UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, DC 20549

Form 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2015

or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission file number: 001-37378

ATYR PHARMA, INC.

(Exact Name of Registrant as Specified in its Charter)

Delaware	**20-3435077**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**
3545 John Hopkins Court, Suite #250, San Diego, CA	**92121**
(Address of Principal Executive Offices)	**(Zip Code)**

(858) 731-8389
(Registrant's Telephone Number, Including Area Code)

Securities registered pursuant to Section 12(b) of the Act:

Title of Each Class	**Name of Each Exchange on Which Registered**
Common Stock, par value $0.001 per share	**The NASDAQ Global Select Market**

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). ☒ Yes ☐ No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer or a smaller reporting company. See definitions of "large accelerated filer", "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ☐ Accelerated filer ☐ Non-accelerated filer ☒ Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Securities Exchange Act of 1934). Yes ☐ No ☒

The aggregate market value of the registrant's common stock held by non-affiliates of the registrant was approximately $282,395,534 based on the closing price of the registrant's common stock on the Nasdaq Global Select Market of $18.52 per share on June 30, 2015. Shares of common stock held by each executive officer and director and each person who beneficially owns 10% or more of the outstanding common stock have been excluded from this calculation. This determination of affiliate status may not be conclusive for other purposes.

The number of outstanding shares of the registrant's common stock, par value $0.001 per share, as of March 24, 2016 was 23,677,303.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's proxy statement to be filed with the Securities and Exchange Commission, or SEC, pursuant to Regulation 14A in connection with the registrant's 2016 Annual Meeting of Stockholders, which will be filed subsequent to the date hereof, are incorporated by reference into Part III of this annual report on Form 10-K. Such proxy statement will be filed with the SEC not later than 120 days following the end of the registrant's fiscal year ended December 31, 2015.

ATYR PHARMA, INC.

ANNUAL REPORT ON FORM 10-K

For the Fiscal Year Ended December 31, 2015

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In this Annual Report on Form 10-K, Annual Report, unless the context requires otherwise, "aTyr Pharma," "aTyr," "Company," "we," "our," and "us" means aTyr Pharma, Inc. and its subsidiary, Pangu BioPharma Limited.

The market data and certain other statistical information used in this Annual Report are based on independent industry publications, governmental publications, reports by market research firms or other independent sources. Some data are also based on our good faith estimates. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information.

We own various U.S. federal trademark applications and unregistered trademarks, including our company name and Resolaris™. All other trademarks or trade names referred to in this Annual Report are the property of their respective owners. Solely for convenience, the trademarks and trade names in this prospectus are referred to without the symbols ® and ™, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto.

Forward-Looking Statements

This Annual Report on Form 10-K contains “forward-looking statements” that involve risks and uncertainties, as well as assumptions that even if they never materialize or prove incorrect, could cause our results to differ materially from those expressed or implied by such forward-looking statements. We make such forward-looking statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. All statements other than statements of historical facts contained in this Annual Report on Form 10-K are forward-looking statements. In some cases, you can identify forward-looking statements by terms such as "may," "will," "expect," "anticipate," "estimate," "intend," "plan," "predict," "potential," "believe," "should" and similar expressions. Forward-looking statements in this Annual Report on Form 10-K include, but are not limited to, statements about:

- the success, cost and timing of our clinical trials, including our ongoing Phase 1b/2 trials of Resolaris, and whether the results of our trials will be sufficient to support domestic or foreign regulatory approvals;
- the likelihood and timing of regulatory approvals for Resolaris, iMod.Fc and any of our other product candidates;
- our ability to identify and discover additional product candidates;
- whether our existing capital resources will be sufficient to enable us to complete any particular portion of our planned clinical development of Resolaris;
- our ability to obtain, maintain, defend and enforce intellectual property rights protecting our product candidates;
- our estimates of our expenses, ongoing losses, future revenue, capital requirements and our needs for or ability to obtain additional financing;
- performance of third-party service providers and independent contractors upon whom we rely to conduct our clinical trials and to manufacture our product candidates or certain components of our product candidates;
- our ability to develop sales and marketing capabilities or to enter into strategic partnerships to develop and commercialize Resolaris or any of our other product candidates;
- the timing and success of the commercialization of Resolaris, iMod.Fc or any of our other product candidates;
- the rate and degree of market acceptance of our product candidates;
- the size and growth of the potential markets for our product candidates and our ability to serve those markets;
- regulatory developments in the United States and foreign countries;
- the success of competing therapies that are or may become available;
- our ability to attract and retain key scientific, medical or management personnel; and
- other risks and uncertainties, including those described under Part I, Item 1A, Risk Factors in this Annual Report on Form 10-K.

The cautionary statements made in this report are intended to be applicable to all related forward-looking statements wherever they may appear in this report. We urge you not to place undue reliance on these forward-looking statements, which speak only as of the date of this report. Except as required by law, we assume no obligation to update our forward-looking statements, even if new information becomes available in the future.

PART I

Item 1. Business

Overview

We engage in the discovery and clinical development of innovative medicines for patients suffering from severe, rare diseases using our knowledge of Physiocrine biology, a newly discovered set of physiological modulators. We have discovered approximately 300 Physiocrines (*physio* for life and *crine* for specific activity), a class of naturally occurring proteins that we believe promote homeostasis, a fundamental process of restoring stressed or diseased tissue to a healthier state. Physiocrines are extracellular signaling regions of tRNA synthetases, an ancient family of enzymes that catalyze a key step in protein synthesis. We believe that Physiocrines have evolved over time to modulate important cellular pathways by interacting with various types of cells, including immune and stem cells. Approximately 100 of these proteins interact with the immune system, which we believe presents a significant therapeutic opportunity to restore affected tissues to a healthier state through natural immuno-modulation mechanisms. We successfully completed a Phase 1 clinical trial of Resolaris, our first development candidate from our discovery engine, and three cohorts of a multi-national exploratory Phase 1b/2 clinical trial of Resolaris in adult patients with facioscapulohumeral muscular dystrophy, or FSHD, a severe, rare genetic myopathy with an immune component, for which there are currently no approved treatments. We are currently conducting three open label trials in patients with early onset FSHD, in adult patients with FSHD or limb-girdle muscular dystrophy 2B, (LGMD2B; dysferlinopathies), and a long term extension study in adult patients with FSHD. By leveraging our discovery engine and our knowledge of rare diseases, we aim to build a proprietary pipeline of novel product candidates with the potential to treat severe, rare diseases characterized by immune dysregulation. We plan to independently commercialize our Physiocrine-based therapeutics.

Our scientists were the first to identify the Resokine pathway (*reso* for restoring skeletal muscle health and *kine* for activity related to cytokines), an extracellular pathway in human skeletal muscle tissue associated with activities arising from various Physiocrine regions of the histidine aminoacyl tRNA synthetase, or HARS. We believe that the Resokine pathway, among its various activities, modulates the immune system to promote tissue homeostasis. We believe the Resokine pathway may play an important role in muscle and lung health. Certain patients with antisynthetase syndrome, a rare auto-immune disease, have antibodies, known as Jo-1 antibodies, to HARS. These Jo-1 antibody patients often develop two significant clinical manifestations, inflammatory skeletal myopathy and interstitial lung disease, or ILD. We believe that the binding of Jo-1 antibodies, particularly to the immuno-modulatory domain of HARS, or iMod domain, blocks HARS immuno-modulatory functions and results in the muscle and lung diseases observed in these Jo-1 antibody patients.

We are harnessing the Resokine pathway and its association in skeletal muscle with homeostasis to develop Resolaris as a potentially first-in-class therapeutic for patients with severe, rare myopathies with an immune component, or RMICs, for which there are limited or no approved treatments. A myopathy is a disease of skeletal muscle tissue, characterized by muscle fiber deterioration, muscle weakness and often an immune response in the affected muscle tissue. In contrast to most current immunology drugs, which are engineered antagonists of immunological pathways, Resolaris is derived from a naturally occurring protein, HARS, which we believe has the potential to reset the immune system in diseased tissue to a more normal state while maintaining the immune system's activity against exogenous, pathogen-based insults. We observed that stimulation of the Resokine pathway through the introduction of Resolaris and its derivatives in rodent models of both severe inflammation and myopathy led to immuno-modulatory effects. We have shown that stimulation of the Resokine pathway by Resolaris alters immune responses and the expression or release of immune-related proteins from cells in response to inflammation. HARS, which contains the immuno-modulatory domain, is also released from human skeletal muscle. In addition to its immuno-modulatory properties, we believe the Resokine pathway may act on other physiological processes, including processes associated with stem cells, fibrosis and endothelial cells.

Since the identification of the Resokine pathway, we have successfully advanced Resolaris through preclinical development, current Good Manufacturing Practice, or cGMP, manufacturing, an initial Phase 1 clinical trial and three cohorts of first exploratory Phase 1b/2 trial in adult FSHD patients. In the first quarter of 2014, we completed a double-blind, placebo-controlled Phase 1 clinical trial of Resolaris, in which we assessed its safety and tolerability in 32 healthy subjects. Resolaris was shown to be well tolerated at all doses tested, and no serious adverse events were reported. Based on the favorable clinical safety, pharmacokinetic and immunogenicity profile of Resolaris in this trial, we decided to advance Resolaris into clinical trials of RMIC patients.

We recently announced results from our multi-national exploratory Phase 1b/2 clinical trial of Resolaris in adult patients with FSHD in the United States and European Union. This randomized, double-blind, placebo-controlled trial was designed to evaluate the safety, tolerability, pharmacokinetics and exploratory pharmacodynamics markers and clinical assessments of multiple intravenous doses of Resolaris in adults with FSHD. We completed three dose escalation cohorts of 0.3, 1.0 and 3.0 mg/kg. We believe the safety, tolerability, immunogenicity and activity profile of Resolaris as demonstrated in this study warrants advancing our program in adult FSHD patients and potentially other rare diseases.

Our initial therapeutic efforts target severe, rare disease indications in which patients suffer from the immune-related consequences of their genetic disease. We have identified over 20 distinct, molecularly definable RMIC indications, including FSHD and LGMD2B, in which we believe Resolaris has the potential to target the immune component of these genetic diseases. In 2015, we made progress in our therapeutic efforts by initiating new clinical studies in patients to further investigate Resolaris. We initiated three additional trials, including a long term safety extension study, a study in adult patients with FSHD or a second rare genetic myopathy, LGMD2B, and a study in patients with early onset FSHD.

During 2015, we made advancements in our pre-clinical research through protein engineering, generating and testing the exposures in animals of multiple configurations of the iMod domain of the Resokine pathway, an immuno-modulatory Physiocrine domain. In the fourth quarter of 2015, we announced the selection of an investigational new drug (IND) candidate based on this iMod domain fused to the Fc region of a human antibody, iMod.Fc. We have selected this iMod.Fc molecule as our second product development candidate and it represents an expansion of our new class of Physiocrine-based therapeutics. With the selection of this iMod.Fc molecule, we are harnessing the Resokine pathway and plan to test its potential role in lung disease, and to develop iMod.Fc as a potential therapeutic for patients with rare pulmonary diseases with an immune component, or RPICs.

We also believe our proprietary inventory of Physiocrines and their diverse functions have potential therapeutic application in a variety of diseases characterized by tissue dysfunction, including severe diseases of the lung, gut, skin, brain and liver. We intend to leverage our unique understanding of Physiocrines and our broad intellectual property portfolio, which we believe covers this entire class of potential protein therapeutics, to build a pipeline of product candidates that we expect to develop and commercialize independently for the treatment of various rare diseases.

We were founded in 2005 by Paul Schimmel, Ph.D. and Xiang-Lei Yang, Ph.D., two leading aminoacyl tRNA synthetase scientists at The Scripps Research Institute in San Diego, California. Our Chief Executive Officer, John D. Mendlein, Ph.D., was formerly the Chief Executive Officer of Adnexus Therapeutics, Inc. (acquired by Bristol-Myers Squibb Company) and Affinium Pharmaceuticals, Ltd. (acquired by Debiopharm Group), and held various roles at Aurora Biosciences Corporation (acquired by Vertex Pharmaceuticals Incorporated). We have assembled an executive team with broad experience in the discovery, development and commercialization of innovative therapeutics, including transformative therapies for rare genetic diseases such as Kalydeco, marketed by Vertex Pharmaceuticals Incorporated for the treatment of cystic fibrosis. We are advised by a Therapeutic Advisory Board and a Scientific Advisory Board, both comprised of leaders in the field of biology for medical applications, including our special advisor in immunology, Bruce Beutler, M.D., recipient of the 2011 Nobel Prize in Physiology or Medicine for his work in immunology.

Our Strategy

We aim to capitalize on Physiocrine biology, a new and important area of human biology, to develop first-in-class medicines to treat patients with severe diseases characterized by an immune component. Key elements of our strategy include the following:

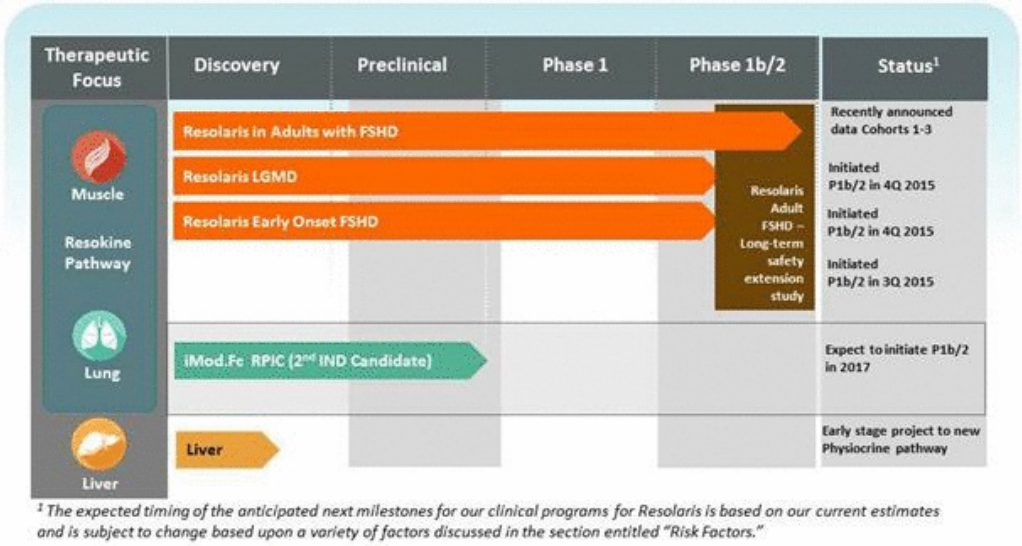
- ***Leverage our leadership position in Physiocrine biology to develop and commercialize novel, first-in-class medicines for patients affected by severe, rare diseases with significant unmet need.*** We focus on patients with severe, rare genetic diseases because we believe that the stimulation of Physiocrine pathways in these patients can restore diseased tissue to a more normal phenotype. Our strategy is to focus initially on indications where current treatment options are limited and our product candidates have the potential to provide transformative therapeutic benefit to patients given the severity of the diseases. We believe our initial focus on rare diseases will allow us to more effectively deploy investor capital for the independent development and commercialization of medicines for the benefit of patients and our stakeholders.
- ***Rapidly and prudently pursue the development, regulatory approval and commercialization of Resolaris and iMod.Fc to treat patients across multiple severe disease indications***. We intend to expeditiously pursue the development and regulatory approval of Resolaris in multiple RMICs. We are currently evaluating Resolaris in two Phase 1b/2 clinical trials and a Phase 1b/2 long term safety extension trial. These studies include adult FSHD and LGMD2B patients, as well as a study in early onset FSHD patients. We recently reported results from our first clinical trial in adult patients with FSHD in which data showed the Resolaris safety, tolerability, immunogenicity, pharmacodynamics and activity profile warrants advancing our program in adult FSHD patients and potentially other rare diseases. We also intend to develop iMod.Fc, our second product candidate based on the Resokine pathway, for RPIC indications. To bolster our clinical understanding of Resolaris, we may additionally evaluate Resolaris in other diseases with an immune component including those that are more common.

- ***Leverage our discovery engine to build a pipeline of first-in-class Physiocrine medicines to address severe conditions characterized by immune pathway dysfunction or fibrosis***. Based on our understanding of the biology of Physiocrines, we believe that this class of naturally occurring proteins has the potential to produce therapeutic benefits across a broad range of disease indications associated with an inappropriately amplified immune response, or where fibrosis contributes to disease associated with specific organs. We plan to leverage our discovery engine to identify other Physiocrine pathways of interest and select additional potential product candidates for preclinical and clinical investigation in a variety of disease settings on a tissue-by-tissue basis, which may include severe, currently inadequately treated diseases of the lung and liver.
- ***Retain exclusive worldwide commercial rights to our product candidates to pursue autonomous commercialization***. We intend to build a pipeline of product candidates, the rights to which we solely own or exclusively license, that we can commercialize independently through a relatively small, dedicated commercial organization focused on patient needs and directed at a limited number of physicians who specialize in the treatment of our target patient populations. While we do not expect to require pharmaceutical partners for commercialization of our product candidates, we may consider partnering for strategic purposes, including enhancing our pipeline efforts.
- ***Expand our knowledge and intellectual property position in Physiocrine biology by emphasizing continuous scientific and business improvements***. We will continue to aggressively pursue new scientific and therapeutic insights into Physiocrine biology through internally developed *in vivo* and *in vitro* screening systems in conjunction with genetic analysis and disease associations of Physiocrines, as well as in partnership with academic institutions and disease societies. We intend to leverage our leadership position in this field to broaden our intellectual property positions both in our most advanced programs and for additional therapeutic applications of Physiocrines. We will continue to vigorously prosecute and defend our patent portfolio, as well as exploit our proprietary position to strategically advance our business.
- ***Build a world class organization oriented to patients and focused on rigorous scientific, clinical and industrial advancements***. We have assembled a world class team with industry-recognized expertise in biology, medicine and the commercialization of innovative and important therapeutics. We intend to continue to build on our leadership position in Physiocrine and immunology-based therapeutics and to grow an organization and culture dedicated to the development and commercialization of medicines with the potential to positively transform the lives of patients with severe, rare diseases. We intend to maintain and expand our relationships with key opinion leaders, patient advocacy groups and other business partners, and to solicit input from payors and others in the healthcare industry, to identify and develop our product opportunities and to design our development programs in order to maximize the availability of our product candidates to patients.

Product Development Programs

Our Pipeline—A New Set of Treatment Mechanisms for Patients

We believe that, as the first and only company engaged in the clinical development of therapeutics based on Physiocrine biology, we are positioned to develop and commercialize a pipeline based on a novel class of protein therapeutics, protected by intellectual property rights that we own or exclusively license, that modulate important physiological processes. Below are summaries of our product development pipeline and discovery engine process:



[1] *The expected timing of the anticipated next milestones for our clinical programs for Resolaris is based on our current estimates and is subject to change based upon a variety of factors discussed in the section entitled "Risk Factors."*

Our research suggests that Physiocrines act through basic mechanisms of innate and adaptive immunity, as well as other pathways, in a way that is distinct from existing classes of protein therapeutics. We believe Physiocrines have evolved, among other things, to balance the immune system, resolving inflammation naturally, in contrast to currently available immuno-modulatory therapeutics, which are engineered inhibitors of pro-inflammatory pathways. We intend to harness these mechanisms of Physiocrines to benefit patients with severe diseases in ways that we believe have advantages over traditional antibody and small molecule approaches.

Physiocrines: Harnessing a Newly Discovered Source of Innovative Therapeutics

The Promise of Physiocrine-Based Medicines in Promoting Homeostasis

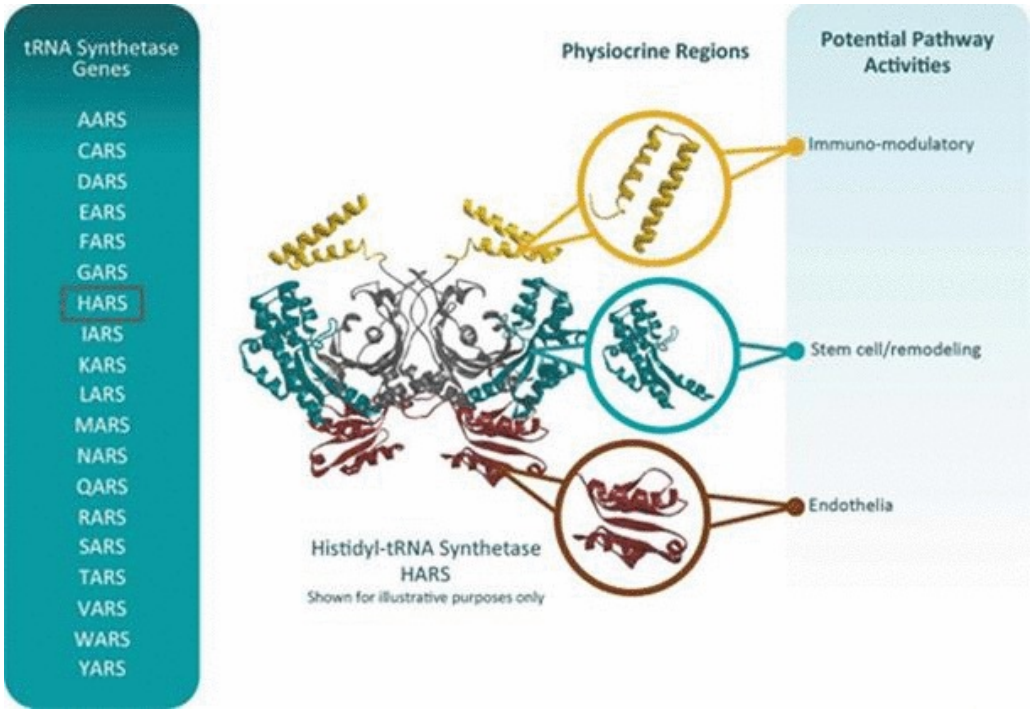
Homeostasis, or the coordinated regulation of tissues within the body, is fundamental to the maintenance of the overall health of an organism and a key feature of multicellular life. Lack of homeostasis can lead to disease and death. The process of homeostasis was first described in 1865 by the French physiologist Claude Bernard and Walter Cannon later coined the term. In the 150 years since this discovery, many proteins associated with homeostatic pathways have been discovered, ranging from insulin to erythropoietin, or EPO.

Using our knowledge of bioinformatics, sequencing, proteomics and structural biology, we identified Physiocrines, a novel class of proteins that are present as biologically active signaling regions of the tRNA synthetases, an ancient protein family. We believe that Physiocrines are involved in orchestrating homeostatic activities to help the body restore diseased or damaged tissue to a healthier state. We have observed that certain Physiocrines exhibit previously undescribed extracellular activities that are involved in restoring and regulating tissues to promote health. We believe that physiological perturbations, such as stress or changes in physiological state, alter or induce the release of Physiocrines from cells or platelets in the human body. Physiocrines have been observed to be released from a wide variety of cells, including in response to such stimuli as starvation-induced apoptotic stress or the introduction of certain cellular ligands, including tumor necrosis factor alpha and vascular endothelial growth factor.

Physiocrine Biology Overview

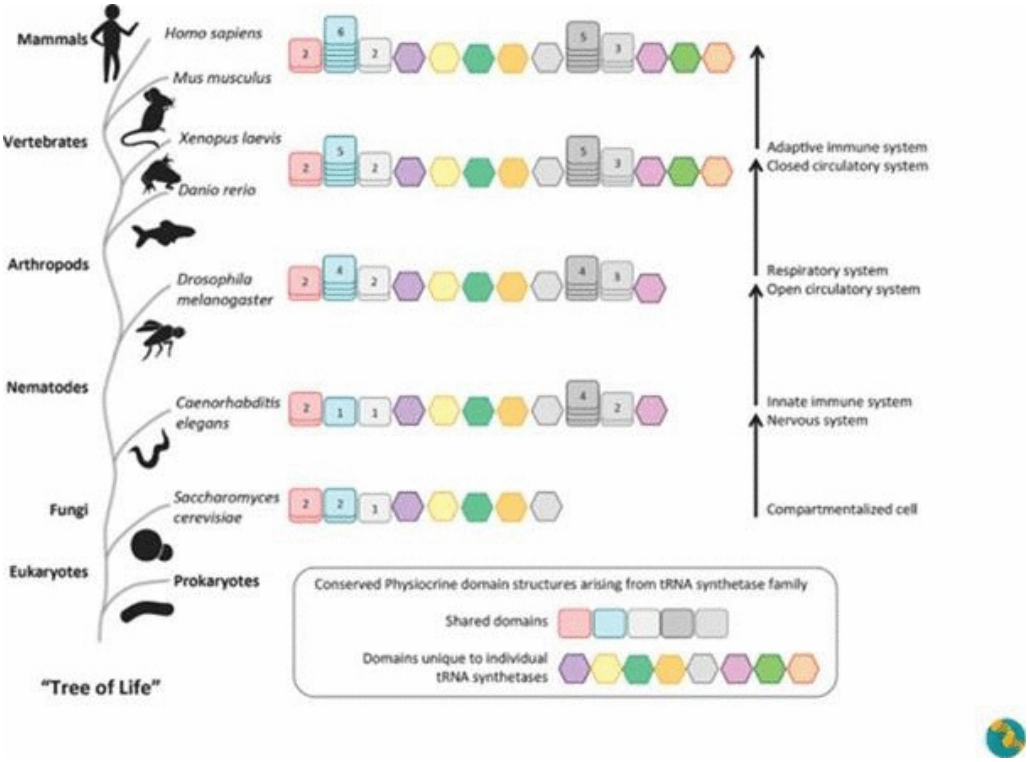
The Discovery of Physiocrines

In 1999, our founder, Dr. Paul Schimmel, published in *Science* a structural and functional description of extracellular signaling regions of a specific aminoacyl tRNA synthetase. tRNA synthetases are an ancient family of enzymes that were generally thought to only be involved in protein synthesis. Since Dr. Schimmel's discovery, numerous papers have been published on the alternative activities of tRNA synthetases. We refer to the extracellular signaling regions of tRNA synthetases illustrated in the figure below, along with other later-discovered or splice variant regions of tRNA synthetases, as Physiocrines. A splice variant is a variation of a gene transcript.



There are 20 known human cytosolic tRNA synthetases, each coding for one of the 20 amino acids. Amino acids, when bonded together, form full-length functional proteins. There are about 15 potential Physiocrines on average per tRNA synthetase, including Physiocrine regions in a full length tRNA synthetase protein, splice variants from a tRNA synthetase gene, or proteolytic fragments from a full length protein. We believe Physiocrines interact with various proteins important in extracellular activities, including G protein-coupled receptors, cytokine receptors, tyrosine kinase receptors and extracellular matrix proteins.

Our founding mandate was to focus on the systematic interrogation of the tRNA synthetase gene family through bioinformatics and structural analysis. Our research, along with that of The Scripps Research Institute, revealed that although the genetic sequence of each of the 20 tRNA synthetase genes changed at multiple times over four billion years by the genetic mutation of tRNA synthetases, including the insertion of DNA sequences, protein synthesis, however, as characterized by tRNA synthetase activity, remained relatively unchanged over that period of time. As illustrated in the figure below, the structural diversity of proteins resulting from the inserted genetic material increased as living organisms became more complex and as fundamental physiological systems, including immunological, stem cell, muscular, circulatory, respiratory and neural systems, developed.



The results of this research suggested to us that tRNA synthetases retained a core function in protein synthesis over four billion years, while developing other important and diverse physiological functions associated with Physiocrines. We believe these functions could serve as a source of therapeutics directed at stimulating pathways involved in the restoration of homeostasis.

The Function of Physiocrines in Fundamental Pathways of Life

Based on the research suggesting that Physiocrines are potentially important modulators of cellular pathways, we hypothesized that Physiocrines may play roles in such fundamental processes as immunology, stem cell biology, neurology, vascular biology, skeletal muscle biology, hepatic (liver) biology and metabolic biology. To test this, we expressed and purified over 200 Physiocrine regions across the family of 20 tRNA synthetase genes and evaluated these purified Physiocrines in numerous cell-based assays to determine their activity in several important human physiological pathways. Some of the data were published in July 2014 in *Science*, with the data categorized according to important areas of biology. The table below describes several key areas of biology in which Physiocrines may present therapeutic opportunities:

Cellular Pathways	Number of Physiocrines	Potential Therapeutic Applications
Immunology	99	Rare Diseases with an Immune Component, Auto-immune Disorders, Oncology and Fibrosis
Stem Cells	129	Regenerative Medicine, Fibrosis and Oncology
Neurology	34	Neurodegenerative Diseases
Vascular	35	Cardiovascular Diseases, Oncology and Immunology
Skeletal Muscle	130	Skeletal Muscle Diseases
Hepatic	76	Liver Fibrosis
Metabolic	22	Diabetes and Obesity

Our current research includes efforts to understand the relationship of various Physiocrine pathways to health and disease and the potential for a particular Physiocrine pathway to provide a valuable therapeutic intervention point. In addition, various independent research sites across the world are conducting genetic analysis of DNA from patients with rare phenotypes and mutations to tRNA synthetases. Laboratories are also investigating the connection between tRNA synthetases and various cancers and auto-immune diseases.

Physiocrine Pathways as Therapeutic Intervention Points

Our Initial Focus on Immuno-Modulation

Many important therapeutics act in connection with physiological pathways, including growth factor and differentiation pathway agonists, such as insulin and erythropoietin, or EPO; growth factor pathway antagonists, such as vascular endothelial growth factor antagonists; immune pathway antagonists, such as tumor necrosis factor antagonists; immune pathway agonists, such as interferon; and metabolic pathway modulators, such as glucagon-like peptide-1 (GLP-1). We are initially focused on the application of Physiocrines to immuno-modulation in rare diseases. We selected immuno-modulation as our initial area of focus for the following reasons:

- We believe immunology plays a significant role in most diseases, including genetic diseases;
- A number of Physiocrines have been shown to be differentially expressed in immune cells;
- A large number of Physiocrine pathways appear to relate to immunology, as at least seven different tRNA synthetase proteins are associated with certain immune-driven diseases; and
- Approximately 100 Physiocrines have demonstrated activity in various cell-based assays related to immunological pathways.

Additionally, we focus on modulators of immune and fibrotic processes for indications that represent severe, rare diseases, particularly genetically based diseases, because:

- Our scientific understanding of Physiocrines as potential immuno-modulators and modulators of fibrotic processes that intersected with multiple rare diseases;
- We believe patients with rare genetic diseases often face challenges related to the responses of their immune and remodeling fibrotic systems to changes in tissues that are caused by their genetic mutations; and
- We believe the pathological immuno-phenotypes in rare diseases present an opportunity for us to therapeutically intervene with greater impact.

Advantages of Physiocrine-Based Therapeutics

Most current immunological based drugs are engineered antagonists of immunological pathways, typically acting to lower elevated immune responses resulting from disease, as in the case of monoclonal antibodies acting against circulating signaling molecules, such as cytokines. Although these signaling molecules may be up-regulated in disease, their natural levels and fluctuations have evolved to include non-disease functions of the immune system, mediating a wide range of physiological activities, as opposed to evolving to cause or contribute to disease. Our discovery and development efforts focus on therapeutics derived from naturally occurring proteins. We believe that Physiocrines have naturally evolved to reset the immune system to control or reduce tissue damage while maintaining the immune system's activity against exogenous pathogen based insults, and may possess the following advantages over engineered antagonists of immunological pathways:

- As proteins designed by nature to reset the immune system, Physiocrines may provide a unique mechanism to improve patient outcomes through their activity in either a single or multiple pathways;
- Physiocrines have the potential to reset the immune system across multiple pathways at the level of an immune cell, rather than lowering the levels of a single immune protein like most engineered antagonists;
- Physiocrines may potentially act as agonists at the level of the immune cell to reduce pro-inflammatory effects and induce resolution of immune activity or inflammation;
- The therapeutic effects of Physiocrines may persist even after the Physiocrines have been cleared from circulation; and
- Physiocrines present the potential for fewer, if any, immuno-suppressive effects, as compared to engineered antagonistic immuno-modulators.

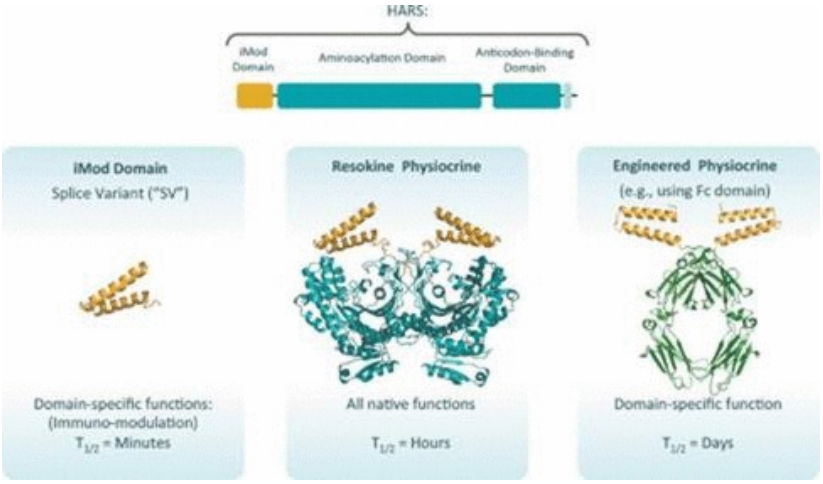
The Resokine Pathway and Resolaris, Our First Clinical Product Candidate

Identification of the Resokine Pathway through In Vivo Screening Approaches

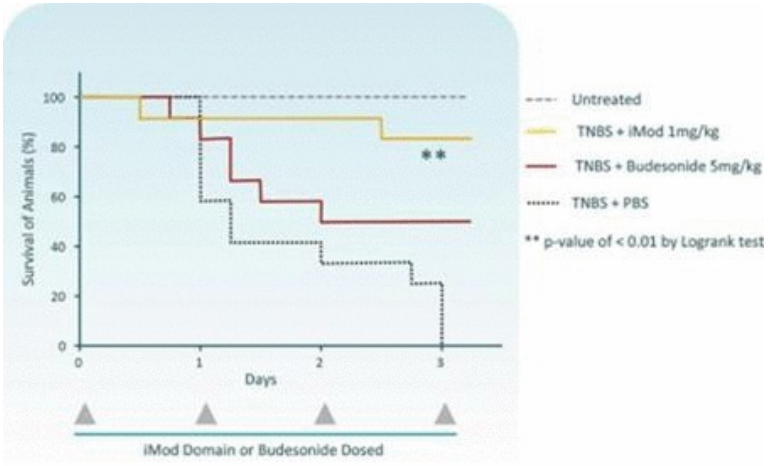
Our scientists discovered the Resokine pathway in human skeletal muscle using our *in vivo* screening systems in models of severe inflammation, combined with our knowledge of the effects of antibody binding to a specific tRNA synthetase in a population of patients with a particular rare myopathy. The Resokine pathway encompasses physiological activities, including potential immuno-modulatory and other muscle health activities, arising from various Physiocrine regions of the histidine aminoacyl tRNA synthetase, or HARS. Animal studies and human pathophysiological data have shown that antibody-based blockade of the Resokine pathway may lead to muscle tissue deterioration and immune cell invasion.

First Demonstration of a Region of HARS as an Immuno-modulator

We conducted *in vivo* screening activities of a splice variant from HARS that we identified in our deep sequencing studies, which we refer to as the immuno-modulatory domain, or iMod domain, of HARS. The figure below depicts the iMod domain and other forms of HARS:



For our studies of the iMod domain, we selected a rodent model of severe immune cell activity or inflammation induced by the administration of trinitrobenzene sulfonic acid, or TNBS, in which the inflammation is thought to be driven by excessive T-cell involvement in the gut, leading to the death of the study animals. Animals administered the iMod domain survived longer than those given either the vehicle control phosphate buffer solution, or PBS, or an approved drug control (Budesonide) ($p<0.01$), demonstrating the potential activity of the iMod domain as an immuno-modulator of excessive T-cell involvement. The results of this study are summarized in the graph below:



Additionally, we have demonstrated in the same rodent model of inflammation in the gut that at least two other related molecules, Resolaris and iMod.Fc, both of which are derived from HARS and contain the iMod domain, are active in models of excessive T-cell involvement. Based on these observations, we believe that blockade of the activity of the iMod domain may contribute to excessive or inappropriate T-cell involvement in immune-driven diseases.

Evidence of the Role of the Resokine Pathway in Rare Muscle and Lung Diseases

In 1983, Matthews and Bernstein published in *Nature* the observation that patients with a rare myopathy possessed antibodies to a single tRNA synthetase, HARS. Since then, it has been observed that patients with auto-antibodies to HARS (but not antibodies to the other 19 tRNA synthetases in the same patients) can develop both a debilitating myopathy characterized by weakness and skeletal muscle loss, and interstitial lung disease, or ILD, both of which are characterized by T-cell invasion. Numerous research laboratories have verified the existence of anti-HARS antibodies, or Jo-1 antibodies, as one of the manifestations of the auto-immune disease, anti-synthetase syndrome.

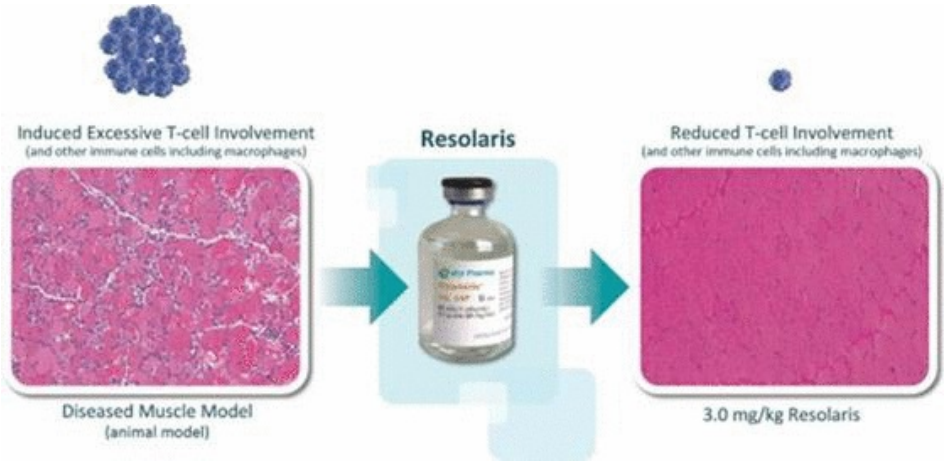
Based on these observations, we chose to study the potential link between HARS antibodies and muscle disease in anti-synthetase syndrome patients with Jo-1 antibodies. Our scientists obtained serum samples from 18 of these patients to determine whether the Jo-1 antibodies specifically bound to the iMod domain. We determined that in each of the 18 Jo-1 antibody positive patients studied, a significant portion of Jo-1 antibody binding was to the iMod domain, compared to binding to other regions of HARS. We believe that in these patients, the binding of Jo-1 antibodies to the iMod domain blocked the immuno-modulatory properties of the iMod domain, therefore contributing to their myopathy and ILD. Independent laboratories have also observed in unrelated studies that the iMod domain is the primary antibody binding region in Jo-1 antibody patients with anti-synthetase syndrome.

Additional Confirmatory Studies of the Blockade of the Resokine Pathway in Animals

We have conducted studies that suggest that antibody blockade of the Resokine pathway contributes to immune cell invasion in skeletal muscle and lung tissue. Recently published animal studies by a third party laboratory are consistent with our findings. In particular, in 2014, Sciorati *et al*. published on the effect in rat skeletal muscle of antibodies to the iMod domain produced by vaccination, generating additional evidence that the Resokine pathway plays a role in skeletal muscle health and the immune system. The Sciorati study demonstrated: (1) antibody generation to the iMod domain of HARS; (2) levels of creatine kinase, or CK, a biomarker of muscle destruction, increased in relation to antibody levels; (3) antibodies to the iMod domain correlated with an increase in muscle inflammation, as observed by magnetic resonance imaging, or MRI; and (4) the MRI signal corresponded to muscle destruction, as judged by histology. The data generated by Sciorati *et al*. are consistent with our conclusions that the Resokine pathway was reduced or blocked in Jo-1 antibody patients as a result of antibodies against the iMod domain.

Altering Excessive T-cell Invasion in Preclinical Studies of Resolaris in Skeletal Muscle

We also tested Resolaris in a rodent model in which statins, which are known to induce myopathies in humans and rodents, were administered to induce a severe, aggressive myopathy. In the study, rats were administered statins for two weeks, and at Day 8, treatment with Resolaris was started. After a week of daily treatment with Resolaris, we observed a dose dependent change in the histologic phenotype of the treated animals, from excessive immune cell invasion to nearly normal histology and immune cell levels, as compared to animals in the control group, as shown in the figure below:



Resolaris Mechanism of Action: T-cell Modulation and Other Potential Pathways

Our *in vivo* studies suggest that stimulation of the Resokine pathway through or with Resolaris combats pathophysiological changes in three established animal models of excessive T-cell involvement in which approved drugs have been tested. Our *in vitro* studies of Resolaris suggest that at least one of the activities of Resolaris includes a direct action on T-cells to reduce, but not completely block, cytokine release. This reduction also lasts for at least 24 hours after Resolaris has been removed from the T-cells. This suggests that the pharmacodynamic effect of Resolaris *in vivo* could be longer than the pharmacokinetics of the protein. It also suggests that there is at least one T-cell associated receptor for Resolaris, such as a cytokine or chemokine receptor. We observed Resolaris' effect on human T-cells by monitoring IL-2 levels over time.

Additional cell-based assays show that specific regions of Resolaris may harbor additional activities similar to Physiocrine regions from the HARS protein, including stem cell/remodeling and endothelia pathways.

Additionally, we have looked for direct antagonist activities of Resolaris on certain cytokines. Resolaris does not appear to act as a direct ligand antagonist, but rather appears to act more globally at the level of immune cells and potentially other cell types. HARS is also released directly from human skeletal muscle *in vitro* , and blocking HARS with antibodies after stimulated release by insulin-like growth factor, or IGF-1, reduces the effect of IGF-1 in muscle differentiation.

Resolaris for the Treatment of Multiple Rare Myopathies with an Immune Component (RMICs)

Overview

We are developing Resolaris as a potentially first-in-class intravenous protein therapeutic for the treatment of rare myopathies with an immune component, or RMICs. We have identified over 20 distinct, molecularly definable RMIC indications that we believe Resolaris has the potential to treat. In each of these indications, skeletal muscle tissue exhibits dysfunction and becomes subject to immune cell invasion, which contributes to the loss of function and deterioration of the muscle tissue. RMIC patients generally present with three common characteristics:

- expression of aberrant protein (in the case of genetically based RMIC indications);
- immune cell invasion; and
- muscle cell damage and deterioration.

In normal muscle, muscle mass and function require a balance between muscle cell stress and damage and muscle cell regeneration and growth. The immune system helps maintain this balance by "cleaning up" damaged muscle cells after muscle damage and during the healing process. In RMIC diseases, the balance is tipped to favor chronic pathophysiological muscle deterioration and persistent immune cell invasion. In genetically based RMIC diseases, aberrant protein expression often occurs, as in the case of FSHD patients with inappropriate expression of a protein not normally expressed in muscle. As discussed above, *in vivo* rodent models of skeletal muscle deterioration and immune cell invasion have shown that Resolaris can combat immune cell invasion into the muscle and muscle deterioration. Conversely, experiments in rodents have shown that antibody blockade of the Resokine pathway can lead to immune cell invasion and muscle tissue deterioration.

We intend to harness the body's power to restore skeletal muscle after stress or damage in the development of Resolaris for RMIC patients who have limited or no approved treatment options. We believe Resolaris can offer a potential multi-pharmacologic therapeutic, synergistically modulating multiple pathways important to muscle health. Our proprietary position for Resolaris includes an issued U.S. patent covering the composition of matter of Resolaris, as well as various patent applications relating to specific methods of use of Resolaris and related proteins.

Resolaris: Potential Specific Therapeutic Applications in RMICs

We believe Resolaris will provide therapeutic benefit to patients in RMIC indications characterized by excessive immune cell involvement, particularly a type of T-cell known as CD8 T-cells and macrophages. Dysregulated immune cell invasion can cause and exacerbate muscle damage and stress. For example, CD8 T-cells have been observed to contribute to muscle damage by the release of proteins that destroy or damage skeletal muscle cells. The table below describes RMIC indications in which the relationship between diseased muscle and the immune system has been observed by others, which we believe may be addressed by the proposed mechanism of action of Resolaris.

Disease Area	Type of RMIC	Molecular Definition of Disease (Estimated U.S. Population)	Immune Features	Potential Resolaris Mechanism of Action
Rare myopathies with an immune component (RMIC)	Genetic	Facioscapulohumoral muscular dystrophy, or FSHD (19,000) 3 genetic forms*	CD8 T-cell infiltration Macrophage infiltration Pro-inflammatory cytokine production, including: MCP-1, IL-6 and IL-12	In preclinical models *in vivo*, Resolaris reduces (i) the infiltration and accumulation of CD8 T-cells; (ii) the expression of cytokines, including MCP-1, IL-6 and others; and (iii) biomarkers, such as MMP9. *In vitro* studies using Resolaris also demonstrate reduction of a variety of pro-inflammatory cytokines, including IFN gamma and IL-17A, as well as the activity of pro-inflammatory macrophages.
		Limb-girdle muscular dystrophy, or LGMD (16,000); LGMD2B (~3,000) >30 genetic forms*	T-cell infiltration	
		Duchenne muscular dystrophy, or DMD (5,600-18,000) >50 genetic forms*	CD8 T-cell infiltration Macrophage infiltration MMP9, TIMP1, TNFα	
		>10 undisclosed muscular dystrophies	To be determined	
	Autoimmune	Sporadic Inclusion Body Myositis, or sIBM	CD8 T-cell infiltration	
		Myositis with at least one molecular marker (such as auto-antibodies)	Macrophage infiltration Pro-inflammatory cytokine production, including MCP-1	

* By use of the term "genetic form," we mean a molecularly defined marker that includes (1) changes in a chromosome structure, (2) different genes that are mutated or (3) a single gene with multiple points of mutation.

Legend:
IL-6: Interleukin-6
IL-12: Interleukin-12
MCP-1: Monocyte Chemotactic Protein 1
MMP9: Matrix Metallopeptidase 9
TIMP1: Tissue Inhibitor of Metalloproteinase-1
TNF-α: Tumor Necrosis Factor alpha

Resolaris: Our Clinical Development Program

We are discovering and developing protein based therapeutics leveraging the novel extra-cellular functions of tRNA synthetases to restore and maintain tissue homeostasis. The initial Physiocrine-based therapeutic from our discovery pipeline, Resolaris, entered clinical development in 2013. We are pursuing a clinical development strategy that not only will inform the therapeutic potential of Resolaris in RMIC indications but will also inform the therapeutic potential of Physiocrine-based therapeutics as a class. The strategy has as its foundation the extensive evaluation of the safety and tolerability of the administration of Physiocrine-based therapeutics to human subjects.

We successfully completed a single ascending dose Phase 1 clinical trial in healthy subjects of Resolaris, our first development candidate from our discovery engine for therapeutic applications of Physiocrines. We recently announced results from our multi-national Phase 1b/2 clinical trial of Resolaris in adult patients with facioscapulohumeral muscular dystrophy, or FSHD, a severe, rare genetic myopathy in which immune cells invade diseased skeletal muscle, for which there are currently no approved treatments. The data from this study showed the Resolaris safety, tolerability, immunogenicity and activity profile warrant advancing our program in adult FSHD patients and potentially other rare diseases. In 2015, we initiated three additional trials, including a long term safety extension study, a study in adult patients with FSHD or LGMD2B, a second rare genetic myopathy, and a study in patients with early onset of FSHD.

Phase 1 Clinical Trial in Healthy Subjects

In the first quarter of 2014, we completed a single ascending dose Phase 1 clinical trial of Resolaris to assess its safety and tolerability in healthy subjects. The planning and design of the trial were guided by the principles that this trial would be the first time that a Physiocrine has been administered to a human subject, and that the therapeutic use of immuno-modulatory drugs are often characterized by poor tolerability and common safety concerns. In particular, we designed this trial as a double-blind, placebo-controlled study in order to rigorously assess safety and tolerability, such as injection site reactions or systemic reactions, and to assess the pharmacokinetics, or PK, immunogenicity and biological activity of single doses of Resolaris in humans. In this trial, 32 healthy adult subjects were randomized to receive a 30 minute intravenous infusion of either placebo or a single dose of 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, or 3.0 mg/kg of Resolaris. Participants were randomly assigned to receive Resolaris or placebo on a 3:1 basis so that within each of the four cohorts, six subjects received Resolaris and two subjects received placebo, and overall, 24 healthy subjects were dosed with Resolaris and eight healthy subjects were dosed with placebo.

Resolaris was found to be well tolerated in all dose cohorts in our Phase 1 clinical trial. There were no serious adverse events or deaths, and the incidence of individual treatment emergent adverse events, or TEAEs, among all groups was low, with no relationship to Resolaris dose level. All TEAEs observed in the trial were mild in intensity and transient, and resolved without treatment-related pathological effects. TEAEs that were considered possibly related to Resolaris were predominantly nervous system symptoms, including single cases of dizziness, headache, and drowsiness. No local tolerability issues related to Resolaris were observed.

We observed no significant changes from normal in over 30 cytokine and other immune-related protein assays after administration of 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, and 3.0 mg/kg of Resolaris in these healthy individuals. These results are consistent with the observed role of the Resokine pathway in resolving inflammation. Systemic exposure and C_{max} were dose proportional, mean total systemic clearance was low and the volume of distribution was small, resulting in a terminal half-life in plasma of approximately three to six hours across all dose levels. Low titer anti-drug antibodies were observed in five subjects out of 24 after administration of Resolaris. One subject out of 24 had similar low titer anti-drug antibodies prior to the administration of Resolaris. The PK of Resolaris was not altered in these subjects. Based on the favorable PK, safety, tolerability and immunogenicity profile of Resolaris in our Phase 1 clinical trial in healthy subjects, we advanced Resolaris into clinical development in RMIC patients.

Resolaris in Facioscapulohumoral Muscular Dystrophy (FSHD)

The process of selecting the first RMIC indication for our Resolaris program involved several steps. First, both genetic and autoimmune forms of RMIC were considered. Then, diseases with high unmet need (no treatment options), severe progressive disease manifestations and clear evidence in scientific literature of an immune component were selected for further exploration. Those in which the muscle tissue itself and the blood clearly reflect the immune dysregulation were prioritized, with those whose immune pathogenesis overlapped with Resolaris activity were further prioritized. These prioritized diseases included several distinct genetic myopathies.

Based on the indication selection process described above, we elected to first pursue FSHD, a rare genetic myopathy in which immune cells invade diseased skeletal muscle and for which there are no approved treatments. The primary clinical phenotype of FSHD is debilitating skeletal muscle deterioration and weakness. The symptoms of FSHD develop in an asymmetric pattern, starting with the face and upper body to the lower body and progressing in a "muscle by muscle" fashion. This is in contrast to other genetic myopathies such as Duchenne muscular dystrophy that usually affect groups of muscles concurrently and symmetrically. These symptoms include musculoskeletal abnormalities such as abnormal protrusion of the shoulder blades or exaggerated bend of the lower spine and, often as the disease progresses, difficulty standing upright, lifting objects, reaching above shoulder level or using the shoulders to support various activities of daily life. Patients also suffer pelvic girdle and lower limb weakness, resulting in progressive difficulty arising from a seated position. Importantly, most patients eventually develop profound weakness in the lower leg and cannot manage to lift the foot of the affected side appropriately. This condition results in frequent falls and related injuries. In addition to debilitating muscle weakness, FSHD patients often experience severe fatigue, muscle deterioration and pain. While FSHD can manifest at any age, the onset of symptoms in many patients occurs before the age of 18. We refer to this patient population as early onset FSHD. We have selected those patients with onset of symptoms before the age of 10 for our current clinical trial. Within the early onset population are individuals with symptom onset at less than five years of age, with progression in disease prior to age ten. These individuals have the most severe muscle symptoms and significant extra-muscular manifestations such as auditory deficits and retinal complications that may result in vision loss. This sub-group of early onset patients are often referred to as having "infantile onset" FSHD.

While estimates of FSHD prevalence vary, studies exploring the topic have identified average prevalence rates of approximately one in 17,000. Applying this rate to the U.S. population, as of November 1, 2014, yields a domestic FSHD population of approximately 19,000, including a domestic "infantile onset" FSHD population of approximately 1,000. FSHD is typically diagnosed by the presence of a characteristic pattern of muscle weakness and other clinical symptoms, as well as through genetic testing of the number of repeats of a specific DNA sequence at the end of Chromosome 4. In normal, unaffected individuals this chromosomal region has from 11 to 100 repeats of the applicable DNA sequence. The term FSHD1 is used to delineate patients in which the genetic basis relates to the deletion of these repeats at the end of Chromosome 4. Patients with FSHD typically have only one to ten of these repeats. The most severe form of FSHD, "infantile onset", is associated with three or fewer repeats. Another form of the disease, FSHD2, occurs in approximately 5% of FSHD patients, and is caused by mutations in the gene *SCHMD1* located on Chromosome 18 of the applicable DNA sequence. In both FSHD1 and FSHD2, the genetic abnormality results in the expression of genes that are normally silent or inactive in skeletal muscle. Consequently, an unusual profile of proteins is produced, which has been linked to FSHD skeletal muscle pathology.

The FSHD immuno-pathology includes an infiltrative inflammatory process (usually dominated by CD8 T-cells and macrophages) that can also be observed by MRI in individual skeletal muscles that are in the early stages of disease. Longitudinal MRI studies in FSHD have recently shown that these muscle by muscle inflammatory changes directly precede the fatty infiltration that characterizes individual muscles that have been affected for a longer period of time. Once this fatty infiltration has progressed to a certain stage in the affected muscle, however, the level of inflammation as detected by MRI decreases. The degree of fatty infiltration measured by MRI correlates with a commonly used measure of functional status, the FSHD clinical severity score.

The inflammatory immune response in FSHD is reflected in individuals with FSHD through activated immune cells and elevated levels of immune and skeletal muscle proteins present in the circulation. Peripheral blood mononuclear cells from individuals with evidence of muscle inflammation via MRI also show evidence of activation in cell culture by spontaneously releasing high amounts of immune proteins into the culture medium compared to controls.

There are currently no approved treatments for FSHD. The standard of care in management of the disease includes physical therapy and, in the presence of severe muscle weakness, orthotic devices or surgical interventions may be needed to maintain musculoskeletal stability.

In the first quarter of 2015, the European Commission granted orphan medicinal product designation for Resolaris (ATYR1940) for the treatment of FSHD following a positive opinion by the EMA's Committee of Orphan Medicinal Products. In the second quarter of 2015, the FDA granted orphan drug designation for Resolaris (ATYR1940) in the United States for the treatment of FSHD.

Resolaris in Limb-Girdle Muscular Dystrophy (LGMD) 2B (Dysferlinopathies)

In addition to clinical trials in FSHD, we are addressing other genetic diseases in which immune cells invade diseased muscle. In the fourth quarter of 2015, we expanded our scope of our studies by initiating a clinical trial of Resolaris in a form of limb-girdle muscular dystrophy (LGMD), a group of uniformly progressive muscular dystrophies characterized predominantly by proximal weakness affecting the pelvic and shoulder girdles and usually sparing the face. This group of disorders, recently re-classified based on the genetic underpinnings of diseases, are categorized by inheritance pattern: dominantly inherited forms (i.e., LGMD1) and those with recessively-inherited forms (i.e., LGMD2). Within these categories, the diseases are further characterized by the causative genetic defect. Currently, LGMD is a collection of approximately 30 genetic muscle diseases caused by mutations at more than 50 genetic loci. The mutations typically create abnormal, malfunctioning proteins that eventually contribute to muscle weakness.

The age of onset, severity, and features of LGMD vary among the subtypes. Overall, LGMD affects men and women equally. LGMD patients typically suffer from:

- skeletal muscle weakness or compromised function in identifiable, specific muscles;
- skeletal muscle immune cell invasion in identifiable, specific muscles; and
- skeletal muscle deterioration in identifiable, specific muscles with insufficient muscle regeneration.

We are now investigating Resolaris in patients with LGMD2B, a recessively inherited LGMD, often termed dysferlinopathy, given that the causative mutations reside within the dysferlin gene (*DYSF*). LGMD2B is characterized mainly by two distinct clinical phenotypes: LGMD syndrome, with early weakness and atrophy of the pelvic and shoulder girdle muscles in adolescence or young adulthood and with slow progression, and Miyoshi myopathy, with muscle weakness and atrophy in young adults, most marked in the distal parts of the legs, especially the gastrocnemius and soleus muscles. Over a period of years, the weakness and atrophy spread to the upper leg muscles. The forearms may become mildly atrophic, with decrease in grip strength, but the small muscles of the hands are spared.

There are multiple lines of evidence supporting a prominent role of inflammation in the pathophysiology of LGMD2B. The genetic mutations in dysferlin appear to create a defect in muscle membrane repair. Alterations in this process may create a pathophysiological environment in muscle that triggers an immune response. LGMD2B has been demonstrated to have a predominant immune cell-mediated pathology. Patients with LGMD2B possess a dysregulated immune response, including immune cell infiltration into affected muscle, increased expression of pro-inflammatory cytokines and altered cellular responses. Analysis of muscle biopsies from LGMD2B patients (including Myoshi myopathy and LGMD syndrome), has revealed that the most prominent cellular immunophenotype in LGMD muscle is infiltration with T-cells (CD4 and CD8 positive, with CD4 predominating) and macrophages. Cytokine patterns that reflect the inflammatory state, include interleukin (IL)-1, interferon-, and tumor necrosis factor (TNF). The muscle in patients with dysferlinopathy is characterized by massive immune cell infiltrates.

Because of the heterogeneity of LGMD and the lack of diagnostic specificity, there are few reports on the prevalence of LGMD; however, it is estimated to range from 1:14,500 to 1:123,000, depending on the genetically defined form. Based on a prevalence rate of 1:20,000, we estimate that LGMD affects an estimated 16,000 patients in the U.S., approximately 3,000 of whom have LGMD2B. The age of onset of certain forms of LGMD is usually between ten and 30, with both genders affected equally. The disease inevitably gets worse over time, although progression is more rapid in some patients. The disease commonly leads to dependence on a wheelchair within 20 to 30 years of symptom onset, but there is high inter-patient variability, with some patients maintaining mobility. LGMD may eventually weaken the respiratory muscles, leading to illness or early death due to complications from this secondary manifestation. Individuals with cardiac involvement may succumb to heart failure.

No definitive treatments exist for LGMD2B or any of the over 30 forms of LGMD. Clinical management is directed to prolong survival and improve quality of life, including avoiding obesity, promoting physical therapy and stretching exercises, using mechanical aids to help ambulation and mobility, surgical intervention for orthopedic complications, using respiratory aids when indicated, monitoring for cardiomyopathy in LGMD types with cardiac involvement, and social and emotional support and stimulation.

The predominant role of the immune system in LGMD2B suggests that focusing on the inflammatory status of muscles in patients *a priori* in a clinical study could increase the likelihood of seeing an impact of non-corticosteroid immunomodulator.

We plan to apply for orphan designation for Resolaris in LGMD in the United States and Europe.

Clinical Trials in Patients

The following table shows our patient clinical trials:

Study ID	Study Population	Phase	Study Design	Dosing Regimen	Duration
ATYR1940-C-002 ("002 Study")	Adult FSHD	1b/2	Placebo Controlled, Randomized, Multiple Ascending Dose Safety Study	Weekly doses of 0.3mg/kg (Cohort 1) Weekly doses of 1.0 mg/kg (Cohort 2) Weekly doses of 3.0mg/kg (Cohort 3)	4 weeks (Cohorts 1 & 2) 12 weeks (Cohort 3)
ATYR1940-C-003 ("003 Study")	Early Onset FSHD	1b/2	Open-Label, Intra-Patient Dose Escalation Study	Weekly and twice weekly starting at 0.3 mg/kg with potential dose escalation up to 3.0 mg/kg	12 weeks
ATYR1940-C-004 ("004 Study")	LGMD2B and FSHD	1b/2	Open-Label, Intra-Patient Dose Escalation Study	Weekly doses starting at 0.3 mg/kg with potential dose escalation up to 1.0 mg/kg and 3.0 mg/kg	12 weeks
ATYR1940-C-005 ("005 Study")	Adult FSHD from 002 Study	1b/2	Open-Label Safety Extension Study	Weekly doses of 3.0 mg/kg	Until Resolaris receives regulatory approval or the program is discontinued

002 Study: Phase 1b/2 Clinical Trial – Adult Patients with FSHD

We recently completed three cohorts of a multi-national Phase 1b/2 clinical trial of Resolaris in adult patients with FSHD in the European Union and the United States. As with our Phase 1 clinical trial, the planning and design of this trial were guided by principles related to safety and tolerability. In particular, we designed this trial as a randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability, immunogenicity and pharmacokinetic (PK) profile of multiple intravenous doses of Resolaris in adults 18 to 65 years of age with FSHD. In addition, the study also evaluated the utility of exploratory pharmacodynamic (PD) markers (including MRI measurements to quantitate areas of potential muscle inflammation) and clinical assessments (including patient reported outcomes).

Resolaris was studied in three dose escalation cohorts (0.3, 1.0 and 3.0 mg/kg) across four sites and 20 patients. In each cohort, patients were randomized at a ratio of 3:1 to receive Resolaris or placebo. Patients in the first two cohorts were dosed weekly over a period of one month, and patients in the third cohort were dosed weekly over a period of three months. As planned, we enrolled a total of four patients in the first cohort and eight patients in each of the second and third cohorts. For the second and third cohorts, inclusion criteria included the presence of at least one skeletal muscle in the legs identified by a non-quantitative MRI technique, which is thought to indicate inflammation. We recently announced results from the first three dose cohorts. The analysis was based on data available through early March 2016.

A number of exploratory PD markers and clinical assessments were conducted to better understand their utility in FSHD. The study was not powered to demonstrate statistically significant evidence of therapeutic utility or a specific activity endpoint. As part of clinical assessments, a validated patient reported outcome measure designed specifically for neuromuscular diseases, the individualized neuromuscular quality of life (INQoL) questionnaire, was utilized in the study. We believe that data from this patient reported outcome measure suggest potential improvement at three months of weekly dosing at 3.0 mg/kg in this relatively small clinical trial of FSHD patients.

Results of the INQoL Overall Score are set forth in the table below:

INQoL Overall Score [1]
(Negative values represent improvement or less disease burden/impact on a patient)

	Change from Baseline (%) ITT Population (n=20)			
Treatment Duration Group	**Placebo**	**0.3 mg/kg**	**1.0 mg/kg**	**3.0 mg/kg**
1 Month	4.12 (n=5)[2]	2.77 (n=3)	-1.22 (n=4)[3]	-3.78 (n=6)
3 Months	15.55 (n=2)	NA[4]	NA[4]	-9.90[5] (n=6)

1) The INQoL Overall Score is comprised of a scoring of five Life domains: Activities, Independence, Social Relationships, Emotions and Body Image. Changes were primarily observed in the categories of patient Activities, Independence and Emotions.
2) Placebo for 1 month data includes patients from all 3 dose cohorts per the aforementioned eligibility criteria.
3) INQoL Overall Score could not be calculated for two patients in the 1.0 mg/kg cohort due to unreported values.
4) NA is not applicable; only 1 month of dosing.
5) The relative improvement between placebo and the 3.0 mg/kg cohort at three months is 25.5% (p=0.03).

The proportion of patients with improved INQoL Overall Scores is set forth in the table below:

	Proportion of Patients with Improved INQoL Overall Scores			
Treatment Duration Group	**Placebo**	**0.3 mg/kg**	**1.0 mg/kg**	**3.0 mg/kg**
1 Month	2/5	1/3	2/4	4/6
3 Months	0/2	NA[1]	NA[1]	5/6

1) NA is not applicable; only 1 month of dosing.

Manual muscle testing (MMT), which measures muscle strength, was performed across 15 selected muscle groups. The composite MMT score showed approximately 0.5% improvement with Resolaris compared to a 1% decline in the placebo treated patients, indicating no reportable disease progression by this technique in either placebo and test article groups after three months of weekly treatment. An exploratory MRI technique, to quantitate inflammation in a targeted lower limb muscle, did not record differences between placebo and test article groups after three months of weekly treatment. No substantial differences between the placebo and test article groups were observed after three months of weekly treatment in certain exploratory circulating PD markers, however only 2/20 patients had elevated levels above the normal range at screening.

Across all dose groups (0.3 , 1.0 and 3.0 mg/kg), we believe the safety, tolerability, immunogenicity and PK profile of Resolaris supports advancement of Resolaris in FSHD and potentially other rare diseases. No serious adverse events were reported by study investigators. Mild to moderate adverse events were observed in both the test article and placebo treated patients. One moderate adverse event in a test article treated patient (a reversible generalized infusion related reaction (IRR) in the third cohort), which was reported by a study investigator, was reclassified to a serious adverse event by aTyr. This patient was discontinued from dosing at week 11 of the 12 weeks of treatment, but completed the study visits. The PK of Resolaris was generally well behaved across all dose cohorts and throughout the study. Anti-drug antibodies (ADAs) were confirmed in approximately 40% of the dosed patients, including the patient that experienced the generalized IRR. ADAs were of low titer and had no significant effect on PK.

Our protocol for this trial includes the option to initiate up to two additional cohorts. We are currently in the planning process for our next trial in FSHD which could include these two cohorts or a separate trial.

003 Study: Phase 1b/2 Clinical Trial –Patients with Early Onset FSHD

In the fourth quarter of 2015, we initiated a multinational, multi-center Phase 1b/2 clinical trial of Resolaris in patients with early onset FSHD. This international Phase 1b/2 clinical trial is an open-label, intra-patient dose escalation study designed to assess the safety, tolerability, immunogenicity and biological activity of Resolaris at weekly doses of 0.3, 1.0 and 3.0 mg/kg to patients with early onset FSHD. We also intend to explore PD markers and clinical assessments to evaluate Resolaris in these patients, based on changes in inflammatory immune state in peripheral blood, muscle strength, upper and lower extremity muscle function, muscle disease burden based on MRI, and patient-reported quality of life measures, such as INQoL.

Up to 16 patients are planned to be enrolled in the study at up to eight centers in the United States and Europe. Patients will receive a single placebo infusion followed by administration of Resolaris as an intravenous infusion once a week for a total of 12 weeks, starting at a dose level of 0.3 mg/kg with the potential for dose escalation to 3.0 mg/kg over the dosing period. Enrollment into the study will be conducted in two stages. In Stage 1, up to eight patients between the ages of 16 and 25 years old with early onset FSHD who meet the study criteria will be enrolled. Inclusion criteria includes a genetically confirmed diagnosis of FSHD and the onset of symptoms prior to the age of 10. Stage 2 of enrollment, which will include up to eight patients between the ages of 12 and 15 years old with early onset FSHD who meet the study criteria, will only be initiated following an amendment to our trial protocol. The amendment will be based on consideration of safety data of Resolaris gathered in Stage 1, along with additional clinical safety data obtained in adults with FSHD.

We recently dosed our first patient in this trial. Enrollment of patients has been slower than anticipated and we believe enrollment will continue to be slow.

004 Study: Phase 1b/2 Clinical Trial –Adult Patients with Limb Girdle Muscular Dystrophy 2B or FSHD

In the fourth quarter of 2015, we initiated a multinational, multi-center Phase 1b/2 clinical trial of Resolaris in adult patients with LGMD2B or FSHD. This international Phase 1b/2 clinical trial is an open-label, intra-patient dose escalation study designed to assess the safety, tolerability, immunogenicity and biological activity of weekly and twice weekly intravenous infusions of Resolaris in adults with either LGMD2B or FSHD. We also intend to explore PD markers and clinical assessments to evaluate Resolaris in these patients, based on changes in serum-based muscle biomarkers, inflammatory immune state in peripheral blood, muscle disease burden based on MRI, skeletal muscle strength, upper and lower extremity muscle function and quality of life measures, such as INQoL.

Patients will be assigned to one of two treatment groups, which differ based on the maximum dose level of Resolaris to be administered. Group A will include up to four patients with FSHD. Group B will include up to four patients with FSHD and up to eight patients with LGMD2B. Enrollment into Groups A and B will be initiated concurrently; however, enrollment of FSHD patients into Group A must be completed before any patients with FSHD may be enrolled into Group B. Patients assigned to Group A will receive a single placebo infusion followed by administration of Resolaris as an intravenous infusion once a week for eight weeks, then twice weekly for four weeks, for a total of 12 weeks, starting at a dose level of 0.3 mg/kg with the potential for dose escalation to 1.0 mg/kg and up to 1.0 mg/kg twice a week over the dosing period. Patients assigned to Group B will receive a single placebo infusion followed by the administration of Resolaris as an intravenous infusion once a week for eight weeks, then twice weekly for four weeks, for a total of 12 weeks, starting at a dose level of 0.3 mg/kg with the potential for dose escalation to 3.0 mg/kg and up to 3.0 mg/kg twice a week over the dosing period. Inclusion criteria for FSHD patients includes a genetically confirmed diagnosis of FSHD and the presence of at least one skeletal muscle in the legs identified by MRI as STIR positive, which is thought to indicate an immune component. Inclusion criteria for LGMD2B patients includes a genetically confirmed diagnosis of LGMD2B and the presence of at least one skeletal muscle in the muscle in the legs identified by MRI as STIR positive or meeting certain circulating biomarker criteria.

005 Study: Phase 1b/2 Clinical Trial –Long-Term Safety Extension Study in Adult Patients with FSHD

In the third quarter of 2015, we initiated a long-term extension study for patients from our 002 Study. This multinational, multi-center, open-label extension study is designed to assess the long-term safety, effects on muscle, PD and systemic exposure of Resolaris in adult FSHD patients from our 002 Study. Eligible patients in jurisdictions where this trial is approved have the opportunity to receive weekly doses of 3.0 mg/kg until Resolaris receives regulatory approval or the program is discontinued. To date, a total of eight patients have enrolled in this 005 Study. Two patients from this 005 Study experienced mild to moderate reversible generalized infusion related reactions (IRRs) and discontinued dosing. Of these patients, one had elevated ADA signals at the time of dosing and one developed elevated ADA signals following the occurrence of the IRR. Current data suggests that the generalized IRRs we have observed are not acute allergic reactions. We have established procedural measures for our ongoing trials, including a decreased concentration and intravenous delivery rate of Resolaris, in an effort to minimize the occurrence of reversible generalized IRRs and the formation of ADAs. Although no other patients have experienced a reversible generalized IRR since these measures were put in place, we cannot assure that these measures will be effective in minimizing the occurrence of generalized IRRs or the formation of ADAs or result in the retention of patients in our trials.

Our Preclinical Immuno-Modulatory Domain Program from the Resokine Pathway: iMod.Fc

We established a discovery program to leverage our knowledge of the Resokine pathway to vary exposure and activity of the iMod domain through protein engineering. The goal of the program was to develop a potential therapeutic that we refer to as iMod.Fc, which would possess only the N-terminal immuno-modulatory and fibro-modulatory activities of Resokine. We conducted a series of experiments to understand how various product form modifications enhance exposure of the iMod domain. Fc fusion proteins have been successfully commercialized previously by others to enhance exposure while enabling biological activity. We explored this approach by fusing the immunoglobin Fc with one iMod domain, which can form a dimer. Enbrel and Zaltrap are commercialized examples of immunoglobulin Fc fusion proteins.

Our Fc fusion experiments have begun to delineate how to enhance the exposure of the iMod domain of Resokine while maintaining activity and provide insights into this domain harboring immuno-modulatory activity. Initial experiments have indicated that Fc fusion proteins can increase exposure and maintain iMod domain activity. Our efforts in this discovery program have led to the selection of our second product candidate.

In the fourth quarter of 2015, we announced the selection of a particular iMod.Fc molecule as an investigational new drug (IND) candidate. We have selected this iMod.Fc molecule as our second product development candidate and it represents an expansion of our new class of Physiocrine-based therapeutics. In preclinical studies, the selected iMod.Fc molecule showed promising results in a well-established mouse model of lung inflammation and pulmonary fibrosis, induced by a chemotherapeutic agent known as bleomycin. When given in two therapeutic doses over 21 days, iMod.Fc was comparable to, or outperformed approved drugs with daily dosing in reducing lung inflammation and fibrosis in the bleomycin model. With the selection of this iMod.Fc, molecule we are harnessing the Resokine pathway and plan to test its potential role in lung disease, and to develop iMod.Fc as a potential therapeutic for patients with rare pulmonary diseases with an immune component, or RPICs.

Currently we are producing our iMod.Fc molecules in E. coli by expression in inclusion bodies and refolding to recreate the native structure. This is in contrast to most other marketed Fc fusion therapeutics that are manufactured in CHO cells. We are in the process of initiating GMP process development with a third party manufacturer.

Non-Muscle Indication Set: Rare Pulmonary Diseases with an Immune Component (RPICs)

The Resokine pathway may play an important role in lung health. We believe the Resokine pathway plays a role in the regulation of tissue homeostasis with respect to immune cell invasion and residence. Jo-1 antibody patients often develop ILD, a pathophysiologic state that involves inflammation and fibrosis of the alveoli, distal airways and septal interstitium of the lungs, includes various patterns of lung pathology and is associated with markedly impaired lung function. We have observed that Jo-1 antibodies isolated from these patients bind to a region of HARS (Resokine) that we believe harbors immuno-modulatory activity with various immune cells.

ILD develops in approximately 85% of anti-synthetase patients with Jo-1 antibodies to Resokine. It can include the presence of focal immune cell infiltrates and an acinar pattern of involvement on chest computed tomography (CT) scan, lymphocytic predominance on broncho-alveolar lavage and lymphocytic invasion of alveolar and interstitial lung tissues on biopsy, and can advance to fibrosis. The pathological patterns in Jo-1 antibody ILD include cellular and fibrotic forms of non-specific interstitial pneumonitis, usual interstitial pneumonitis and diffuse alveolar damage. The development of ILD in Jo-1 antibody patients, particularly the acute severe forms of the disease, portends high morbidity and mortality. Elevations in a number of circulating immune proteins are observed in Jo-1 antibody associated ILD including interferon (IFN)-inducible chemokines CXCL9, or MIG, and CXCL10 or IP-10, IL-8 and IL-6.

ILD occurs in other settings such as rare genetic disorders, environmental exposures, as a side effect of certain therapeutics and as a manifestation of certain connective tissue disorders. Among these forms of ILD, we have identified several that result in severe and progressive lung disease and share immune-pathophysiology features that overlap with our demonstrated Resolaris activities. We have classified these disorders as rare pulmonary diseases with an immune component, or RPIC. Examples of RPICs include idiopathic non-specific interstitial pneumonias, idiopathic pulmonary fibrosis, lymphocytic interstitial pneumonia, bleomycin (the chemotherapeutic agent)-induced pulmonary fibrosis, and ILD in the setting of systemic sclerosis, or scleroderma, and sarcoidosis. A number of circulating immune proteins are observed in these diseases that overlap with Resolaris activity. These include IP-10, MCP1, IL-8 and IL-6.

To test our hypothesis that augmenting the Resokine pathway has therapeutic potential in ILD, we have generated data in a mouse model of lung inflammation and pulmonary fibrosis. The mouse equivalent of Resolaris has shown promising therapeutic activity in this bleomycin-induced model which has been used previously in the development of therapeutics for different forms of ILD, including the drug pirfenidone, or Esbriet, which was approved by the FDA in October 2014 for the treatment of idiopathic pulmonary fibrosis. We noted that Resolaris administration attenuated the radiographic and histological manifestations of pathophysiology in this model when it was dosed therapeutically. These mouse Resolaris pharmacology data, along with data discussed above delineating our immuno-modulatory activity in other settings, provide pre-clinical evidence supporting our hypothesis that augmenting the Resokine pathway has therapeutic potential in ILD.

Our Discovery Engine for Therapeutic Applications of Physiocrines: Lung and Liver Focused

We plan to leverage our discovery engine to identify other Physiocrine pathways of interest and select additional potential product candidates for preclinical and clinical investigation in a variety of disease settings. The engine that drives our discovery efforts is based on our scientific investigation of Physiocrine pathways and their proteins, coupled with a process of identifying disease indications that may benefit from a Physiocrine therapeutic. Through a combination of deep sequencing and bioinformatics panning, augmented by proteomic analysis, we identified over 300 naturally occurring Physiocrines. We then expressed and purified over 200 of these Physiocrines. Our strategy for identifying function and potential indications begins with developing a series of phenotypic assays for *in vitro* evaluations of function. Many of our purified Physiocrines were evaluated in numerous cell-based phenotypic assays that encompassed 14 distinct human cell types. In July 2014, a publication in *Science* described a portion of the results from our research, along with the research of our collaborators at Scripps La Jolla, Scripps Florida, Stanford University and the Hong Kong University of Science and Technology.

A key step in the discovery engine requires mining data from rare disease patients and linking this to the data generated in our phenotypic profiling experiments either *in vitro* or *in vivo*. For example, with HARS we studied published reports regarding Jo-1 antibody patients, also known as anti-synthetase patients. These clinical phenotypes led us to consider additional roles that extracellular HARS plays in muscle and lung. Thus, Resolaris, a HARS derivative, was evaluated in a number of *in vivo* pharmacology models that portray immune-driven inflammatory processes, including myopathy. The ability to restore homeostasis in multiple pharmacology models prompted us to catalog a number of rare myopathies that are immune driven as indications for therapeutic intervention with Resolaris.

We believe our strategy of understanding Physiocrine function by using *in vivo* experiments early and often while using patient data to focus this *in vivo* exploration has been validated by Resolaris. Additionally, we believe our discovery engine can be applied to other members of the Physiocrine class to help identify additional indications that may benefit from therapeutic intervention with Physiocrines.

We believe the biology of Physiocrines presents a novel protein therapeutic development opportunity based on the modulation of important physiological processes applicable to multiple diseases. This “pathway” approach or “physiology first” paradigm as we call it, which leverages the understanding of a basic physiological process, has been used successfully to create some of the most important therapeutics in such diverse areas as oncology and ophthalmology. Given the breadth of our discoveries, we currently focus on Physiocrine pathways related to immune and regeneration responses to explore for product candidates with rare disease applications.

Discovery Programs in Lung and Liver

In addition, we believe some Physiocrine pathways may relate to fibrosis. Fibrosis is the formation of excess fibrous connective tissue in an organ or tissue in a reparative or reactive physiological process. Immune cells and their secreted molecules have been shown to play a critical role in the fibrotic process in a number of human tissues, including liver and lung. Persistent or unregulated inflammation is a hallmark of many chronic diseases, and is implicated in the development of fibrosis. Extracellular factors such as cytokines and chemokines act in the development of fibrosis by activating and recruiting inflammatory cells to developing fibrotic lesions.

As described previously, Resolaris had shown activity in *in vivo* pharmacology models of lung inflammation and pulmonary fibrosis. We are using this same model to evaluate other Physiocrine molecules in our pipeline. This coupled with ongoing functional knockout studies will be used to prioritize active Physiocrines and novel pathways for further studies.

Immune-mediated processes are also thought to be a driver in various forms of liver fibrosis. A connection between Physiocrines and fibrosis has also been demonstrated in functional knockout studies. In these experiments, conducted at aTyr, antibodies to individual mouse Physiocrines were induced in mice and the phenotypes related to the absence of the Physiocrine or blockade of its pathway were observed. Mice with antibodies to specific Physiocrines developed liver fibrosis and impaired liver function, as measured by decreased glycogen content, decreased albumin:globulin ratio and other functional features.

These experiments demonstrate that the blockade of Physiocrine pathways in rodents resulted in an *in vivo* phenotype characterized by immune cell infiltration or fibrotic disease in the lung or the liver. These data support the concept that Physiocrines may have the potential to inhibit, limit or otherwise regulate immune cell activity in both the lung and the liver, as well as the subsequent development of fibrosis in these tissues. Accordingly, we are continuing to investigate certain Physiocrines for potential therapeutic applications in both lung and liver indications.

Other Potential Discovery Programs

We have applied our discovery engine to identify a variety of medical conditions that we believe may be due to altered Physiocrine function, and are associated with mutations of members of the tRNA synthetase gene family, as set forth in the table below:

tRNA Synthetase Gene	Type of Mutation	Phenotype
AARS	Heterozygous (two forms)	CMT2N
	Heterozygous	Sporadic Axonal CMT
	Heterozygous	dHMN/CMT Variant
	Compound Heterozygous	Early Infantile Encephalopathy
DARS	Compound Heterozygous	Hypomyelination
	Homozygous (two forms)	Hypomyelination
GARS	Heterozygous (three forms)	dSMA-V
	Heterozygous (two forms)	CMT2D/dSMA-V
	Heterozygous (two forms)	CMT2D
	Heterozygous (two forms)	CMT2
	Heterozygous	CMT2D/dHMN-V
	Heterozygous (three forms)	dHMN
	Compound Heterozygous	Non-Compaction Cardiomyopathy
HARS	Homozygous	HARS Genetic Syndrome
	Heterozygous	Peripheral Neuropathy
KARS	Compound Heterozygous	CMTRIB
	Homozygous (two forms)	Deafness
LARS	Homozygous	Infantile Liver Failure (ILFS1)
MARS	Compound Heterozygous	Infantile Liver Failure (ILFS2)
	Heterozygous	CMT2A1
	Compound Heterozygous	Hereditary Spastic Paraplegia
QARS	Compound Heterozygous (two forms)	Microcephaly
RARS	Compound Heterozygous (three forms)	Hypomyelination
YARS	Heterozygous (three forms)	DI-CMTC

Legend:

"_"ARS	=	"amino acid code" Aminoacyl tRNA synthetase. Alanine is represented by the letter A, hence alanine aminoacyl tRNA synthetase is abbreviated to AARS.
CMT	=	Charcot-Marie-Tooth Disease
CMT2A1	=	Charcot-Marie-Tooth Disease Type 2A1
CMT2D	=	Charcot-Marie-Tooth Disease Type 2D
CMT2N	=	Charcot-Marie-Tooth Disease Type 2N
CMTRIB	=	Intermediate Charcot-Marie-Tooth Disease B
dHMN	=	Distal Hereditary Motor Neuropathies
DI-CMTC	=	Intermediate Charcot-Marie-Tooth Disease C
dSMA-V	=	Distal Spinal Muscular Atrophy Type V

In addition, the following table summarizes research published regarding a variety of medical conditions that appear to be associated with autoantibodies targeting various tRNA synthetases (See Solomon, J., et al., (2011) Myositis-related interstitial lung disease and anti-synthetase syndrome, J. Bras. Pneumol. (2011) 37(1) 100-109):

tRNA synthetase target	Anti-tRNA synthetase antibody	# Patients Studied	% with Muscle Inflammation	% with Lung involvement
HARS	Jo-1	308	78-100	84
AARS	PL-12	69	60	95
TARS	PL-7	21	84	84
IARS	OJ	9	100	55
NARS	KS	6	0	100
GARS	EJ	1	100	100
FARSA, FARSB	ZO	1	100	100

Sales and Marketing

We currently intend to build the commercial infrastructure in the United States and Europe necessary to effectively support the commercialization of all of our product candidates, if and when we believe a regulatory approval of the first of such product candidates in a particular geographic market appears imminent. The commercial infrastructure for products directed at rare disease indications typically consists of a targeted, specialty sales force that calls on a limited and focused group of physicians supported by sales management, medical liaisons, internal sales support, an internal marketing group, and distribution support. One challenge unique to commercializing therapies for rare diseases is the difficulty in identifying eligible patients due to the very small and sometimes heterogeneous disease populations.

Additional capabilities important to the marketing of therapeutics for rare diseases include the management of key accounts such as managed care organizations, group-purchasing organizations, specialty pharmacies, and government accounts. To develop the appropriate commercial infrastructure, we will have to invest significant amounts of financial and management resources, some of which will be committed prior to any confirmation that any of our product candidates will be approved.

Although we currently intend to commercialize Resolaris and any other product candidates that we may develop on our own, we may elect in the future to utilize strategic partners, distributors, or contract sales forces to assist in the commercialization of our products in selected geographic locations or for particular indications.

Manufacturing

We currently contract with third parties for the manufacturing and testing of our product candidates for preclinical studies and clinical trials and intend to do so in the future. We do not own or operate manufacturing facilities for the production of clinical quantities of our product candidates. We currently have no plans to build our own clinical or commercial scale manufacturing capabilities. The use of contracted manufacturing organizations, or CMOs, and reliance on collaboration partners is relatively cost-efficient and has eliminated the need for our direct investment in manufacturing facilities and additional staff early in development. Although we rely on contract manufacturers, we have personnel with extensive manufacturing experience to oversee our contract manufacturers.

Resolaris is produced in recombinant bacteria, purified, filled and packaged for clinical use. The drug substance for Resolaris is currently manufactured in India by Syngene International Limited, or Syngene, pursuant to a Master Services Agreement and a Quality Agreement executed in November 2012. We have a non-exclusive license to the host cell line used to produce drug substance for Resolaris at Syngene. All other raw materials for Resolaris are commercially available. We intend to continue to work with Syngene for the production of Resolaris for preclinical studies and clinical testing. We contract with other third parties to conduct fill and finish and labeling, as well as for the storage and distribution of Resolaris to clinical sites and plan to do so for other product candidates that we may develop.

To date, our third-party manufacturers have met our manufacturing requirements for clinical development, and we expect that our current third-party manufacturers are capable of providing sufficient quantities of our product candidates to meet anticipated clinical development needs through to the start of the pivotal clinical trials.

To meet our projected needs for clinical trials and larger scale commercial manufacturing, we are currently working with Fujifilm Diosynth Biotechnologies USA, Inc., or Fujifilm, to complete the development of the manufacturing process for, and for the production of, drug substance for Resolaris, pursuant to a Master Services Agreement, or MSA, executed in June 2015. Pursuant to the MSA, Fujifilm will provide drug substance for Resolaris to support future clinical trials, including potential pivotal trials. Under the initial scope of work executed pursuant to the MSA, Fujifilm will conduct process optimization, scale-up and demonstration, and cGMP manufacturing of the drug substance of Resolaris. We have a non- exclusive license to the host cell line used to produce the drug substance for Resolaris at Fujifilm. The drug substance will be filled as drug product at a third party contract research organization, or CRO, and we are currently in the process of scaling-up the drug product batch production.

Additionally, we are negotiating with additional storage and labelling CROs to enable the commercial storage and supply of Resolaris. We believe that manufacturing at these CMOs/CROs can satisfy our clinical, regulatory and commercial requirements for Resolaris. We cannot be certain, however, that the transfer and commercial scale up of the manufacturing process for Resolaris will not result in significant delay or add material additional costs.

Patents and Proprietary Rights

We strive to protect the proprietary technologies that we believe are important to our business, including seeking and maintaining patent protection intended to cover the composition of matter of our product candidates, their methods of use, related technology and other inventions that are important to our business. As of March 23, 2016, we own, or have exclusive licenses to, 67 issued U.S. and foreign patents, 7 allowed U.S. and foreign patent applications, and over 240 pending U.S. and foreign patent applications, with predicted expiration dates ranging from 2026 to 2034. In addition to patent protection, we also rely on trade secrets and careful monitoring of our proprietary information to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business, defend and enforce our patents, maintain our licenses to use intellectual property owned by third parties, preserve the confidentiality of our trade secrets and operate without infringing the valid and enforceable patents and other proprietary rights of third parties. We also rely on know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen, and maintain our proprietary position in the field of Physiocrine therapeutics.

A third party may hold intellectual property, including patent rights, which is important or necessary to the development of our products. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our products, in which case we would be required to obtain a license from these third parties on commercially reasonable terms, or our business could be harmed, possibly materially.

We plan to continue to expand our intellectual property estate by filing patent applications directed to new methods of treatment, therapeutics and additional new product forms thereof with new therapeutic or pharmacokinetic properties. Specifically, we seek patent protection in the United States and internationally for novel compositions of matter covering our protein therapeutics, next generation product forms and the use of these compositions in a variety of therapies.

The patent positions of biopharmaceutical companies like us are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Consequently, we do not know whether any of our product candidates will be protectable or remain protected by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient proprietary protection from competitors. Any patents that we hold may be challenged, circumvented or invalidated by third parties.

Because patent applications in the United States and certain other jurisdictions are maintained in secrecy for 18 months, and since publication of discoveries in the scientific or patent literature often lags behind actual discoveries, we cannot be certain of the priority of inventions covered by pending patent applications. Moreover, we may have to participate in interference proceedings declared by the United States Patent and Trademark Office, or USPTO, or a foreign patent office to determine priority of invention or in post-grant challenge proceedings, such as oppositions, that challenge priority of invention or other features of patentability. Such proceedings could result in us incurring substantial costs, even if the eventual outcome is favorable to us.

The patent portfolios for our most advanced programs are summarized below.

Resolaris. Our Resolaris patent portfolio is comprised of a number of patent families and includes U.S. Patent No. 8,835,387 covering Resolaris, which issued on September 16, 2014 and is predicted to expire in 2033; and U.S. Patent No. 9,273,302, which issued on March 1, 2016 and is predicted to expire in 2033. This patent family is jointly owned by us and Pangu Biopharma. Patent applications in the same family as U.S. Patent No. 8,835,387 are pending in a variety of worldwide jurisdictions, including the United States, Australia, Brazil, Canada, China, Europe, India, Japan, Korea, Mexico, New Zealand, Russia and South Africa. The Resolaris patent portfolio also encompasses additional issued patents and pending patent applications that cover Resolaris and related proteins; these patents and patent applications are wholly owned by us. This second patent family includes U.S. Patent No. 9,127,268, which issued on September 8, 2015; European Patent No. 2509625, which granted on January 28, 2015; Japanese Patent No. 5819314, which granted on October 9, 2015; and Australian Patent No. 2010327926, which issued August 21, 2014, and related applications that are pending in the United States, Australia, Canada, Europe, China, Japan, and Hong Kong. Patents that issue from these applications, if any, are expected to expire in 2030 plus any patent term extension. Also included with the Resolaris patent portfolio are pending patent applications to specific methods of use of Resolaris and related proteins, and disease polymorphisms of HARS. These applications have been filed in the United States as U.S. provisional applications and in some cases under the Patent Cooperation Treaty, or PCT. U.S. provisional applications may be used to establish non-provisional U.S. applications, PCT applications and other national filings worldwide. PCT applications are eligible for filing in most worldwide jurisdictions, including the United States. If issued, these patents are predicted to expire between 2033 and 2034.

iMod.Fc. Our iMod.Fc patent portfolio, which covers derivatives of Resokine, including the iMod domain, related splice variants, and next-generation product forms with modified therapeutic activity or pharmacokinetic characteristics, is comprised of a number of patent families and includes U.S. Patent No. 8,404,242, and U.S. Patent No 8,753,638, which issued on March 26, 2013 and June 17, 2014, respectively, and are expected to expire in 2031 and 2030. Also included in this patent family are Japanese Patent No. 5756751, which granted on June 5, 2015; and Australian Patent No. 2010226726, which issued on October 16, 2014. This patent family is jointly owned by us and Pangu Biopharma, and includes pending applications in United States, Australia, Canada, Europe, China, Japan, and Hong Kong. Patents that issue from these applications, if any, are expected to expire in 2030, plus any patent term extension. The iMod.Fc patent family also includes patent applications filed on related splice variants of HARS. This patent family includes applications that are pending in the United States, Australia, Canada, Europe, China, India, Japan, Korea, New Zealand, Russia and Hong Kong. This patent family is jointly owned by us, and our subsidiary Pangu Biopharma. Also included within the iMod.Fc patent portfolio are pending applications to specific product forms of iMod.Fc, Resolaris and other HARS splice variants which include patent families to Fc fusion proteins, pegylated forms and variants with substituted D amino acids. These applications have been filed in the United States as U.S. provisional applications and in some cases under the PCT. If issued, these patents are predicted to expire between 2033 and 2034.

Our pipeline of Physiocrines is covered by a series of 21 patent families, which covers all 20 human cytosolic tRNA synthetases. At least 19 Physiocrine patents are issued in the United States, and applications are pending to the corresponding Physiocrine polynucleotide sequences. These cases are jointly owned by us and Pangu Biopharma, and include pending applications in the United States, Australia, Canada, India, Europe, China and Japan. Patents that issue from these applications, if any, would be expected to expire in 2031. Additional patent applications have also been separately filed on GARS (Glycyl-tRNA synthetase), DARS (Aspartyl-tRNA synthetase), YARS (tyrosyl-tRNA synthetase), and other tRNA synthetases, and any patents issuing from these patent applications would be expected to expire between 2026 and 2030. We have also exclusively in-licensed from TSRI, patents and patent applications related to YARS and specific monomeric forms of tRNA synthetases.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is generally 20 years from the earliest date of filing the non-provisional patent application from which the patent issued.

In the United States, the patent term of a patent that covers a drug approved by the U.S. Food and Drug Administration, or FDA, may also be eligible for patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. Patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and other non-United States jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our pharmaceutical products receive FDA approval, we expect to apply for patent term extensions on patents covering those products. We intend to seek patent term extensions to any of our issued patents in any jurisdiction where these are available, however there is no guarantee that the applicable authorities, including the FDA in the United States, will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions.

We also rely on trade secret protection for our confidential and proprietary information. Although we take steps to protect our proprietary information and trade secrets, including through contractual means with our employees and consultants, third parties may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or disclose our technology. Thus, we may not be able to meaningfully protect our trade secrets. It is our policy to require our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements provide that all confidential information concerning our business or financial affairs developed or made known to the individual during the course of the individual's relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual, and which are related to our current or planned business or research and development or made during normal working hours, on our premises or using our equipment or proprietary information, are our exclusive property.

Research and License Agreements

The Scripps Research Institute

We are party to an amended and restated research funding and option agreement with The Scripps Research Institute, or TSRI. Under the agreement, we provide funding to TSRI to conduct certain research activities related to aminoacyl tRNA synthetases. The agreement renews automatically for successive 12 month periods starting on May 31 of each year unless we provide written notice of our desire to terminate the agreement at least 30 days prior to the end of the applicable 12-month period. Under the agreement, the parties agree to update the amount of annual funding for such successive 12-month periods as mutually agreed in good faith by the parties. We have the right to terminate the agreement at any time upon six months' written notice, and TSRI has the right to terminate the agreement if we fail to make any payment under the agreement within ten days of being notified by TSRI that such payment is overdue. Additionally, each party may terminate the agreement in the event of an uncured material breach by the other party or for insolvency of the other party.

Under the amended and restated research funding and option agreement, TSRI has granted us options to enter into license agreements to acquire rights and exclusive licenses to develop, make, have made, use, have used, import, have imported, offer to sell, sell and have sold certain licensed products, processes and services based on certain technology arising from the sponsored research activities. Pursuant to the terms of these license agreements, TSRI is entitled to receive tiered royalties as a percentage of net sales, ranging from the low to mid-single digits, with these royalty rates subject to increase if we challenge the validity or enforceability of any of the licensed patent rights under certain circumstances. The royalty rates are subject to reduction to the extent we need to obtain any rights from third parties to make, use, or sell the licensed products, processes or services, subject to a minimum floor in the single digits. Additionally, we have agreed to pay TSRI a percentage of non-royalty revenue we receive from our sublicensees or partners, with the amount owed decreasing if we enter into the applicable sublicense or partnering agreement after meeting a specified clinical milestone. In addition, we are obligated to make payments to TSRI of up to an aggregate of $2.75 million under each license agreement upon the achievement of specific clinical and regulatory milestone events.

Under the terms of the license agreements, we are obligated to use commercially reasonable efforts and diligence to develop and commercialize licensed products, processes and services and to obtain regulatory approvals as necessary.

We may terminate the license agreements upon mutual agreement with TSRI or unilaterally upon 90 days' notice, and TSRI has the right to terminate the agreements under certain circumstances, including our uncured material breach of the agreements and if TSRI determines that we are not engaged in research, development, manufacturing, marketing or sublicensing activities reasonably appropriate to put the licensed patents into commercial use, and to make the licensed subject matter reasonably available to the public, in the countries covered by the license.

Pangu Biopharma

In October 2007, we formed our Hong Kong subsidiary, Pangu BioPharma Limited, or Pangu BioPharma, a company registered in Hong Kong, to collaborate with the Hong Kong University of Science and Technology, or HKUST, on the discovery and development of aminoacyl tRNA synthetase protein therapeutics. We hold 98% of the outstanding shares of Pangu BioPharma, and a subsidiary of HKUST holds the remaining outstanding shares. Beginning in July 2008, Pangu BioPharma, in collaboration with HKUST, entered into a series of three research grant agreements with the Government of the Hong Kong Special Administrative Region to carry out research in the discovery and development of Physiocrines. In December 2015, Pangu BioPharma renewed its annual joint research agreement with a subsidiary of HKUST, under which Pangu BioPharma agrees to fund research to be performed in 2016 under the agreement by the subsidiary of HKUST with respect to development of aminoacyl tRNA synthetase protein therapeutics. Pangu BioPharma is the sole beneficial owner of all resulting intellectual property rights from the research performed under these agreements, subject to the right of HKUST's subsidiary to use certain background intellectual property of HKUST in conducting the research and, in the event Pangu BioPharma applies for individual funding of any work under the research programs, compliance with the terms and conditions of any written agreement covering ownership of such funded works. Pangu BioPharma funds the annual research on a quarterly basis. Either party may terminate the agreement during the annual period upon an uncured breach of the agreement by the other party. We are also party to a license agreement with Pangu BioPharma, pursuant to which Pangu BioPharma has granted us an exclusive, royalty-bearing license (with a right to sublicense) in and to certain of Pangu BioPharma's solely and jointly owned patent rights and know-how to research, develop, manufacture, use, import, export, distribute, offer for sale, sell and have sold products incorporating such patent rights and know-how for any therapeutic, prognostic or diagnostic use throughout the world.

Competition

The biotechnology and pharmaceutical industries are intensely competitive. We will face competition with respect to Resolaris and any other protein therapeutics we may develop or commercialize in the future from pharmaceutical companies, biotechnology companies and universities and other research institutions. Our competitors may have substantially greater financial, technical and other resources, such as larger research and development staff and experienced marketing and manufacturing organizations. Additional mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or licensing on an exclusive basis drug products that are more effective or less costly than any product candidate that we may develop.

Although we believe we are the only company engaged in the discovery and development of therapeutics based on Physiocrine pathways, we are aware of other companies that are developing products that could compete as treatments for our targeted indications, as described below.

In the area of RMICs, we expect to face competition from a number of companies, academic institutions and other organizations, including Akashi Therapeutics, Inc., BioMarin Pharmaceutical Inc., Catabasis Pharmaceuticals, Inc., FibroGen Inc., F. Hoffmann-La Roche AG, Milo Biotechnology, LLC., Nobelpharma Co.Ltd., Novartis AG, Pfizer, Inc., PTC Therapeutics, Inc., Sarepta Therapeutics, Inc. and Ultragenyx Pharmaceuticals, that are engaged in the clinical development of therapeutics to address muscle loss and muscle weakness in a variety of indications. More specifically, while there are currently no approved products for the treatment of FSHD, Acceleron Pharma Inc. is developing a clinical candidate, ACE-083, a locally acting protein therapeutic designed to increase muscle mass and strength in patients with neuromuscular disorders and other diseases characterized by a loss of muscle function, including FSHD. In addition, Facio Therapies recently announced its plans to screen chemical libraries to identify chemical compounds that will boost the expression of proteins known to repress one of the causal genes responsible for FSHD. In the area of LGMD, we are aware of a number of academic institutions engaged in the clinical development of therapeutics, including Genethon, a not-for-profit research laboratory created by the Association Française contre les Myopathies, or French Muscular Dystrophy Association, which has completed an experimental Phase 1 clinical trial in LGMD2C using gene therapy; Nationwide Children's Hospital, which is currently conducting a Phase 1/2a clinical trial of an AAV vector to transport the alpha-sarcoglycan gene into muscles in in LGMD2D; and NeuroGen Brain and Spine Institute in India, which is currently conducting a Phase 1 clinical trial in an unspecified form of LGMD using stem cell therapy.

In the area of RPICs, including ILD, we expect to face competition from pirfenidone, which is marketed by several companies worldwide, including InterMune Inc. (acquired by F. Hoffmann-La Roche AG Roche), Shionogi Ltd. and GNI Group Ltd., as well as nintedanib, a small molecule tyrosine-kinase inhibitor marketed by Boehringer Ingelheim, both of which were approved by the FDA in October 2014. We are also aware of a number of companies engaged in the clinical development of therapeutics for lung diseases, including Astra Zeneca plc., Biogen Inc., Bristol-Myers Squibb, FibroGen Inc., Gilead Sciences Inc., Promedior, Inc. and Sanofi S. A.

Government Regulation

Government authorities in the United States, including federal, state, and local authorities, and in other countries, extensively regulate, among other things, the manufacturing, research and clinical development, marketing, labeling and packaging, storage, distribution, post-approval monitoring and reporting, advertising and promotion, pricing, and export and import of pharmaceutical and biological products, such as those we are developing. Pricing of such products is also subject to regulation in many countries. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local, and foreign statutes and regulations require the expenditure of substantial time and financial resources.

U.S. Government Regulation

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations, and biologics under the FDCA and the Public Health Service Act, or PHSA, and its implementing regulations. FDA approval is required before any new unapproved drug or biologic or dosage form, including a new use of a previously approved drug, can be marketed in the United States. Drugs and biologics are also subject to other federal, state, and local statutes and regulations. If we fail to comply with applicable FDA or other requirements at any time during the product development process, clinical testing, the approval process or after approval, we may become subject to administrative or judicial sanctions. These sanctions could include the FDA's refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, untitled or warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties or criminal prosecution. Any FDA enforcement action could have a material adverse effect on us.

The process required by the FDA before product candidates may be marketed in the United States generally involves the following:

- completion of extensive preclinical laboratory tests and preclinical animal studies, all performed in accordance with the Good Laboratory Practices, or GLP, regulations;
- submission to the FDA of an investigational new drug application, or IND, which must become effective before human clinical trials may begin and must be updated annually;
- approval by an independent institutional review board, or IRB, or ethics committee representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials to establish the safety and efficacy of the product candidate for each proposed indication;
- preparation of and submission to the FDA of a biologics license application, or BLA, or a new drug application, or NDA, after completion of all pivotal clinical trials;
- potential review of the product application by an FDA advisory committee, where appropriate and if applicable;
- a determination by the FDA within 60 days of its receipt of a BLA or NDA to file the application for review;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facilities where the proposed product is produced to assess compliance with current Good Manufacturing Practices, or cGMP; and
- FDA review and approval of a BLA or NDA prior to any commercial marketing or sale of the product in the United States.

The preclinical and clinical testing and approval process requires substantial time, effort, and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all.

An IND is a request for authorization from the FDA to administer an investigational new drug product to humans in clinical trials. The central focus of an IND submission is on the general investigational plan and the protocol(s) for human trials. The IND also includes results of animal and in vitro studies assessing the toxicology, pharmacokinetics, pharmacology, and pharmacodynamic characteristics of the product; chemistry, manufacturing, and controls information; and any available human data or literature to support the use of the investigational new drug. An IND must become effective before human clinical trials may begin. An IND will automatically become effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to the proposed clinical trials. In such a case, the IND may be placed on clinical hold and the IND sponsor and the FDA must resolve any outstanding concerns or questions before clinical trials can begin. Accordingly, submission of an IND may or may not result in the FDA allowing clinical trials to commence. The FDA may impose a clinical hold at any time during clinical trials and may impose a partial clinical hold that would limit trials, for example, to certain doses or for a certain length of time.

Clinical Trials

Clinical trials involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with Good Clinical Practices, or GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety, and the efficacy criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. Additionally, approval must also be obtained from each clinical trial site's IRB before the trials may be initiated, and the IRB must monitor the trial until completed. There are also requirements governing the reporting of ongoing clinical trials and clinical trial results to public registries.

The clinical investigation of a drug is generally divided into three phases. Although the phases are usually conducted sequentially, they may overlap or be combined.

- *Phase 1.* The drug is initially introduced into healthy human subjects or patients with the target disease or condition. These studies are designed to evaluate the safety, dosage tolerance, metabolism and pharmacologic actions of the investigational new drug in humans, the side effects associated with increasing doses, and if possible, to gain early evidence on effectiveness.
- *Phase 2.* The drug is administered to a limited patient population to evaluate dosage tolerance and optimal dosage, identify possible adverse side effects and safety risks, and preliminarily evaluate efficacy.
- *Phase 3.* The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites to generate enough data to evaluate dosage, clinical effectiveness and safety, to establish the overall benefit-risk relationship of the investigational new drug product, and to provide an adequate basis for product approval.

In some cases, the FDA may condition approval of a BLA or NDA for a product candidate on the sponsor's agreement to conduct additional clinical trials after approval. In other cases, a sponsor may voluntarily conduct additional clinical trials after approval to gain more information about the drug. Such post-approval studies are typically referred to as Phase 4 clinical trials.

A pivotal trial is a clinical trial that adequately meets regulatory agency requirements for the evaluation of a drug candidate's efficacy and safety such that it can be used to justify the approval of the product. Generally, pivotal trials are Phase 3 trials, but the FDA may accept results from Phase 2 clinical trials if the trial design provides a well-controlled and reliable assessment of clinical benefit, particularly in situations where there is an unmet medical need and the results are sufficiently robust.

Sponsors must also report to the FDA, within certain timeframes, serious and unexpected adverse reactions, any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator's brochure, or any findings from other studies or animal or in vitro testing that suggest a significant risk in humans exposed to the product candidate. The FDA, the IRB, or the clinical trial sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access to certain data from the trial. We may also suspend or terminate a clinical trial based on evolving business objectives or competitive climate.

The clinical trial process can take three to ten years or more to complete, and there can be no assurance that the data collected will support FDA approval or licensure of the product. Results from one trial are not necessarily predictive of results from later trials.

Submission of a BLA or NDA to the FDA

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, detailed investigational new drug product information is submitted to the FDA in the form of a BLA or NDA requesting approval to market the product for one or more indications. Under federal law, the submission of most BLAs and NDAs is subject to an application user fee. For fiscal year 2016, the application user fee exceeds $2.3 million, and the sponsor of an approved BLA or NDA is also subject to annual product and establishment user fees, set at $114,450 per product and $585,200 per establishment. These fees are typically increased annually. Applications for orphan drug products are exempted from the BLA and NDA user fees and may be exempted from product and establishment user fees, unless the application includes an indication for other than a rare disease or condition.

A BLA or NDA must include all relevant data available from pertinent preclinical studies and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls, and proposed labeling, among other things. Data can come from company-sponsored clinical trials intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including trials initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational new drug product to the satisfaction of the FDA.

Once a BLA or NDA has been submitted, the FDA's goal is to review the application within ten months after it accepts the application for filing, or, if the application relates to an unmet medical need in a serious or life-threatening indication, six months after the FDA accepts the application for filing. The review process is often significantly extended by the FDA's requests for additional information or clarification.

Before approving a BLA or NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving a BLA or NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP.

The FDA is required to refer an application for a novel drug to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

The FDA's Decision on a BLA or NDA

The FDA evaluates a BLA to determine whether the data demonstrate that the biologic is safe, pure, and potent, or effective, and an NDA to determine whether the drug is safe and effective. After the FDA evaluates the BLA or NDA and conducts inspections of manufacturing facilities where the product will be produced, it may issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete and the application is not ready for approval. A Complete Response Letter may require additional clinical data or an additional pivotal Phase 3 clinical trial(s), or other significant, expensive and time-consuming requirements related to clinical trials, preclinical studies or manufacturing. Even if such additional information is submitted, the FDA may ultimately decide that the BLA or NDA does not satisfy the criteria for approval and issue a denial. The FDA could also approve the BLA or NDA with a Risk Evaluation and Mitigation Strategy, or REMS, plan to mitigate risks, which could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling, development of adequate controls and specifications, or a commitment to conduct one or more post-market studies or clinical trials. Such post-market testing may include Phase 4 clinical trials and surveillance to further assess and monitor the product's safety and effectiveness after commercialization. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our products under development.

Expedited Review and Accelerated Approval Programs

A sponsor may seek approval of its product candidate under programs designed to accelerate FDA's review and approval of BLAs and NDAs. For example, Fast Track Designation may be granted to a drug intended for treatment of a serious or life-threatening disease or condition that has potential to address unmet medical needs for the disease or condition. The key benefits of fast track designation are more frequent interactions with the FDA during development and testing, the eligibility for priority review, and rolling review, which is submission of portions of an application before the complete marketing application is submitted. Based on results of the Phase 3 clinical trial(s) submitted in a BLA or NDA, upon the request of an applicant, the FDA may grant the BLA or NDA a priority review designation, which sets the target date for FDA action on the application at six months after the FDA accepts the application for filing. Priority review is granted where there is evidence that the proposed product would be a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition. If criteria are not met for priority review, the application is subject to the standard FDA review period of ten months after FDA accepts the application for filing. Priority review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

Under the accelerated approval program, the FDA may approve a BLA or NDA on the basis of either a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Post-marketing trials or completion of ongoing trials after marketing approval are generally required to verify the drug's clinical benefit in relationship to the surrogate endpoint or ultimate outcome in relationship to the clinical benefit. In addition, the Food and Drug Administration Safety and Innovation Act, or FDASIA, which was enacted and signed into law in 2012, established the new Breakthrough Therapy designation. A sponsor may seek FDA designation of its product candidate as a breakthrough therapy if the drug is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. If so designated, the FDA shall act to expedite the development and review of the product's marketing application, including by meeting with the sponsor throughout the product's development, providing timely advice to the sponsor to ensure that the development program to gather pre-clinical and clinical data is as efficient as practicable, involving senior managers and experienced review staff in a cross-disciplinary review, and assigning a cross-disciplinary project lead for the FDA review team to facilitate an efficient review of the development program and to serve as a scientific liaison between the review team and the sponsor.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

Drug manufacturers are subject to periodic unannounced inspections by the FDA and state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon us and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance.

We rely, and expect to continue to rely, on third parties for the production of clinical quantities of our product candidates, and expect to rely in the future on third parties for the production of commercial quantities. Future FDA and state inspections may identify compliance issues at our facilities or at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of previously unknown problems with a product or the failure to comply with applicable requirements may result in restrictions on a product, manufacturer or holder of an approved BLA or NDA, including withdrawal or recall of the product from the market or other voluntary, FDA-initiated or judicial action that could delay or prohibit further marketing. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our products under development.

The FDA may withdraw approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution restrictions or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, untitled or warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending BLAs or NDAs or supplements to approved BLAs or NDAs, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising, and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

Orphan Designation and Exclusivity

The FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the United States, or if it affects more than 200,000 individuals in the United States, there is no reasonable expectation that the cost of developing and making the drug for this type of disease or condition will be recovered from sales in the United States.

Orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages, and user-fee waivers. In addition, if a product is the first to receive FDA approval for the indication for which it has orphan designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity.

Pediatric Trials and Exclusivity

Under the Pediatric Research Equity Act of 2003, or PREA, BLAs and NDAs must contain data to assess the safety and effectiveness of an investigational new drug product for the claimed indications in all relevant pediatric populations and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. A sponsor who is planning to submit a marketing application for a drug product that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration must submit an initial Pediatric Study Plan, or PSP, within sixty days of an end-of-phase 2 meeting or as may be agreed between the sponsor and the FDA. The initial PSP must include an outline of the pediatric study or studies that the sponsor plans to conduct, including study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults or full or partial waivers if certain criteria are met. The FDA and the sponsor must reach agreement on the PSP. A sponsor can submit amendments to an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from pre-clinical studies, early phase clinical trials, and/or other clinical development programs. The requirements for pediatric data do not apply to any drug for an indication for which orphan designation has been granted.

Pediatric exclusivity is another type of non-patent exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the five-year and three-year non-patent and orphan exclusivity. This six-month exclusivity may be granted if a BLA or NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of FDA-requested pediatric trials are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection covering the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot accept or approve another application relying on the BLA or NDA sponsor's data.

Patent Term Restoration

Depending upon the timing, duration, and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of a BLA or NDA, plus the time between the submission date and the approval of that application, except that the review period is reduced by any time during which the applicant failed to exercise due diligence. Only one patent applicable to an approved product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent and within 60 days of the product's approval. The U.S. Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may apply for restoration of patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant BLA or NDA.

Biosimilars and Exclusivity

The Patient Protection and Affordable Care Act, or Affordable Care Act, signed into law on March 23, 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCI Act, which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. This amendment to the PHSA attempts to minimize duplicative testing. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical trial or trials. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic.

A reference biologic is granted twelve years of exclusivity from the time of first licensure of the reference product. The first biologic product submitted under the abbreviated approval pathway that is determined to be interchangeable with the reference product has exclusivity against other biologics submitting under the abbreviated approval pathway for the lesser of (i) one year after the first commercial marketing, (ii) eighteen months after approval if there is no legal challenge, (iii) eighteen months after the resolution in the applicant's favor of a lawsuit challenging the biologics' patents if an application has been submitted, or (iv) 42 months after the application has been approved if a lawsuit is ongoing within the 42-month period.

Abbreviated New Drug Applications for Generic Drugs

In 1984, with passage of the Hatch-Waxman Amendments, Congress authorized the FDA to approve generic drugs that are the same as drugs previously approved by the FDA under the NDA provisions of the statute. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. In support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference listed drug, or RLD.

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, and the strength of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug is bioequivalent to an RLD if "the rate and extent of absorption of the [generic] drug do not show a significant difference from the rate and extent of absorption of the listed drug. . . ."

Upon approval of an ANDA, the FDA indicates that the generic product is "therapeutically equivalent" to the RLD and it assigns a therapeutic equivalence rating to the approved generic drug in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider an "AB" therapeutic equivalence rating to mean that a generic drug is fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA's designation of an "AB" rating often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

The FDCA provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity. In cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval. The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication.

Hatch-Waxman Patent Certification and the 30-Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or a method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval.

Specifically, the applicant must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;

- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired.

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant.

European Union/Rest of World Government Regulation

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of our products. The cost of establishing a regulatory compliance system for numerous varying jurisdictions can be very significant. Although many of the issues discussed above with respect to the United States apply similarly in the context of the European Union and in other jurisdictions, the approval process varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials. In the European Union, for example, a clinical trial application, or CTA, must be submitted for each clinical protocol to each country's national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the CTA is accepted in accordance with a country's requirements, the clinical trial may proceed.

The requirements and process governing the conduct of clinical trials vary from country to country. In all cases, the clinical trials are conducted in accordance with good clinical practices, or GCP, the applicable regulatory requirements, and the ethical principles that have their origin in the Declaration of Helsinki.

To obtain regulatory approval of an investigational medicinal product under European Union regulatory systems, we must submit a marketing authorization application. The content of the BLA or NDA filed in the United States is similar to that required in the European Union, with the exception of, among other things, country-specific document requirements.

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing product licensing, pricing, and reimbursement vary from country to country.

Countries that are part of the European Union, as well as countries outside of the European Union, have their own governing bodies, requirements, and processes with respect to the approval of pharmaceutical and biologic products. If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Authorization Procedures in the European Union

Medicines can be authorized in the European Union by using either the centralized authorization procedure or national authorization procedures.

- *Centralized procedure*. The EMA implemented the centralized procedure for the approval of human medicines to facilitate marketing authorizations that are valid throughout the European Economic Area, or EEA, which is comprised of the 28 member states of the European Union plus Norway, Iceland, and Lichtenstein. This procedure results in a single marketing authorization issued by the EMA that is valid across the EEA. The centralized procedure is compulsory for human medicines that are: derived from biotechnology processes, such as genetic engineering, contain a new active substance indicated for the treatment of certain diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions, and officially designated orphan medicines.
- For medicines that do not fall within these categories, an applicant has the option of submitting an application for a centralized marketing authorization to the European Commission following a favorable opinion by the EMA, as long as the medicine concerned is a significant therapeutic, scientific or technical innovation, or if its authorization would be in the interest of public health.
- *National authorization procedures*. There are also two other possible routes to authorize medicinal products in several European Union countries, which are available for investigational medicinal products that fall outside the scope of the centralized procedure:
- *Decentralized procedure*. Using the decentralized procedure, an applicant may apply for simultaneous authorization in more than one European Union country of medicinal products that have not yet been authorized in any European Union country and that do not fall within the mandatory scope of the centralized procedure.
- *Mutual recognition procedure*. In the mutual recognition procedure, a medicine is first authorized in one European Union Member State, in accordance with the national procedures of that country. Following this, further marketing authorizations can be sought from other European Union countries in a procedure whereby the countries concerned agree to recognize the validity of the original, national marketing authorization.

In some cases, a Pediatric Investigation Plan, or PIP, or a request for waiver or deferral, is required for submission prior to submitting a marketing authorization application. A PIP describes, among other things, proposed pediatric trials and their timing relative to clinical trials in adults.

New Chemical Entity Exclusivity

In the European Union, new chemical entities, sometimes referred to as new active substances, qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. This data exclusivity, if granted, prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic (abbreviated) application for eight years, after which a generic application can be submitted, and the innovator's data may be referenced, but not approved for two years. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies.

Orphan Designation and Exclusivity

In the European Union, the European Commission, after reviewing the opinion of the EMA's Committee for Orphan Medicinal Products, or COMP, grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions that affect not more than 5 in 10,000 persons in the European Union Community, or when, without incentives, it is unlikely that sales of such products in the European Union would be sufficient to justify the necessary investment in developing the products. Additionally, orphan drug designation is only available where no satisfactory method of diagnosis, prevention, or treatment of the condition has been authorized (or the product would be a significant benefit to those affected).

In the European Union, orphan drug designation entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity is granted following medicinal product approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. Market exclusivity would not prevent the approval of a similar drug that is shown to be safer, more effective or otherwise clinically superior.

Orphan drug designation must be requested before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

Exceptional Circumstances/Conditional Approval

Orphan drugs or drugs with unmet medical needs may be eligible for European Union approval under exceptional circumstances or with conditional approval. Approval under exceptional circumstances may be applicable to orphan products and is used when an applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use because the indication for which the product is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, when the present state of scientific knowledge does not allow comprehensive information to be provided, or when it is medically unethical to collect such information. Conditional marketing authorization may be applicable to orphan medicinal products, medicinal products for seriously debilitating or life-threatening diseases, or medicinal products to be used in emergency situations in response to recognized public threats. Conditional marketing authorization can be granted on the basis of less complete data than is normally required in order to meet unmet medical needs and in the interest of public health, provided the risk-benefit balance is positive, it is likely that the applicant will be able to provide the comprehensive clinical data, and unmet medical needs will be fulfilled. Conditional marketing authorization is subject to certain specific obligations to be reviewed annually.

Accelerated Review

Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of a marketing authorization application is 210 days (excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the EMA's Committee for Medicinal Products for Human Use, or CHMP). Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, particularly from the point of view of therapeutic innovation. In this circumstance, EMA ensures that the opinion of the CHMP is given within 150 days, excluding clock stops.

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any products for which we obtain regulatory approval. In the United States and in other countries, sales of any products for which we receive regulatory approval for commercial sale will depend in part on the availability of coverage and reimbursement from third-party payors. Third-party payors include government authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the reimbursement rate that the payor will pay for the product. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the FDA-approved products for a particular indication. Moreover, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third- party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. In order to obtain coverage and reimbursement for any product that might be approved for sale, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain regulatory approvals. Our product candidates may not be considered medically necessary or cost-effective. If third-party payors do not consider a product to be cost-effective compared to other available therapies, they may not cover the product after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit.

The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. By way of example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, collectively, the Affordable Care Act, contains provisions that may reduce the profitability of drug products, including, for example, increased rebates for drugs sold to Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies' share of sales to federal health care programs. Adoption of government controls and measures, and tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceuticals.

In the European Community, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed to by the government. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, an increasing emphasis on cost containment measures in the United States and other countries has increased and we expect will continue to increase the pressure on pharmaceutical pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Other Healthcare Laws and Compliance Requirements

If we obtain regulatory approval for any of our product candidates, we may be subject to various federal and state laws targeting fraud and abuse in the healthcare industry. These laws may impact, among other things, our proposed sales, marketing and education programs. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce, or in return for, the purchase or recommendation of an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;
- federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payors that are false or fraudulent;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;
- the federal transparency laws, including the provision of the Affordable Care Act referred to as the federal Physician Payment Sunshine Act, that requires drug and biologics manufacturers to disclose payments and other transfers of value provided to physicians and teaching hospitals;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, which imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information; and
- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws that may apply to items or services reimbursed by any third-party payor, including commercial insurers, and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

The Affordable Care Act broadened the reach of the fraud and abuse laws by, among other things, amending the intent requirement of the federal Anti-Kickback Statute and the applicable criminal healthcare fraud statutes contained within 42 U.S.C. § 1320a-7b. Pursuant to the statutory amendment, a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the Affordable Care Act provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act or the civil monetary penalties statute. Many states have adopted laws similar to the federal Anti-Kickback Statute, some of which apply to the referral of patients for healthcare items or services reimbursed by any source, not only the Medicare and Medicaid programs.

We are also subject to the U.S. Foreign Corrupt Practices Act, or FCPA, which prohibits improper payments or offers of payments to foreign governments and their officials for the purpose of obtaining or retaining business. Safeguards we implement to discourage improper payments or offers of payments by our employees, consultants, and others may be ineffective, and violations of the FCPA and similar laws may result in severe criminal or civil sanctions, or other liabilities or proceedings against us, any of which would likely harm our reputation, business, financial condition and result of operations.

If our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, exclusion from participation in government healthcare programs, such as Medicare and Medicaid and imprisonment, damages, fines and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

Employees

As of March 24, 2016, we had 55 full-time employees. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

Financial Information about Segments

We operate in a single accounting segment. Refer to Note 1, "Organization, Business and Basis of Presentation" in the Notes to Consolidated Financial Statements included elsewhere in this report..

Emerging Growth Company

We completed our initial public offering, or IPO, in May 2015, in which we sold 6,164,000 shares of common stock, at a public offering price of $14.00 per share, the net proceeds of which totaled $75.9 million, after deducting underwriting discounts and commissions and offering expenses incurred by us. We qualify as an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, as amended, or the JOBS Act. As an emerging growth company, we may take advantage of specified reduced disclosure and other requirements that are otherwise applicable generally to public companies. We would cease to be an emerging growth company on the date that is the earliest of: (i) the last day of the fiscal year in which we have total annual gross revenues of $1 billion or more; (ii) December 31, 2020; (iii) the date on which we have issued more than $1 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the SEC.

Corporate Information

We were incorporated under the laws of the State of Delaware in September 2005. Our principal executive office is located at 3545 John Hopkins Court, Suite #250, San Diego, California 92121, and our telephone number is (858) 731-8389. Our website address is www.atyrpharma.com. We do not incorporate the information on or accessible through our website into this Annual Report, and you should not consider any information on, or that can be accessed through, our website as part of this Annual Report.

You are advised to read this Annual Report in conjunction with other reports and documents that we file from time to time with the SEC. In particular, please read our final prospectus filed with the SEC on May 7, 2015 under Rule 424(b) of the Securities Act of 1933, as amended, our Quarterly Reports on Form 10-Q and any Current Reports on Form 8-K that we may file from time to time. You may obtain copies of these reports directly from us or from the SEC at the SEC's Public Reference Room at 100 F Street, N.E. Washington, D.C. 20549. In addition, the SEC maintains information for electronic filers (including aTyr Pharma, Inc.) at its website at www.sec.gov. The public may obtain information regarding the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. We make our periodic and current reports available on our internet website, free of charge, as soon as reasonably practicable after such material is electronically filed with, or furnished to, the SEC.

Item 1A. Risk Factors

You should carefully consider the following risk factors, as well as the other information in this Annual Report on Form 10-K, and in our other public filings. The occurrence of any of these risks could harm our business, financial condition, results of operations and/or growth prospects or cause our actual results to differ materially from those contained in forward-looking statements we have made in this report and those we may make from time to time. You should consider all of the risk factors described in our public filings when evaluating our business.

Risks related to the discovery, development and regulation of our Physiocrine-based product candidates

Resolaris, iMod.Fc and any other product candidates that we may develop from our discovery engine represent novel therapeutic approaches, which may cause significant delays or may not result in any commercially viable drugs.

We have concentrated our research and development efforts on Physiocrine biology, a new area of biology, and our future success is highly dependent on the successful development of Physiocrine-based product candidates, including Resolaris, iMod.Fc and additional product candidates arising from the Resokine pathway or other pathways. Physiocrine-based biology represents a novel approach to drug discovery and development, and to our knowledge, no drugs have been developed using, or based upon, this approach. Despite the successful development of other naturally occurring proteins, such as erythropoietin and insulin, as therapeutics, Physiocrines represent a novel class of protein therapeutics, and our development of these therapeutics is based on our new understanding of human physiology. In particular, the mechanism of action of Physiocrines and their role in immuno-modulation and tissue regeneration have not been studied extensively, nor has the safety of this class of protein therapeutics been evaluated extensively in humans. The Physiocrines that we elect to develop may not have the physiological functions that we currently ascribe to them, may have limited or no therapeutic applications, or may present safety problems of which we are not yet aware. We cannot be sure that our discovery engine will yield product candidates with therapeutic applications of Physiocrines that are safe, effective, approvable by regulatory authorities, manufacturable, scalable, or profitable.

Because our work in Physiocrine biology and our product candidates represent a new therapeutic approach, developing and commercializing our product candidates subjects us to a number of challenges, including:

- defining indications within our targeted rare diseases and clinical endpoints within each indication that are appropriate to support regulatory approval;
- obtaining regulatory approval from the U.S. Food and Drug Administration, or the FDA, and other regulatory authorities that have little or no experience with the development of Physiocrine-based therapeutics;
- educating medical personnel regarding the potential side effect profile of each of our product candidates, such as the potential for the development of antibodies against our purified protein therapeutics;
- developing processes for the safe administration of these product candidates, including long-term follow-up for all patients who receive our product candidates;
- sourcing clinical and, if approved, commercial supplies for the materials used to manufacture and process our product candidates;
- developing a manufacturing process and distribution network that ensures consistent manufacture of our product candidates in compliance with current Good Manufacturing Practices, or cGMPs, and related requirements, with a cost of goods that allows for an attractive return on investment;
- establishing sales and marketing capabilities after obtaining any regulatory approval to gain market acceptance; and
- developing therapeutics for rare and more common diseases or indications beyond those addressed by our current product candidates.

Moreover, public perception of safety issues, including adoption of new therapeutics or novel approaches to treatment, may adversely influence the willingness of subjects to participate in clinical trials, or if approved, of physicians to adopt and prescribe novel therapeutics. Physicians, hospitals and third-party payors often are slow to adopt new products, technologies and treatment practices. Physicians may decide the therapy is too complex or unproven to adopt and may choose not to administer the therapy. Based on these and other factors, healthcare providers and payors may decide that the benefits of any Physiocrine-based therapeutic for which we receive regulatory approval do not or will not outweigh its costs. Any inability to successfully develop commercially viable drugs would have an adverse impact on our business, prospects, financial condition and results of operations.

We are highly dependent on the success of Resolaris, our first clinical product candidate, which is still in early clinical development. If we are unable to successfully complete or otherwise advance clinical development, obtain regulatory or marketing approval for, or successfully commercialize, Resolaris, or experience significant delays in doing so, our business will be materially harmed.

To date, we have expended significant time, resources and effort on the discovery and development of Resolaris, including conducting preclinical studies, our Phase 1 clinical trial, our initial FSHD trial and ongoing clinical trials. We have not yet commenced or completed any evaluation of Resolaris in human clinical trials designed to demonstrate efficacy to the satisfaction of the FDA. We currently generate no revenue from the sale of any product, and our ability to generate product revenues and to achieve commercial success, which we do not expect will occur for many years, if ever, will initially depend on our ability to successfully develop, obtain regulatory approval for and commercialize Resolaris for the treatment of one or more of our target rare disease indications in the United States and any foreign jurisdictions. Before we can market or sell Resolaris in the United States or foreign jurisdictions, we will need to commence and complete additional clinical trials (including larger, pivotal trials, which we have not yet commenced), manage clinical and manufacturing activities, obtain necessary regulatory approvals from the FDA in the United States and from similar regulatory authorities in other jurisdictions, obtain adequate clinical and commercial manufacturing supplies, build commercial capabilities, which may include entering into a marketing collaboration with a third party, and in some jurisdictions, obtain reimbursement authorization, among other things. We cannot assure you that we will be able to successfully complete the necessary clinical trials, obtain regulatory approvals, secure an adequate commercial supply for, or otherwise successfully commercialize, Resolaris. If we do not receive regulatory approvals for Resolaris, and even if we do obtain regulatory approvals, we may never generate significant revenues, if any, from commercial sales. If we fail to successfully commercialize Resolaris, we may be unable to generate sufficient revenues to sustain and grow our company, and our business, prospects, financial condition and results of operations will be adversely affected.

Data generated in our preclinical studies and patient sample data relating to the Resokine pathway may not be predictive or indicative of the immuno-modulatory activity or therapeutic effects, if any, of Resolaris in patients.

Our scientists discovered the Resokine pathway using *in vivo* screening systems designed to test potential immuno-modulatory activity in animal models of severe immune activity or inflammation, combined with data relating to the potential blockade of the Resokine pathway in a population of patients with myopathy that occurs in a particular rare disease, anti-synthetase syndrome, with Jo-1 antibodies. Translational medicine, or the application of basic scientific findings to develop therapeutics that promote human health, is subject to a number of inherent risks. In particular, scientific hypotheses formed from non-clinical observations may prove to be incorrect, and the data generated in animal models or observed in limited patient populations may be of limited value, and may not be applicable in clinical trials conducted under the controlled conditions required by applicable regulatory requirements and our protocols. For example, we have not extensively studied the activity of the Resokine pathway in patients with rare genetic myopathies with an immune component, which forms the basis for our clinical trials of Resolaris in facioscapulohumeral dystrophy, or FSHD, and limb-girdle muscular dystrophy 2B, or LGMD2B, nor have we evaluated the activity of the Resokine pathway in patients with interstitial lung disease, or ILD. Our knowledge of the activity of this pathway in Jo-1 antibody patients may not be applicable to our target patient populations in rare myopathies with an immune component, or RMICs, or rare pulmonary diseases with an immune component, or RPICs. In addition, our classification of diseases based on the existence of immune cell invasion (RMICs and RPICs) and our hypothesis that these represent potential indications for Resolaris and iMod.Fc may not prove to be therapeutically relevant. Accordingly, the conclusions that we have drawn from animal studies and patient sample data regarding the potential immuno-modulatory activity of molecules containing the immuno-modulatory domain, or iMod domain, may not be substantiated in other animal models or in clinical trials. Any failure to demonstrate in controlled clinical trials the requisite safety and efficacy of Resolaris, iMod.Fc or other product candidates that we may develop will adversely affect our business, prospects, financial condition and results of operations.

We have not studied Resolaris, iMod.Fc or any of our other product candidates in any human clinical trials designed primarily to show efficacy.

Preclinical and clinical data are often susceptible to varying interpretations and analyses, which may delay, limit or prevent regulatory approval. Many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products. Accordingly, our earlier preclinical and clinical studies should not be relied upon as evidence that our current or future clinical trials will succeed. Study designs and results from previous studies are not necessarily predictive of our future clinical trial designs or results, and initial results may not be confirmed upon full analysis of the complete study data. In particular, Resolaris may not achieve positive results in our current and planned Phase 1b/2 clinical trials in RMICs, and any results observed in our ongoing Phase 1b/2 clinical trials of Resolaris in patients with FSHD and LGMD2B may not be predictive of results for subsequent cohorts or of the overall results of the trials. iMod.Fc may not achieve positive results in our planned clinical trials in healthy subjects and in RPICs or any other clinical studies. In addition, study data from our clinical trials in adult patients might not be predictive of safety, tolerability, immunogenicity or activity in young adults and children. Additionally, Resolaris and iMod.Fc may fail to show the desired safety and efficacy in later stages of clinical development, such as pivotal clinical trials, despite having successfully advanced through initial clinical trials. Any failure of Resolaris, iMod.Fc or any other product candidates that we may develop at any stage in the clinical development process would have a material adverse impact on our business, prospects, financial condition and results of operations.

Because we are developing novel product candidates for the treatment of diseases in which there is little clinical drug development experience and, in some cases, are using new endpoints or methodologies, the regulatory pathways for approval are not well defined, and as a result, there is greater risk that our clinical trials will not result in our desired outcomes.

Our initial clinical focus is on the development of Physiocrine-based therapeutics for the treatment of rare diseases, including FSHD and LGMD2B, where patients may benefit from the activation of immuno-modulatory pathways. There are currently no approved treatments for FSHD, LGMD2B, or other rare disease indications that we intend to initially pursue. As a result, the design and conduct of clinical trials for these indications are subject to increased risk, and we may experience setbacks with our ongoing or planned clinical trials for Resolaris or other product candidates that we may develop because of the limited clinical experience in our target indications. In particular, regulatory authorities in the United States and European Union have not issued definitive guidance as to how to measure and achieve efficacy. In addition, the protocols for our Phase 1b/2 clinical trials of Resolaris in patients with FSHD or LGMD2B include the use of magnetic resonance imaging, or MRI, data as a measure of potential immuno-modulatory effects of Resolaris in diseased muscle tissue. Regulators have not yet determined that such data in FSHD patients signifies a clinically meaningful result or can support regulatory approvals. In later stage trials, we may not achieve a pre-specified endpoint with statistical significance in our planned clinical trials of Resolaris in this indication or in other indications where there is limited or no regulatory guidance regarding appropriate clinical endpoints, which would decrease the chance of obtaining marketing approval for Resolaris. Additionally, it is difficult to establish clinically relevant endpoints for some of these indications because it may take a long time before any therapeutic effects of a drug can be observed.

We could also face challenges in designing clinical trials and obtaining regulatory approval for product candidates from our discovery engine due to the lack of historical clinical trial experience for this novel class of therapeutics. At the moment, because no Physiocrine-based products have received regulatory approval anywhere in the world, it is difficult to determine whether regulatory agencies will be receptive to the approval of our product candidates and to predict the time and cost associated with obtaining regulatory approval. The clinical trial requirements of the FDA and other regulatory agencies and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of the potential products. The regulatory approval process for novel product candidates such as ours can be more expensive and take longer than for other, better known or more extensively studied classes of product candidates. Any inability to design clinical trials with protocols and endpoints acceptable to applicable regulatory authorities, and to obtain regulatory approvals for our product candidates, would have an adverse impact on our business, prospects, financial condition and results of operations.

We may encounter substantial delays and other challenges in our clinical trials or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates in humans. Clinical trials are expensive, time- consuming, often delayed and uncertain as to outcome. We cannot guarantee that our ongoing and planned clinical trials of Resolaris in RMICs, planned clinical trials of iMod.Fc in RPICs, or any other clinical trials that we may plan to conduct, will be initiated or conducted as planned or completed on schedule, if at all. Following our submission of an investigational new drug application, or IND, to the Division of Neurology Products at the FDA to evaluate Resolaris in our Phase 1b/2 trial in adult patients with FSHD in the United States, our IND was placed on full clinical hold to address the non-clinical issue of the comparability of the drug substance used in our preclinical toxicology studies to that used in our Phase 1 clinical trial and proposed for use in the U.S. clinical trial in FSHD patients. We responded to the FDA's comparability request, and, in January 2015, our IND was removed from full clinical hold, allowing us to initiate the Phase 1b/2 trial in the United States. Our IND was placed on partial clinical hold, which prohibits the evaluation of Resolaris at doses higher than our proposed 3.0 mg/kg dose pending our submission of additional non-clinical data to the FDA and the FDA's review of that data. We submitted a response to address the partial clinical hold in September 2015. In October 2015, the FDA requested that we provide additional information to support a lifting of the partial hold. We are finalizing an action plan to provide that information to the FDA in an appropriately timed manner. Although we do not expect the partial clinical hold to have a material impact on our current clinical development timeline for Resolaris in FSHD because we do not intend to evaluate Resolaris at doses higher than 3.0 mg/kg in our current clinical trials in the United States, any inability to initiate or complete our clinical trials of Resolaris in the United States, as a result of the partial clinical hold or otherwise, would delay our clinical development plans, may require us to incur additional clinical development costs and could impair our ability to obtain U.S. regulatory approval for Resolaris.

A failure of one or more clinical trials can occur at any stage of testing, and our clinical trials may not be successful. Events that may prevent successful or timely completion of clinical development include, but are not limited to:

- inability to generate sufficient preclinical, toxicology, or other in vivo or in vitro data to support the initiation of human clinical trials, including trials of certain dosages;
- delays in reaching consensus with regulatory agencies on trial design;
- delays in reaching agreement on acceptable terms with prospective CROs and clinical trial sites;
- delays in obtaining required Institutional Review Board, or IRB, or Ethics Committee approval at each clinical trial site;
- delays in recruiting suitable patients to participate in our clinical trials, or delays that may result if the number of patients required for a clinical trial is larger than we anticipate;
- imposition of a clinical hold by regulatory agencies, which may occur after our submission of data to these agencies or an inspection of our clinical trial operations or trial sites;
- failure by our CROs, investigators, other third parties or us to adhere to clinical trial requirements;
- failure to perform in accordance with the FDA's good clinical practices, or GCPs, or applicable regulatory requirements in other countries;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites;
- delays in having patients complete participation in a trial or return for post-treatment follow-up;
- disagreements with regulators regarding our interpretation of data from preclinical studies or clinical trials;
- occurrence of adverse events associated with the product candidate that are viewed to outweigh its potential benefits; or
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

Any delay in or inability to successfully complete preclinical and clinical development could result in additional costs to us and impair our ability to generate revenue. In addition, if we make manufacturing or formulation changes to our product candidates (including currently contemplated changes in our contract manufacturer, production capacity and manufacturing cell line), we may need to conduct additional studies to bridge our modified product candidates to earlier versions. Clinical trial delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which could impair our ability to obtain orphan exclusivity and successfully commercialize our product candidates and may harm our business and results of operations.

If the results of our clinical trials are perceived to be negative or inconclusive, or if there are safety concerns or adverse events associated with our product candidates, we may:

- be required to perform additional clinical trials to support approval or be subject to additional post-marketing testing requirements;
- be delayed in obtaining marketing approval for our product candidates, if at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;
- be subject to changes in the way the product is manufactured or administered;
- have regulatory authorities withdraw their approval of the product or impose restrictions on its distribution in the form of a modified risk evaluation and mitigation strategy, or REMS;
- be subject to litigation; or
- experience damage to our reputation.

To date, the safety and efficacy of Physiocrine-based therapeutics in humans has not been studied to any significant extent. Accordingly, our product candidates could potentially cause adverse events that have not yet been predicted. In addition, the inclusion of critically ill patients in our clinical trials may result in deaths or other adverse medical events due to the natural progression of the disease. As described above, any of these events could prevent us from successfully completing the clinical development of our product candidates and impair our ability to commercialize any products.

Resolaris, iMod.Fc and any other product candidates that we may discover and develop may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following marketing approval, if any.

Undesirable side effects caused by Resolaris, iMod.Fc and any other product candidates that we may discover or develop, or safety, tolerability or toxicity issues that may occur in our preclinical studies, clinical trials or in the future, could cause us or regulatory authorities to interrupt, restrict, delay, or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign authorities. For example, in its partial clinical hold letter, the FDA requested that, to support clinical trials of Resolaris at doses higher than our proposed 3.0 mg/kg dose, we will need to provide additional non-clinical data demonstrating that certain rodent deaths in our good laboratory practices, or GLP, safety studies of Resolaris at the highest doses administered to rodents were not drug-related or to propose a human clinical monitoring strategy acceptable to the FDA to prevent serious toxicity in humans. We submitted a response to address this concern regarding rodent deaths in September 2015, including the results from a nude rat study in which we reported no deaths. In October 2015, the FDA stated we had not provided sufficient data to resolve the concerns raised by the unexplained deaths and did not lift the partial clinical hold. The FDA requested that we provide additional information to support the lifting of the partial hold. We are finalizing an action plan to provide that information to the FDA in an appropriately timed manner. Any failure to proceed with clinical testing of Resolaris at the doses required to demonstrate efficacy will impair our ability to obtain regulatory approval.

In our Phase 1 clinical trial, we observed low levels of antibodies to Resolaris in some subjects in response to the administration of Resolaris. The development of higher levels of such antibodies over a longer course of treatment may ultimately limit the efficacy of Resolaris and trigger a negative autoimmune response, including the development of anti-synthetase syndrome. Anti-synthetase syndrome can include one or more of the following clinical features: ILD, inflammatory myopathy and inflammatory polyarthritis. Other symptoms which may occur in this setting include fever, weight loss, fatigue, Raynaud's phenomenon of the digits, rash and difficulty swallowing. In our recent Phase 1b/2 clinical trial in adult FSHD patients, or our 002 Study, and the long-term safety extension study, or our 005 Study, we observed low levels of antibodies in some patients. Three patients in these studies experienced generalized infusion related reactions, or IRRs, and discontinued dosing. Of the three patients who experienced generalized IRRs, two had elevated anti-drug antibodies, or ADA, signals at the time of dosing and one developed elevated ADA signals following the occurrence of the IRR. We have established procedural measures for our ongoing trials, including a decreased concentration and intravenous delivery rate of Resolaris, in an effort to minimize the occurrence of generalized IRRs and the formation of ADAs. Although no other patients have experienced a generalized IRR since these measures were put in place, we cannot assure that these measures will be effective in minimizing the occurrence of generalized IRRs or the formation of ADAs, or result in the retention of patients in our trials. Generalized IRRs and other complications or side effects could harm further development and/or commercialization of Resolaris, iMod.Fc and any other product candidates. Additionally, our product candidates are designed to be administered by intravenous injection, which may cause side effects, including acute immune responses and injection site reactions. The risk of adverse immune responses remains a significant concern for protein therapeutics, and we cannot assure that these or other risks will not occur in any of our clinical trials for Resolaris or other product candidates we may develop. There is also a risk of delayed adverse events as a result of long-term exposure to protein therapeutics that must be administered repeatedly for the management of chronic conditions, such as the development of antibodies, which may occur over time. If any such adverse events occur, which may include the development of anti-synthetase syndrome from antibodies or the occurrence of IRRs associated with antibodies, further advancement of our clinical trials could be halted or delayed, which would have a material adverse effect on our business, prospects, financial condition and results of operations.

If one or more of our product candidates receives marketing approval, and we or others later identify undesirable side effects or other safety concerns caused by such products, a number of potentially significant negative consequences could result, including but not limited to:

- regulatory authorities may withdraw approvals or suspend licenses of such products;
- regulatory authorities may require additional warnings on the label;
- we may be required to create a REMS plan, which could include a medication guide outlining the risks of such side effects for distribution to patients, a communication plan for healthcare providers, or other elements to assure safe use;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and could significantly harm our business, prospects, financial condition and results of operations.

We may not be successful in our efforts to identify or discover additional product candidates.

A key element of our strategy is to leverage our discovery engine to identify tRNA synthetases that exhibit activity in physiological disease pathways of interest, and to develop purified forms of these proteins that are suitable for therapeutic application. A significant portion of the research that we are conducting involves new compounds and drug discovery methods, including our proprietary technology. Our drug discovery activities using our proprietary technology may not be successful in identifying proteins that are useful in treating rare or more common diseases. Our research programs may initially show promise in identifying potential product candidates, including iMod.Fc, yet fail to yield product candidates for clinical development for a number of reasons, including:

- the research methodology used may not be successful in identifying appropriate potential product candidates; or
- potential product candidates may, on further study, be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be medicines that will receive marketing approval and achieve market acceptance.

Research programs to identify new product candidates require substantial technical, financial and human resources. We may choose to focus our efforts and resources on a potential product candidate that ultimately proves to be unsuccessful. If we are unable to identify suitable product candidates for preclinical and clinical development and regulatory approval, we will not be able to generate product revenues, which would have an adverse impact on our business, prospects, financial condition and results of operations.

We may encounter difficulties enrolling patients in our clinical trials for a variety of reasons, including the limited number of patients who have the diseases for which our product candidates are being studied, which could delay or halt the clinical development of our product candidates.

Identifying and qualifying patients to participate in our ongoing and planned clinical trials of Resolaris and any other clinical trials that we may conduct for our product candidates is critical to our success. In particular, each of the conditions for which we currently plan to evaluate Resolaris is a rare disease with limited patient pools from which to draw for clinical trials. For example, while estimates of FSHD prevalence vary, studies exploring the topic have identified average prevalence rates of approximately one in 17,000. Applying this rate to the U.S. population, as of November 1, 2014, yields a domestic FSHD population of approximately 19,000. In addition, we estimate that LGMD affects an estimated 16,000 patients in the U.S., approximately 3,000 of whom have LGMD2B. The eligibility criteria for our clinical trials, such as the requirement of at least one skeletal muscle in the legs identified by MRI as STIR positive for enrollment in our ongoing Phase 1b/2 clinical trials of Resolaris in adult patients with FSHD or the requirement for onset of symptoms before the age of 10 in our recently initiated Phase 1b/2 clinical trial of Resolaris in patients with early onset FSHD, may further limit the pool of available participants in our trial. We may be unable to identify and enroll a sufficient number of patients with the disease in question and who meet the eligibility criteria for, and are willing to participate in, our clinical trials. Once enrolled, patients may decide or be required to discontinue from our clinical trials due to inconvenience, burden of trial requirements, adverse events associated with our product candidates or limitations required by trial protocols.

Our ability to identify, recruit enroll and maintain a sufficient number of patients, or those with required or desired characteristics to achieve diversity in a study, to complete our clinical trials in a timely manner may also be affected by other factors, including:

- proximity and availability of clinical trial sites for prospective patients;
- severity of the disease under investigation;
- design of the study protocol and the burdens to patients of compliance with our study protocols;
- perceived risks and benefits of the product candidate under study;
- availability of competing therapies and clinical trials for the patient populations and indications under study;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians; and
- ability to monitor patients adequately during and after treatment.

We are initially focused on the development of Physiocrine-based therapeutics to treat rare conditions. We plan to seek initial marketing approval in the United States. We may not be able to initiate or continue clinical trials if we cannot enroll a sufficient number of eligible patients to participate in the clinical trials required by the FDA or other regulatory agencies. Our ability to successfully initiate, enroll and complete a clinical trial in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including:

- difficulty in establishing or managing relationships with CROs and physicians;
- different requirements and standards for the conduct of clinical trials;
- our inability to locate qualified local consultants, physicians and partners; and
- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment.

Additionally, if patients are unwilling to participate in our clinical trials because of negative publicity from adverse events in our clinical trials or in the biotechnology or protein therapeutics industries or for other reasons, including competitive clinical trials for similar patient populations, the timeline for recruiting patients, conducting studies and obtaining regulatory approval of potential products may be delayed. These delays could result in increased costs, delays in advancing our product development or termination of our clinical trials altogether. If we have difficulty enrolling and maintaining a sufficient number of patients to conduct our clinical trials as planned for any reason, we may need to delay, limit or terminate ongoing or planned clinical trials, any of which would have an adverse effect on our business, prospects, financial condition and results of operations.

We may face manufacturing stoppages and other challenges associated with the clinical or commercial manufacture of our Physiocrine-based therapeutics.

All entities involved in the preparation of therapeutics for clinical trials or commercial sale, including our existing contract manufacturers for our product candidates, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or use in late-stage clinical trials must be manufactured in accordance with cGMP. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of contaminants or to inadvertent changes in the properties or stability of our product candidates that may not be detectable in final product testing. We or our contract manufacturers must supply all necessary documentation in support of a biologics license application, or BLA, or a new drug application, or NDA, on a timely basis and must adhere to the FDA's GLP and cGMP regulations enforced by the FDA through its facilities inspection program. The facilities and quality systems of our contract manufacturers and other third-party contractors must pass a pre-approval inspection for compliance with applicable regulations as a condition of regulatory approval of our product candidates. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our product candidates or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If these facilities do not pass a pre-approval plant inspection, FDA approval of the products will not be granted.

The regulatory authorities also may, at any time following approval of a product for sale, audit the facilities in which the product is manufactured. If any such inspection or audit of our facilities or those of our third-party contractors identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independently of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly or time-consuming for us or a third party to implement and that may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

If we or any of our third-party manufacturers fail to maintain regulatory compliance, the FDA can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new biologic product or drug product, or revocation of a pre-existing approval. Additionally, if supply from one approved manufacturer is interrupted, there could be a significant disruption in clinical or commercial supply. An alternative manufacturer would need to be qualified through a BLA or NDA supplement which could result in further delay. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

In addition, the manufacture of Resolaris and any other Physiocrine-based therapeutics that we may develop presents challenges associated with biologics production, including the inherent instability of larger, more complex molecules and the need to ensure uniformity of the drug substance produced in different facilities or across different batches. We are also currently in the process of changing cell lines for the production of Resolaris in connection with our engagement of a new contract manufacturer to meet our projected needs for pivotal clinical trials and a commercial chemistry, manufacturing and controls specification, which may present production challenges or delays. Furthermore, although Physiocrines represent a class of proteins that may share immuno-modulatory properties in various physiological pathways, each Physiocrine has a different structure and may have unique manufacturing requirements that are not applicable across the entire class. For example, Fc fusion proteins, such as iMod.Fc, include an additional antibody domain to improve pharmacokinetic, or PK, characteristics, and may therefore require a more complex and time-consuming manufacturing process than other Physiocrines. Currently, we are producing our iMod.Fc molecule in E.Coli by expression in inclusion bodies and refolding to recreate the native structure. As a result, the manufacturing processes for one of our product candidates may not be readily adaptable to other product candidates that we develop, and we may need to engage multiple third-party manufacturers to produce our product candidates. Any manufacturing stoppage or delay, or any inability to consistently manufacture adequate supplies of our product candidates for our ongoing or planned clinical trials or on a commercial scale will harm our business, prospects, financial condition and results of operations.

Although the FDA and the European Commission have granted orphan drug designation to Resolaris for the treatment of FSHD, we may not receive orphan drug designation for Resolaris in other jurisdictions or for other indications that we may pursue, or for any other product candidates we may develop under any new applications for orphan drug designation that we may submit, and any orphan drug designations that we have received or may receive may not confer marketing exclusivity or other expected commercial benefits.

The FDA and the European Commission have granted orphan drug designation to Resolaris for the treatment of FSHD. We plan to apply for orphan drug designation for Resolaris for the treatment of LGMD in the United States and European Union and may also apply for orphan drug designation in other territories and for other indications and product candidates. Orphan drug status confers up to ten years of marketing exclusivity in Europe, and up to seven years of marketing exclusivity in the United States, for a particular product in a specified indication. To date, we have been granted orphan drug designation for only one product candidate in the United States and the European Union. We cannot assure you that we will be able to obtain orphan drug designation, or rely on orphan drug or similar designations to exclude other companies from manufacturing or selling products using the same principal mechanisms of action for the same indications that we pursue beyond these timeframes. Furthermore, marketing exclusivity in Europe can be reduced from ten years to six years if the initial designation criteria have significantly changed since the market authorization of the orphan product. Even if we are the first to obtain marketing authorization for an orphan drug indication, there are circumstances under which a competing product may be approved for the same indication during the period of marketing exclusivity, such as if the later product is shown to be clinically superior to the orphan product, or if the later product is deemed a different product than ours. Further, the marketing exclusivity would not prevent competitors from obtaining approval of the same product candidate as ours for indications other than those in which we have been granted orphan drug designation, or for the use of other types of products in the same indications as our orphan product.

Even if we complete the necessary preclinical studies and clinical trials, we cannot predict when or if we will obtain regulatory approval to commercialize a product candidate, and the scope of any approval may be narrower than we expect.

We cannot commercialize a product until the appropriate regulatory authorities have reviewed and approved the product candidate. Even if our product candidates demonstrate safety and efficacy in clinical trials, the regulatory agencies may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Additional delays may result if an FDA Advisory Committee or regulatory authority recommends non-approval or restrictions on approval. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory agency policy during the period of product development, clinical trials and the review process. Regulatory agencies also may approve a product candidate for fewer or more limited indications than requested, may impose restrictions on dosing or may grant approval subject to the performance of post-marketing studies. In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of our product candidates.

Failure to obtain marketing approval in international jurisdictions would prevent our medicines from being marketed in such jurisdictions.

In order to market and sell our medicines in the European Union and many other jurisdictions, we must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing, and we have limited regulatory experience in many jurisdictions. The time required to obtain approval in one jurisdiction may differ substantially from that required to obtain approval in other jurisdictions. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by one regulatory authority does not ensure approval by regulatory authorities in other countries or jurisdictions, and we may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our medicines in any market.

We may not elect or be able to take advantage of any expedited development or regulatory review and approval processes available to product candidates granted breakthrough therapy or fast track designation by the FDA.

We are evaluating the possibility of seeking breakthrough therapy or fast track designation for Resolaris and any other product candidates that we may develop, although we may elect not to do so. A breakthrough therapy program is for a product candidate intended to treat a serious or life-threatening condition, and preliminary clinical evidence indicates that the product candidate may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies. A fast track program is for a product candidate that treats a serious or life-threatening condition, and nonclinical or clinical data demonstrate the potential to address an unmet medical need. Although we believe Resolaris and other product candidates that we may develop from our discovery engine may qualify under either or both of the breakthrough therapy and fast track programs, we may elect not to pursue either of these programs, and even if we do, the FDA has broad discretion whether or not to grant these designations. Accordingly, even if we believe a particular product candidate is eligible for breakthrough therapy or fast track designation, we cannot assure you that the FDA would decide to grant it. Even if we do receive breakthrough therapy or fast track designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw breakthrough therapy or fast track designation if it believes that the product no longer meets the qualifying criteria. In addition, the breakthrough therapy program is a relatively new program. As a result, we cannot be certain whether any of our product candidates can or will qualify for breakthrough therapy designation. Our business may be harmed if we are unable to avail ourselves of these or any other expedited development and regulatory pathways.

Even if we obtain regulatory approval for a product candidate, our products will remain subject to regulatory scrutiny.

Even if Resolaris or any other product candidates that we discover and develop are approved, they will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping, conduct of post-marketing studies, and submission of safety, efficacy, and other post-market information, including both federal and state requirements in the United States and requirements of comparable foreign regulatory authorities.

Manufacturers and manufacturers' facilities are required to comply with extensive FDA, and comparable foreign regulatory authority, requirements, including ensuring that quality control and manufacturing procedures conform to cGMP regulations. As such, we and our contract manufacturers will be subject to continual review and inspections to assess compliance with cGMP and adherence to commitments made in any BLA, NDA, or marketing authorization application, or MAA. Accordingly, we and others with whom we work will need to continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production, and quality control.

Any regulatory approvals that we receive for our product candidates may be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials, and surveillance to monitor the safety and efficacy of the product candidate. We will be required to report certain adverse reactions and production problems, if any, to the FDA and comparable foreign regulatory authorities. Any new legislation addressing drug safety issues could result in delays in product development or commercialization, or increased costs to assure compliance.

We will have to comply with requirements concerning advertising and promotion for our products. Promotional communications with respect to prescription drugs are heavily scrutinized by the FDA, the Department of Justice, state attorneys general and comparable foreign regulatory authorities. For example, we may face claims associated with the use or promotion of our products for uses outside the scope of their approved label indications. Violations, including actual or alleged promotion of our products for unapproved, or off-label, uses are subject to enforcement letters, inquiries and investigations, and civil and criminal sanctions. Any actual or alleged failure to comply with labeling and promotion requirements may have a negative impact on our business. In the United States, engaging in impermissible promotion of our products for off-label uses can also subject us to false claims litigation under federal and state statutes, which can lead to civil and criminal penalties and fines and agreements that would materially restrict the manner in which we promote or distribute our drug products. These false claims statutes include the federal False Claims Act, which allows any individual to bring a lawsuit against a pharmaceutical company on behalf of the federal government alleging submission of false or fraudulent claims, or causing to present such false or fraudulent claims, for payment by a federal program such as Medicare or Medicaid. If the government prevails in the lawsuit, the individual will share in any fines or settlement funds. Since 2004, these False Claims Act lawsuits against pharmaceutical companies have increased significantly in volume and breadth, leading to several substantial civil and criminal settlements based on certain sales practices promoting off-label drug uses. This growth in litigation has increased the risk that a pharmaceutical company will have to defend a false claims action, pay settlement fines or restitution, agree to comply with burdensome reporting and compliance obligations, and be excluded from Medicare, Medicaid and other federal and state healthcare programs. If we do not lawfully promote our approved products, we may become subject to such litigation and, if we are not successful in defending against such actions, those actions could compromise our ability to become profitable.

The holder of an approved BLA, NDA or MAA must submit new or supplemental applications and obtain approval for certain changes to the approved product, product labeling, or manufacturing process. We could also be asked to conduct post-marketing clinical trials to verify the safety and efficacy of our products in general or in specific patient subsets. If original marketing approval were obtained through an accelerated approval pathway, we could be required to conduct a successful post-marketing clinical trial to confirm clinical benefit for our products. An unsuccessful post-marketing study or failure to complete such a trial could result in the withdrawal of marketing approval.

If a regulatory agency discovers previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, or disagrees with the promotion, marketing or labeling of a product, such regulatory agency may impose restrictions on that product or us, including requiring withdrawal of the product from the market. If we fail to comply with applicable regulatory requirements, a regulatory agency or enforcement authority may, among other things:

- issue untitled or warning letters;
- impose civil or criminal penalties;
- suspend or withdraw regulatory approval;
- suspend any of our ongoing clinical trials;
- refuse to approve pending applications or supplements to approved applications submitted by us;
- impose restrictions on our operations, including closing our contract manufacturers' facilities; or
- seize or detain products, or require or request a product recall.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response, and could generate negative publicity. Any failure to comply with ongoing regulatory requirements may significantly and adversely affect our ability to commercialize and generate revenue from our products. If regulatory sanctions are applied or if regulatory approval is withdrawn, the value of our company and our operating results will be adversely affected.

Because of our focus on treatments for severe, rare diseases, Resolaris and other product candidates that we develop may be subject to requests for treatment use under individual patient INDs, which would present a variety of risks.

FDA regulations permit an investigational drug or biologic to be used for the treatment of an individual patient by a licensed physician under certain circumstances if the patient has a serious disease or condition, generally defined as a disease or condition associated with morbidity that has a substantial impact on day-to-day functioning. We believe that Resolaris and other product candidates that we develop may be susceptible to physician requests for use in these settings given the severity of the disease indications that we are targeting and the limited availability of approved and other investigational therapeutics for these indications. The treatment use of our product candidates under individual patient INDs would present a number of risks, including the following:

- The treatment use of our product candidates under individual patient INDs may be subject to less stringent or otherwise different protocols from our clinical trials, subjecting the patient to additional risk, which could negatively affect the perception of our product candidates among physicians, patients and regulators;
- The actual or perceived availability of a product candidate for use under individual patient INDs may impair patient enrollment in our clinical trials; and
- Any decision to make quantities of our product candidates available for use under individual patient INDs may impair our or our third-party manufacturers' ability to timely supply adequate quantities of our product candidates for our clinical trials.

Physicians may independently file individual patient INDs for Resolaris or one of our other product candidates. We may disagree with a physician's or the FDA's conclusion that our product candidate is suitable for evaluation under a particular individual patient IND, and any decision by us not to make our product candidate available for evaluation under this setting may subject us to negative publicity or market perception.

Risks related to our financial condition and capital requirements

We have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future.

We are a clinical stage biotherapeutics company, and we have not yet generated any revenues from product sales. We have incurred net losses in each year since our inception in 2005, including net losses of $48.0 million, $24.4 million and $20.0 million for the years ended December 31, 2015, 2014 and 2013, respectively. As of December 31, 2015, we had an accumulated deficit of $158.1 million.

We have devoted most of our financial resources to research and development, including our clinical and preclinical development activities. To date, we have financed our operations primarily through the sale of equity securities and convertible debt and through commercial bank debt. The amount of our future net losses will depend, in part, on the rate of our future expenditures and our ability to obtain funding through equity or debt financings, grant funding or strategic collaborations. We have not commenced pivotal clinical trials for any product candidate and it will be several years, if ever, before we have a product candidate ready for commercialization. Even if we obtain regulatory approval to market a product candidate, our future revenues will depend upon the size of any markets in which our product candidates have received approval, and our ability to achieve sufficient market acceptance, reimbursement from third-party payors and adequate market share for our product candidates in those markets. However, even if we obtain adequate market share for our product candidates, because the potential markets in which our product candidates may ultimately receive regulatory approval are very small, we may never become profitable despite obtaining such market share and acceptance of our products.

We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. We anticipate that our expenses will increase substantially if and as we:

- continue our research and preclinical and clinical development of Resolaris, our lead product candidate, or any other product candidates that we may develop, including iMod Fc;
- continue our current clinical trials of Resolaris in patients with FSHD and LGMD2B and initiate and conduct additional clinical trials of Resolaris in other RMICs, and iMod.Fc in RPICs, or any other clinical trials;
- initiate and conduct any additional preclinical studies, clinical trials or other studies for Resolaris and any other product candidates that we may develop;
- further develop the manufacturing process for our product candidates;
- change or add additional manufacturers, including manufacturers of quantities of drug substance suitable for pivotal clinical trials and commercialization;
- seek regulatory approvals for our product candidates that successfully complete clinical trials;
- establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval;
- seek to identify and validate additional product candidates;
- make milestone or other payments under our in-license agreements;
- maintain, protect and expand our portfolio of owned and in-licensed intellectual property;
- acquire or in-license other product candidates and technologies;
- attract and retain skilled personnel;
- create additional infrastructure to support our operations as a public company and our product development and planned future commercialization efforts; and
- experience any delays or encounter challenges with any of the above.

The net losses we incur may fluctuate significantly from quarter to quarter and year to year, such that a period-to-period comparison of our results of operations may not be a good indication of our future performance. In any particular quarter or quarters, our operating results could be below the expectations of securities analysts or investors, which could cause our stock price to decline.

We have never generated any revenue from product sales and may never be profitable.

Our ability to generate revenue and achieve profitability depends on our ability to successfully complete the development of, and obtain the regulatory approvals necessary to commercialize, Resolaris and any other product candidates that we may develop. We do not anticipate generating revenues from product sales for the foreseeable future, if ever. Our ability to generate future revenues from product sales depends heavily on our success in:

- completing research, preclinical development and clinical development of Resolaris, iMod Fc and other product candidates;
- seeking and obtaining regulatory approvals for product candidates for which we complete clinical trials;
- developing a sustainable, scalable, reproducible, and transferable manufacturing process for Resolaris and any other product candidates that we may develop;
- establishing and maintaining supply and manufacturing relationships with third parties that can provide products and services that are adequate in both amount and quality to support clinical development and the market demand for our product candidates, if approved;
- launching and commercializing product candidates for which we obtain regulatory approval, by establishing a sales force, marketing and distribution infrastructure;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trademarks, trade secrets and know-how;
- obtaining market acceptance of Physiocrine therapeutics and our product candidates as viable treatment options for our target indications;
- addressing any competing technological and market developments;
- implementing additional internal systems and infrastructure, as needed;
- identifying and validating new Physiocrine therapeutic product candidates;
- attracting, hiring and retaining qualified personnel; and
- negotiating favorable terms in any licensing, collaboration or other arrangements into which we may enter.

Even if Resolaris, iMod.Fc or any of the other product candidates that we may develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Our expenses could increase beyond expectations if we are required by the FDA or other regulatory agencies, domestic or foreign, to perform clinical trials and other studies in addition to those that we currently anticipate. In cases where we are successful in obtaining regulatory approvals to market one or more of our product candidates, our revenue will be dependent, in part, upon the size of the markets in the territories for which we gain regulatory approval, the accepted price for the product, the ability to get reimbursement at any price, the competition we face, and whether we own the commercial rights for that territory. If the number of our addressable rare disease patients is not as significant as we estimate, the indication approved by regulatory authorities is narrower than we expect, or the reasonably accepted population for treatment is narrowed by competition, physician choice or treatment guidelines, we may not generate significant revenue from sales of such products, even if approved. Even if we are able to generate revenues from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations.

We will need to raise additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.

We are currently advancing Resolaris through clinical development and conducting preclinical development activities directed at the identification and selection of additional Physiocrine-based therapeutic candidates. The development of protein therapeutics is expensive, and we expect our research and development expenses to increase substantially in connection with our ongoing activities, particularly as we advance Resolaris into further clinical trials in multiple indications.

As of December 31, 2015, our cash, cash equivalents and investments were approximately $125.3 million. We expect that our existing cash, cash equivalents and investments will be sufficient to fund our current operations through at least the next 12 months. However, our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or a combination of these approaches. Our future funding requirements will depend on many factors, including but not limited to:

- the scope, rate of progress, results and cost of our clinical trials, nonclinical testing, and other related activities;

- the cost of manufacturing clinical supplies, and establishing commercial supplies, of our product candidates and any products that we may develop;
- the number and characteristics of product candidates that we pursue;
- the cost, timing, and outcomes of regulatory review of our product candidates;
- the cost and timing of establishing sales, marketing, and distribution capabilities; and
- the terms and timing of any collaborative, licensing, and other arrangements that we may establish, including any required milestone and royalty payments thereunder.

In any event, we will require additional capital to complete additional clinical trials, including larger, pivotal clinical trials, to obtain regulatory approval for, and to commercialize, our product candidates. Raising funds in the current economic environment may present additional challenges. Even if we believe we have sufficient funds for our current or future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic considerations. If we are unable to obtain funding on a timely basis, we may be required to significantly curtail, delay or discontinue one or more of our research or development programs or the commercialization of any product candidates, or we may be unable to expand our operations or otherwise capitalize on our business opportunities, as desired, which could materially affect our business, financial condition and results of operations.

Raising additional capital may cause dilution to our existing stockholders, restrict our operations, require us to relinquish rights to our technologies or product candidates on terms unfavorable to us and divert management's attention from our product development activities.

The terms of any financing may adversely affect the holdings or the rights of our stockholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities would cause dilution to all of our stockholders. The incurrence of indebtedness would increase our fixed payment obligations and may require us to agree to certain restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. We could also be required to seek funds through arrangements with collaborative partners or otherwise at an earlier stage than desirable and we may be required to relinquish rights to some of our technologies or product candidates or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results and prospects. In addition, any fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates.

Risks related to our reliance on third parties

We rely, and expect to continue to rely, on third parties to conduct some or all aspects of our product manufacturing, protocol development, research and preclinical and clinical testing, and these third parties may not perform satisfactorily.

We currently rely, and expect to continue to rely, on third parties to conduct some or all aspects of product manufacturing, protocol development, research and preclinical and clinical testing with respect to our product candidates. Any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it could delay our product development activities. Our reliance on these third parties for research and development activities reduces our control over these activities but does not relieve us of our responsibility to ensure compliance with all required regulations and study protocols. For example, for Resolaris and any other product candidates that we develop and commercialize on our own, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable study plan and protocols and cGCPs.

If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our research and development activities, including clinical trials, in accordance with regulatory requirements or our stated study plans and protocols, we will not be able to complete, or may be delayed in completing, the preclinical studies and clinical trials required to support future BLA or NDA submissions and approval of our product candidates.

We rely on third parties to manufacture our clinical supply of Resolaris, and we intend to rely on third parties to produce non-clinical, clinical and commercial supplies of any future product candidate.

We do not have, nor do we plan to acquire, the infrastructure or capability internally to manufacture our nonclinical and clinical quantities of our product candidates, and we lack the internal resources and capability to manufacture any of our product candidates on a clinical or commercial scale. Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured the product candidates ourselves, including:

- the inability to negotiate manufacturing agreements with third parties under commercially reasonable terms;
- reduced control as a result of using third-party manufacturers for all aspects of manufacturing activities;

- termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us; and
- disruptions to the operations of our third-party manufacturers or suppliers caused by conditions unrelated to our business or operations, including the insolvency or bankruptcy of the manufacturer or supplier.

Any of these events could lead to clinical trial delays or failure to obtain regulatory approval, or impact our ability to successfully commercialize future products. Some of these events could be the basis for FDA action, including injunction, recall, seizure or total or partial suspension of production.

Additionally, each manufacturer may require licenses to manufacture our product candidates or components thereof if the applicable manufacturing processes are not owned by the manufacturer or in the public domain, and we may be unable to transfer or sublicense the intellectual property rights we may have with respect to such activities. These factors could cause the delay of clinical development, regulatory submissions, required approvals or commercialization of our product candidates, cause us to incur higher costs and prevent us from commercializing our products successfully.

We currently rely on a single manufacturer for bulk drug substance for Resolaris in our current and planned Phase 1b/2 clinical trials and have recently initiated cGMP drug substance manufacturing activities with an additional contract manufacturer for our projected needs for ongoing and anticipated pivotal clinical trials. Subject to the satisfactory completion of process validation and other requirements, we may contract with this manufacturer for larger scale commercial manufacturing. We do not have long-term contracts with our manufacturers, and our manufacturers may terminate their agreements with us for a variety of reasons including technical issues or our material breach of our obligations under the applicable agreement. Furthermore, our manufacturers may reallocate resources away from the production of our product candidates if we delay manufacturing under certain circumstances, and the manufacturing facilities in which our product candidates are made could be adversely affected by earthquakes and other natural disasters, labor shortages, power failures, and numerous other factors. If our manufacturers fail to meet contractual requirements, and we are unable to secure one or more replacement manufacturers capable of production at a substantially equivalent cost, our clinical development activities may be delayed, or we could lose potential revenue. Manufacturing biologic drugs is complicated and tightly regulated by the FDA and comparable regulatory authorities around the world, and although alternative third-party manufacturers with the necessary manufacturing and regulatory expertise and facilities exist, it could be expensive and take a significant amount of time to arrange for alternative manufacturers, transfer manufacturing procedures to these alternative manufacturers, and demonstrate comparability of material produced by such new manufacturers. New manufacturers of any product would be required to comply with applicable regulatory requirements. These manufacturers may not be able to manufacture our product candidates at costs, or in quantities, or in a timely manner necessary to complete the clinical development of our product candidates or make commercially successful products.

We rely, and expect to continue to rely, on third parties to conduct, supervise and monitor our clinical trials, and if these third parties perform in an unsatisfactory manner, it may harm our business.

We have relied, and expect to continue to rely, on third-party CROs and clinical trial sites to ensure our clinical trials are conducted properly and on time. While we have and will continue to enter into agreements governing their activities, we will have limited influence over their actual performance. We will control only certain aspects of our CROs' activities. Nevertheless, we will be responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, legal and regulatory requirements, and scientific standards, and our reliance on the CROs does not relieve us of our regulatory responsibilities.

We and our CROs are required to comply with GCPs for conducting, recording and reporting the results of clinical trials to assure that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. The FDA enforces GCPs through periodic inspections of study sponsors, principal investigators and clinical trial sites. If we or our CROs fail to comply with applicable GCPs, the clinical data generated in our future clinical trials may be deemed unreliable and the FDA may require us to perform additional unanticipated clinical trials before approving any marketing applications. Upon inspection, the FDA may determine that our clinical trials did not comply with GCPs. In addition, our future clinical trials will require a sufficient number of test subjects to evaluate the safety and effectiveness of our product candidates. Accordingly, if our CROs fail to comply with these regulations or fail to recruit a sufficient number of patients, we may be required to repeat such clinical trials, which would delay the regulatory approval process.

Our CROs are not our employees, and we are therefore unable to directly monitor whether or not they devote sufficient time and resources to our clinical and nonclinical programs. These CROs may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other drug development activities that could harm our competitive position. If our CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements, or for any other reasons, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize our product candidates. As a result, our financial results would be harmed, our costs could increase, our ability to generate revenues could be delayed and the commercial prospects for our product candidates will be adversely affected.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

We rely on third parties to manufacture our product candidates, and we collaborate with various academic institutions in the development of our discovery engine for therapeutic applications of Physiocrines. In connection with these activities, we are required, at times, to share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our collaborators, advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business, prospects, financial condition and results of operations.

In addition, these agreements typically restrict the ability of our collaborators, advisors, employees and consultants to publish data potentially relating to our trade secrets. Our academic collaborators typically have rights to publish data, provided that we are notified in advance and may delay publication for a specified time in order to secure intellectual property rights to which we are entitled arising from the collaboration. In other cases, publication rights are controlled exclusively by us, although in some cases we may share these rights with other parties. We also conduct joint research and development programs that may require us to share trade secrets under the terms of our research and development partnerships or similar agreements. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of these agreements, independent development or publication of information including our trade secrets in cases where we do not have proprietary or otherwise protected rights at the time of publication. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business, prospects, financial condition and results of operations.

Risks related to the commercialization of our product candidates

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell our product candidates, we may be unable to generate any revenues.

We do not currently have any infrastructure for the sales, marketing and distribution of pharmaceutical products. In order to market our product candidates, if approved by the FDA or any other regulatory body, we must build our sales, marketing, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. There are risks involved with both establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our medicines on our own include:

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future medicines;
- the lack of complementary medicines to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we enter into arrangements with third parties to perform sales, marketing and distribution services, our product revenues or the profitability of these product revenues to us are likely to be lower than if we were to market and sell any medicines that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our medicines effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

We rely on third-party manufacturers to produce Resolaris, iMod.Fc and any other product candidates that we may develop, but we have not entered into agreements with any such manufacturers to support commercialization.

We have not yet secured manufacturing capabilities for commercial quantities of Resolaris, iMod.Fc or any other product candidates. Although we intend to rely on third-party manufacturers for commercialization, we have only entered into agreements with such manufacturers to support our human proof-of-concept clinical trials. We have not yet entered into a long-term commercial supply agreement to support full scale commercial production, and we or our contract manufacturers may be unable to process validation activities necessary to enter into commercial supply agreements or otherwise negotiate agreements with the manufacturers to support our commercialization activities at commercially reasonable terms.

We may run into technical or scientific issues related to development or manufacturing that we may be unable to resolve in a timely manner or with available funds. If we or our manufacturing partners are unable to scale the manufacturing process to produce commercial quantities of our product candidates, or our manufacturing partners do not pass required regulatory pre-approval inspections, our commercialization efforts will be harmed.

In addition, any significant disruption in our relationships with our manufacturers could harm our business. There are a relatively small number of potential manufacturers for Resolaris and any other product candidates that we may develop, and such manufacturers may not be able to supply our drug products at the times we need them or on commercially reasonable terms. Any disruption to our relationship with our current manufacturers and any manufacturers that we contract with in the future will result in delays in our ability to complete the clinical development of, or to commercialize, Resolaris and any other product candidates we may develop, and may require us to incur additional costs.

We face intense competition and rapid technological change and the possibility that our competitors may develop therapies that are more advanced or effective than ours, which may adversely affect our financial condition and our ability to successfully commercialize our product candidates.

We are engaged in the development of medicines for severe, rare diseases, which is a competitive and rapidly changing field. We have competitors both in the United States and internationally, including major multi-national pharmaceutical companies, biotechnology companies and universities and other research institutions. We expect to compete with various companies, academic institutions and other organizations that have products in development for some of our target RMIC indications. For example, although there are currently no approved products for the treatment of FSHD, Acceleron Pharma Inc. is developing a clinical candidate, ACE-083, a locally acting protein therapeutic designed to increase muscle mass and strength in patients with neuromuscular disorders and other diseases characterized by a loss of muscle function, including FSHD in which it intends to initiate a Phase 2 trial in mid-2016. In addition, Facio Therapies and Novogen are screening chemical libraries to identify chemical compounds that will boost the expression of proteins known to repress one of the causal genes responsible for FSHD. While the limb-girdle muscular dystrophies are comprised of over 20 rare genetically-defined myopathies, we are unaware of any companies with programs specific to LGMD2B. We may also face competition from numerous companies in the field of RPICs, including several companies that currently market Esbriet (pirfenidone) and Ofev (nintedanib), both of which were approved by the FDA for the treatment of ILD in October 2014. Many larger companies, universities and private and public research institutions are also actively engaged in the development of therapeutics to address muscle loss and muscle weakness in a variety of indications.

Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff and experienced marketing and manufacturing organizations. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or licensing on an exclusive basis products that are more effective, safer, more convenient or less costly than any product candidate that we may develop, or achieve earlier patent protection, regulatory approval, product commercialization and market penetration than us. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors.

Even if we are successful in achieving regulatory approval to commercialize a product candidate faster than our competitors, we may face competition from biosimilars due to the changing regulatory environment. In the United States, the Biologics Price Competition and Innovation Act of 2009 created an abbreviated approval pathway for biological products that are demonstrated to be "highly similar," or biosimilar, to or "interchangeable" with an FDA-approved biological product. This new pathway could allow competitors to reference data from biological products already approved after 12 years from the time of approval. In Europe, the European Commission has granted marketing authorizations for several biosimilars pursuant to a set of general and product class-specific guidelines for biosimilar approvals issued over the past few years. In Europe, a competitor may reference data from biological products already approved, but will not be able to get on the market until ten years after the time of approval. This ten year period will be extended to 11 years if, during the first eight of those ten years, the marketing authorization holder obtains an approval for one or more new therapeutic indications that bring significant clinical benefits compared with existing therapies. In addition, companies may be developing biosimilars in other countries that could compete with our products. If competitors are able to obtain marketing approval for biosimilars referencing our products, our products may become subject to competition from such biosimilars, with the attendant competitive pressure and consequences. Expiration or successful challenge of our applicable patent rights could also trigger competition from other products, assuming any relevant exclusivity period has expired.

Finally, as a result of the expiration or successful challenge of our patent rights, we could face more litigation with respect to the validity or scope of patents relating to our competitors' products. The availability of our competitors' products could limit the demand, and the price we are able to charge, for any products that we may develop and commercialize.

The commercial success of any current or future product candidate will depend upon the degree of market acceptance by physicians, patients, third-party payors and others in the medical community.

Even with the requisite approval from the FDA and comparable foreign regulatory authorities, the commercial success of our product candidates will depend in part on the medical community, patients, and third-party payors accepting our product candidates as medically useful, cost-effective, and safe. Any product that we bring to the market may not gain market acceptance by physicians, patients, third-party payors and others in the medical community. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable. The degree of market acceptance of these product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the potential efficacy and potential advantages over alternative treatments;
- the prevalence and severity of any side effects, including any limitations or warnings contained in a product's approved labeling;
- the prevalence and severity of any side effects resulting from the administration of our product candidates by injection;
- the clinical indications for which approval is granted;
- relative convenience and ease of administration;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- publicity concerning our products or competing products and treatments; and
- the availability of sufficient third-party insurance coverage or reimbursement.

Even if a potential product displays a favorable efficacy and safety profile in preclinical studies and clinical trials, market acceptance of the product will not be known until after it is launched. Our efforts to educate the medical community and third-party payors on the benefits of the product candidates may require significant resources and may never be successful. Such efforts to educate the marketplace may require more resources than are required by the conventional technologies marketed by our competitors, and our competitors may have substantially greater resources or brand recognition to effectively market their products. If our product candidates are approved but fail to achieve an adequate level of acceptance by physicians, patients, third-party payors, and others in the medical community, we will not be able to generate sufficient revenue to become or remain profitable.

The insurance coverage and reimbursement status of newly-approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for new or current products could limit our ability to market those products and decrease our ability to generate revenue.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, as CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors often follow CMS with respect to coverage policy and payment limitations in setting their own reimbursement policies. It is difficult to predict what CMS will decide with respect to reimbursement for fundamentally novel products such as ours, as there is no body of established practices and precedents for these new products. Reimbursement agencies in Europe may be more conservative than CMS. For example, a number of cancer drugs have been approved for reimbursement in the United States, but have not been approved for reimbursement in certain European countries. There may be significant delays in obtaining reimbursement for newly approved medicines, and our inability to promptly obtain coverage and profitable payment rates from third-party payors for any approved medicines could have a material adverse effect on our business, prospects, financial condition and results of operations.

Outside the United States, international sales are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe, Canada, and other countries has and will continue to put pressure on the pricing and usage of our product candidates. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. In general, the prices of medicines under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for medicines, but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenues and profits. Net prices for medicines may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that currently restrict imports of medicines from countries where they may be sold at lower prices than in the United States.

Moreover, increasing efforts by governmental and third-party payors, in the United States and abroad, to cap or reduce healthcare costs may cause such organizations to limit both coverage and level of reimbursement for new products and, as a result, they may not cover or provide adequate payment for our product candidates. We expect to experience pricing pressures in connection with the sale of any of our product candidates, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

In addition, drug prices are under significant scrutiny in the markets in which our products may be sold. Drug pricing and other health care costs continues to be subject to intense political and societal pressures which we anticipate will continue and escalate on a global basis. As a result, our business and reputation may be harmed, our stock price may be adversely impacted and experience periods of volatility, we may have difficulty raising funds and our results of operations may be adversely impacted.

If the market opportunities for our product candidates are smaller than we believe they are, our revenues may be adversely affected and our business may suffer. Because the target patient populations of our product candidates are small, we must be able to successfully identify patients and capture a significant market share to achieve and maintain profitability.

We focus our research and product development on treatments for rare diseases. Given the small number of patients who have the diseases that we are targeting, it is critical to our ability to grow and become profitable that we continue to successfully identify patients with these rare diseases. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including the scientific literature, surveys of clinics, patient foundations, or market research, and may prove to be incorrect. New studies may change the estimated incidence or prevalence of these diseases. The number of patients may turn out to be lower than expected. The effort to identify patients with diseases we seek to treat is in early stages, and we cannot accurately predict the number of patients for whom treatment might be possible. Additionally, the potentially addressable patient population for each of our product candidates may be limited or may not be amenable to treatment with our product candidates, and new patients may become increasingly difficult to identify or gain access to, which would adversely affect our results of operations and our business. Further, even if we obtain significant market share for our product candidates, because the potential target populations are very small, we may never achieve profitability despite obtaining such significant market share.

Our target patient populations are relatively small, and there is currently no standard of care treatment directed at some of our target indications, such as FSHD and LGMD2B. As a result, the pricing and reimbursement of our product candidates, if approved, is uncertain, but must be adequate to support commercial infrastructure. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell our product candidates will be adversely affected. The manner and level at which reimbursement is provided for services related to our product candidates (e.g., for administration of our product to patients) is also important. Inadequate reimbursement for such services may lead to physician resistance and adversely affect our ability to market or sell our products.

Risks related to our intellectual property

If we are unable to obtain, maintain or protect intellectual property rights related to our product candidates, or if the scope of such intellectual property protection is not sufficiently broad, we may not be able to compete effectively in our markets.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our technologies and product candidates. Our success depends in large part on our and our licensors' abilities to obtain and maintain patent and other intellectual property protection in the United States and in other countries for our proprietary technology and product candidates.

We have sought to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies and product candidates that are important to our business. This process is expensive and time consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection.

The patentability of inventions, and the validity, enforceability and scope of patents in the biotechnology and pharmaceutical fields involves complex legal and scientific questions and can be uncertain. As a result, patent applications that we own or in-license may not issue as patents with claims that cover our product candidates, or at all, in the United States or in foreign countries for many reasons. For example, there is no assurance that we were the first to invent or the first to file patent applications in respect of the inventions claimed in our patent applications or that our patent applications claim patentable subject matter. We may also be unaware of potentially relevant prior art relating to our patents and patent applications, and this prior art, if any, may be used by third parties as grounds to seek to invalidate a patent or to prevent a patent from issuing from a pending patent application. Even if patents do successfully issue and even if such patents disclose aspects of our product candidates, third parties may challenge their validity, enforceability or scope, which may result in such patents being narrowed or invalidated. Furthermore, even if they are unchallenged, our patents and patent applications may not adequately protect our intellectual property, provide exclusivity for our product candidates or prevent others from designing around our claims. If the breadth or strength of protection provided by the patents and patent applications we hold, license or pursue with respect to our product candidates is threatened, it could threaten our ability to commercialize our product candidates. Further, if we encounter delays in our clinical trials, the period of time during which we could market any of our product candidates under patent protection, if approved, would be reduced. Since patent applications in the United States and most other countries are confidential for a period of time after filing, we cannot be certain that we were the first to file any patent application related to our product candidates. Changes to the patent laws in the United States and other jurisdictions could also diminish the value of our patents and patent applications or narrow the scope of our patent protection. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

If the patent applications we own or have in-licensed that relate to our programs or product candidates do not issue as patents, if their breadth or strength of protection is threatened, or if they fail to provide exclusivity for our product candidates, it could dissuade companies from collaborating with us to develop product candidates, and threaten our ability to commercialize future products. We cannot offer any assurances about which, if any, patents will issue, the breadth of any such patents or whether any issued patents will be found invalid and unenforceable or will be threatened by third parties. Any successful opposition to these patents or any other patents owned by or licensed to us could deprive us of rights necessary for the successful commercialization of any product candidates that we may develop. In addition, patents have a limited term. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Although various extensions may be available, the life of a patent, and the protection it affords, is limited. Even if a patent does issue for any of our pending patent applications, possible delays in regulatory approvals could mean that the period of time during which we could market a product candidate under patent protection could be reduced from what we generally would expect. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we were the first to file any patent application related to a product candidate. Furthermore, if third parties have filed such patent applications, an interference proceeding in the United States can be initiated by a third party to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. Even if patents covering aspects of our product candidates are obtained, once the patent life has expired for a product, we may be open to competition from generic medications.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems, but it is possible that these security measures could be breached. Although we expect all of our employees and consultants to assign their inventions to us, and all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed or that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. For example, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Misappropriation or unauthorized disclosure of our trade secrets could impair our competitive position and may have a material adverse effect on our business. Additionally, if the steps we take to maintain the confidentiality of our trade secrets are inadequate, we may have insufficient recourse against third parties for misappropriating our proprietary information and processes. In addition, others may independently discover our trade secrets and proprietary information. For example, the FDA, as part of its Transparency Initiative, is currently considering whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time how the FDA's disclosure policies may change in the future, if at all.

If we are unable to prevent material disclosure of the non-patented intellectual property related to our technologies to third parties, and there is no guarantee that we will have any such enforceable trade secret protection, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition.

Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in preventing third parties from practicing our inventions in countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions.

Claims that our product candidates or the manufacture, sale or use of our future products infringe the patent or other intellectual property rights of third parties could result in costly litigation or could require substantial time and money to resolve, even if litigation is avoided.

Our commercial success depends in part on our avoiding infringement of the patents and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, oppositions and inter partes reexamination proceedings before the United States Patent and Trademark Office, or USPTO, and corresponding foreign patent offices. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are pursuing development candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may infringe. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. If any third-party patents were held by a court of competent jurisdiction to cover the manufacturing process of any of our product candidates, any molecules formed during the manufacturing process or any final product itself, the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire.

Similarly, if any third-party patents are held by a court of competent jurisdiction to cover aspects of our formulations, processes for manufacture or methods of use, the holders of any such patents may be able to block our ability to develop and commercialize the applicable product candidate unless we obtain a license or until such patent expires. In either case, such a license may not be available on commercially reasonable terms or at all.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, pay royalties, redesign our infringing products or obtain one or more licenses from third parties, which may not be able to be obtained on reasonable commercial terms or at all, or require substantial time and monetary expenditure.

We may not be successful in obtaining or maintaining necessary rights to our Physiocrine therapeutic product candidates and processes for our development pipeline through acquisitions and in-licenses.

We believe that we have rights to intellectual property, through licenses from third parties and under patents that we own, that is necessary or useful to develop our product candidates. Because our programs may involve additional product candidates that may require the use of proprietary rights held by third parties, the growth of our business will likely depend in part on our ability to acquire, in-license or use these proprietary rights. In addition, our product candidates may require specific formulations to work effectively and efficiently and these rights may be held by others. We may be unable to acquire or in-license any compositions, methods of use, processes or other third-party intellectual property rights from third parties that we identify on reasonable commercial terms or at all. The licensing and acquisition of third-party intellectual property rights is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities.

We sometimes collaborate with U.S. and foreign academic institutions to accelerate our preclinical research or development under written agreements with these institutions. These institutions may provide us with an option to negotiate a license to the institution's rights in technology resulting from the collaboration. Regardless of any such right of first negotiation for intellectual property, we may be unable to negotiate a license within the specified time frame or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program.

In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment. If we are unable to successfully obtain rights to required third-party intellectual property rights, our business, financial condition and prospects for growth could suffer.

If we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.

We are a party to a number of intellectual property license agreements that are important to our business and expect to enter into additional license agreements in the future. Our existing license agreements impose, and we expect that future license agreements will impose, various diligence, milestone payment, royalty and other obligations on us. If we fail to comply with our obligations under these agreements, or we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to market products covered by the license. For example, under the terms of the license agreements that we may enter into pursuant to our amended and restated research funding and option agreement with The Scripps Research Institute, or TSRI, TSRI has the right to terminate the license under various circumstances, including our failure to make payments to TSRI when due, our default in our indemnification and insurance obligations under the agreement, our failure to meet diligence obligations, as determined by TSRI, our underreporting or underpayment of amounts due to TSRI, our conviction of a felony related to the manufacture, use or sale of licensed products, services or processes and our institution of any challenges to the validity or enforceability of any of the licensed patents.

We may need to obtain licenses from third parties to advance our research or allow commercialization of our product candidates, and we have done so from time to time. We may fail to obtain any of these licenses at a reasonable cost or on reasonable commercial terms, if at all. In that event, we may be required to expend significant time and resources to develop or license replacement technology. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates, which could harm our business significantly. We cannot provide any assurances that third-party patents do not exist which might be enforced against our current product candidates or future products, resulting in either an injunction prohibiting our sales, or, with respect to our sales, an obligation on our part to pay royalties or other forms of compensation to third parties.

In some cases, patent prosecution of our licensed technology is controlled by the licensor. Under the license agreements that we may enter into pursuant to our amended and restated research funding and option agreement with TSRI, TSRI is responsible for the prosecution and maintenance of the licensed patent rights, subject to our right to be consulted and to be informed of the progress of patent applications, patents and related submissions. If our licensors fail to obtain and maintain patent or other protection for the proprietary intellectual property we license from them, we could lose our rights to the intellectual property or our exclusivity with respect to those rights, and our competitors could market competing products using such intellectual property. In certain cases, we may control the prosecution of patents resulting from licensed technology. In the event we breach any of our obligations related to such prosecution, we may incur significant liability to our licensors. Licensing of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues and is complicated by the rapid pace of scientific discovery in our industry. Disputes may arise regarding intellectual property subject to a license agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the license agreement;
- the sublicensing of patent and other rights under our collaborative development relationships;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our sublicensees or partners, if any; and
- the priority of invention of patented technology.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

We may become involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time-consuming and unsuccessful.

Competitors may infringe or otherwise violate our patents, the patents of our licensors or our other intellectual property rights. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. Any claims that we assert against perceived infringers could also provoke these parties to assert counterclaims against us alleging that we infringe their intellectual property rights. In addition, in an infringement proceeding, a court may decide that a patent of ours or our licensors is not valid, is unenforceable or is not infringed, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly and could put our patent applications at risk of not issuing.

Interference or derivation proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions or other matters of inventorship with respect to our patents or patent applications or those of our licensors. We may also become involved in other proceedings, such as re-examination or opposition proceedings, before the USPTO or its foreign counterparts relating to our intellectual property or the intellectual property rights of others. An unfavorable outcome in any such proceedings could require us to cease using the related technology or to attempt to license rights to it from the prevailing party, or could cause us to lose valuable intellectual property rights. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms, if any license is offered at all. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our research programs, license necessary technology from third parties, or enter into development partnerships that would help us bring our product candidates to market. We may also become involved in disputes with others regarding the ownership of intellectual property rights. For example, we jointly develop intellectual property with certain parties, and disagreements may therefore arise as to the ownership of the intellectual property developed pursuant to these relationships. If we are unable to resolve these disputes, we could lose valuable intellectual property rights.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our common stock.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties or that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

We employ individuals who were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and independent contractors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed intellectual property, including trade secrets or other proprietary information, of any of our employee's former employer or other third parties. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could adversely impact our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

We may be subject to claims challenging the inventorship or ownership of our patents and other intellectual property.

Although we are not currently experiencing any claims challenging the inventorship of our patents or ownership of our intellectual property, we may in the future be subject to claims that former employees, collaborators or other third parties have an ownership interest in our patents or other intellectual property. For example, we may have inventorship disputes arise from conflicting obligations of consultants or others who are involved in developing our product candidates. Litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents or applications will be due to be paid to the USPTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents or applications. We have systems in place to remind us to pay these fees, and we employ an outside firm and rely on our outside counsel to pay these fees due to non-U.S. patent agencies. The USPTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. We employ law firms and other professionals to help us comply, and in many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, there are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business.

Issued patents covering our product candidates could be found invalid or unenforceable if challenged in court.

If we or one of our licensors initiated legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that the patent covering our product candidate is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). Such proceedings could result in revocation or amendment to our patents in such a way that they no longer cover our product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates. Such a loss of patent protection would have a material adverse impact on our business.

Changes in patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with many other biotechnology companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biotechnology industry involve both technological and legal complexity, and is therefore obtaining, maintaining and enforcing biotechnology patents is costly, time-consuming and inherently uncertain. In addition, recent legislative and judicial developments in the United States and elsewhere have in some cases removed the protection afforded to patent owners, made patents more difficult to obtain, or increased the uncertainty regarding the ability to obtain, maintain and enforce patents. For example, Congress has recently passed, and the United States is currently implementing, wide-ranging patent reform legislation, and may pass further patent reform legislation in the future. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. For example, in a recent case, *Association for Molecular Pathology v. Myriad Genetics, Inc.*, the U.S. Supreme Court held that certain claims to naturally occurring substances are not patentable. Although we do not believe that any of the patents owned or licensed by us will be found invalid based on this decision, we cannot predict how future decisions by the courts, the U.S. Congress, or the USPTO may impact the value of our patents. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents generally, once obtained. Depending on decisions and actions by the U.S. Congress, the federal courts, the USPTO and their respective foreign counterparts, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to maintain and enforce our existing patents and patents that we might obtain in the future.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the validity or defense of our issued patents.

On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law, including provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. The USPTO is currently developing regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, were enacted March 16, 2013. Although it is not clear what, if any, impact the Leahy-Smith Act will have on the operation of our business, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

We have not yet registered Resolaris as a trademark, and failure to secure or maintain adequate protection for our trademarks could adversely affect our business.

We have filed a U.S. trademark application for the Resolaris mark but it has not yet matured to registration, and we have yet to file any foreign trademark applications for the Resolaris mark. Although, the USPTO has examined our U.S. application for the Resolaris mark and there are no outstanding objections to the application, comparable agencies in foreign jurisdictions may raise objections to our applications. Although we would be given an opportunity to respond to those objections, we may be unable to overcome such objections. In addition, in the USPTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings have been filed and may in the future be filed against certain of our trademarks, and our trademarks may not survive such proceedings. Furthermore, third parties have alleged, and may allege in the future, that Resolaris in particular or any other trademark or trade name that we elect to use for our product candidates, may cause confusion in the marketplace. Specifically, in April 2015, Alexion Pharmaceuticals ("Alexion") sent a letter to our counsel alleging that our anticipated use of the Resolaris trademark would cause patients, practitioners and researchers to mistakenly associate us with Alexion or its Soliris product. Alexion claims ownership of a U.S. trademark registration for its Soliris mark. Alexion concluded its letter by requesting that we select a new name for our Resolaris product and withdraw our pending trademark application for the mark. We evaluate such actual and potential allegations in the course of our business, and such evaluations may cause us to change our commercialization or branding strategy for our product candidates, which may require us to incur additional costs. In particular, we are assessing Alexion's allegations and will determine whether we need to, or should, select a different name for the product or contest any trademark enforcement actions by Alexion. Moreover, any name we propose to use with our product candidates in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. The FDA typically conducts a review of proposed product names, including an evaluation of potential for confusion with other product names. If the FDA objects to any of our proposed proprietary product names, we may be required to expend significant additional resources in an effort to identify a suitable substitute name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA.

We may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Risks related to our business operations

Our future success depends on our ability to retain key employees, consultants and advisors and to attract, retain and motivate qualified personnel.

We are highly dependent on principal members of our executive team, the loss of whose services may adversely impact the achievement of our objectives. While we have entered into employment agreements with each of our other executive officers, any of them could leave our employment at any time, as all of our employees are "at will" employees. Recruiting and retaining other qualified employees, consultants and advisors for our business, including scientific and technical personnel, will also be critical to our success. There is currently a shortage of skilled executives in our industry, which is likely to continue. As a result, competition for skilled personnel is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. In addition, failure to succeed in preclinical studies or clinical trials may make it more challenging to recruit and retain qualified personnel. The inability to recruit or loss of the services of any executive, key employee, consultant or advisor may impede the progress of our research, development and commercialization objectives. Furthermore, many of our employees have become or will soon become vested in a substantial amount of stock or number of stock options. Our employees may be more likely to leave us if the shares they own or the shares underlying their vested options have significantly appreciated in value relative to the original purchase prices of the shares or the exercise prices of the options, or if the exercise prices of the options that they hold are significantly below the market price of our common stock. Further, our employees' ability to exercise those options and sell their stock in the public market may result in an increased turnover rate.

We are subject to a variety of risks associated with international operations that could materially adversely affect our business.

We currently conduct research activities through our majority-owned Hong Kong subsidiary, Pangu BioPharma Limited, in collaboration with the Hong Kong University of Science and Technology and maintain a representative office for this subsidiary in China. Additionally, we are currently conducting our Phase 1b/2 clinical trials of Resolaris in patients with FSHD and LGMD2B in the European Union, and the supply of Resolaris for our clinical trials is currently produced in India by a third-party manufacturer. We are also working with FujiFilm in the United Kingdom and a CRO in Germany. If any of our product candidates are approved for commercialization outside of the United States, we expect to either use our own sales organization or selectively enter into agreements with third parties to market our products on a worldwide basis or in more limited geographical regions. We are, and we expect that we will continue to be, subject to a variety of risks related to international operations, including:

- different regulatory requirements for approval of drugs and biologics in foreign countries;
- reduced or uncertain protection for intellectual property;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;

- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad; and
- foreign currency fluctuations, which could result in reduced revenues, and other obligations incident to doing business in another country.

Any failure to continue our international operations or to commercialize our product candidates outside of the United States may impair our ability to generate revenues and harm our business, prospects and results of operations.

We will need to expand our organization and we may experience difficulties in managing this growth, which could disrupt our operations.

As we continue our Phase 1b/2 clinical trials of Resolaris in patients with FSHD and LGMD2B, prepare for additional clinical trials of Resolaris and iMod.Fc and expand our other clinical development activities, as well as continue our operations as a public company, we expect to increase our full-time employee base and to hire more consultants and contractors. In addition to certain members of our management team being relatively new to our company, our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the conduct of additional clinical activities for Resolaris and the development of additional product candidates. If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate or grow revenues could be reduced, and we may not be able to implement our business strategy. Our future financial performance and our ability to develop and commercialize product candidates and compete effectively will depend, in part, on our ability to effectively manage any future growth.

We may use our financial and human resources to pursue a particular business strategy, research program or product candidate and fail to capitalize on strategies, programs or product candidates that may be more profitable or for which there is a greater likelihood of success.

Because we have limited resources, we may forego or delay pursuit of certain strategic opportunities or opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. In addition, we may elect to pursue a research, clinical or commercial strategy that ultimately does not yield the results that we desire. Our spending on current and future research and development programs for product candidates may not result in any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate, or we may allocate internal resources to a product candidate in a therapeutic area or market in which it would have been more advantageous to enter into a partnering arrangement. Any failure to allocate resources or capitalize on strategies in a successful manner will have an adverse impact on our business.

Our employees, principal investigators, consultants and commercial partners may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of fraud or other misconduct by our employees, principal investigators, consultants and commercial partners. Misconduct by these parties could include intentional failures to comply with the regulations of the FDA and non-U.S. regulators, provide accurate information to the FDA and non-U.S. regulators, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of conduct applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

We face potential product liability, and, if successful claims are brought against us, we may incur substantial liability and costs. If the use of our product candidates harms patients, or is perceived to harm patients even when such harm is unrelated to our product candidates, our regulatory approvals could be revoked or otherwise negatively impacted and we could be subject to costly and damaging product liability claims.

The use of our product candidates in clinical trials and the sale of any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by patients, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. There is a risk that our product candidates may induce adverse events. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- impairment of our business reputation;
- withdrawal of clinical trial participants;
- costs due to related litigation;
- distraction of management's attention from our primary business;
- substantial monetary awards to patients or other claimants;
- the inability to commercialize our product candidates; and
- decreased demand for our product candidates, if approved for commercial sale.

We carry product liability insurance for our clinical trials covering $5.0 million per occurrence and up to $5.0 million in the aggregate, subject to certain deductibles and exclusions. Although we believe the amount of our insurance coverage is typical for companies similar to us in our industry, we may not have adequate insurance coverage or be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. If and when we obtain marketing approval for product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. On occasion, large judgments have been awarded in class action lawsuits based on drugs or medical treatments that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could cause our stock price to decline and adversely affect our reputation and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business.

Patients with the diseases targeted by our product candidates are often already in severe and advanced stages of disease and may have both known and unknown significant pre-existing and potentially life-threatening health risks. During the course of treatment, patients may suffer adverse events, including death, for reasons that may be related to our product candidates. Such events could subject us to costly litigation, require us to pay substantial amounts of money to injured patients, delay, negatively impact or end our opportunity to receive or maintain regulatory approval to market our products, or require us to suspend or abandon our commercialization efforts. Even in a circumstance in which we do not believe that an adverse event is related to our products, the investigation into the circumstance may be time-consuming or inconclusive. These investigations may interrupt our sales efforts, delay our regulatory approval process in other countries, or impact and limit the type of regulatory approvals our product candidates receive or maintain. As a result of these factors, a product liability claim, even if successfully defended, could have a material adverse effect on our business, financial condition or results of operations.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work-related injuries, this insurance may not provide adequate coverage against potential liabilities. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

We are subject to anti-corruption laws in the jurisdictions in which we operate.

We are subject to a number of anti-corruption laws, including the U.S. Foreign Corrupt Practices Act, or the FCPA, and various other anti-corruption laws. The FCPA generally prohibits companies and their intermediaries from making improper payments to foreign officials for the purpose of obtaining or keeping business and/or other benefits. Our business relies on approvals and licenses from government and regulatory entities, and as a result, we are subject to certain elevated risks associated with interactions with these entities. Although we have adopted a code of business conduct and ethics that includes provisions governing the interactions of employees with government entities to mitigate these risks. If we are not in compliance with anti-corruption laws and other laws governing the conduct of business with government entities (including local laws), we may be subject to criminal and civil penalties and other remedial measures, which could harm our reputation and have a material adverse impact on our business, financial condition, results of operations and prospects. Any investigation of any actual or alleged violations of such laws could also harm our reputation or have an adverse impact on our business, prospects, financial condition and results of operations.

We will incur significant increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives.

As a public company, we will incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act of 2002, or Sarbanes-Oxley Act, as well as rules subsequently implemented by the Securities and Exchange Commission, or SEC, and The Nasdaq Global Select Market have imposed various requirements on public companies. In July 2010, the Dodd-Frank Wall Street Reform and Consumer Protection Act, or the Dodd-Frank Act, was enacted. There are significant corporate governance and executive compensation related provisions in the Dodd-Frank Act that require the SEC to adopt additional rules and regulations in these areas such as "say on pay" and proxy access. Recent legislation permits smaller "emerging growth companies" to implement many of these requirements over a longer period and up to five years from the pricing of our IPO. We have elected to take advantage of this legislation but cannot guarantee that we will not be required to implement these requirements sooner than budgeted or planned and thereby incur unexpected expenses. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, we expect these rules and regulations to make it more difficult and more expensive for us to maintain director and officer liability insurance and we may be required to incur substantial costs to maintain our current levels of such coverage.

Unfavorable global economic conditions could adversely affect our business, financial condition or results of operations.

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. The recent global financial crisis caused extreme volatility and disruptions in the capital and credit markets. A severe or prolonged economic downturn, such as the recent global financial crisis, could result in a variety of risks to our business, including inability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could also strain our manufacturers, possibly resulting in supply disruption. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

We or the third parties upon whom we depend may be adversely affected by earthquakes, droughts, floods, fires or other natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

We are located in San Diego, California, and our clinical supply of Resolaris is currently produced in India. We currently anticipate that if Resolaris receives marketing approval, commercial production may take place in the United States and/or the United Kingdom. Some of these geographic locations have in the past experienced natural disasters, including severe earthquakes. Earthquakes, droughts, floods, fires, disease epidemics or other natural disasters could severely disrupt our operations, and have a material adverse effect on our business, results of operations, financial condition and prospects. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our facilities, that damaged critical infrastructure, such as the manufacturing facilities of our third-party contract manufacturers, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place currently are limited and are unlikely to prove adequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, as well as limits on our insurance coverage, which could have a material adverse effect on our business, prospects, financial condition and results of operations.

Risks related to the ownership of our common stock

The market price of our common stock may be highly volatile, and you could lose all or part of your investment.

The market price of our common stock is likely to be volatile. Our stock price could be subject to wide fluctuations in response to a variety of factors, including the following:

- adverse results or delays in preclinical studies or clinical trials;
- the imposition of a clinical hold on our product candidates or our inability to cause the clinical hold to be lifted;
- any delay in filing a BLA, NDA or IND for any of our product candidates and any adverse development or perceived adverse development with respect to the FDA's review of that BLA, NDA or IND;
- failure to successfully develop and commercialize our product candidates;
- the perception of limited market sizes or pricing for our product candidates;
- failure by us or our licensors to prosecute, maintain or enforce intellectual property rights covering our product candidates and processes;
- changes in laws or regulations applicable to future products;
- inability to obtain adequate product supply for our product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- introduction of new products, services or technologies by our competitors;
- inability to obtain additional funding;
- failure to meet or exceed financial or operational projections we may provide to the public;
- failure to meet or exceed the financial or operational projections of the investment community;
- the perception of the pharmaceutical industry by the public, politicians, legislatures, regulators and the investment community;
- significant acquisitions, strategic partnerships, joint ventures or capital commitments by us or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or stockholder litigation;
- if securities or industry analysts do not publish research or reports about our business, or they issue an adverse or misleading opinion regarding our stock;
- changes in the market valuations of similar companies;
- general market or macroeconomic conditions;
- sales of our common stock by us or our stockholders in the future; and
- trading volume of our common stock.

In addition, companies trading in the stock market in general, and The Nasdaq Global Select Market and biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance.

Our executive officers, directors, principal stockholders and their affiliates own a significant percentage of our stock and will be able to exert significant control over matters submitted to stockholders for approval.

As of March 24, 2016, based on the latest information publicly available to the Company, our executive officers, directors, five percent stockholders and their affiliates beneficially own approximately 73.6% of our voting stock. Therefore, these stockholders will have the ability to influence us through their ownership positions and may be able to determine all matters requiring stockholder approval. For example, these stockholders, acting together, may be able to control elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that you may believe are in your best interest as one of our stockholders.

We are an "emerging growth company," and we cannot be certain if the reduced reporting requirements applicable to emerging growth companies will make our common stock less attractive to investors.

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For as long as we continue to be an emerging growth company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act reduced disclosure obligations regarding executive compensation and our periodic reports and proxy statements and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. We could be an emerging growth company for up to five years from the pricing of our IPO, although circumstances could cause us to lose that status earlier, including if the market value of our common stock held by non-affiliates exceeds $700.0 million as of any June 30 before that time or if we have total annual gross revenue of $1.0 billion or more during any fiscal year before that time, in which cases we would no longer be an emerging growth company as of the following December 31 or, if we issue more than $1.0 billion in non-convertible debt during any three-year period before that time, we would cease to be an emerging growth company immediately. Even after we no longer qualify as an emerging growth company, we may still qualify as a "smaller reporting company" which would allow us to take advantage of many of the same exemptions from disclosure requirements, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

Under the JOBS Act, emerging growth companies can also delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

Future sales and issuances of equity or debt securities could result in dilution to our stockholders, impose restrictions or limitations on our business and could cause our stock price to fall.

We will need additional capital in the future to continue our planned operations, and we may seek additional funding through a combination of equity offerings, debt financings, government or other third-party funding and other collaborations, strategic alliances and licensing arrangements. These financing activities may have an adverse effect on our stockholders' rights, the market price of our common stock and on our operations, and may require us to relinquish rights to some of our technologies, intellectual property or product candidates, issue additional equity or debt securities, or otherwise agree to terms unfavorable to us. Any future debt financings may impose restrictive covenants or otherwise adversely affect the holdings or the rights of our stockholders, and any equity financings will be dilutive to our stockholders. Furthermore, additional equity or debt financing might not be available to us on reasonable terms, if at all.

In additional, sales of a substantial number of shares of our common stock by our existing stockholders in the public market or the perception that these sales might occur, could depress the market price of our common stock and could impair our ability to raise capital through the sale of additional equity securities. Certain holders of our securities are entitled to rights with respect to the registration of their shares under the Securities Act pursuant to a registration and voting rights agreement. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act. Any sales of securities by these stockholders could have a material adverse effect on the trading price of our common stock, even if there is no relationship between such sales and the performance of our business.

We have also registered all common stock that we may issue under our employee benefits plans. As a result, these shares can be freely sold in the public market upon issuance, subject to restrictions under the securities laws. In addition, our directors and executive officers may establish programmed selling plans under Rule 10b5-1 of the Securities Exchange Act for the purpose of effecting sales of our common stock. If any of these events cause a large number of our shares to be sold in the public market, the sales could reduce the trading price of our common stock and impede our ability to raise future capital.

If securities analysts do not publish research or reports about our business or if they publish negative evaluations of our stock, the price of our stock could decline.

The trading market for our common stock will rely in part on the research and reports that industry or financial analysts publish about us or our business. We may never obtain research coverage by industry or financial analysts. If no or few analysts commence coverage of us, the trading price of our stock would likely decrease. Even if we do obtain analyst coverage, if one or more of the analysts covering our business downgrade their evaluations of our stock, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price to decline.

We could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

We have broad discretion in the use of our cash and cash equivalents and may not use them effectively.

We have considerable discretion in the application of our existing cash and cash equivalents. We expect to use our existing cash to fund research and development activities and for working capital and general corporate purposes, including funding the costs of operating as a public company. In addition, pending their use, we may invest our existing cash in short-term, investment-grade, interest-bearing securities. We may use these proceeds for purposes that do not yield a significant return or any return at all for our stockholders.

Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.

We have incurred substantial losses during our history, we do not expect to become profitable in the near future and we may never achieve profitability. Unused losses generally are available to be carried forward to offset future taxable income, if any, until such unused losses expire. Under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards, or NOLs, and other pre-change tax attributes (such as research tax credits) to offset its post-change taxable income or taxes may be limited. We completed an analysis through September 7, 2011, and determined that on November 30, 2006 an ownership change occurred, for which we have adjusted our NOL and research and development tax credit carryforwards. We may have experienced an ownership change subsequent to September 7, 2011, including as a result of our IPO, and we may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. As a result, our ability to use our pre-change NOLs to offset U.S. federal taxable income may be subject to limitations, which could potentially result in increased future tax liability to us. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

We do not intend to pay dividends on our common stock, and therefore any returns will be limited to the value of our stock.

We have never declared or paid any cash dividends on our common stock. We anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock.

Provisions in our amended and restated certificate of incorporation and bylaws, as well as provisions of Delaware law, could make it more difficult for a third party to acquire us or increase the cost of acquiring us, even if doing so would benefit our stockholders or remove our current management.

Our amended and restated certificate of incorporation, amended and restated bylaws and Delaware law contain provisions that may have the effect of delaying or preventing a change in control of us or changes in our management. Our amended and restated certificate of incorporation and bylaws include provisions that:

- authorize "blank check" preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend and other rights superior to our common stock;
- create a classified board of directors whose members serve staggered three-year terms;
- specify that special meetings of our stockholders can be called only by our board of directors, the chairperson of our board of directors, our chief executive officer or our president;
- prohibit stockholder action by written consent;
- establish an advance notice procedure for stockholder approvals to be brought before an annual meeting of our stockholders, including proposed nominations of persons for election to our board of directors;
- provide that our directors may be removed only for cause;
- provide that vacancies on our board of directors may be filled only by a majority of directors then in office, even though less than a quorum;
- specify that no stockholder is permitted to cumulate votes at any election of directors;
- expressly authorize our board of directors to modify, alter or repeal our amended and restated bylaws; and
- require supermajority votes of the holders of our common stock to amend specified provisions of our amended and restated certificate of incorporation and amended and restated bylaws.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management.

In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us.

Any provision of our amended and restated certificate of incorporation or amended and restated bylaws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

Our administrative offices and research laboratory are located in San Diego, California. We lease approximately 17,083 square feet of office and laboratory space under a lease that currently expires in May 2017. We believe that our facility is sufficient to meet our needs and that suitable additional space will be available as and when needed.

Item 3. Legal Proceedings

We are not a party to any material legal proceedings at this time. From time to time, we may be subject to various legal proceedings and claims that arise in the ordinary course of our business activities. Although the results of litigation and claims cannot be predicted with certainty, we do not believe we are party to any claim or litigation the outcome of which, if determined adversely to us, would individually or in the aggregate be reasonably expected to have a material adverse effect on our results of operations or financial condition. Regardless of the outcome, litigation can have an adverse effect on us because of defense and settlement costs, diversion of management resources and other factors.

Item 4. Mine Safety Disclosure

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our common stock began trading on The NASDAQ Global Select Market on May 7, 2015 and trades under the symbol "LIFE". Prior to such time, there was no public market for our common stock. The following table sets forth the high and low sales prices per share of our common stock for the periods indicated as reported on The NASDAQ Global Select Market.

	Price Range	
	High	Low
Year Ended December 31, 2015:		
Second Quarter (commencing May 7, 2015)	$ 28.29	$ 12.90
Third Quarter	$ 21.00	$ 9.59
Fourth Quarter	$ 13.26	$ 7.37

Holders of Record

As of March 24, 2016, there were approximately 97 holders of record of our common stock. The approximate number of holders is based upon the actual number of holders registered in our records at such date and excludes holders in "street name" or persons, partnerships, associations, corporations, or other entities identified in security positions listings maintained by depository trust companies.

Dividend Policy

We have never declared or paid any cash dividends on our common stock. We currently intend to retain all available funds and any future earnings to support our operations and finance the growth and development of our business. We do not intend to pay cash dividends on our common stock for the foreseeable future. Any future determination related to our dividend policy will be made at the discretion of our board of directors and will depend upon, among other factors, our results of operations, financial condition, capital requirements, contractual restrictions, business prospects and other factors our board of directors may deem relevant.

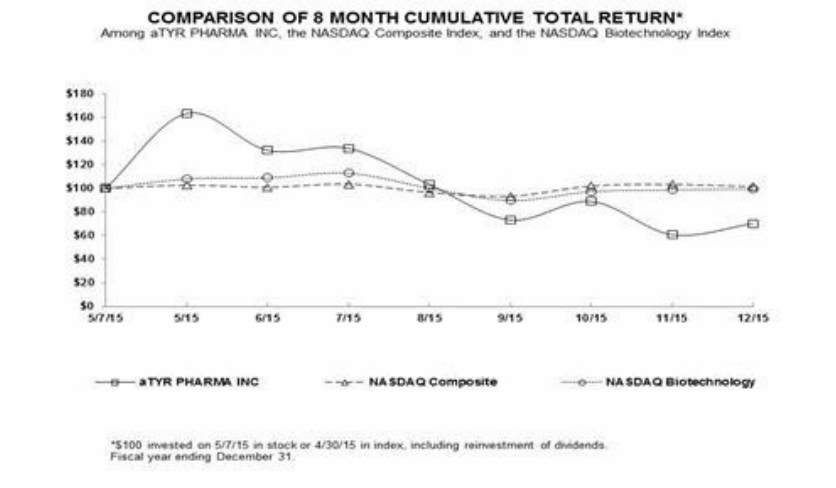
Securities Authorized for Issuance Under Equity Compensation Plans

Information about our equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report.

Performance Graph

The following is not deemed "filed" with the Securities and Exchange Commission and is not to be incorporated by reference into any filing we make under the Securities Act of 1933, as amended, whether made before or after the date hereof and irrespective of any general incorporation by reference language in such filing.

The following graph shows a comparison from May 7, 2015 (the date our common stock commenced trading on The NASDAQ Global Select Market) through December 31, 2015 of the cumulative total return for our common stock, the NASDAQ Biotechnology Index (NBI) and the NASDAQ Composite Index (CCMP). The graph assumes an initial investment of $100 on May 7, 2015. The comparisons in the graph are not intended to forecast or be indicative of possible future performance of our common stock



Recent Sales of Unregistered Securities

During the year ended December 31, 2015, we did not issue or sell any unregistered securities not previously disclosed in a Quarterly Report on Form 10-Q or in a Current Report on Form 8-K.

Issuer Purchases of Equity Securities

We did not repurchase any securities during the quarter ended December 31, 2015.

Item 6. Selected Financial Data.

The selected financial data set forth below is derived from our audited consolidated financial statements and may not be indicative of future operating results. The following selected financial data should be read in conjunction with the Consolidated Financial Statements and notes thereto and Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations" included elsewhere in this Annual Report on Form 10-K. Amounts are in thousands, except per share amounts.

	Years Ended December 31,		
	2015	2014	2013
Statements of Operations Data:			
Operating expenses:			
Research and development	$ 34,504	$ 16,777	$ 13,832
General and administrative	13,112	6,777	5,710
Total operating expenses	47,616	23,554	19,542
Loss from operations	$ (47,616)	(23,554)	(19,542)
Other income (expense)	(357)	(796)	(472)
Net loss	(47,973)	(24,350)	(20,014)
Accretion to redemption value of redeemable convertible preferred stock	(15)	(416)	(1,637)
Net loss attributable to common stockholders	$ (47,988)	$ (24,766)	$ (21,651)
Net loss per share attributable to common stockholders, basic and diluted	$ (3.03)	$ (29.69)	$ (28.39)
Weighted average shares outstanding, basic and diluted	15,838,353	834,221	762,761

	As of December 31,		
	2015	2014	2013
Consolidated Balance Sheet Data:			
Cash, cash equivalents and investments	$ 125,349	$ 15,853	$ 36,457
Total assets	129,675	20,644	39,786
Preferred stock warrant liabilities	—	319	207
Convertible promissory note	—	2,000	2,000
Working capital	85,802	6,396	31,814
Commercial bank debt, net of current portion	1,776	5,142	4,158
Redeemable convertible preferred stock	—	95,619	93,165
Accumulated deficit	(158,124)	(110,151)	(85,801)
Noncontrolling interest	—	—	2,414
Total stockholders' deficit	115,050	(91,010)	(66,082)

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations.

You should read the following discussion and analysis together with "Item 6. Selected Financial Data" and the consolidated financial statements and related notes included elsewhere in this Annual Report on Form 10-K. The following discussion contains forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from those expressed or implied in any forward-looking statements as a result of various factors, including those set forth under the caption "Item 1A. Risk Factors."

Overview

We engage in the discovery and clinical development of innovative medicines for patients suffering from severe, rare diseases using our knowledge of Physiocrine biology, a newly discovered set of physiological modulators. We have discovered approximately 300 Physiocrines, a class of naturally occurring human proteins that we believe promote homeostasis, a fundamental process of restoring stressed or diseased tissue to a healthier state. By leveraging our discovery engine and our knowledge of rare diseases, we aim to build a proprietary pipeline of novel product candidates with the potential to treat severe, rare diseases characterized by immune dysregulation. We plan to independently commercialize our Physiocrine-based therapeutics.

Since the identification of the Resokine pathway, we have successfully advanced Resolaris through preclinical development, current Good Manufacturing Practice, or cGMP, manufacturing, an initial Phase 1 clinical trial and three cohorts of first exploratory Phase 1b/2 trial in adult FSHD patients. In the first quarter of 2014, we completed a double-blind, placebo-controlled Phase 1 clinical trial of Resolaris, in which we assessed its safety and tolerability in 32 healthy subjects. Resolaris was shown to be well tolerated at all doses tested, and no serious adverse events were reported. Based on the favorable clinical safety, pharmacokinetic and immunogenicity profile of Resolaris in this trial, we decided to advance Resolaris into clinical trials of RMIC patients.

We recently announced results from our multi-national exploratory Phase 1b/2 clinical trial of Resolaris in adult patients with FSHD in the United States and European Union. This randomized, double-blind, placebo-controlled trial was designed to evaluate the safety, tolerability, pharmacokinetics and exploratory pharmacodynamics markers and clinical assessments of multiple intravenous doses of Resolaris in adults with FSHD. We completed three dose escalation cohorts of 0.3, 1.0 and 3.0 mg/kg. We believe the safety, tolerability, immunogenicity and activity profile of Resolaris as demonstrated in this study warrants advancing our program in adult FSHD patients and potentially other rare diseases.

Our initial therapeutic efforts target severe, rare disease indications in which patients suffer from the immune-related consequences of their genetic disease. We have identified over 20 distinct, molecularly definable RMIC indications, including FSHD and LGMD2B, in which we believe Resolaris has the potential to target the immune component of these genetic diseases. In 2015, we made progress in our therapeutic efforts by initiating new clinical studies in patients to further investigate Resolaris. We initiated three additional trials, including a long term safety extension study, a study in adult patients with FSHD or a second rare genetic myopathy, LGMD2B, and a study in patients with early onset FSHD.

During 2015, we made advancements in our pre-clinical research through protein engineering, generating and testing the exposures in animals of multiple configurations of the iMod domain of the Resokine pathway, an immuno-modulatory Physiocrine domain. In the fourth quarter of 2015, we announced the selection of an investigational new drug (IND) candidate based on this iMod domain fused to the Fc region of a human antibody, iMod.Fc. We have selected this iMod.Fc molecule as our second product development candidate and it represents an expansion of our new class of Physiocrine-based therapeutics. With the selection of the this iMod.Fc molecule, we are harnessing the Resokine pathway and plan to test its potential role in lung disease and to develop iMod.Fc as a potential therapeutic for patients with rare pulmonary diseases with an immune component, or RPICs.

In May 2015, we completed our IPO whereby we sold 6,164,000 shares of common stock at a public offering price of $14.00 per share. As a result of the IPO, we raised a total of $75.9 million in net proceeds after deducting underwriting discounts and commissions of approximately $6.0 million and offering expenses of approximately $4.4 million. In addition, in connection with the IPO, all outstanding redeemable convertible preferred stock converted into 16,279,859 shares of our common stock.

Since our inception in 2005, we have devoted substantially all of our resources to the therapeutic application of Physiocrines, including the preclinical development of and clinical trials for Resolaris, the creation, licensing and protection of related intellectual property and the provision of general and administrative support for these operations. We have not generated any revenue from product sales and, through December 31, 2015, have funded our operations primarily with the aggregate proceeds from the sales of our common stock in our IPO, private placement of redeemable convertible preferred stock and convertible promissory notes, commercial bank debt and a convertible promissory note issued to our landlord.

We have never been profitable and have incurred net losses in each annual and quarterly period since our inception. For the years ended December 31, 2015, 2014 and 2013, we have incurred consolidated net losses of $48.0 million, $24.4 million and $20.0 million, respectively. As of December 31, 2015, we had an accumulated deficit of $158.1 million.

Substantially all of our net losses resulted from costs incurred in connection with our development of and clinical trials for Resolaris, our other research and development programs and from general and administrative costs associated with our operations. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future, at least until we apply for and receive regulatory approval for Resolaris or another product candidate and generate substantial revenues from its commercialization, if ever. Our net losses may fluctuate significantly from quarter to quarter and year to year, depending on the nature and extent of our research and development expenses and clinical trials. We expect our expenses will increase substantially in connection with our ongoing activities as we:

- conduct clinical trials of Resolaris and any additional product candidates we may develop;
- continue our research and product development efforts;
- manufacture preclinical study and clinical trial materials;
- expand, protect and maintain our intellectual property portfolio;
- seek regulatory approvals for our product candidates that successfully complete clinical trials;
- hire additional staff, including clinical, operational, financial and technical personnel to execute on our business plan and create additional infrastructure to support our operations as a public company; and
- implement operational, financial and management systems.

We do not expect to generate any revenues from product sales unless and until we successfully complete development and obtain regulatory approval for one or more of our product candidates, which we expect will take a number of years at a minimum. If we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. Accordingly, we will need to raise substantial additional capital beyond the net proceeds from our IPO. The amount and timing of our future funding requirements will depend on many factors, including the pace and results of our preclinical and clinical development efforts and the timing and nature of the regulatory approval process for our product candidates. We anticipate that we will seek to fund our operations through public or private equity or debt financings or other sources. However, we may be unable to raise additional funds or enter into such other arrangements when needed on favorable terms or at all. Our failure to raise capital or enter into such other arrangements when needed would have a negative impact on our financial condition and ability to develop our product candidates.

Financial Operations Overview

Organization and Business; Principles of Consolidation and Affiliates

We conduct substantially all of our activities through aTyr Pharma, Inc., a Delaware corporation, at our facility in San Diego, California. aTyr Pharma, Inc. was incorporated in the state of Delaware in September 2005. The consolidated financial statements include the accounts of aTyr Pharma, Inc., and its 98% majority-owned subsidiary in Hong Kong, Pangu BioPharma Limited as of December 31, 2015. The consolidated financial statements in the prior years included six variable interest entities, which we referred to as the Affiliates. The Affiliates were dissolved in the fourth quarter of 2014. Our consolidated financial statements for periods after the effectiveness of the dissolutions of the Affiliates no longer include a noncontrolling interest, and we continued the operating activities of the Affiliates. All intercompany transactions and balances are eliminated in consolidation.

Research and Development Expenses

To date, our research and development expenses have related primarily to the development of and clinical trials for Resolaris and to research efforts targeting the potential therapeutic application of other Physiocrine-based immuno-modulators in rare disease indications. These expenses consist primarily of:

- salaries and employee-related expenses, including stock-based compensation and benefits for personnel in research and product development functions;
- costs associated with conducting our preclinical, development and regulatory activities, including fees paid to third-party professional consultants, service providers and our scientific, therapeutic and clinical advisory board;
- costs to acquire, develop and manufacture preclinical study and clinical trial materials;
- costs incurred under clinical trial agreements with clinical research organizations, or CROs, and investigative sites;
- costs for laboratory supplies;
- payments and stock issuances related to licensed products and technologies; and
- allocated facilities, depreciation and other allocable expenses.

Research and development costs are expensed as incurred. Clinical trial and other development costs incurred by third parties are expensed as the contracted work is performed. We accrue for costs incurred as the services are being provided by monitoring the status of the trial or project and the invoices received from our external service providers. We adjust our accrual as actual costs become known.

Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect that the levels of our research and development expenses will increase during the foreseeable future as we: (i) continue to advance Resolaris in clinical development; (ii) advance our iMod.Fc discovery program; and (iii) engage in additional research, discovery and development activities relating to our discovery engine for therapeutic applications of Physiocrines.

We cannot determine with certainty the timing of initiation, the duration or the completion costs of current or future preclinical studies and clinical trials of our product candidates. At this time, due to the inherently unpredictable nature of preclinical and clinical development and given the early stage of our programs, we are unable to estimate with any certainty the costs we will incur or the timelines we will require in the continued development of Resolaris and any other product candidates that we may develop. Clinical and preclinical development timelines, the probability of success and development costs can differ materially from expectations. We anticipate that we will make determinations as to which product candidates to pursue and how much funding to direct to each product candidate on an ongoing basis in response to the results of ongoing and future preclinical studies and clinical trials, regulatory developments and our ongoing assessments as to each product candidate's commercial potential. In addition, we cannot forecast which product candidates may be subject to future collaborations, when such arrangements will be secured, if at all, and to what degree such arrangements would affect our development plans and capital requirements.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and related costs for employees in executive, finance and administration, corporate development and administrative support functions, including stock-based compensation expenses and benefits. Other significant general and administrative expenses include accounting and legal services, expenses associated with applying for and maintaining patents, the cost of various consultants, occupancy costs, information systems costs and depreciation.

We anticipate that our general and administrative expenses will substantially increase for the foreseeable future as we increase support the continued development of our product candidates and the increased costs of operating as a public company, including expenses related to services associated with maintaining compliance with NASDAQ listing rules and SEC requirements, insurance and investor relations costs. These increases will likely include increased costs related to personnel, fees to outside consultants, lawyers and accountants, among other expenses.

Other Income (Expense)

Other income (expense) primarily consists of interest income and expense and changes in the fair value of preferred stock warrant liabilities related to warrants we issued in connection with commercial bank debt. No further fair value adjustments for these warrants will be recorded subsequent to our IPO, when these liabilities were reclassified to additional paid-in capital.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States, or GAAP. The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities as of the date of the consolidated financial statements, as well as the reported expenses during the reporting periods. We monitor and analyze these items for changes in facts and circumstances, and material changes in these estimates could occur in the future. We base our estimates on our historical experience and on various other factors we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Changes in estimates are reflected in reported results for the period in which they become known. Actual results may differ materially from these estimates under different assumptions or conditions.

We discuss our accounting policies and assumptions that involve a higher degree of judgment and complexity within Note 2 to our audited consolidated financial statements appearing elsewhere in this Annual Report. We believe the following accounting policies related to research and development expenses accruals and stock-based compensation involve the most significant estimation and judgment in accounting for our reported consolidated financial results.

Research and Development Expense Accruals

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date in our consolidated financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. Examples of estimated accrued research and development expenses include fees paid to investigative sites and Clinical Research Organizations (CROs) in connection with clinical trials; service providers in connection with preclinical development activities; and service providers related to product manufacturing, development and distribution of clinical supplies.

We currently rely on third parties for the clinical development of Resolaris and the manufacture of Resolaris to support our ongoing clinical trials. We pay these third parties, including consultants, CROs, manufacturers and other service providers, pursuant to contractual arrangements, which may include provisions for time and materials-based payments, project-based fees and milestone payments. We base our accrual for these expenses on our estimates of the services received and efforts expended pursuant to our contractual arrangements. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our service providers will exceed the level of services provided and result in a prepayment of the clinical expense. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical milestones. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid accordingly.

Although we do not expect our estimates to be materially different from amounts actually incurred, if our estimates of the status and timing of services performed differs from the actual status and timing of services performed, we may report amounts that are too high or too low in any particular period. To date, there has been no material differences between our estimates and the amounts actually incurred.

Stock-Based Compensation

Stock-based compensation expense represents the grant date fair value of employee stock option grants recognized as expense over the requisite service period of the awards (usually the vesting period) on a straight-line basis, net of estimated forfeitures. For stock option grants with performance-based milestones, the expense is recorded over the service period after the achievement of the milestone is probable or the performance is achieved. For stock option grants with market-based conditions, the expense is recorded using the accelerated attribution method over the requisite service period for each vesting tranches. We account for stock options granted to non-employees using the fair value approach. These options are subject to periodic revaluation over their vesting terms. We estimate fair value of employee and non-employee stock option grants using the Black-Scholes option pricing model. We estimate the fair value of the market-based stock option grants using Monte Carlo simulations. We generally estimate the fair value using assumptions, including the risk-free interest rate, the expected volatility of a peer group of similar companies, the expected term of the awards and the expected dividend yield. These estimates involve inherent uncertainties and the application of management's judgment. If factors change and different assumptions are used, our stock-based compensation expense could be materially different in the future.

Results of Operations

Comparison of the Years Ended December 31, 2015 and 2014

The following table summarizes our results of operations for the years ended December 31, 2015 and 2014 (in thousands):

	Years Ended December 31,		Increase /
	2015	2014	(Decrease)
Research and development expenses	$ 34,504	$ 16,777	$ 17,727
General and administrative expenses	13,112	6,777	6,335
Other income (expense)	(357)	(796)	439

Research and development expenses. Research and development expenses were $34.5 million and $16.8 million for the years ended December 31, 2015 and 2014, respectively. The increase of $17.7 million was due primarily to a $11.4 million increase related to manufacturing costs and clinical development incurred in support of various activities for Resolaris, a $4.1 million increase related to compensation expenses (including $2.0 million of non-cash stock-based compensation) as a result of increased headcount across our research and development organization and a $1.4 million increase related to the issuance of common stock in connection with the amendment and restatement of our research funding and option agreement with the The Scripps Research Institute, or TSRI.

General and administrative expenses. General and administrative expenses were $13.1 million and $6.8 million for the years ended December 31, 2015 and 2014, respectively. The increase of $6.3 million was due primarily to a $3.8 million increase in personnel costs resulting from increased headcount (including $1.1 million of non-cash stock-based compensation), a $1.7 million increase in costs associated with being a public company and a $0.3 million increase related to intellectual property-related projects.

Other income (expense). Other income (expense) was $(0.4) million and $(0.8) million for the years ended December 31, 2015 and 2014, respectively. The decrease of $0.4 million in other expense was primarily a result of $0.3 million increase in interest income related to short-term and long-term investments and a $0.1 million decrease in interest expense related to the $5.0 million we borrowed in June 2014 under a loan agreement with Silicon Valley Bank, or SVB.

Comparison of the Years Ended December 31, 2014 and 2013

The following table summarizes our results of operations for the years ended December 31, 2014 and 2013 (in thousands):

	Years Ended December 31,		Increase /
	2014	2013	(Decrease)
	(in thousands)		
Research and development expenses	$ 16,777	$ 13,832	$ 2,945
General and administrative expenses	6,777	5,710	1,067
Other income (expense)	(796)	(472)	324

Research and development expenses. Research and development expenses were $16.8 million and $13.8 million for the years ended December 31, 2014 and 2013, respectively. The increase of $2.9 million was due primarily to a $2.2 million increase in regulatory and clinical activities related to the completion of our Phase 1 clinical trial of Resolaris and the initiation of our multi-national Phase 1b/2 clinical trial of Resolaris in adult patients with FSHD in the European Union, a $1.5 million increase related to compensation expenses (including stock-based compensation) as a result of increased headcount across our research and development organization and a $1.0 million increase in pre-clinical expenditures, facilities and other research costs. These increases were offset by a decrease of $1.8 million related to the timing of manufacturing costs incurred in support of various Resolaris clinical development activities.

General and administrative expenses. General and administrative expenses were $6.8 million and $5.7 million for the years ended December 31, 2014 and 2013, respectively. The increase of $1.1 million was due primarily to a $1.2 million increase in personnel costs resulting from increased headcount in our executive leadership team and stock-based compensation and a $0.2 million increase in travel and facility-related expenses, offset by a decrease of $0.3 million related to market studies that did not recur in 2014.

Other income (expense). Other income (expense) was $(0.8) million and $(0.5) million for the years ended December 31, 2014 and 2013, respectively. The increase of $0.3 million in other expense was primarily the result of additional interest expense related to the $5.0 million we borrowed under a loan agreement with Silicon Valley Bank in June 2014 and a $36,000 decrease in other expense related to decreases in the fair value of outstanding warrant liabilities as the underlying preferred stock fair value decreased.

Liquidity and Capital Resources

We have incurred losses and negative cash flows from operations since our inception. As of December 31, 2015, we had an accumulated deficit of $158.1 million and we expect to continue to incur net losses for the foreseeable future. As of December 31, 2015, we had cash, cash equivalents and short-term and long-term investments of $125.3 million. As discussed above, our IPO and related transactions resulted in net proceeds of $75.9 million. We believe that our existing cash and cash equivalents as of December 31, 2015 will be sufficient to meet our anticipated cash requirements through at least the next 12 months.

Sources of Liquidity

From our inception through December 31, 2015, we have funded our operations primarily with aggregate proceeds from the sales of our common stock through our IPO, the private placement of redeemable convertible preferred stock and convertible promissory notes, commercial bank debt and a convertible promissory note issued to our landlord.

Debt Financing

In each of July 2013 and June 2014, we borrowed $5.0 million under a $10.0 million loan and security agreement with SVB, which we refer to as the SVB Loan. Beginning in July 2014, we began to make payments of principal and interest which are due through the maturity date of June 1, 2017. The interest rate is a per annum fixed rate of 5.0% and 5.88% for the $5.0 million drawn in each of July 2013 and June 2014, respectively. The final payment due in June 2017 includes an additional fee of $0.5 million. The SVB Loan is collateralized by all of our assets, other than our intellectual property, and contains customary affirmative and negative covenants, reporting requirements and events of default. As of December 31, 2015, we have no available credit under the SVB Loan.

In December 2011, in conjunction with our facility lease, we issued a $2.0 million subordinated convertible unsecured promissory note to the venture arm of our landlord, BioMed Realty, L.P., which was subsequently transferred to its affiliate, BMV Direct RE LP. The convertible note carried an annual interest rate of 8.0% and matured on May 12, 2015, at which time we repaid the outstanding principal and accrued interest on the convertible note of $2.0 million and $0.5 million, respectively.

Cash Flows

The following table sets forth a summary of the net cash flow activity for each of the periods indicated (in thousands):

	Years Ended December 31,		
	2015	2014	2013
Net cash provided by (used in):			
Operating activities	$ (36,797)	$ (22,824)	$ (17,311)
Investing activities	(71,994)	(2,246)	(644)
Financing activities	147,917	2,512	50,737
Net increase (decrease) in cash	$ 39,126	$ (22,558)	$ 32,782

Operating activities. Net cash used in operating activities was $36.8 million, $22.8 million and $17.3 million for the years ended December 31, 2015, 2014 and 2013, respectively. The net cash used in operating activities in each of these periods was primarily due to our net losses. The primary differences between net cash used in operating activities and our net loss in the year ended December 31, 2015 related to non-cash charges including: $0.9 million for depreciation, $4.9 million for stock-based compensation, $1.4 million for the issuance of common stock for technology to TSRI and $3.3 million of cash provided by changes in our prepaid and other assets, accounts payable and accrued expense accounts. The primary differences between net cash used in operating activities and our net loss in the year ended December 31, 2014 related to non-cash charges including: $0.8 million for depreciation and amortization, $1.8 million for stock-based compensation offset by $1.3 million of cash used by changes in our prepaid and other assets, accounts payable and accrued expense accounts. The primary differences between net cash used in operating activities and our net loss in the year ended December 31, 2013 related to non-cash charges including: $0.7 million for depreciation and amortization and $1.8 million of cash provided by changes in our prepaid and other assets, accounts payable and accrued expense accounts.

Investing activities. Net cash used in investing activities for the year ended December 31, 2015 consisted of $71.3 million of net purchases of investment securities, consisting primarily of money market funds, corporate debt securities, asset-backed securities, United States Treasury securities and commercial paper and $0.7 million of property and equipment purchases. Net cash used in investing activities for the year ended December 31, 2014 consisted of $2.0 million of net purchases of investments, consisting primarily of corporate debt and commercial paper and $0.2 million of property and equipment purchases. Net cash used in investing activities for the year ended December 31, 2013 was due to our purchases of property and equipment.

Financing activities. Net cash provided by financing activities for the year ended December 31, 2015 was $147.9 million and consisted primarily of $75.6 million of net proceeds from the issuance of Series E redeemable convertible preferred stock and $76.9 million of net proceeds from the IPO net of offering costs paid in the period, offset by $3.2 million of principal payments on the SVB Loan and $2.0 million repayment of convertible debt and related accrued interest. Net cash provided by financing activities during the year ended December 31, 2014 was $2.5 million consisted primarily of $5.0 million of proceeds from the SVB Loan offset by $1.6 million of principal payments on the SVB Loan and $1.0 million of costs paid in connection with our planned initial public offering. Net cash provided by financing activities for the year ended December 31, 2013 was $50.7 million and consisted primarily of $38.7 million of net proceeds from the issuance of Series D redeemable convertible preferred stock, $9.5 million of net proceeds from the issuance of convertible notes that were converted into Series D redeemable convertible preferred stock and $2.5 million of net proceeds from the SVB Loan.

Funding Requirements

To date, we have not generated any revenues from product sales. We expect our expenses to increase in connection with our ongoing activities, particularly as we continue to advance Resolaris in clinical development, continue our research and development activities with respect to potential Physiocrine-based therapeutics, and seek marketing approval for Resolaris and other product candidates that we may develop. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. We currently have no sales or marketing capabilities and would need to expand our organization to support these activities. Furthermore, we expect to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. Our forecast of the period of time through which our financial resources will be adequate to support our operations is a forward-looking statement that involves risks and uncertainties, and actual results could vary materially.

Our future capital requirements are difficult to forecast and will depend on many factors, including:

- our ability to initiate, and the progress and results of, our planned clinical trials of Resolaris;
- the scope, progress, results and costs of preclinical development, and clinical trials for our other product candidates;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims;
- the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for any of our product candidates for which we receive marketing approval; and
- the extent to which we acquire or in-license other products and technologies.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic partnerships and/or licensing arrangements. To the extent we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through collaborations, strategic partnerships or licensing arrangements with third parties, we may have to relinquish valuable rights to our product candidates, our other technologies, future revenue streams or research programs or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market our product candidates even if we would otherwise prefer to develop and market such product candidates ourselves.

Contractual Obligations and Commitments

The following table summarizes our contractual obligations as of December 31, 2015:

	Total	Payments Due by Period			
		Less than 1 Year	1-3 Years	3-5 Years	More than 5 Years
		(in thousands)			
Commercial bank debt, including interest and final payment obligations	$ 5,933	$ 3,622	$ 2,311	$ —	$ —
Operating lease (1)	841	610	231	—	—
Total	$ 6,774	$ 4,232	$ 2,542	$ —	$ —

(1) Our operating lease obligations relate to our corporate headquarters in San Diego, California. We lease 17,083 square feet of office and laboratory space under an operating lease that expires in May 2017.

We enter into contracts in the normal course of business with clinical trial sites and clinical supply manufacturing organizations and with vendors for preclinical safety and research studies, research supplies and other services and products purposes. These contracts generally provide for termination after a notice period, and therefore are cancelable contracts and not included in the table of contractual obligations and commitments.

We may have payment obligations under our agreements with TSRI certain of which are contingent upon future events such as our achievement of specified development, regulatory and commercial milestones, and we are required to make development milestone payments and royalty payments in connection with the sale of products developed under these agreements. As of December 31, 2015, we were unable to estimate the timing or likelihood of achieving the milestones or making future product sales and, therefore, any related payments are not included in the table above.

We are party to an amended and restated research funding and option agreement with TSRI, under which we provide funding to TSRI to conduct certain research activities related to aminoacyl tRNA synthetases. Under the research funding and option agreement, TSRI has granted us options to enter into license agreements to acquire rights and exclusive licenses to develop, make, have made, use, have used, import, have imported, offer to sell, sell and have sold certain licensed products, processes and services based on certain technology arising from the sponsored research activities. Pursuant to the terms of these license agreements, TSRI is entitled to receive tiered royalties as a percentage of net sales, ranging from the low to mid-single digits, with these royalty rates subject to adjustment under certain circumstances. Additionally, we have agreed to pay TSRI a percentage of non-royalty revenue we receive from our sublicensees or partners, with the amount owed decreasing if we enter into the applicable sublicense agreement or partnering agreement after meeting a specified clinical milestone. We are obligated to make payments to TSRI of up to an aggregate of $2.75 million under each license agreement upon the achievement of specific clinical and regulatory milestone events.

We have payment obligations under our agreement with FUJIFILM Diosynth Biotechnologies, U.S.A., Inc. (Fujifilm) related to development and production milestones of up to the mid seven figures for process optimization, scale-up and demonstration, and cGMP manufacturing of the drug substance of Resolaris. In addition, we are billed for consumables on a pass-through basis.

Recent Accounting Pronouncements

In August 2014, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update (ASU) No. 2014-15, Presentation of Financial Statements — Going Concern. ASU 2014-15 provides that in connection with preparing financial statements for each annual and interim reporting period, an entity's management should evaluate whether there are conditions or events, considered in the aggregate, that raise substantial doubt about the entity's ability to continue as a going concern within one year after the date that the financial statements are issued (or within one year after the date that the financial statements are available to be issued when applicable). ASU 2014-15 is effective for the annual reporting period ending after December 15, 2016, and for annual and interim periods thereafter. Early adoption is permitted. The adoption of ASU 2014-15 is not expected to have a material impact on our consolidated financial position or results of operations.

In April 2015, the FASB issued ASU No. 2015-03, Interest - Imputation of Interest (Subtopic 835-30): Simplifying the Presentation of Debt Issuance Costs. ASU 2015-03 requires that debt issuance costs related to a recognized debt liability be presented in the balance sheet as a direct deduction from that debt liability, consistent with the presentation of a debt discount. The recognition and measurement guidance for debt issuance costs is not affected by ASU 2015-03. ASU 2015-03 is effective for fiscal years beginning after December 15, 2015, and interim periods within those fiscal years. Early application is permitted. The adoption of ASU 2015-03 is not expected to have a material impact on our consolidated financial position or results of operations.

In November 2015, the FASB issued ASU No. 2015-17, "Balance Sheet Classification of Deferred Taxes," which requires all deferred tax assets and liabilities to be classified as noncurrent on the balance sheet. The new accounting guidance is effective for annual reporting periods beginning after December 15, 2016 and interim periods therein. Early adoption is permitted as of the beginning of interim or annual reporting periods. We elected to early adopt this guidance prospectively beginning in the year ended December 31, 2015 and prior periods were not retrospectively adjusted. There was no material impact on our consolidated financial statements upon adoption.

In January 2016, the FASB issued ASU No. 2016-01, "Financial Instruments-Overall: Recognition and Measurement of Financial Assets and Financial Liabilities," which requires that (i) all equity investments, other than equity-method investments, in unconsolidated entities generally be measured at fair value through earnings and (ii) when the fair value option has been elected for financial liabilities, changes in fair value due to instrument-specific credit risk will be recognized separately in other comprehensive income. Additionally, the ASU changes the disclosure requirements for financial instruments. The new standard will be effective for fiscal years beginning after December 15, 2018, and interim periods within fiscal years beginning after December 15, 2019. Early adoption is permitted for certain provisions. The adoption of ASU 2015-03 is not expected to have a material impact on our consolidated financial position or results of operations.

In February 2016, the FASB issued ASU 2016-02, Leases, to increase transparency and comparability among organizations by requiring recognition of lease assets and lease liabilities on the balance sheet and disclosure of key information about leasing arrangements. The standard will become effective for interim and annual periods beginning after December 15, 2018, with early adoption permitted. The guidance is required to be adopted at the earliest period presented using a modified retrospective approach. We are currently evaluating the impact the provisions will have on our consolidated financial statements and whether we will adopt the guidance early.

Off-Balance Sheet Arrangements

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined in the rules and regulations of the SEC.

JOBS Act

In April 2012, the JOBS Act was enacted. Section 107 of the JOBS Act provides that an emerging growth company can take advantage of the extended transition period provided in Section 7(a)(2)(B) of the Securities Act for complying with new or revised accounting standards. Thus, an emerging growth company can delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this extended transition period and, as a result, we will adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for other companies.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

Interest Rate Risk

We are exposed to market risk related to changes in interest rates. As of December 31, 2015, we had cash and cash equivalents, and available-for-sale investments totaling of $125.3 million. We invest our excess cash in investment-grade, interest-bearing securities. The primary objective of our investment activities is to preserve principal and liquidity. To achieve this objective, we invest in money market funds, U.S. treasury and high quality marketable debt instruments of corporations and financial institutions, government sponsored and asset backed securities with contractual maturity dates of less than two years. If interest rates were to increase instantaneously and uniformly by 100 basis points, compared to interest rates as of December 31, 2014, the increase would not have had a material effect on the fair market value of our portfolio.

We do not believe that our cash, cash equivalents and investments have significant risk of default or illiquidity. While we believe our cash and cash equivalents do not contain excessive risk, we cannot provide absolute assurance that in the future our investments will not be subject to adverse changes in market value. In addition, we maintain significant amounts of cash and cash equivalents at one or more financial institutions that are in excess of federally insured limits.

Our debt obligations bear interest at fixed rates and therefore have no exposure to changes in interest rates.

Foreign Currency Exchange Risk

We incur expenses, including for CROs and clinical trial sites, outside the United States based on contractual obligations denominated in currencies other than the U.S. dollar, including Pounds Sterling. At the end of each reporting period, these liabilities are converted to U.S. dollars at the then-applicable foreign exchange rate. As a result, our business is affected by fluctuations in exchange rates between the U.S. dollar and foreign currencies. We do not enter into foreign currency hedging transactions to mitigate our exposure to foreign currency exchange risks. Exchange rate fluctuations may adversely affect our expenses, results of operations, financial position and cash flows. However, to date, these fluctuations have not been significant and a movement of 10% in the U.S. dollar to Pounds Sterling or U.S. dollar to Euro exchange rates would not have a material effect on our results of operations or financial condition.

Effects of Inflation

Inflation generally affects us by increasing our cost of labor, manufacturing, clinical trial, and other research and development and administration costs. We do not believe that inflation has had a material effect on our results of operations or financial condition during the periods presented.

Item 8. Financial Statements and Supplementary Data

Report of Independent Registered Public Accounting Firm

The Board of Directors and Stockholders of
aTyr Pharma, Inc.

We have audited the accompanying consolidated balance sheets of aTyr Pharma, Inc. as of December 31, 2015 and 2014, and the related consolidated statements of operations, comprehensive loss, redeemable convertible preferred stock and stockholders' equity (deficit) and cash flows for each of the three years in the period ended December 31, 2015. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company's internal control over financial reporting. Our audits included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of aTyr Pharma, Inc. at December 31, 2015 and 2014, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2015, in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP
San Diego, California
March 30, 2016

aTyr Pharma, Inc.
Consolidated Balance Sheets
(in thousands, except share and per share data)

	December 31,	
	2015	**2014**
Assets		
Current assets:		
Cash and cash equivalents	$ 53,025	$ 13,899
Short-term investments	42,510	1,954
Prepaid expenses and other assets	2,415	656
Total current assets	97,950	16,509
Long-term investments	29,814	—
Property and equipment, net	1,793	1,925
Other assets	118	2,210
Total assets	$ 129,675	$ 20,644
Liabilities, Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)		
Current liabilities:		
Accounts payable	$ 3,872	$ 1,433
Accrued expenses	4,595	2,932
Current portion of deferred rent	315	295
Current portion of commercial bank debt	3,366	3,134
Convertible promissory note	—	2,000
Preferred stock warrant liabilities	—	319
Total current liabilities	12,148	10,113
Deferred rent, net of current portion	130	445
Commercial bank debt, net of current portion	1,776	5,142
Other long-term liabilities	571	335
Commitments and contingencies (Note 5)		
Redeemable convertible preferred stock, $0.001 par value; authorized shares – 7,285,456 and 75,772,871 at December 31, 2015 and 2014, respectively; issued and outstanding shares – none and 73,487,415 at December 31, 2015 and 2014, respectively; liquidation preference of $0 and $95,619 at December 31, 2015 and 2014, respectively	—	95,619
Stockholders' equity (deficit):		
Undesignated preferred stock, $0.001 par value; authorized shares – 5,000,000 at December 31, 2015 and none at December 31, 2014; issued and outstanding shares – none at December 31, 2015 and 2014	—	—
Common stock, $0.001 par value; authorized shares – 150,000,000 and 95,500,000 at December 31, 2015 and 2014, respectively; issued and outstanding shares – 23,670,079 and 909,880 at December 31, 2015 and 2014, respectively	24	1
Additional paid-in capital	273,321	19,209
Stockholder note receivable	—	(69)
Accumulated other comprehensive loss	(171)	—
Accumulated deficit	(158,124)	(110,151)
Total stockholders' equity (deficit)	115,050	(91,010)
Total liabilities, redeemable convertible preferred stock and stockholders' equity (deficit)	$ 129,675	$ 20,644

See accompanying notes.

aTyr Pharma, Inc.
Consolidated Statements of Operations
(in thousands, except share and per share data)

	Years Ended December 31,		
	2015	**2014**	**2013**
Operating expenses:			
Research and development	$ 34,504	$ 16,777	$ 13,832
General and administrative	13,112	6,777	5,710
Total operating expenses	47,616	23,554	19,542
Loss from operations	(47,616)	(23,554)	(19,542)
Other income (expense):			
Interest income (expense), net	(386)	(832)	(444)
Change in fair value of warrant liabilities	29	36	(28)
Total other income (expense)	(357)	(796)	(472)
Net loss	(47,973)	(24,350)	(20,014)
Accretion to redemption value of redeemable convertible preferred stock	(15)	(416)	(1,637)
Net loss attributable to common stockholders	$ (47,988)	$ (24,766)	$ (21,651)
Net loss per share attributable to common stockholders, basic and diluted	$ (3.03)	$ (29.69)	$ (28.39)
Weighted average common stock shares outstanding, basic and diluted	15,838,353	834,221	762,761

See accompanying notes.

aTyr Pharma, Inc.
Consolidated Statements of Comprehensive Loss
(in thousands)

	Years Ended December 31,		
	2015	**2014**	**2013**
Net loss	$ (47,973)	$ (24,350)	$ (20,014)
Other comprehensive loss:			
Change in unrealized loss on available for sale investments	(171)	—	—
Comprehensive loss	$ (48,144)	$ (24,350)	$ (20,014)

See accompanying notes.

aTyr Pharma, Inc.
Consolidated Statements of Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)
(in thousands, except share data)

	Redeemable Convertible Preferred Stock		Common Stock		Additional Paid-In Capital	Stockholder Note Receivable	Non-Controlling Interest	Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount						
Balance as of December 31, 2012	55,211,585	$ 63,225	788,946	$ 1	$ 5	$ (69)	$ 25	$ —	$ (64,516)	$ (64,554)
Issuance of Series D redeemable convertible preferred stock for cash	14,504,841	36,683	—	—	—	—	2,431	—	—	2,431
Issuance of Series D redeemable convertible preferred stock for conversion of debt and interest	3,770,989	9,537	—	—	—	—	—	—	—	—
Series D redeemable preferred stock issuance costs	—	(389)	—	—	—	—	(65)	—	—	(65)
Exercise of common stock options	—	—	67,645	—	54	—	23	—	—	77
Changes in share repurchase liability	—	—	—	—	(3)	—	—	—	—	(3)
Stock-based compensation	—	—	—	—	155	—	—	—	—	155
Accretion to redemption value of redeemable convertible preferred stock	—	1,637	—	—	(366)	—	—	—	(1,271)	(1,637)
Capital contribution related to reversal of historical accretion of redeemable convertible preferred stock	—	(17,528)	—	—	17,528	—	—	—	—	17,528
Net loss	—	—	—	—	—	—	—	—	(20,014)	(20,014)
Balance as of December 31, 2013	73,487,415	93,165	856,591	1	17,373	(69)	2,414	—	(85,801)	(66,082)
Exercise of common stock options	—	—	53,289	—	43	—	29	—	—	72
Changes in share repurchase liability	—	—	—	—	13	—	—	—	—	13
Stock-based compensation	—	—	—	—	1,791	—	—	—	—	1,791
Dissolution of Affiliates	—	2,038	—	—	405	—	(2,443)	—	—	(2,038)
Accretion to redemption value of redeemable convertible preferred stock	—	416	—	—	(416)	—	—	—	—	(416)
Net loss	—	—	—	—	—	—	—	—	(24,350)	(24,350)
Balance as of December 31, 2014	73,487,415	95,619	909,880	1	19,209	(69)	—	—	(110,151)	(91,010)
Issuance of Series E redeemable convertible preferred stock for cash	68,166,894	75,650	—	—	—	—	—	—	—	—
Conversion of redeemable convertible preferred stock in connection with IPO	(141,654,309)	(171,284)	16,279,859	16	171,268	—	—	—	—	171,284
Issuance of common stock through initial public offering, net	—	—	6,164,000	6	75,897	—	—	—	—	75,903
Repayment of stockholder note receivable	—	—	—	—	(9)	69	—	—	—	60
Exercise of common stock options	—	—	196,500	1	534	—	—	—	—	535
Reclassification of preferred stock warrant liability to additional paid-in-capital	—	—	—	—	290	—	—	—	—	290
Issuance of common stock to The Scripps Research Institute	—	—	119,840	—	1,411	—	—	—	—	1,411
Changes in share repurchase liability	—	—	—	—	(120)	—	—	—	—	(120)
Stock-based compensation	—	—	—	—	4,856	—	—	—	—	4,856
Accretion to redemption value of redeemable convertible preferred stock	—	15	—	—	(15)	—	—	—	—	(15)

Net unrealized loss on investments	—	—	—	—	—	—	—	(171)	—	(171)
Net loss	—	—	—	—	—	—	—		(47,973)	(47,973)
Balance as of December 31, 2015	—	$ —	23,670,079	$ 24	$ 273,321	$ —	$ —	$ (171)	$ (158,124)	$ 115,050

See accompanying notes.

aTyr Pharma, Inc.
Consolidated Statements of Cash Flows
(in thousands)

	Years Ended December 31,		
	2015	**2014**	**2013**
Cash flows from operating activities:			
Net loss	$ (47,973)	$ (24,350)	$ (20,014)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	869	829	714
Issuance of common stock for technology	1,411	—	—
Stock-based compensation	4,856	1,791	155
Amortization of debt discount	297	426	211
Change in fair value of preferred stock warrant liability	(29)	(36)	28
Amortization of investment premium	789	43	—
Deferred rent	(295)	(277)	(254)
Changes in operating assets and liabilities			
Prepaid expenses and other assets	(666)	(1,043)	323
Accounts payable and accrued expenses	3,944	(207)	1,526
Net cash used in operating activities	(36,797)	(22,824)	(17,311)
Cash flows from investing activities:			
Purchase of property and equipment	(664)	(249)	(644)
Purchases of investment securities	(109,445)	(5,397)	—
Maturities of investment securities	38,115	3,400	—
Net cash used in investing activities	(71,994)	(2,246)	(644)
Cash flows from financing activities:			
Issuance of preferred stock for cash, net of issuance costs	75,648	—	38,660
Issuance of common stock through initial public offering, net of offering costs	76,902	—	—
Costs paid in connection with initial public offering	—	(999)	—
Proceeds from issuance of common stock through option exercises	604	72	77
Proceeds from notes payable to bank	—	5,000	5,000
Repayments on notes payable to bank	(3,237)	(1,561)	(2,500)
Proceeds from convertible debt	—	—	10,000
Repayment of convertible debt	(2,000)	—	(500)
Net cash provided by financing activities	147,917	2,512	50,737
Net change in cash and cash equivalents	39,126	(22,558)	32,782
Cash and cash equivalents at beginning of the period	13,899	36,457	3,675
Cash and cash equivalents at the end of the period	$ 53,025	$ 13,899	$ 36,457
Supplemental disclosure of cash flow information:			
Interest paid	$ 925	$ 415	$ 254
Supplemental schedule of noncash investing and financing activities:			
Issuance of warrants in connection with long-term debt	$ —	$ 148	$ 137
Changes in share repurchase liability	$ (120)	$ 13	$ (3)
Capital contribution related to reversal of historical accretion of redeemable convertible preferred stock	$ —	$ —	$ 17,528
Conversion of convertible debt and accrued interest	$ —	$ —	$ 9,537

See accompanying notes.

1. Organization, Business and Basis of Presentation

Organization and Business

We were incorporated in the state of Delaware on September 8, 2005. We are focused on the discovery and clinical development of innovative medicines for patients suffering from severe rare diseases.

Initial Public Offering

On May 12, 2015, we completed our initial public offering (IPO) of 6,164,000 shares of common stock at $14.00 per share, resulting in gross proceeds of approximately $86.3 million and net proceeds of $75.9 million, after underwriting and other expenses of approximately $10.4 million (consisting of approximately $6.0 million in underwriting discounts and commissions and approximately $4.4 million in other offering expenses). In connection with the IPO, all outstanding shares of redeemable convertible preferred stock were converted into 16,279,859 shares of our common stock and warrants to purchase 206,581 shares of redeemable convertible preferred stock were converted into warrants to purchase 25,970 shares of our common stock with a resultant reclassification of the warrant liabilities to additional paid-in capital. In addition, we filed an amended and restated certificate of incorporation on May 12, 2015, authorizing 150,000,000 shares of common stock and 7,285,456 shares of preferred stock, 5,000,000 of which is undesignated preferred stock.

Upon the closing of the IPO, 1,574,566 shares of common stock were reserved for future issuance under the 2015 Stock Option and Incentive Plan (the 2015 Plan) and 227,623 shares of common stock were reserved for future issuance under the 2015 Employee Stock Purchase Plan (the 2015 ESPP).

Principles of Consolidation

Our consolidated financial statements include our accounts, our 98% majority-owned subsidiary in Hong Kong, Pangu BioPharma Limited (Pangu BioPharma). All intercompany transactions and balances are eliminated in consolidation.

Reverse Stock Split

On May 5, 2015, we filed an amendment to our amended and restated certificate of incorporation to effect a one-for-7.95413 reverse stock split of our common stock (the Reverse Stock Split). The par value and the authorized shares of the common and convertible preferred stock were not adjusted as a result of the Reverse Stock Split. All share information has been retroactively restated to reflect the Reverse Stock Split.

Use of Estimates

Our consolidated financial statements are prepared in accordance with generally accepted accounting principles (GAAP). The preparation of our consolidated financial statements requires us to make estimates and assumptions that impact the reported amounts of assets, liabilities and expenses and the disclosure of contingent assets and liabilities in our consolidated financial statements and accompanying notes. The most significant estimates in our consolidated financial statements relate to the fair value of equity issuances and awards, and clinical trial and research and development expenses. Although these estimates are based on our knowledge of current events and actions we may undertake in the future, actual results may ultimately differ materially from these estimates and assumptions.

Segment Reporting

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision-maker in making decisions regarding resource allocation and assessing performance. We view our operations and manage our business in one operating segment.

2. Summary of Significant Accounting Policies

Cash and Cash Equivalents

Cash and cash equivalents consist primarily of readily available checking, money market accounts and money market funds. We consider all highly liquid investments that mature in three months or less when purchased to be cash equivalents.

Investment Securities

Investment securities primarily consist of investment grade corporate debt securities, asset-backed securities, commercial paper and United States Treasury securities. We classify all investment securities as available-for-sale. Investment securities are carried at fair value, with the unrealized gains and losses, if any, reported as a component of other comprehensive income (loss) in stockholders' equity (deficit) until realized. Realized gains and losses from the sale of investment securities, if any, are determined on a specific identification basis. A decline in the market value of any investment security below cost that is determined to be other than temporary will result in an impairment charge to earnings and a new cost basis for the security is established. No such impairment charges were recorded for any period presented. Premiums and discounts are amortized or accreted over the life of the related security as an adjustment to yield using the straight-line method and are included in interest income. Interest income is recognized when earned. As of December 31, 2015, we held an aggregate total of $72.3 million of investment securities which consisted of corporate debt securities, asset-backed securities, commercial paper and United States Treasury securities, all of which will mature in less than two years and there was $0.2 million difference between the amortized cost and fair value of these investment securities. As of December 31, 2014, we held $2.0 million of corporate debt securities, all of which mature in less than three months, and there was no difference between the amortized cost and fair value of these investment securities.

Concentration of Credit Risk

Financial instruments that potentially subject us to significant concentration of credit risk consist primarily of cash, cash equivalents and investment securities. We have established guidelines regarding diversification of investments and their maturities, which are designed to maintain principal and maximize liquidity. We maintain deposits in federally insured financial institutions in excess of federally insured limits. We have not experienced any losses in such accounts and we believe that we are not exposed to significant credit risk due to the financial position of the depository institutions in which those deposits are held.

Property and Equipment

Property and equipment are stated at cost and depreciated on a straight-line basis over the estimated useful life of the related assets (generally three to seven years). Leasehold improvements are stated at cost and amortized on a straight-line basis over the lesser of the remaining term of the related lease or the estimated useful life of the leasehold improvements. Repairs and maintenance costs are charged to expense as incurred.

Impairment of Long-Lived Assets

Long-lived assets consist primarily of property and equipment. An impairment loss is recorded if and when events and circumstances indicate that assets might be impaired and the undiscounted cash flows estimated to be generated by those assets are less than the carrying amount of those assets. While our current and historical operating losses are indicators of impairment, we believe that future cash flows to be received support the carrying value of our long-lived assets and, accordingly, have not recognized any impairment losses since inception.

Accrued Expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate accrued expenses, including accrued research and development expenses for fees paid to investigative sites and CROs in connection with clinical trials; service providers in connection with preclinical development activities; service providers related to product manufacturing; and other professional services. The accrual process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. We make estimates of accrued expenses as of each balance sheet date in our consolidated financial statements based on facts and circumstances known to us at that time. Although we do not expect the estimates to be materially different from amounts actually incurred, if the estimates of the status and timing of services performed differs from the actual status and timing of services performed, we may report amounts that are too high or too low in any particular period.

Deferred Rent

Rent expense, including the value of tenant improvement allowances received, is recorded on a straight-line basis over the term of the lease. The difference between rent expense and amounts paid under the lease agreements is recorded as deferred rent in the accompanying consolidated balance sheets.

Research and Development Costs

Research and development costs are expensed as incurred. Research and development costs include: salaries and employee-related expenses, including stock-based compensation and benefits for personnel in research and product development functions; costs associated with conducting our preclinical, development and regulatory activities, including fees paid to third-party professional consultants, service providers and our scientific, therapeutic and clinical advisory boards; costs to acquire, develop and manufacture preclinical study and clinical trial materials; costs incurred under clinical trial agreements with clinical research organizations and investigative sites; costs for laboratory supplies; payments related to licensed products and technologies; allocated facilities and information technology costs; and depreciation.

Patent Costs

Costs related to filing and pursuing patent applications are recorded as general and administrative expense and expensed as incurred since recoverability of such expenditures is uncertain.

Stock-Based Compensation

Stock-based compensation expense represents the cost of the grant date fair value of employee stock option grants recognized over the requisite service period of the awards (usually the vesting period) on a straight-line basis, net of estimated forfeitures. For stock option grants with performance-based milestones, the expense is recorded over the service period after the achievement of the milestone is probable or the performance condition is achieved. For stock option grants with market-based conditions, the expense is recorded using the accelerated attribution method over the requisite service period for each vesting tranche. We account for stock options granted to non-employees using the fair value approach. These option grants are subject to periodic revaluation over their vesting terms. We estimate the fair value of employee and non-employee stock option grants using the Black-Scholes option pricing model. We estimate the fair value of the market-based stock option grants using a Monte Carlo simulation.

Income Taxes

We account for income taxes under the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements. Under this method, deferred tax assets and liabilities are determined on the basis of the differences between the financial statements and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. The effect of a change in tax rates on deferred tax assets and liabilities is recognized as income in the period that includes the enactment date.

We recognize net deferred tax assets to the extent that we believe these assets are more likely than not to be realized. In making such a determination, we consider all available positive and negative evidence, including future reversals of existing taxable temporary differences, projected future taxable income, tax-planning strategies and results of recent operations. If we determine that we would be able to realize the deferred tax assets in the future in excess of their net recorded amount, we would make an adjustment to the deferred tax asset valuation allowance, which would reduce the provision for income taxes.

We record uncertain tax positions on the basis of a two-step process whereby (1) we determine whether it is more likely than not that the tax positions will be sustained on the basis of the technical merits of the position and (2) for those tax positions that meet the more-likely-than-not recognition threshold, we recognize the largest amount of tax benefit that is more than 50% likely to be realized upon ultimate settlement with the related tax authority. We recognize interest and penalties related to unrecognized tax benefits within income tax expense. Any accrued interest and penalties are included within the related tax liability.

In November 2015, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update (ASU) No. 2015-17, “Balance Sheet Classification of Deferred Taxes,” which requires all deferred tax assets and liabilities to be classified as noncurrent on the balance sheet. The new accounting guidance is effective for annual reporting periods beginning after December 15, 2016 and interim periods therein. Early adoption is permitted as of the beginning of interim or annual reporting periods. We elected to early adopt this guidance prospectively beginning in the year ended December 31, 2015 and prior periods were not retrospectively adjusted. There was no material impact on the financial statements upon adoption.

Net Loss Per Share

Basic net loss per share is calculated by dividing the net loss attributable to common stockholders by the weighted average number of common shares outstanding for the period, without consideration for common stock equivalents and adjusted for the weighted average number of common shares outstanding that are subject to repurchase. We have excluded 61,814, 61,457 and 76,587 shares subject to repurchase from the weighted average number of common shares outstanding for the years ended December 31, 2015, 2014 and 2013, respectively. Diluted net loss per share attributable to common stockholders is calculated by dividing the net loss attributable to common stockholders by the weighted average number of common stock equivalents outstanding for the period determined using the treasury-stock method. Dilutive common stock equivalents are comprised of redeemable convertible preferred stock, redeemable convertible preferred stock issuable upon conversion of convertible promissory note, warrants for the purchase of redeemable convertible preferred stock, warrants for common stock and options outstanding under our stock option plan. For all periods presented, there is no difference in the number of shares used to calculate basic and diluted shares outstanding due to our net loss position.

Potentially dilutive securities not included in the calculation of diluted net loss per share because to do so would be anti-dilutive are as follows (in common share equivalents):

	Years Ended December 31,		
	2015	2014	2013
Redeemable convertible preferred stock outstanding	—	9,238,868	9,238,868
Redeemable convertible preferred stock issuable upon conversion of convertible promissory note	—	94,455	94,455
Warrants for redeemable convertible preferred stock	—	25,970	18,514
Warrants for common stock	25,970	—	—
Common stock options	2,625,280	1,514,471	821,057
Employee stock purchase plan	17,363	—	—
	2,668,613	10,873,764	10,172,894

The following table summarizes our net loss per share (in thousands, except per share data):

	Years Ended December 31,		
	2015	2014	2013
Numerator:			
Consolidated net loss	(47,973)	(24,350)	(20,014)
Accretion to redemption value	(15)	(416)	(1,637)
Net loss attributable to common stockholders	(47,988)	(24,766)	(21,651)
Denominator:			
Weighted average common shares outstanding	15,900,167	895,678	839,348
Weighted average common shares subject to repurchase	(61,814)	(61,457)	(76,587)
Weighted average common shares outstanding - basic and diluted	15,838,353	834,221	762,761
Net loss per share - basic and diluted	$ (3.03)	$ (29.69)	$ (28.39)

Recent Accounting Pronouncements

In August 2014, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update (ASU) No. 2014-15, Presentation of Financial Statements — Going Concern. ASU 2014-15 provides that in connection with preparing financial statements for each annual and interim reporting period, an entity's management should evaluate whether there are conditions or events, considered in the aggregate, that raise substantial doubt about the entity's ability to continue as a going concern within one year after the date that the financial statements are issued (or within one year after the date that the financial statements are available to be issued when applicable). ASU 2014-15 is effective for the annual reporting period ending after December 15, 2016, and for annual and interim periods thereafter. Early adoption is permitted. The adoption of ASU 2014-15 is not expected to have a material impact on our consolidated financial position or results of operations.

In April 2015, the FASB issued ASU No. 2015-03, Interest - Imputation of Interest (Subtopic 835-30): Simplifying the Presentation of Debt Issuance Costs. ASU 2015-03 requires that debt issuance costs related to a recognized debt liability be presented in the balance sheet as a direct deduction from that debt liability, consistent with the presentation of a debt discount. The recognition and measurement guidance for debt issuance costs is not affected by ASU 2015-03. ASU 2015-03 is effective for fiscal years beginning after December 15, 2015, and interim periods within those fiscal years. Early application is permitted. The adoption of ASU 2015-03 is not expected to have a material impact on our consolidated financial position or results of operations.

In November 2015, the FASB issued ASU No. 2015-17, "Balance Sheet Classification of Deferred Taxes," which requires all deferred tax assets and liabilities to be classified as noncurrent on the balance sheet. The new accounting guidance is effective for annual reporting periods beginning after December 15, 2016 and interim periods therein. Early adoption is permitted as of the beginning of interim or annual reporting periods. We elected to early adopt this guidance prospectively beginning in the year ended December 31, 2015 and prior periods were not retrospectively adjusted. There was no material impact on our consolidated financial statements upon adoption.

In January 2016, the FASB issued ASU No. 2016-01, "Financial Instruments-Overall: Recognition and Measurement of Financial Assets and Financial Liabilities," which requires that (i) all equity investments, other than equity-method investments, in unconsolidated entities generally be measured at fair value through earnings and (ii) when the fair value option has been elected for financial liabilities, changes in fair value due to instrument-specific credit risk will be recognized separately in other comprehensive income. Additionally, the ASU changes the disclosure requirements for financial instruments. The new standard will be effective for fiscal years beginning after December 15, 2018, and interim periods within fiscal years beginning after December 15, 2019. Early adoption is permitted for certain provisions. The adoption of ASU 2015-03 is not expected to have a material impact on our consolidated financial position or results of operations.

In February 2016, the FASB issued ASU 2016-02, Leases, to increase transparency and comparability among organizations by requiring recognition of lease assets and lease liabilities on the balance sheet and disclosure of key information about leasing arrangements. The standard will become effective for interim and annual periods beginning after December 15, 2018, with early adoption permitted. The guidance is required to be adopted at the earliest period presented using a modified retrospective approach. We are currently evaluating the impact the provisions will have on our consolidated financial statements and whether we will adopt the guidance early.

3. Fair Value Measurements

The carrying amounts of cash equivalents, prepaid and other assets, accounts payable and accrued liabilities are considered to be representative of their respective fair values because of the short-term nature of those instruments. Based on the borrowing rates currently available to us for loans with similar terms, which is considered a Level 2 input, we believe that the fair value of our commercial bank debt and convertible promissory notes approximate their carrying values. Investment securities and preferred stock warrant liabilities are recorded at fair value.

The accounting guidance defines fair value, establishes a consistent framework for measuring fair value and expands disclosure for each major asset and liability category measured at fair value on either a recurring or nonrecurring basis. Fair value is defined as an exit price, representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. As such, fair value is a market-based measurement that should be determined based on assumptions that market participants would use in pricing an asset or liability. As a basis for considering such assumptions, the accounting guidance establishes a three-tier fair value hierarchy, which prioritizes the inputs used in measuring fair value as follows:

Level 1: Observable inputs such as quoted prices in active markets.

Level 2: Inputs, other than the quoted prices in active markets that are observable either directly or indirectly.

Level 3: Unobservable inputs in which there is little or no market data, which require the reporting entity to develop its own assumptions.

Financial assets measured at fair value on a recurring basis consist of investment securities. Investment securities are recorded at fair value, defined as the exit price in the principal market in which we would transact, representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. Level 2 securities are valued using quoted market prices for similar instruments, non-binding market prices that are corroborated by observable market data, or discounted cash flow techniques and include our investments in corporate debt securities, commercial paper, asset-backed securities and United States Treasury securities. Financial liabilities measured at fair value on a recurring basis include our preferred stock warrant liabilities. None of our non-financial assets and liabilities is recorded at fair value on a non-recurring basis. No transfers between levels have occurred during the periods presented.

Assets and liabilities measured at fair value on a recurring basis are as follows (in thousands):

		Fair Value Measurements Using		
		Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
As of December 31, 2015:				
Assets:				
Current:				
Cash and cash equivalents	$ 53,025	$ 53,025	$ —	$ —
Short-term investments:				
Commercial paper	2,996	—	2,996	—
Corporate debt securities	39,514	—	39,514	—
Sub-total short-term investments	42,510	—	42,510	—
Long-term investments:				
United States Treasury securities	1,999	1,999	—	—
Asset-backed securities	10,912	—	10,912	—
Corporate debt securities	16,903	—	16,903	—
Sub-total long-term investments	29,814	1,999	27,815	—
Total assets measured at fair value	$ 125,349	$ 55,024	$ 70,325	$ —
As of December 31, 2014:				
Assets:				
Cash and cash equivalents	$ 13,899	$ 13,899	$ —	$ —
Short-term investments - Corporate debt securities	1,954	—	1,954	—
Total assets measured at fair value	$ 15,853	$ 13,899	$ 1,954	$ —
Liabilities:				
Preferred stock warrant liabilities	$ 319	$ —	$ —	$ 319

As of December 31, 2015 and 2014, available-for-sale investments are detailed as follows (in thousands):

	December 31, 2015			
	Gross Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Market Value
Short-term investments:				
Commercial paper	$ 2,996	$ —	$ —	$ 2,996
Corporate debt securities	39,575	—	(61)	39,514
	$ 42,571	$ —	$ (61)	$ 42,510
Long-term investments:				
United States Treasury securities	$ 2,006	$ —	$ (7)	$ 1,999
Asset-backed securities	10,928	—	(16)	10,912
Corporate debt securities	16,990	—	(87)	16,903
	$ 29,924	$ —	$ (110)	$ 29,814

	December 31, 2014			
	Gross Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Market Value
Short-term:				
Corporate debt securities	$ 1,954	$ —	$ —	$ 1,954

Available-for-sale investments that are in an unrealized loss position as of December 31, 2015 are as follows (in thousands):

	Estimated Fair Value	Gross Unrealized Losses
United States Treasury securities	$ 1,999	$ (7)
Asset-backed securities	10,912	(16)
Corporate debt securities	56,416	(148)
	$ 69,327	$ (171)

As of December 31, 2015, all available-for-sale investments have contractual maturity dates within two years. As of December 31, 2015, there are 39 available-for-sale investments in gross unrealized loss position, all of which have been in such position for less than twelve months.

At each reporting date, we perform an evaluation of impairment to determine if the unrealized losses are other-than-temporary. Factors considered in determining whether a loss is other-than-temporary include the length of time and extent to which fair value has been less than the cost basis, the financial condition of the issuer, and our intent and ability to hold the investment until recovery of its amortized cost basis. We intend, and have the ability, to hold our investments in unrealized loss positions until their amortized cost basis has been recovered. Based on our evaluation, we determined that the unrealized losses were not other-than-temporary as of December 31, 2015.

All warrant liabilities were recorded at fair value utilizing the Black-Scholes option pricing model using significant unobservable inputs consistent with the inputs used for our stock-based compensation expense adjusted for the warrants' expected life.

The following table provides a reconciliation of all liabilities measured at fair value using Level 3 significant unobservable inputs (in thousands):

	Warrant Liabilities
Balance as of December 31, 2014	$ 319
Change in fair value	(29)
Balance as of May 5, 2015	$ 290
Reclassification to additional paid-in capital as of IPO on May 6, 2015	(290)
Balance as of December 31, 2015	$ —

4. Balance Sheet Details

Property and equipment consist of the following (in thousands):

	December 31,	
	2015	2014
Computer and office equipment	$ 336	$ 372
Scientific and laboratory equipment	3,518	2,848
Tenant improvements	1,687	1,668
	5,541	4,888
Less accumulated depreciation and amortization	(3,748)	(2,963)
	$ 1,793	$ 1,925

Accrued expenses consist of the following (in thousands):

	December 31,	
	2015	2014
Accrued salaries, wages and benefits	1,710	684
Other accrued expenses	2,885	2,248
	$ 4,595	$ 2,932

5. Debt, Commitments and Contingencies

Commercial Bank Debt

Commercial bank debt and unamortized discount balances are as follows (in thousands):

	December 31,	
	2015	2014
Commercial bank debt	$ 5,202	$ 8,439
Less debt discount, net of current portion	(6)	(60)
Commercial bank debt, net of debt discount	5,196	8,379
Less current portion of commercial bank debt	(3,420)	(3,237)
Commercial bank debt, net of current portion	$ 1,776	$ 5,142
Current portion of commercial bank debt	$ 3,420	$ 3,237
Current portion of debt discount	(54)	(103)
Current portion of commercial bank debt	$ 3,366	$ 3,134

In each of April 2012 and August 2012, we borrowed $1.25 million under a loan and security agreement with Silicon Valley Bank (SVB Loan), at fixed interest rates of 4.89% and 4.85%, respectively. We were obligated to make interest-only payments through December 2012 and, beginning in December 2013, monthly payments of principal and interest through the maturity date in December 2015. The SVB Loan was amended in July 2013 to increase the available credit under the agreement to $10.0 million. In July 2013, we borrowed $5.0 million under the SVB Loan at a fixed interest rate of 5.0% and received $2.9 million of cash proceeds after repayment of the existing principal balance and related accrued interest and fees. In June 2014, we borrowed the remaining $5.0 million of available credit at a fixed interest rate of 5.88% and, subsequent to June 2014, had no available credit under the SVB Loan. We were obligated to make interest-only payments on each $5.0 million borrowing through June 2014 and, beginning in July 2014, monthly payments of principal and interest through the maturity date in June 2017. The final payment due in June 2017 includes an additional fee of $0.5 million, which is being accreted over the term of the debt using the effective interest method and is included in interest expense. The loan is collateralized by all of our assets, other than intellectual property, and contains customary affirmative and negative covenants, reporting requirements and events of default.

In July 2013, in connection with the SVB Loan, we issued a warrant to purchase 59,312 shares of Series D redeemable convertible preferred stock at an exercise price of $2.529 per share. In June 2014, the warrant became exercisable for a total of 118,624 shares of Series D redeemable convertible preferred stock when we borrowed the remaining $5.0 million of available credit under the SVB Loan. In May 2015, upon the effectiveness of our IPO, the Series D redeemable convertible preferred stock warrants with Silicon Valley Bank (SVB) were converted to purchase 14,913 shares common stock.

Future minimum principal and interest payments under our loan and security agreement with SVB, including the final payment, are as follows (in thousands):

	As of December 31, 2015
2016	$ 3,622
2017	2,311
	$ 5,933
Less interest and final payment	(731)
Commercial bank debt	$ 5,202

Facility Lease

In December 2011, we entered into a noncancelable operating lease that included certain tenant improvement allowances and is subject to base lease payments, which escalate over the term of the lease, additional charges for common area maintenance and other costs. The lease expires in May 2017 and we have an option to extend the lease for a period of five years. Rent expense for the years ended December 31, 2015, 2014 and 2013 was $0.4 million, $0.2 million and $0.2 million, respectively.

In conjunction with this lease, we borrowed $2.0 million under a subordinated unsecured convertible promissory note issued to the venture arm of our landlord. The convertible promissory note carried an annual interest rate of 8.0%. In May 2015, the $2.0 million outstanding principal balance of the convertible promissory note and the $0.5 million accrued interest on the convertible promissory note was repaid in full in connection with our IPO.

Future minimum payments under the non-cancelable operating lease as of December 31, 2015 are as follows (in thousands):

	Operating Lease
2016	$ 610
2017	231
	$ 841

Research Agreements and Funding Obligations

In October 2007, we entered into a research funding and option agreement for certain technologies from The Scripps Research Institute (TSRI). Under the agreement, we provide funding to TSRI to conduct certain research activities. The agreement renews automatically for successive 12 month periods starting on May 31st of each year unless we provide 30 days' prior written notice to terminate the agreement. TSRI has the right to terminate the agreement if we fail to make any payment under the agreement or for breach or insolvency. Under the research funding and option agreement, TSRI has granted us options to enter into license agreements to acquire rights and exclusive licenses to develop, make, have made, use, have used, import, have imported, offer to sell, sell, and have sold certain licensed products, processes and services based on certain technology arising from the sponsored research activities. Pursuant to the terms of these license agreements, TSRI is entitled to receive tiered royalties as a percentage of net sales and a percentage of nonroyalty revenue we may receive from our sublicensees or partners, with the amount owed decreasing if we enter into the applicable sublicense or partnering agreement after meeting a specified clinical milestone. In addition, we are obligated to pay TSRI up to an aggregate of $2.75 million under each license agreement upon the achievement of specific clinical and regulatory milestone events. In January 2015, we and TSRI entered into an amended and restated research funding and option agreement pursuant to which we agreed to issue 119,840 shares of our common stock to TSRI in consideration for the adjustment of sublicense payments and the assignment of certain intellectual property rights by TSRI to us. The $1.4 million fair value of the common stock issued to TSRI was recorded to research and development expense. We issued the shares of common stock to TSRI on March 31, 2015.

During the years ended December 31, 2015, 2014 and 2013, excluding the fair value of the common stock issued to TSRI described above, we recognized expense under the agreement in the amount of $0.7 million, $0.7 million and $0.6 million, respectively. A member of our board of directors is a faculty member at TSRI and such payments fund a portion of his research activities conducted at TSRI.

During the years ended December 31, 2015, 2014 and 2013, we provided charitable donations to the National Foundation for Cancer Research of $0.4 million. We have requested that the donations be restricted to certain basic research in cancer biology and therapeutics, a portion of which funds research activities conducted at TSRI in the laboratory of a member of our board of directors.

FUJIFILM Diosynth Biotechnologies U.S.A., Inc. Agreement

On June 16, 2015, we entered into a Master Services Agreement (the MSA) with FUJIFILM Diosynth Biotechnologies U.S.A., Inc. (Fujifilm) to complete the development of the manufacturing process and for the production of the drug substance for Resolaris, our drug in clinical development. Pursuant to the MSA, Fujifilm will provide the drug substance for Resolaris to support future clinical trials, including potential pivotal trials. Under the initial scope of work executed pursuant to the MSA, Fujifilm will conduct process optimization, scale-up and demonstration, and cGMP manufacturing of the drug substance of Resolaris, and we are required to pay Fujifilm based on development and production milestones up to the mid seven figures. In addition, we are billed for consumables on a pass-through basis. During the year ended December 31, 2015, expenses associated with this agreement were $5.1 million.

6. Stockholders' Equity

Sale of Series E Redeemable Convertible Preferred Stock

On March 31, 2015, pursuant to a Series E stock purchase agreement, we issued an aggregate of 68,166,894 shares of our Series E redeemable convertible preferred stock at a purchase price of $1.119 per share, for aggregate cash consideration of $76.3 million and incurred $0.6 million of issuance costs. Each share of Series E redeemable convertible preferred stock was convertible into 0.12572 shares of our common stock. The purchase agreement also included an automatic conversion into approximately 0.10329 shares of common stock for each share of Series E redeemable convertible preferred stock upon completion of a qualified public offering on or before March 1, 2016. On May 12, 2015, all outstanding shares of Series E redeemable convertible preferred stock was converted into 7,040,991 shares of our common stock in connection with our IPO.

Common Stock

In March 2015, we amended and restated our certificate of incorporation to, among other things, (1) increase its authorized shares of common stock from 95,500,000 to 185,000,000 shares, (2) increase its authorized shares of preferred stock from 75,772,871 to 143,939,765 shares, of which 68,166,894 shares are designated as Series E preferred stock, and (3) set forth the rights, preferences and privileges of the Series E preferred stock.

In May 2015, in connection with our IPO, we filed an amended and restated certificate of incorporation, authorizing 150,000,000 shares of common stock and 7,285,456 shares of preferred stock, 5,000,000 of which is undesignated preferred stock. In addition, all outstanding shares of redeemable convertible preferred stock, including Series E, were converted into 16,279,859 shares of our common stock and warrants to purchase 206,581 shares of redeemable convertible preferred stock were converted into warrants to purchase 25,970 shares of our common stock with a resultant reclassification of the warrant liabilities to additional paid-in capital.

2014 Stock Plan

We adopted a stock option plan in 2007 (the 2007 Plan), which was subsequently amended, restated and renamed in July 2014 (the 2014 Plan) to provide for the incentive stock options, nonstatutory stock options, stock and rights to purchase restricted stock to eligible recipients. Recipients of incentive stock options are eligible to purchase shares of our common stock at an exercise price equal to no less than the estimated fair market value of such stock on the date of grant. The maximum term of options under the 2014 Plan is ten years. Options granted generally vest over four years.

2015 Stock Plan

In April 2015, our board of directors adopted, and our stockholders approved, the 2015 Plan. The 2015 Plan became effective on May 6, 2015 and we ceased granting any new awards under our 2014 Plan. Awards granted under the 2014 Plan prior to our IPO that are forfeited, canceled, reacquired by us prior to vesting satisfied without the issuance of stock or otherwise terminated (other than by exercise) will be added to shares available for issuance under the 2015 Plan. A total of 1,574,566 shares of our common stock were initially reserved for issuance under the 2015 Plan. In addition, the number of shares reserved and available for issuance under the 2015 Plan will automatically increase each January 1, beginning on January 1, 2016 and thereafter until January 1, 2019, by the lesser of (i) 1,840,000 shares, (ii) 4% of the outstanding number of shares of our common stock on the immediately preceding December 31 or (iii) an amount determined by our board of directors. Shares underlying any awards under the 2015 Plan that are forfeited, canceled, reacquired by us prior to vesting, satisfied without the issuance of stock or otherwise terminated (other than by exercise) will be added to shares available for issuance under the 2015 Plan.

Employee Stock Purchase Plan

In April 2015, our board of directors adopted, and our stockholders approved, our 2015 Employee Stock Purchase Plan (the 2015 ESPP). The 2015 ESPP became effective on May 6, 2015. A total of 227,623 shares of our common stock were initially reserved for issuance under the 2015 ESPP. In addition, the number of shares reserved and available for purchase under the 2015 ESPP will automatically increase each January 1, beginning on January 1, 2016 and thereafter until January 1, 2019, by 1% of the outstanding number of shares of our common stock on the immediately preceding December 31 or such lesser number of shares as determined by the administrator of the 2015 ESPP.

Stock option activity is summarized as follows:

	Number of Outstanding Options	Weighted Average Price	Weighted Remaining Contractual Term	Aggregate Intrinsic Value (in 000s)
Outstanding as of December 31, 2014	1,514,471	$ 4.60		
Granted	1,715,028	$ 11.29		
Exercised	(197,253)	$ 2.78		
Canceled	(406,966)	$ 6.37		
Outstanding as of December 31, 2015	2,625,280	$ 8.83	8.02	$ 6,684
Options vested and expected to vest as of December 31, 2015	2,625,280	$ 8.83	8.02	$ 6,684
Options exercisable as of December 31, 2015	899,931	$ 4.91	6.64	$ 5,063

The assumptions used in the Black-Scholes option pricing model to determine the fair value of the employee stock option grants were as follows:

	Years Ended December 31,		
	2015	2014	2013
Expected term (in years)	5.50 – 6.08	5.77 – 6.56	6.52 – 6.56
Risk-free interest rate	1.5% – 1.9%	1.7% – 2.7%	2.0% – 2.2%
Expected volatility	79.2% – 100.9%	111.0%	109.0%
Expected dividend yield	0.0%	0.0%	0.0%

The assumptions used in the Black-Scholes option pricing model to determine the fair value of the ESPP offering were as follows:

	Year Ended December 31, 2015
Expected term (in years)	0.50
Risk-free interest rate	0.33%
Expected volatility	67.3%
Expected dividend yield	0.0%

Expected term. The expected term represents the period of time that options are expected to be outstanding. Because we do not have sufficient history of exercise behavior, we determine the expected life assumption using the simplified method, which is an average of the contractual term of the option and its vesting period.

Risk-free interest rate. We base that risk-free interest rate assumption on the U.S. Treasury's rates for U.S. Treasury zero-coupon bonds with maturities similar to those of the expected term of the award being valued.

Expected volatility. The expected volatility assumption is based on volatilities of a peer group of similar companies whose share prices are publicly available. The peer group was developed based on companies in the biotechnology industry.

Expected dividend yield. We base the expected dividend yield assumption on the fact that we have never paid cash dividends and have no present intention to pay cash dividends.

The allocation of stock-based compensation for all options, including performance options,with market condition is as follows (in thousands):

	Years Ended December 31,		
	2015	2014	2013
Research and development	$ 2,524	$ 527	$ 96
General and administrative	2,332	1,264	59
	$ 4,856	$ 1,791	$ 155

The weighted–average grant date fair value per share of stock options granted by us during the years ended December 31, 2015, 2014 and 2013 was $11.29 per share, $10.18 per share and $3.42 per share, respectively. The aggregate intrinsic value of stock options exercised during the years ended December 31, 2015, 2014 and 2013 was $1.9 million, $0.4 million and $47,000, respectively. As of December 31, 2015, total unrecognized share-based compensation expense related to unvested stock options was approximately $12.7 million. This unrecognized cost is expected to be recognized over a weighted-average period of approximately 2.9 years ratably on a straight-line basis.

During the fourth quarter of 2014, we modified certain vesting conditions of performance-based equity awards for our Chief Executive Officer which resulted in incremental share-based compensation costs of $0.7 million, of which $0.6 million was recognized as expense during the year ended December 31, 2014.

In October 2015, our Compensation Committee of the Board of Directors approved an amendment to accelerate the vesting schedule of certain outstanding stock options representing 931,749 shares granted to active employees and certain consultants under the 2014 Plan to change the vesting schedule of such options from six-years to four-years retroactive to the original vesting commencement dates. We recorded $0.8 million of stock compensation expense in connection with the modification during the year ended December 31, 2015.

In October 2015, we granted our employees and certain consultants performance options with a market condition to purchase up to an aggregate 169,402 shares of common stock at an exercise price of $10.24. Upon achievement of specified performance goals by October 2017, such performance-based options shall begin to vest over four years in equal monthly installments, otherwise the options will be subject to forfeiture. The fair value of the stock options awarded that include market-based performance conditions is estimated on the date of the grant using a Monte Carlo simulation, based on the market price of the underlying common stock, expected performance measurement period, expected peer group stock price volatility and expected risk-free interest rate. The weighted average grant date fair value was $4.23.The performance options with market conditions grants are expensed using the accelerated attribution method over the requisite service period of 5.0 years regardless of whether the market condition is achieved or earned and vest.

The assumptions used to determine the fair value of the performance options with market condition were as follows:

	Year Ended December 31, 2015
Expected term (in years)	4.8
Risk-free interest rate	2.05%
Expected volatility	80.6%
Expected dividend yield	0.0%

401(k) Plan

We maintain a defined contribution 401(k) plan available to eligible employees. Employee contributions are voluntary and are determined on an individual basis, limited to the maximum amount allowable under federal tax regulations. In April 2015, our Board of Directors approved a policy, beginning on June 1, 2015, to match employee contributions equal to 50% of the participant's contribution of up to a maximum of 6% of the participants's annual salary. We made discretionary contributions totaling $0.1 million during the year ended December 31, 2015.

Warrants

Warrants outstanding as of December 31, 2015:

Number Outstanding		Exercise Price Per Share	Expiration Date
9,051	$	6.63	September 2017
2,006	$	7.48	March 2021
14,913	$	20.12	July 2023
25,970			

Common Stock Reserved for Future Issuance

Common stock reserved for future issuance is as follows:

	As of December 31,	
	2015	2014
Conversion of redeemable convertible preferred stock	—	9,238,868
Conversion of redeemable convertible preferred stock issuable upon conversion of promissory note	—	94,455
Redeemable convertible preferred stock warrants	—	25,970
Common stock warrants	25,970	—
Common stock options outstanding	2,625,280	1,514,471
Shares available under the 2014 Plan	984,357	180,190
Shares available under the 2015 Plan	903,350	—
Shares available under the 2015 ESPP Plan	227,623	—
	4,766,580	11,053,954

7. Income Taxes

Pretax earnings (loss) were generated by both domestic and foreign operations as follows (in thousands):

	Years Ended December 31,		
	2015	2014	2013
United States	$ (47,490)	$ (34,885)	$ (11,085)
Foreign	(483)	10,535	(8,929)
	$ (47,973)	$ (24,350)	$ (20,014)

A reconciliation of the expected statutory federal income tax provision to the actual income tax provision is summarized as follows (in thousands):

	Years Ended December 31,		
	2015	2014	2013
Expected income taxes benefit at federal statutory rate	$ (16,311)	$ (8,279)	$ (6,804)
State income taxes, net of federal benefit	—	(2,023)	(634)
Permanent items and other	19	(321)	2
Stock-based compensation	734	396	—
Research credits	(2,674)	(372)	(397)
Unrecognized tax benefits	1,070	144	159
Foreign rate differential	84	(3,391)	2,978
Change in tax rate	3,551	—	—
Other, net	112	293	(26)
Change in valuation allowance	13,415	13,553	4,722
Income tax (benefit) expense	$ —	$ —	$ —

Deferred income taxes are provided for temporary differences in recognizing certain income and expense items for financial and tax reporting purposes. The deferred tax assets consisted primarily of the income tax benefits from net operating loss (NOL) carryforwards, research and development credits and capitalized research and development expenses, along with other accruals and reserves. Valuation allowances of $48.3 million, $34.8 million and $21.3 million as of December 31, 2015, 2014 and 2013, respectively, have been recorded to offset deferred tax assets as realization of such assets does not meet the more-likely-than-not threshold under ASC 740, *Accounting for Income Taxes*.

Significant components of our deferred tax assets are summarized as follows (in thousands):

	December 31,		
	2015	2014	2013
Net operating loss carryforwards	$ 24,869	$ 20,066	$ 13,093
Capitalized research and development expenses	14,181	7,855	6,684
Research credits and other state credits	3,565	1,368	1,171
Intangible assets	4,176	4,926	28
Depreciation and amortization	(120)	(260)	(360)
Reserve and accruals	1,648	891	677
Valuation allowance	(48,319)	(34,846)	(21,293)
Net deferred tax assets	$ —	$ —	$ —

The consolidated financial statements in the prior years included six variable interest entities which we referred to as the Affiliates. In the fourth quarter of 2014, we dissolved all of the Affiliates and, as a result, acquired intellectual property originally developed by the Affiliates. For book purposes, as this was a transaction between consolidated entities, no intangible asset was recognized. For tax purposes, the intellectual property will be amortized over 15 years resulting in an increase to deferred tax assets as of December 31, 2014. The increase in deferred tax assets was offset by a corresponding adjustment to the valuation allowance. As a result of the dissolution, we forgave intercompany loans and recorded a corresponding tax deduction; whereas the Affiliates recognized cancellation of debt income which was offset by net operating losses.

As of December 31, 2015, we had approximately $65.4 million, $48.9 million, and $5.8 million of net operating loss carryforwards for federal, state, and foreign purposes, respectively, net of Section 382 limitations, available to offset future taxable income. The federal and state net operating loss carryforwards begin to expire in 2025 and 2016, respectively. California net operating loss carryforwards of $0.2 million and $1.4 million will expire in 2016 and 2017, respectively. California net operating loss carryforwards of $47.3 million will expire from 2028 through 2034. The foreign net operating losses carry over indefinitely. As of December 31, 2015, we had federal and state research and development credit carryforwards of approximately $1.8 million and $1.9 million, respectively, net of Section 382 limitations, which begin to expire in 2026 for federal purposes and carry over indefinitely for state purposes. We had $2.9 million of federal Orphan Drug Credits as of December 31, 2015, which will begin to expire in 2035.

In November 2015, the FASB issued ASU No. 2015-17, "Balance Sheet Classification of Deferred Taxes," which requires all deferred tax assets and liabilities to be classified as noncurrent on the balance sheet. The new accounting guidance is effective for annual reporting periods beginning after December 15, 2016 and interim periods therein. Early adoption is permitted as of the beginning of interim or annual reporting periods. We elected to early adopt this guidance prospectively beginning in the year ended December 31, 2015 and prior periods were not retrospectively adjusted. There was no material impact on the financial statements upon adoption.

Utilization of the domestic NOL and research and development credit carryforwards may be subject to a substantial annual limitation due to ownership change limitations that may have occurred or that could occur in the future, as required by Section 382 and 383 of the Internal Revenue Code of 1986, as amended (the Code), as well as similar state and foreign provisions. These ownership changes may limit the amount of NOL and research and development credit carryforwards that can be utilized annually to offset future taxable income and tax, respectively. In general, an "ownership change" as defined by Section 382 of the Code results from a transaction or series of transactions over a three-year period resulting in an ownership change of more than 50 percentage points of the outstanding stock of a company by certain stockholders. Since the Company's formation, we raised capital through the issuance of capital stock on several occasions which on its own or combined with the purchasing stockholders' subsequent disposition of those shares, has resulted in such an ownership change, and could result in an ownership change in the future.

Upon the occurrence of an ownership change under Section 382 as outlined above, utilization of the NOL and research and development credit carryforwards become subject to an annual limitation under Section 382 of the Code, which is determined by first multiplying the value of our stock at the time of the ownership change by the applicable long-term, tax-exempt rate, which could be subject to additional adjustments. Any limitation may result in expiration of a portion of the NOL or research and development credit carryforwards before utilization. We completed an analysis through September 7, 2011, and had adjusted our NOL and research and development tax credit carryforwards accordingly. Ownership changes that may have occurred subsequent to September 7, 2011, and future ownership changes, including any ownership change resulting from this offering, may further limit our ability to utilize its remaining tax attributes.

We recognize a tax benefit from an uncertain tax position when it is more likely than not that the position will be sustained upon examination, including resolutions of any related appeals or litigation processes, based on the technical merits. Income tax positions must meet a more-likely-than-not recognition threshold to be recognized.

Our practice is to recognize interest and penalties related to income tax matters in income tax expense. We had no accrual for interest and penalties on our balance sheet and had not recognized interest or penalties in the consolidated statements of operations for the years ended December 31, 2015, 2014 and 2013.

Due to the existence of the valuation allowance, future changes in unrecognized tax benefits will not impact our effective tax rate.

Uncertain tax positions are evaluated based upon the facts and circumstances that exist at each reporting period. Subsequent changes in judgment based upon new information may lead to changes in recognition, derecognition, and measurement. Adjustments may result, for example, upon resolution of an issue with the taxing authorities, or expiration of a statute of limitations barring an assessment for an issue.

The activity related to our unrecognized tax benefits is summarized as follows (in thousands):

Balance as of December 31, 2012	$ 774
Increase related to prior year tax positions	79
Increase related to current year tax positions	94
Balance as of December 31, 2013	947
Increase related to prior year tax positions	—
Increase related to current year tax positions	177
Other decreases	(18)
Balance as of December 31, 2014	1,106
Increase related to prior year tax positions	2,404
Increase related to current year tax positions	1,523
Balance as of December 31, 2015	5,033

We do not anticipate that the amount of unrecognized tax benefits as of December 31, 2015 will change within the next twelve months.

We are subject to taxation in the United States, Hong Kong and state jurisdictions. Our tax years from inception are subject to examination by the United States, Hong Kong and California authorities due to the carry forward of unutilized NOLs and research and development credits.

8. Quarterly Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in our opinion, necessary for a fair statement of the results of the interim periods. Summarized quarterly data for 2015 and 2014 are as follows (in thousands, except per share data):

	For the quarters ended			
	March 31	June 30	September 30	December 31
2015:				
Operating expenses	$ 8,922	$ 10,898	$ 11,313	$ 16,483
Net loss	(9,071)	(11,080)	(11,329)	(16,493)
Basic and diluted net loss per share	$ (9.39)	$ (0.74)	$ (0.48)	(0.70)
2014:				
Operating expenses	$ 5,930	$ 5,363	$ 6,231	$ 6,030
Net loss	(6,093)	(5,588)	(6,631)	(6,038)
Basic and diluted net loss per share	$ (7.87)	$ (6.85)	$ (8.02)	$ (7.04)

Net loss per share is computed independently for each of the quarters presented. Therefore, the sum of the quarterly per-share calculations will not necessarily equal the annual per share calculation.

9. Subsequent Events

In January 2016, we granted to our executives, employees and certain consultants performance options with a market condition to purchase up to an aggregate 386,210 shares of common stock at an exercise price of $9.13. Upon achievement of specified goals by January 4, 2018, such performance options shall begin to vest over four years in equal monthly installments, otherwise the options will be subject to forfeiture. The grant date fair value of $1.93 was determined using a Monte Carlo simulation and will be expensed using the accelerated attribution method over the requisite service period of 5.0 years.

In addition, our Compensation Committee of the Board of Directors approved annual option grants to our executives, members of board of directors, employees and certain consultants to purchase an aggregate of 574,482 shares of common stock at an exercise price of $6.14. The weighted average grant date fair value of the options granted to our executives, members of board of directors and employees was $4.76.

Item 9. Changes in and Disagreements With Accountants on Accounting and Financial Disclosure

None

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

We maintain disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, that are designed to ensure that information required to be disclosed in our periodic and current reports that we file with the SEC is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our Principal Executive Officer and Principal Financial Officer, as appropriate, to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable and not absolute assurance of achieving the desired control objectives. In reaching a reasonable level of assurance, management necessarily is required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures. In addition, the design of any system of controls also is based in part upon certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions; over time, control may become inadequate because of changes in conditions, or the degree of compliance with policies or procedures may deteriorate. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

We carried out an evaluation, under the supervision and with the participation of our management, including our Principal Executive Officer and Principal Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act. Based on this evaluation, our Principal Executive Officer and Principal Financial Officer concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2015.

Management's Report on Internal Control Over Financial Reporting

This Annual Report on Form 10-K does not include a report of management's assessment regarding internal control over financial reporting or an attestation report of our independent registered public accounting firm due to the existence of a transition period, established by rules of the SEC, for newly public companies.

Changes in Internal Control Over Financial Reporting

During the quarter ended December 31, 2015, there have been no changes in our internal control over financial reporting, as such term is defined in Rules 13a-15(f) and 15(d)-15(f) promulgated under the Securities Exchange Act of 1934, that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

Except as set forth below, the information required by this item will be contained in our Proxy Statement to be filed with the SEC in connection with our 2016 Annual Meeting of Stockholders within 120 days after the end of the fiscal year ended December 31, 2015, or Proxy Statement and is incorporated herein by reference.

We have adopted a written code of ethics for directors, officers (including our principal executive officer, principal financial officer and principal accounting officer or persons performing similar functions) and employees, known as the Code of Business Conduct and Ethics. The Code of Business Conduct and Ethics is available on our website at *http://www.atyrpharma.com* under the Corporate Governance section of our Investor Relations page. If we make any substantive amendments to, or grant any waivers from, the Code of Business Conduct and Ethics for any officer or director, we will disclose the nature of such amendment or waiver on our website or in a Current Report on Form 8-K.

Item 11. Executive Compensation

The information required by this item will be contained in our Proxy Statement and is incorporated herein by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this item will be contained in our Proxy Statement and is incorporated herein by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this item will be contained in our Proxy Statement and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services

The information required by this item will be contained in our Proxy Statement and is incorporated herein by reference.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a) The following documents are filed as part of this report.

1. *Index list to Financial Statements*:

2. *Financial Statement Schedules.*

Schedules have been omitted as all required information has been disclosed in the financial statements and related footnotes.

3. *Exhibits.*

The Exhibits listed in the Exhibit Index are filed as a part of this Form 10-K.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this Annual Report on Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized.

aTyr Pharma, Inc.

Date: March 30, 2016

By /s/ John D. Mendlein
John D. Mendlein, Ph.D.
Chief Executive Officer
(Principal Executive Officer)

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints John D. Mendlein and John T. Blake, jointly and severally, and each of them, his or her true and lawful attorneys-in-fact, each with full power of substitution, for him or her in any and all capacities, to sign any amendments to this Annual Report on Form 10-K and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact or their substitute or substitutes may do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this Annual Report on Form 10-K has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ John D. Mendlein John D. Mendlein, Ph.D.	Chief Executive Officer and Executive Chairman, Board of Director (Principal Executive Officer)	March 30, 2016
/s/ John T. Blake John T. Blake	Vice President, Finance (Principal Financial and Accounting Officer)	March 30, 2016
/s/ John K. Clarke John K. Clarke	Chairman of the Board	March 30, 2016
/s/ Srinivas Akkaraju Srinivas Akkaraju, M.D., Ph.D.	Director	March 30, 2016
/s/ James C. Blair James C. Blair, Ph.D.	Director	March 30, 2016
/s/ Kathryn E. Falberg Kathryn E. Falberg	Director	March 30, 2016
/s/ Mark Goldberg Mark Goldberg, M.D.	Director	March 30, 2016
/s/ Amir H. Nashat Amir H. Nashat, Sc.D.	Director	March 30, 2016
/s/ Paul Schimmel Paul Schimmel, Ph.D.	Director	March 30, 2016

EXHIBIT INDEX

Exhibit Number	Exhibit Title	Incorporated by Reference			
		Form	File No.	Exhibit	Filing Date
3.1	Restated Certificate of Incorporation of the Registrant	S-1/A	333-203272	3.2	May 1, 2015
3.2	Amended and Restated Bylaws of the Registrant	S-1/A	333-203272	3.4	April 27, 2015
4.1	Specimen Common Stock Certificate	S-1/A	333-203272	4.1	April 27, 2015
4.2	Warrant to Purchase Stock issued to Comerica Bank on September 18, 2007	S-1	333-203272	4.2	April 6, 2015
4.3	Warrant to Purchase Stock issued to Comerica Bank on March 18, 2011	S-1	333-203272	4.3	April 6, 2015
4.4	Warrant to Purchase Stock issued to Silicon Valley Bank on July 24, 2013	S-1	333-203272	4.4	April 6, 2015
10.1#	2014 Stock Plan and forms of agreements thereunder	S-1/A	333-203272	10.1	April 27, 2015
10.2#	2015 Stock Option and Incentive Plan and forms of agreements thereunder	S-1/A	333-203272	10.2	April 27, 2015
10.3#	Amended and Restated Employment Agreement by and between the Registrant and John D. Mendlein, Ph.D., dated as of December 23, 2015	—	—	—	Filed herewith
10.4#	Amended and Restated Restricted Stock Purchase Agreement by and between the Registrant and John D. Mendlein, Ph.D., dated as of December 18, 2014	S-1	333-203272	10.6	April 6, 2015
10.5†	Amended and Restated Research Funding and Option Agreement by and between the Registrant and The Scripps Research Institute, dated January 19, 2015	S-1	333-203272	10.7	April 6, 2015
10.6	Master Services Agreement by and between the Registrant and Syngene International Limited, dated November 5, 2012	S-1	333-203272	10.8	April 6, 2015
10.7	Lease by and between the Registrant and BMR-John Hopkins Court LLC, dated December 22, 2011	S-1	333-203272	10.9	April 6, 2015
10.8	Loan and Security Agreement by and between the Registrant and Silicon Valley Bank, dated April 25, 2012, as amended by First Amendment to Loan and Security Agreement by and between the Registrant and Silicon Valley Bank, dated July 24, 2013	S-1	333-203272	10.10	April 6, 2015
10.9	Registration and Voting Rights Agreement by and among the Registrant and the stockholders named therein, dated March 31, 2015	S-1/A	333-203272	10.11	April 27, 2015
10.10	Form of Indemnification Agreement entered into between the Registrant and its directors	S-1/A	333-203272	10.12	April 27, 2015
10.11	Form of Indemnification Agreement entered into between the Registrant and its officers	S-1/A	333-203272	10.13	April 27, 2015
10.12#	2015 Employee Stock Purchase Plan	S-1/A	333-203272	10.14	April 27, 2015

Exhibit Number	Exhibit Title	Incorporated by Reference			
		Form	File No.	Exhibit	Filing Date
10.13†	Master Services Agreement by and between the Registrant and Fujifilm Diosynth Biotechnologies U.S.A., Inc., dated June 16, 2015	10-Q/A	001-37378	10.1	November 25, 2015
10.14#	Separation Agreement and Release made by and between the Registrant and David M. Weiner, M.D., dated September 10, 2015	10-Q	001-37378	10.1	November 10, 2015
10.15#	Senior Executive Cash Incentive Bonus Plan	8-K	001-37378	10.1	January 29, 2016
10.16#	Executive Severance and Change in Control Policy	—	—	—	Filed herewith
10.17#	Employment Offer Letter by and between the Registrant and Dr. Melissa Ashlock, dated April 28, 2011	—	—	—	Filed herewith
10.18#	Employment Offer Letter by and between the Registrant and Ms. Kelly Blackburn, dated April 22, 2013	—	—	—	Filed herewith
10.19#	Consulting Agreement by and between the Registrant and David M. Weiner, M.D., dated September 10, 2015	10-Q	001-37378	10.1 (Appendix A)	November 10, 2015
14.1	Code of Business Conduct and Ethics	10-Q	001-37378	14.1	June 18, 2015
21.1	Subsidiaries of the Registrant	S-1	333-203272	21.1	April 6, 2015
23.1	Consent of Independent Registered Public Accounting Firm	—	—	—	Filed herewith
24.1	Power of Attorney (included on signature page to this Annual Report)	—	—	—	Filed herewith
31.1	Certification of Principal Executive Officer required by Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.	—	—	—	Filed herewith
31.2	Certification of Principal Financial Officer required by Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.	—	—	—	Filed herewith
32.1	Certification of Principal Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.	—	—	—	Filed herewith
32.2	Certification of Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.	—	—	—	Filed herewith
101.INS	XBRL Instance Document	—	—	—	Filed herewith
101.SCH	XBRL Taxonomy Extension Schema Document	—	—	—	Filed herewith
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document	—	—	—	Filed herewith
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document	—	—	—	Filed herewith
101.LAB	XBRL Taxonomy Extension Label Linkbase Document	—	—	—	Filed herewith
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document	—	—	—	Filed herewith

# Indicates a management contract or compensatory plan, contract or arrangement.

† Application has been made to the Securities and Exchange Commission for confidential treatment of certain provisions. Omitted material for which confidential treatment has been requested has been filed separately with the Securities and Exchange Commission.

AMENDED AND RESTATED EMPLOYMENT AGREEMENT

This Amended and Restated Employment Agreement ("Agreement") is made as of the 23rd day of December, 2015 (the "Effective Date"), between aTyr Pharma, Inc., a Delaware corporation (the "Company"), and John D. Mendlein (the "Executive").

WHEREAS, the Executive and the Company previously entered into that certain Employment Agreement dated as of January 1, 2010 (the "Prior Agreement");

WHEREAS, the Executive and the Company desire to amend and restate the Prior Agreement on the terms and conditions set forth herein.

NOW, THEREFORE, in consideration of the mutual covenants and agreements herein contained and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, the parties agree as follows:

1. Employment.

(a) Term. The term of this Agreement shall commence as of the Effective Date and will continue until terminated in accordance with Section 3 (the "Term").

(b) Position and Duties. During the Term, the Executive shall serve as a member of the Board of Directors of the Company (the "Board") and Chief Executive Officer of the Company, and shall have supervision and control over and responsibility for the day-to-day business and affairs of the Company and shall have such other powers and duties as may from time to time be prescribed by the Board, provided that such duties are consistent with the Executive's position or other positions that he may hold from time to time. The Executive shall devote his full working time and efforts to the business and affairs of the Company. Notwithstanding the foregoing, the Executive may serve on other boards of directors, with the approval of the Board, or engage in religious, charitable or other community activities as long as such services and activities are disclosed to the Board and do not materially interfere with the Executive's performance of his duties to the Company as provided in this Agreement.

2. Compensation and Related Matters.

(a) Base Salary. During the Term, the Executive's initial annual base salary shall be $472,750. The Executive's base salary shall be subject to annual increases as determined annually by the Compensation Committee of the Board. The base salary in effect at any given time is referred to herein as "Base Salary." The Base Salary shall be payable in a manner that is consistent with the Company's usual payroll practices for senior executives.

(b) Incentive Compensation. During the Term, the Executive shall be eligible to receive cash incentive compensation as determined by the Compensation Committee of the Board from time to time. The Executive's target annual incentive compensation shall be 50 percent of his Base Salary. To earn incentive compensation, except as otherwise set forth herein, the Executive must be employed by the Company on the day such incentive compensation is

paid. Any such incentive compensation shall be paid no later than March 15 of the year following the year to which such compensation relates.

(c) Expenses. The Executive shall be entitled to receive prompt reimbursement for all reasonable expenses incurred by him during the Term in performing services hereunder, in accordance with the policies and procedures then in effect and established by the Company for its senior executive officers. The Company acknowledges that the foregoing reasonable expenses shall include business or first class airfare for all flights over 60 minutes.

The Company will also reimburse the Executive for all reasonable expenses (including attorney and tax advisor fees) incurred by him in connection with the negotiation and preparation of this Agreement, up to an aggregate maximum of $10,000.

(d) Other Benefits. During the Term, the Executive shall be eligible to participate in or receive benefits under the Company's employee benefit plans in effect from time to time, subject to the terms of such plans.

(e) Vacations. During the Term, the Executive shall be entitled to accrue vacation in accordance with the Company's vacation policy as in effect from time to time. The Executive shall also be entitled to all paid holidays given by the Company to its executives.

3. Termination. During the Term, the Executive's employment hereunder may be terminated without any breach of this Agreement under the following circumstances:

(a) Death. The Executive's employment hereunder shall terminate upon his death.

(b) Disability. The Company may terminate the Executive's employment if he is becomes Disabled. For purposes of this Agreement, Disabled means the inability of the Executive to perform his duties under this Agreement, whether with or without reasonable accommodation, because he has become permanently disabled within the meaning of any policy of disability income insurance covering employees of the Company then in force. If the Company has no policy of disability income insurance covering employees of the Company in force when he becomes disabled, the term "Disabled" shall mean disabled and unable to perform the essential functions of the Executive's then existing position or positions under this Agreement with or without reasonable accommodation for a period of 180 days (which need not be consecutive) in any 12-month period. If the Company has no policy of disability income insurance covering employees of the Company in force when he becomes disabled and any question shall arise as to whether during any period the Executive is disabled so as to be unable to perform the essential functions of the Executive's then existing position or positions with or without reasonable accommodation, the Executive may, and at the request of the Company shall, submit to the Company a certification in reasonable detail by a physician selected by the Company to whom the Executive or the Executive's guardian has no reasonable objection as to whether the Executive is so disabled or how long such disability is expected to continue, and such certification shall for the purposes of this Agreement be conclusive of the issue. The Executive shall cooperate with any reasonable request of the physician in connection with such

certification. If such question shall arise and the Executive shall fail to submit such certification, the Company's determination of such issue shall be binding on the Executive. Nothing in this Section 3(b) shall be construed to waive the Executive's rights, if any, under existing law including, without limitation, the Family and Medical Leave Act of 1993, 29 U.S.C. §2601 *et seq*. and the Americans with Disabilities Act, 42 U.S.C. §12101 *et seq*.

(c) Termination by Company for Cause. The Company may terminate the Executive's employment hereunder for Cause. For purposes of this Agreement, "Cause" shall mean: (i) conduct by the Executive constituting a material act of willful misconduct in connection with the performance of his duties (provided that if such misconduct is reasonably capable of cure, Executive has failed to cure the same within 30 days following written notice of such purported misconduct requesting its cure); (ii) Executive's conviction of, or the entry of a pleading of guilty or nolo contendere by Executive to, any crime involving (A) fraud or embezzlement in either case that results in material damage to the Company or any of its subsidiaries or affiliates or (B) any felony; (iii) willful and repeated failure by the Executive to substantially perform the duties, functions and responsibilities of the Executive's positions that result in material damage to the Company or any of its subsidiaries and affiliates, that continues after the Executive has received prior written notice from the Board of such purported repeated failure, which notice details the grounds of such purported repeated failure and requests its cure, and the Executive has been given a reasonable opportunity to cure which will not be less than 30 days; or (iv) a material breach by the Executive of any of the material provisions contained in this Agreement which has continued for more than 30 days following written notice of such purported breach, provided, however, that no such notice is required in the event of a material breach of Section 7 that is not reasonably capable of being cured as determined in good faith by a majority of the Board.

(d) Termination Without Cause. The Company may terminate the Executive's employment hereunder at any time without Cause. Any termination by the Company of the Executive's employment under this Agreement which does not constitute a termination for Cause under Section 3(c) and does not result from the death or Disability of the Executive under Section 3(a) or (b) shall be deemed a termination without Cause.

(e) Termination by the Executive. The Executive may terminate his employment hereunder at any time for any reason or for no reason, including but not limited to Good Reason. For purposes of this Agreement, "Good Reason" shall mean that the Executive has complied with the "Good Reason Process" (hereinafter defined) following the occurrence of any of the following events: (i) a material diminution in the Executive's responsibilities, authority or duties; (ii) a material diminution in the Executive's Base Salary except for across-the-board salary reductions based on the Company's financial performance similarly affecting all or substantially all senior management employees of the Company; (iii) relocation of the Company's executive headquarters to a location more than 50 miles from San Diego, California; or (iv) the material breach of this Agreement by the Company. "Good Reason Process" shall mean that (i) the Executive reasonably determines in good faith that a "Good Reason" condition has occurred; (ii) the Executive notifies the Company in writing of the first occurrence of the Good Reason condition within 60 days of the first occurrence of such condition; (iii) the Executive cooperates in good faith with the Company's efforts, for a period not less than 30 days following such notice (the "Cure Period"), to remedy the condition; (iv) notwithstanding such

efforts, the Good Reason condition continues to exist; and (v) the Executive terminates his employment within 60 days after the end of the Cure Period. If the Company cures the Good Reason condition during the Cure Period, Good Reason shall be deemed not to have occurred.

(f) Notice of Termination. Except for termination as specified in Section 3(a), any termination of the Executive's employment by the Company or any such termination by the Executive shall be communicated by written Notice of Termination to the other party hereto. For purposes of this Agreement, a "Notice of Termination" shall mean a notice which shall indicate the specific termination provision in this Agreement relied upon.

(g) Date of Termination. "Date of Termination" shall mean: (i) if the Executive's employment is terminated by his death, the date of his death; (ii) if the Executive's employment is terminated on account of Disability under Section 3(b) or by the Company for Cause under Section 3(c), the date on which Notice of Termination is given; (iii) if the Executive's employment is terminated by the Company under Section 3(d), the date on which a Notice of Termination is given; (iv) if the Executive's employment is terminated by the Executive under Section 3(e) without Good Reason, 30 days after the date on which a Notice of Termination is given, and (v) if the Executive's employment is terminated by the Executive under Section 3(e) with Good Reason, the date on which a Notice of Termination is given after the end of the Cure Period. Notwithstanding the foregoing, in the event that the Executive gives a Notice of Termination to the Company, the Company may unilaterally accelerate the Date of Termination and such acceleration shall not result in a termination by the Company for purposes of this Agreement.

4. Compensation Upon Termination.

(a) Termination Generally. If the Executive's employment with the Company is terminated for any reason, the Company shall pay or provide to the Executive (or to his authorized representative or estate) (i) any Base Salary earned through the Date of Termination, unpaid expense reimbursements (subject to, and in accordance with, Section 2(c) of this Agreement) and unused vacation that accrued through the Date of Termination on or before the time required by law but in no event more than 30 days after the Executive's Date of Termination; (ii) any vested benefits the Executive may have under any employee benefit plan of the Company through the Date of Termination, which vested benefits shall be paid and/or provided in accordance with the terms of such employee benefit plans and (iii) to the extent the Executive's employment with the Company terminates for any reason other than due to the termination of Executive's employment for Cause as provided in Section 3(c), any earned but unpaid incentive compensation from the prior calendar year pursuant to Section 2(b) (collectively, the "Accrued Benefit"). In addition, if the Executive's employment with the Company is terminated due to the Executive's death or Disability as provided in Sections 3(a) or (b), the Company shall pay the Executive or the Executive's estate (i) the pro-rata portion (based on days worked during the calendar year) of the Executive's target incentive compensation pursuant to Section 2(b) for the calendar year in which the Date of Termination occurs, payable within 30 days after the date of Termination and (ii) if the Executive was participating in the Company's group health plan immediately prior to the Date of Termination, a monthly cash payment for 6 months in an amount equal to the monthly employer contribution that the

Company would have made to provide health insurance to the Executive and his dependents if the Executive had remained employed by the Company.

(b) Termination by the Company Without Cause or by the Executive with Good Reason. During the Term, if the Executive's employment is terminated by the Company without Cause as provided in Section 3(d), or the Executive terminates his employment for Good Reason as provided in Section 3(e), then the Company shall pay the Executive his Accrued Benefit. In addition, subject to the Executive signing a separation agreement and general release of claims in the form attached as Exhibit A (the "Separation Agreement and Release"), and the Separation Agreement and Release becoming irrevocable, all within 60 days after the Date of Termination:

(i) the Company shall pay the Executive an amount equal to the sum of (A) the Executive's Base Salary plus (B) the Executive's target annual incentive compensation for the year of termination (together, the "Severance Amount"). Notwithstanding the foregoing, if the Executive breaches any of the provisions contained in Section 7 of this Agreement, all payments of the Severance Amount shall immediately cease; and

(ii) upon the Date of Termination, the time-based vesting provisions of all stock options and other stock-based awards held by the Executive in which the Executive would have vested if he had remained employed for an additional 12 months following the Date of Termination shall accelerate as of the Date of Termination; provided, however, that for avoidance of doubt, for any awards that include both a performance-based vesting condition (which would include the achievement of a certain stock price) and a time-based vesting condition, no acceleration shall be provided unless such performance-based vesting provision has been satisfied as of the Date of Termination; and

(iii) if the Executive was participating in the Company's group health plan immediately prior to the Date of Termination and elects COBRA health continuation, then the Company shall pay to the Executive a monthly cash payment for 12 months or the Executive's COBRA health continuation period, whichever ends earlier, in an amount equal to the amount that would reasonably be required by the Executive to obtain not less than the same health, dental, health, vision, disability and other insurance coverage for the Executive and his dependents as was in effect at the Date of Termination; and

(iv) the amounts payable under this Section 4(b) shall be paid out in substantially equal installments in accordance with the Company's payroll practice over 12 months commencing within 60 days after the Date of Termination; provided, however, that if the 60-day period begins in one calendar year and ends in a second calendar year, the Severance Amount shall begin to be paid in the second calendar year by the last day of such 60-day period; provided, further, that the initial payment shall include a catch-up payment to cover amounts retroactive to the day immediately following the Date of Termination. Each payment pursuant to this Agreement is intended to constitute a separate payment for purposes of Treasury Regulation Section 1.409A-2(b)(2).

5. Change in Control Payment. The provisions of this Section 5 set forth certain terms of an agreement reached between the Executive and the Company regarding the Executive's rights and obligations upon the occurrence of a Change in Control of the Company. These provisions are intended to assure and encourage in advance the Executive's continued attention and dedication to his assigned duties and his objectivity during the pendency and after the occurrence of any such event. These provisions shall apply in lieu of, and expressly supersede, the provisions of Section 4(b) regarding severance pay and benefits upon a termination of employment, if such termination of employment occurs within 2 months prior to and 12 months after the occurrence of the first event constituting a Change in Control. These provisions shall terminate and be of no further force or effect beginning 12 months after the occurrence of a Change in Control.

(a) Change in Control. During the Term, if within 2 months prior to and 12 months after a Change in Control, the Executive's employment is terminated by the Company without Cause as provided in Section 3(d) or the Executive terminates his employment for Good Reason as provided in Section 3(e), then, subject to the signing of the Separation Agreement and Release by the Executive and the Separation Agreement and Release becoming irrevocable, all within 60 days after the Date of Termination,

(i) the Company shall pay the Executive in cash an amount equal to the sum of (A) 1.5 times the Executive's then-current Base Salary (or the Executive's Base Salary in effect immediately prior to the Change in Control, if higher) plus (B) the Executive's annual target incentive compensation for the year of termination; and

(ii) notwithstanding anything to the contrary in any applicable option agreement or stock-based award agreement, all time-based vesting provisions of stock options and other stock-based awards held by the Executive shall immediately accelerate as of the Date of Termination; provided, however, that for avoidance of doubt, for any awards that include both a performance-based vesting condition (which would include the achievement of a certain stock price) and a time-based vesting condition, no acceleration shall be provided unless such performance-based vesting provision has been satisfied as of the Date of Termination; and provided further that in determining whether the achievement of a specified closing stock price as reported on the NASDAQ Stock Market has been satisfied, such price shall be deemed satisfied to the extent that the consideration payable per share of Common Stock of the Company in connection with such Change in Control, as determined in good faith by the Compensation Committee, equals or exceeds such stock price; and

(iii) if the Executive was participating in the Company's group health plan immediately prior to the Date of Termination and elects COBRA health continuation, then the Company shall pay to the Executive a monthly cash payment for 18 months or the Executive's COBRA health continuation period, whichever ends earlier, in an amount equal to the amount that would reasonably be required by the Executive to obtain not less than the same medical, dental, health, vision, disability and other insurance coverage for the Executive and his dependents as was in effect at the Date of Termination; and

(iv) The amounts payable under this Section 5(a) shall be paid out in substantially equal installments in accordance with the Company's payroll practice over 18 months commencing within 60 days after the Date of Termination; provided, however, that if the 60-day period begins in one calendar year and ends in a second calendar year, the Severance Amount shall begin to be paid in the second calendar year by the last day of such 60-day period; provided, further, that the initial payment shall include a catch-up payment to cover amounts retroactive to the day immediately following the Date of Termination. Each payment pursuant to this Agreement is intended to constitute a separate payment for purposes of Treasury Regulation Section 1.409A-2(b)(2).

(b) Additional Limitation.

(i) Anything in this Agreement to the contrary notwithstanding, in the event that the amount of any compensation, payment or distribution by the Company to or for the benefit of the Executive, whether paid or payable or distributed or distributable pursuant to the terms of this Agreement or otherwise, calculated in a manner consistent with Section 280G of the Code and the applicable regulations thereunder (the "Aggregate Payments"), would be subject to the excise tax imposed by Section 4999 of the Code, then the Aggregate Payments shall be reduced (but not below zero) so that the sum of all of the Aggregate Payments shall be $1.00 less than the amount at which the Executive becomes subject to the excise tax imposed by Section 4999 of the Code; provided that such reduction shall only occur if it would result in the Executive receiving a higher After Tax Amount (as defined below) than the Executive would receive if the Aggregate Payments were not subject to such reduction. In such event, the Aggregate Payments shall be reduced in the following order, in each case, in reverse chronological order beginning with the Aggregate Payments that are to be paid the furthest in time from consummation of the transaction that is subject to Section 280G of the Code: (1) cash payments not subject to Section 409A of the Code; (2) cash payments subject to Section 409A of the Code; (3) equity-based payments and acceleration; and (4) non-cash forms of benefits; provided that in the case of all the foregoing Aggregate Payments all amounts or payments that are not subject to calculation under Treas. Reg. §1.280G-1, Q&A-24(b) or (c) shall be reduced before any amounts that are subject to calculation under Treas. Reg. §1.280G-1, Q&A-24(b) or (c).

(ii) For purposes of this Section 5(b), the "After Tax Amount" means the amount of the Aggregate Payments less all federal, state, and local income, excise and employment taxes imposed on the Executive as a result of the Executive's receipt of the Aggregate Payments. For purposes of determining the After Tax Amount, the Executive shall be deemed to pay federal income taxes at the highest marginal rate of federal income taxation applicable to individuals for the calendar year in which the determination is to be made, and state and local income taxes at the highest marginal rates of individual taxation in each applicable state and locality, net of the maximum reduction in federal income taxes which could be obtained from deduction of such state and local taxes.

(iii) The determination as to whether a reduction in the Aggregate Payments shall be made pursuant to Section 5(b)(i) shall be made by a nationally recognized accounting firm selected by the Company (the "Accounting Firm"), which

shall provide detailed supporting calculations both to the Company and the Executive within 15 business days of the Date of Termination, if applicable, or at such earlier time as is reasonably requested by the Company or the Executive. Any determination by the Accounting Firm shall be binding upon the Company and the Executive.

(c) Definitions. For purposes of this Section 5, the following terms shall have the following meanings:

"Change in Control" shall mean any of the following:

(i) any "person," as such term is used in Sections 13(d) and 14(d) of the Securities Exchange Act of 1934, as amended (the "Act") (other than the Company, any of its subsidiaries, or any trustee, fiduciary or other person or entity holding securities under any employee benefit plan or trust of the Company or any of its subsidiaries), together with all "affiliates" and "associates" (as such terms are defined in Rule 12b-2 under the Act) of such person, shall become the "beneficial owner" (as such term is defined in Rule 13d-3 under the Act), directly or indirectly, of securities of the Company representing 50percent or more of the combined voting power of the Company's then outstanding securities having the right to vote in an election of the Board ("Voting Securities") (in such case other than as a result of an acquisition of securities directly from the Company); or

(ii) the date a majority of the members of the Board is replaced during any 12-month period by directors whose appointment or election is not endorsed by a majority of the members of the Board before the date of the appointment or election; or

(iii) the consummation of (A) any consolidation or merger of the Company or any subsidiary of the Company where the stockholders of the Company, immediately prior to the consolidation or merger, would not, immediately after the consolidation or merger, beneficially own (as such term is defined in Rule 13d-3 under the Act), directly or indirectly, shares representing in the aggregate more than 50 percent of the voting shares of the Company issuing cash or securities in the consolidation or merger (or of its ultimate parent corporation, if any), or (B) any sale or other transfer (in one transaction or a series of transactions contemplated or arranged by any party as a single plan) of all or substantially all of the assets of the Company; provided, however, that with respect to clause (A) above and as approved by the Board, a Change of Control shall be deemed to have occurred upon the consummation of a transaction whereby shares representing in the aggregate of more than 30 percent but less than 50 percent of the voting shares of the Company are beneficially owned by the acquiring party or parties and such transaction includes a contingent right for the acquiring party or parties to acquire additional voting shares of the Company that would represent more than 50% of the Company's voting shares in the aggregate.

In no event shall the Executive be required to mitigate the amount of any payment provided for in this Agreement by seeking other employment or otherwise, nor will the amount of any payment provided for herein be reduced by any compensation earned by the Executive as

a result of employment by another employer or by retirement benefits after the date of termination of the executive's employment.

Notwithstanding the foregoing, a "Change in Control" shall not be deemed to have occurred for purposes of the foregoing clause (i) solely as the result of an acquisition of securities by the Company which, by reducing the number of shares of Voting Securities outstanding, increases the proportionate number of Voting Securities beneficially owned by any person to 50 percent or more of the combined voting power of all of the then outstanding Voting Securities; provided, however, that if any person referred to in this sentence shall thereafter become the beneficial owner of any additional shares of Voting Securities (other than pursuant to a stock split, stock dividend, or similar transaction or as a result of an acquisition of securities directly from the Company) and immediately thereafter beneficially owns 50 percent or more of the combined voting power of all of the then outstanding Voting Securities, then a "Change in Control" shall be deemed to have occurred for purposes of the foregoing clause (i).

6. Section 409A.

(a) Anything in this Agreement to the contrary notwithstanding, if at the time of the Executive's separation from service within the meaning of Section 409A of the Code, the Company determines that the Executive is a "specified employee" within the meaning of Section 409A(a)(2)(B)(i) of the Code, then to the extent any payment or benefit that the Executive becomes entitled to under this Agreement on account of the Executive's separation from service would be considered deferred compensation otherwise subject to the 20 percent additional tax imposed pursuant to Section 409A(a) of the Code as a result of the application of Section 409A(a)(2)(B)(i) of the Code, such payment shall not be payable and such benefit shall not be provided until the date that is the earlier of (A) six months and one day after the Executive's separation from service, or (B) the Executive's death. If any such delayed cash payment is otherwise payable on an installment basis, the first payment shall include a catch-up payment covering amounts that would otherwise have been paid during the six-month period but for the application of this provision, and the balance of the installments shall be payable in accordance with their original schedule.

(b) All in-kind benefits provided and expenses eligible for reimbursement under this Agreement shall be provided by the Company or incurred by the Executive during the time periods set forth in this Agreement. All reimbursements shall be paid as soon as administratively practicable, but in no event shall any reimbursement be paid after the last day of the taxable year following the taxable year in which the expense was incurred. The amount of in-kind benefits provided or reimbursable expenses incurred in one taxable year shall not affect the in-kind benefits to be provided or the expenses eligible for reimbursement in any other taxable year (except for any lifetime or other aggregate limitation applicable to medical expenses). Such right to reimbursement or in-kind benefits is not subject to liquidation or exchange for another benefit.

(c) To the extent that any payment or benefit described in this Agreement constitutes "non-qualified deferred compensation" under Section 409A of the Code, and to the extent that such payment or benefit is payable upon the Executive's termination of employment, then such payments or benefits shall be payable only upon the Executive's "separation from

service." The determination of whether and when a separation from service has occurred shall be made in accordance with the presumptions set forth in Treasury Regulation Section 1.409A-1(h).

(d) The parties intend that this Agreement will be administered in accordance with Section 409A of the Code. To the extent that any provision of this Agreement is ambiguous as to its compliance with Section 409A of the Code, the provision shall be read in such a manner so that all payments hereunder comply with Section 409A of the Code. Each payment pursuant to this Agreement is intended to constitute a separate payment for purposes of Treasury Regulation Section 1.409A-2(b)(2). The parties agree that this Agreement may be amended, as reasonably requested by either party, and as may be necessary to fully comply with Section 409A of the Code and all related rules and regulations in order to preserve the payments and benefits provided hereunder without additional cost to either party.

(e) The Company makes no representation or warranty and shall have no liability to the Executive or any other person if any provisions of this Agreement are determined to constitute deferred compensation subject to Section 409A of the Code but do not satisfy an exemption from, or the conditions of, such Section.

7. Confidential Information and Noncompetition. The Executive hereby acknowledges and agrees that he shall remain subject to and comply with the provisions of Section 7 of the Prior Agreement, which provisions are hereby incorporated by reference into this Agreement.

8. Arbitration of Disputes. Any controversy or claim arising out of or relating to this Agreement or the breach thereof or otherwise arising out of the Executive's employment or the termination of that employment (including, without limitation, any claims of unlawful employment discrimination whether based on age or otherwise) shall, to the fullest extent permitted by law, be settled by arbitration in any forum and form agreed upon by the parties or, in the absence of such an agreement, under the auspices of the American Arbitration Association ("AAA") in San Diego, California in accordance with the Employment Dispute Resolution Rules of the AAA, including, but not limited to, the rules and procedures applicable to the selection of arbitrators. In the event that any person or entity other than the Executive or the Company may be a party with regard to any such controversy or claim, such controversy or claim shall be submitted to arbitration subject to such other person or entity's agreement. Judgment upon the award rendered by the arbitrator may be entered in any court having jurisdiction thereof. This Section 8 shall be specifically enforceable. Notwithstanding the foregoing, this Section 8 shall not preclude either party from pursuing a court action for the sole purpose of obtaining a temporary restraining order or a preliminary injunction in circumstances in which such relief is appropriate; provided that any other relief shall be pursued through an arbitration proceeding pursuant to this Section 8.

9. Consent to Jurisdiction. To the extent that any court action is permitted consistent with or to enforce Section 8 of this Agreement, the parties hereby consent to the jurisdiction of the state courts of the State of California and the United States District Court for the Northern District of California. Accordingly, with respect to any such court action, the Executive (a) submits to the personal jurisdiction of such courts; (b) consents to service of process; and (c)

waives any other requirement (whether imposed by statute, rule of court, or otherwise) with respect to personal jurisdiction or service of process.

10. Integration. This Agreement constitutes the entire agreement between the parties with respect to the subject matter hereof and supersedes all prior agreements between the parties concerning such subject matter, including the Prior Agreement, except that Section 7 of the Prior Agreement is incorporated by reference into Section 7 of this Agreement and will remain in full force and effect.

11. Withholding. All payments made by the Company to the Executive under this Agreement shall be net of any tax or other amounts required to be withheld by the Company under applicable law.

12. Successor to the Executive. This Agreement shall inure to the benefit of and be enforceable by the Executive's personal representatives, executors, administrators, heirs, distributees, devisees and legatees. In the event of the Executive's death after his termination of employment but prior to the completion by the Company of all payments due him under this Agreement, the Company shall continue such payments to the Executive's beneficiary designated in writing to the Company prior to his death (or to his estate, if the Executive fails to make such designation).

13. Enforceability. If any portion or provision of this Agreement (including, without limitation, any portion or provision of any section of this Agreement) shall to any extent be declared illegal or unenforceable by a court of competent jurisdiction, then the remainder of this Agreement, or the application of such portion or provision in circumstances other than those as to which it is so declared illegal or unenforceable, shall not be affected thereby, and each portion and provision of this Agreement shall be valid and enforceable to the fullest extent permitted by law.

14. Survival. The provisions of this Agreement shall survive the termination of this Agreement and/or the termination of the Executive's employment to the extent necessary to effectuate the terms contained herein.

15. Waiver. No waiver of any provision hereof shall be effective unless made in writing and signed by the waiving party. The failure of any party to require the performance of any term or obligation of this Agreement, or the waiver by any party of any breach of this Agreement, shall not prevent any subsequent enforcement of such term or obligation or be deemed a waiver of any subsequent breach.

16. Notices. Any notices, requests, demands and other communications provided for by this Agreement shall be sufficient if in writing and delivered in person or sent by a nationally recognized overnight courier service or by registered or certified mail, postage prepaid, return receipt requested, to the Executive at the last address the Executive has filed in writing with the Company or, in the case of the Company, at its main offices, attention of the Board.

17. Amendment. This Agreement may be amended or modified only by a written instrument signed by the Executive and by a duly authorized representative of the Company.

18. Governing Law. This is a California contract and shall be construed under and be governed in all respects by the laws of the State of California, without giving effect to the conflict of laws principles of such State. With respect to any disputes concerning federal law, such disputes shall be determined in accordance with the law as it would be interpreted and applied by the United States Court of Appeals for the Sixth Circuit.

19. Counterparts. This Agreement may be executed in any number of counterparts, each of which when so executed and delivered shall be taken to be an original; but such counterparts shall together constitute one and the same document.

20. Successor to Company. The Company shall require any successor (whether direct or indirect, by purchase, merger, consolidation or otherwise) to all or substantially all of the business or assets of the Company expressly to assume and agree to perform this Agreement to the same extent that the Company would be required to perform it if no succession had taken place. Failure of the Company to obtain an assumption of this Agreement at or prior to the effectiveness of any succession shall be a material breach of this Agreement.

21. Gender Neutral. Wherever used herein, a pronoun in the masculine gender shall be considered as including the feminine gender unless the context clearly indicates otherwise.

IN WITNESS WHEREOF, the parties have executed this Agreement effective on the date and year first above written.

ATYR PHARMA, INC.

By: /s/ Nancy D. Krueger
Its: Nancy D. Krueger
V.P. Legal Affairs & Secretary

EXECUTIVE

/s/ John D. Mendlein
John D. Mendlein

EXHIBIT A

RELEASE

I enter into this Separation Agreement and Release (the "Release") pursuant to Section 4(b) or 5(a), as applicable, of the Amended and Restated Employment Agreement between aTyr Pharma, Inc., a Delaware corporation (the "Employer") and me dated December ___, 2015 (the "Employment Agreement"). I acknowledge that my timely execution and return and my non-revocation of this Release are conditions to the payments and benefits pursuant to Section 4(b) or 5(a), as applicable, of the Employment Agreement. I therefore agree to the following terms:

1. Release of Claims. I voluntarily release and forever discharge the Employer, its affiliated and related entities, its and their respective predecessors, successors and assigns, its and their respective employee benefit plans and fiduciaries of such plans, and the current and former officers, directors, shareholders, members, employees, attorneys, accountants and agents of each of the foregoing in their official and personal capacities (collectively referred to as the "Releasees") generally from all claims, demands, debts, damages and liabilities of every name and nature, known or unknown ("Claims") that, as of the date when I sign this Release, I have, ever had, now claim to have or ever claimed to have had against any or all of the Releasees. This release includes, without limitation, all Claims:

- relating to my employment by the Employer and/or any affiliate of the Employer and the termination of my employment;
- of wrongful discharge;
- of breach of contract;
- of retaliation or discrimination under federal, state or local law (including, without limitation, Claims of age discrimination or retaliation under the Age Discrimination in Employment Act, Claims of disability discrimination or retaliation under the Americans with Disabilities Act, Claims of discrimination or retaliation under Title VII of the Civil Rights Act of 1964, Claims of any form of discrimination or retaliation that is prohibited by the California Fair Employment and Housing Act;
- under any other federal or state statute;
- of defamation or other torts;
- of violation of public policy;
- for wages, bonuses, incentive compensation, stock, stock options, vacation pay or any other compensation or benefits (except for such wages, bonuses, incentive compensation, stock, stock options, vacation pay or other compensation or benefits otherwise due to me under the Employment Agreement); and
- for damages or other remedies of any sort, including, without limitation, compensatory damages, punitive damages, injunctive relief and attorney's fees;

I agree that the release set forth in this section shall be and remain in effect in all respects as a complete general release as to the matters released. This release does not extend to any obligations incurred under this Employment Agreement, under any ongoing Company benefit plans or for indemnification under any indemnification agreement, the Company's Bylaws or applicable law. This release does not release claims that cannot be released as a matter of law,

including, but not limited to, my right to file a charge with or participate in a charge by the Equal Employment Opportunity Commission, or any other local, state, or federal administrative body or government agency that is authorized to enforce or administer laws related to employment, against the Company (with the understanding that any such filing or participation does not give me the right to recover any monetary damages against the Company; my release of claims herein bars me from recovering such monetary relief from the Company).

I agree that I shall not seek or accept damages of any nature, other equitable or legal remedies for my own benefit, attorney's fees, or costs from any of the Releasees with respect to any Claim released by this Agreement. I represent that I have not assigned to any third party and I have not filed with any agency or court any Claim released by this Agreement.

2. Ongoing Obligations. I reaffirm my ongoing obligations under the Employment Agreement, including without limitation my obligations under Section 7 ("Confidential Information and Noncompetition") and under Section 7 of the Prior Agreement (as defined in the Employment Agreement).

3. No Assignment. I represent that I have not assigned to any other person or entity any Claims against any Releasee.

4. Right to Consider and Revoke Release. I acknowledge that I have been given the opportunity to consider this Release for a period of twenty-one (21) days from the date when it is tendered to me. In the event that I executed this Release within less than twenty-one (21) days, I acknowledge that such decision was entirely voluntary and that I had the opportunity to consider this Release until the end of the twenty-one (21) day period. To accept this Release, I shall deliver a signed Release to the Employer's Vice President of Operations within such twenty-one (21) day period; *provided* that I acknowledge that the Employer may change the designated recipient by notice. For a period of seven (7) days from the date when I execute this Release (the "Revocation Period"), I shall retain the right to revoke this Release by written notice that is received by the Employer's Vice President of Operations or other Employer-designated recipient on or before the last day of the Revocation Period. This Release shall take effect only if it is executed within the twenty-one (21) day period as set forth above and if it is not revoked pursuant to the preceding sentence. If those conditions are satisfied, this Release shall become effective and enforceable on the date immediately following the last day of the Revocation Period (the "Effective Date").

5. California Civil Code Section 1542. I acknowledge that I have been advised to consult with legal counsel and am familiar with the provisions of California Civil Code Section 1542, a statute that otherwise prohibits the release of unknown claims, which provides as follows:

> A GENERAL RELEASE DOES NOT EXTEND TO CLAIMS WHICH THE CREDITOR DOES NOT KNOW OR SUSPECT TO EXIST IN HIS OR HER FAVOR AT THE TIME OF EXECUTING THE RELEASE, WHICH IF KNOWN BY HIM OR HER MUST HAVE MATERIALLY AFFECTED HIS OR HER SETTLEMENT WITH THE DEBTOR.

I, being aware of said code section, agree to expressly waive any rights I may have thereunder, as well as under any other statute or common law principles of similar effect.

6. Other Terms.

(a) Legal Representation; Review of Release. I acknowledge that I have been advised to discuss all aspects of this Release with my attorney, that I have carefully read and fully understand all of the provisions of this Release and that I am voluntarily entering into this Release.

(b) Binding Nature of Release. This Release shall be binding upon me and upon my heirs, administrators, representatives and executors.

(c) Amendment. This Release may be amended only upon a written agreement executed by the Employer and me.

(d) Severability. In the event that at any future time it is determined by an arbitrator or court of competent jurisdiction that any covenant, clause, provision or term of this Release is illegal, invalid or unenforceable, the remaining provisions and terms of this Release shall not be affected thereby and the illegal, invalid or unenforceable term or provision shall be severed from the remainder of this Release. In the event of such severance, the remaining covenants shall be binding and enforceable.

(e) Governing Law and Interpretation. This Release shall be deemed to be made and entered into in the State of California, and shall in all respects be interpreted, enforced and governed under the laws of the State of California, without giving effect to the conflict of laws principles of such State. The language of all parts of this Release shall in all cases be construed as a whole, according to its fair meaning, and not strictly for or against either the Employer or me.

(f) Entire Agreement; Absence of Reliance. I acknowledge that I am not relying on any promises or representations by the Employer or any of its agents, representatives or attorneys regarding any subject matter addressed in this Release.

So agreed.

_____ _____

John D. Mendlein Date

ATYR PHARMA, INC.
EXECUTIVE SEVERANCE AND CHANGE IN CONTROL POLICY

ADOPTED ON DECEMBER 21, 2015

The purpose of this Executive Severance and Change in Control Policy (the "Policy") of aTyr Pharma, Inc. (the "Company") is to provide certain senior management employees of the Company with certain compensation and benefits in the event of a termination of employment without Cause (as defined below) or for Good Reason (as defined below), under the terms and conditions described in this Policy.

1. Termination Not in Connection with a Sale Event

If the employment of an Eligible Employee (as defined below) is terminated by the Company without Cause (as defined below) or the Eligible Employee resigns for Good Reason (as defined below), then subject to such Eligible Employee's execution and non-revocation of a severance agreement within 60 days following the date of such termination, including a general release of claims acceptable to the Company, such Eligible Employee shall be entitled to receive the following benefits:

- Acceleration of the time-based vesting provisions of outstanding stock options and other equity awards in which the employee would have vested if he or she had remained employed for an additional 12 months following the date of termination; provided, however, that for avoidance of doubt, for any equity award that includes both a performance-based vesting condition (which would include the achievement of a certain stock price) and a time-based vesting provision, no acceleration shall be provided unless such performance-based vesting condition has been satisfied as of the date of termination; and

- Payment of (a) severance in a lump sum in the amounts set forth below and (b) if the employee was participating in the Company's group health plan immediately prior to the date of termination of his or her employment and elects COBRA health continuation, payment of a monthly cash payment for the period set forth below or the employee's COBRA health continuation period, whichever ends earlier, in an amount equal to the monthly employer contribution that the Company would have made to provide health insurance to the employee if the employee had remained employed by the Company:

Severance (Amount of Base Salary)	**Benefits Continuation**
12 months	12 months

2. Termination in Connection with a Sale Event

If the employment of an Eligible Employee is terminated by the Company (or its successor) without Cause or such Eligible Employee resigns for Good Reason, in either case within two months prior to or one year after the closing of a Sale Event (as defined in the Company's 2015

Stock Option and Incentive Plan, as may be amended from time to time), then subject to such Eligible Employee's execution and non-revocation of a severance agreement within 60 days following the date of such termination, including a general release of claims acceptable to the Company or its successor or acquirer, such Eligible Employee shall be entitled to receive the following benefits:

- Full acceleration of the time-based vesting provisions of outstanding stock options and other equity awards; provided, however, that for avoidance of doubt, for any equity award that includes both a performance-based vesting condition (which would include the achievement of a certain stock price) and a time-based vesting provision, no acceleration shall be provided unless such performance-based vesting condition has been satisfied as of the date of termination; and

- Payment of (a) severance in a lump sum in the amounts set forth below, (b) target bonus in the amounts set forth below and (c) if the employee was participating in the Company's group health plan immediately prior to the date of termination of his or her employment and elects COBRA health continuation, payment of a monthly cash payment for the period set forth below or the employee's COBRA health continuation period, whichever ends earlier, in an amount equal to the monthly employer contribution that the Company would have made to provide health insurance to the employee if the employee had remained employed by the Company:

Severance (Base Salary)	Bonus	Benefits Continuation
12 months	1x bonus target	12 months

For the avoidance of doubt, if an employee is eligible to receive benefits pursuant to this Section 2, the employee shall not be eligible to receive any benefits pursuant to Section 1 of this Policy.

3. Definitions.

(a) "Cause" shall mean (i) the employee's dishonest statements or acts with respect to the Company or any affiliate of the Company, or any current or prospective customers, suppliers, vendors or other third parties with which such entity does business; (ii) the employee's commission of (A) a felony or (B) any misdemeanor involving moral turpitude, deceit, dishonesty or fraud; (iii) the employee's failure to perform his or her assigned duties and responsibilities to the reasonable satisfaction of the Company which failure continues, in the reasonable judgment of the Company, after written notice given to the employee by the Company; (iv) the employee's gross negligence, willful misconduct or insubordination with respect to the Company or any affiliate of the Company; or (v) the employee's material violation of any provision of any agreement(s) between the employee and the Company relating to noncompetition, nonsolicitation, nondisclosure and/or assignment of inventions.

(b) "Committee" shall mean the Compensation Committee of the Board of Directors of the Company.

(c) "Eligible Employees" shall mean the senior management employees of the Company designated by the Committee from time to time as eligible to receive benefits under this Policy. Eligible Employees at the time of adoption of this Policy include the members of the Company's Executive Leadership Team (other than the Company's Chief Executive Officer, who shall receive severance benefits pursuant to his employment agreement with the Company and not this Policy): Melissa A. Ashlock, M.D., John C. McKew, Ph.D., Kelly Blackburn, Andrew Cubitt, Ph.D., Holly D. Chrzanowski, Marcy Graham, John Blake, Nancy Krueger and Ashraf Amanullah, Ph.D. and, effective as of January 4, 2016, Sanuj Ravindran. Any additional executive officers who become members of the Company's Executive Leadership Team, who qualify as "named executive officers" for purposes of the Company's filings with the U.S. Securities and Exchange Commission under the Securities Exchange Act of 1934, as amended, or who otherwise report directly to the Chief Executive Officer shall be deemed to be Eligible Employees for purposes of this Policy.

(d) "Good Reason" shall mean (i) a material diminution in the employee's responsibilities, authority or duties; (ii) a material diminution in the employee's base compensation except for across-the-board compensation reductions similarly affecting all or substantially all similarly situated service providers of the Company; or (iii) a change of more than fifty (50) miles in the geographic location at which the employee provides services to the Company, in each case so long as the employee provides at least ninety (90) days' notice to the Company following the initial occurrence of any such event, the Company fails to cure such event within thirty (30) days thereafter and the employee terminates his or her employment within thirty (30) days after the end of such cure period.

4. General Terms and Conditions.

(a) The amounts payable pursuant to this Policy shall be paid or commence to be paid within 60 days following the date of termination of employment, provided that if the 60-day period begins in one calendar year and ends in a second calendar year, such payments shall be paid or commence to be paid in the second calendar year by the last day of such 60-day period.

(b) In addition, upon the consummation of a Sale Event, to the extent Section 280G of the Internal Revenue Code is applicable to such employee, each employee shall be entitled to receive either: (a) payment of the full amounts set forth above to which the employee is entitled or (b) payment of such lesser amount that does not trigger excise taxes under Section 280G, whichever results in the employee receiving a higher amount after taking into account all federal, state, and local income, excise and employment taxes.

(c) This Policy shall be administered by the Committee, and the Committee shall have the power and authority to interpret the terms and provisions of this Policy, to make all determinations it deems advisable for the administration of this Policy, to decide all disputes arising in connection with this Policy and to otherwise supervise

administration of this Policy. The Committee retains the right to amend, revise, change or end this Policy at any point in the future; provided that the Committee may not amend or end the Policy during the period commencing on the date that it enters into a definitive agreement that if consummated, would result in a Sale Event and ending on the earlier of (i) 12 months after a Sale Event and (ii) the termination of the definitive agreement without the consummation of a Sale Event. This Policy does not change the "at-will" employment status of any employee.

(d) In the event an Eligible Employee of the Company is party to an agreement or other arrangement with the Company that provides greater benefits in the aggregate than set forth in this Policy, such Eligible Employee shall be entitled to receive the payments or benefits under such other agreement or arrangement and shall not be eligible to receive any payments or benefits under this Policy.

aTyr Pharma
Advancing medicine. Improving lives.

Exhibit 10.17

April 28, 2011

Melissa Ashlock, M.D.

Dear Melissa:

This letter is a formal offer setting forth the principal terms for you to join aTyr Pharma, Inc. (the "Company"), a Delaware corporation, which is located in San Diego, California.

Position: Vice President, External Scientific Affairs & Human Genetics
Your primary directives and responsibilities are outlined in Attachment "A".

Status: Full-Time, Exempt. This means you are paid for the job and not by the hour. Accordingly, you will not receive overtime pay if you work more than 8 hours in a work day or 40 hours in a workweek.

Reporting to: John D. Mendlein, Ph.D., Executive Chairman

Base Salary Rate: $9,292.00 per pay period (which equals $223,000.00 per year) less applicable withholdings, paid in accordance with Company's normal payroll practices. Future adjustments in compensation, if any, will be made by the Company in its sole and absolute discretion.

Bonus: In addition to your annual salary, you will be eligible to earn an annual performance bonus of up to 20% of your base salary. This will be paid based upon corporate achievement of goals and achievement of your individual goals. The corporate goals are established by the Company and approved by the Board of Directors. Your goals shall be mutually agreed to by you and the Company. The achievement of corporate goals and your individuals goals shall be determined by the Board of Directors (or the compensation committee thereof) in its sole discretion. This bonus will be paid on an annual basis and will be prorated during your first year of employment.

Equity: Shortly after commencement of your employment with the Company, and subject to approval by the board of directors, you will be granted an Option to purchase 322,055 shares of the Common Stock of the Company

pursuant to the 2007 Stock Plan. The exercise price per share of the Option shall be the fair market value of the Common Stock, as determined by the board of directors at the time of the Option grant.

The specific terms and conditions of your Option will be subject to the terms of then 2007 Stock Plan, as well as the terms set forth in a Stock Option Agreement between you and the Company. This Stock Option Agreement will be entered into and executed after you commence your employment with the Company.

Benefits: You will be entitled to receive standard medical, life and dental insurance benefits for yourself and your dependents in accordance with Company policy. Company reserves the right to change or eliminate these benefits on a prospective basis at any time.

401(k) Plan: You will be eligible to participate in the aTyr Pharma, Inc. 401(k) Savings Plan immediately following the start of your employment.

Vacation & Sick Time: You will be entitled to accrue 15 days of vacation per year. You will have 6 days of sick time available each year.

Holidays: You will be eligible for aTyr's paid holidays. The schedule is published prior to the beginning of each calendar year.

Employment at Will: Your employment will be at will, which means it may be terminated at any time by you or the Company with or without cause and that your employment is not for any specific period of time. Any change to the at-will employment relationship must be by a specific, written agreement signed by you and the Company's Chief Executive Officer.

Start Date: May 9, 2011 or a mutually agreed upon date.

As a condition of your employment, you will be required to sign and abide by our Employee Nondisclosure and Assignment Agreement when you begin your employment. A copy is attached for your reference. In addition, in order to comply with the Immigration Reform and Control Act of 1986, within three (3) days of your Start Date you will be required to provide

sufficient documentation to verify your identity and legal authorization to work in the United States. Please bring with you on your Start Date, the original of one of the documents noted in List A or one document from List B and one document from List C as itemized in the enclosed "Lists of Acceptable Documents". If you do not have the originals of any of these documents, please contact me immediately.

In the event of any dispute or claim relating to or arising out of your employment relationship with the Company, this agreement, or the termination of your employment with the Company for any reason (including, but not limited to, any claims of breach of contract, defamation, wrongful termination or age, sex, sexual orientation, race, color, national origin, ancestry, marital status, religious creed, physical or mental disability or medical condition or other discrimination, retaliation or harassment), you and the Company agree that all such disputes shall be fully resolved by confidential, binding arbitration conducted by a single arbitrator through the American Arbitration Association ("AAA") under the AAA's National Rules for the Resolution of Employment Disputes then in effect, which are available online at the AAA's website at www.adr.org. The arbitrator shall permit adequate discovery and is empowered to award all remedies otherwise available in a court of competent jurisdiction and any judgment rendered by the arbitrator may be entered by any court of competent jurisdiction. By executing this letter, you and the Company are both waiving the right to a jury trial with respect to any such disputes. Company shall bear the costs of the arbitrator, forum and filing fees. Each party shall bear its own respective attorney fees and all other costs, unless otherwise provided by law and awarded by the arbitrator.

It is aTyr's policy to respect fully the rights of your previous employers in their proprietary or confidential information. No employee is expected to disclose, or is allowed to use for aTyr's purposes, any confidential or proprietary information he or she may have acquired as a result of previous employment.

I am pleased to extend this offer to you and look forward to your acceptance. Please sign and return the enclosed copy of this offer letter as soon as possible to indicate your agreement with the terms of this offer. This offer will lapse if not signed and returned by May 2, 2011

Once signed by you, this letter will constitute the complete agreement between you and aTyr Pharma, Inc. regarding employment matters and will supersede all prior written or oral agreements or understandings on these matters.

I believe you will be able to make an immediate contribution to aTyr's effort, and I think you will enjoy the rewards of working for an innovative, fast-paced company. One of the keys to our accomplishments is good people. We hope you accept our offer to be one of those people.

Yours sincerely,

/s/ John D. Mendlein
John D. Mendlein, Ph.D.
Executive Chairman

Enclosures

I accept the terms of employment as described in this offer letter dated April 28, 2011 ***and will start my employment on*** May 9, 2011. ***I confirm that by my start date at aTyr Pharma, Inc. I will be under no contract or agreement with any other entity which would in any way restrict my ability to work at aTyr Pharma, Inc. or perform the functions of my job for aTyr, including, but not limited to, any employment agreement and/or non-compete agreement.***

/s/ Melissa Ashlock ***Date*** 5/13/2011
Melissa Ashlock

aTyr Pharma, Inc.
3565 General Atomics Court Suite 103 San Diego CA 92121
Phone 858 731 8389 Fax 858 731 8394

aTyr Pharma
Advancing medicine. Improving lives.

Exhibit 10.18

April 22, 2013

Ms. Kelly Blackburn

Dear Kelly,

This letter is a formal offer setting forth the principal terms for you to join aTyr Pharma, Inc. (the "Company"), a Delaware corporation, which is located in San Diego, California. This offer is contingent upon satisfactory completion of a background check.

Position: Vice President, Clinical Affairs

Status: Full-Time, Exempt. This means you are paid for the job and not by the hour. Accordingly, you will not receive overtime pay if you work more than 8 hours in a work day or 40 hours in a workweek.

Reporting to: John Mendlein, Ph.D., Executive Chairman and Chief Executive Officer

Base Salary Rate: $11,458.34 semi-monthly (which equals $275,000.00 per year) less applicable withholdings, paid in accordance with Company's normal payroll practices. Future adjustments in compensation, if any, will be made by the Company in its sole and absolute discretion.

Target Bonus: Your annual target bonus will be 20% of your base salary with a range of 0-40% based upon the achievement of your individual goals, the achievement of team goals and the achievement of corporate goals. Your annual target bonus is subject to review and approval by the aTyr Board of Directors.

Equity: Shortly after commencement of your employment with the Company, and subject to approval by the board of directors, you will be granted an Option to purchase 439,000 shares of the Common Stock of the Company pursuant to the 2007 Stock Plan. The exercise price per share of the Option shall be the fair market value of the Common Stock, as determined by the board of directors at the time of the Option grant. The specific terms and conditions of your Option will be subject to the terms of then 2007 Stock Plan, as well as the terms set forth in a Stock Option Agreement between you and the Company. This Stock Option Agreement will be entered into and executed after you commence your employment with the Company.

Benefits:	You will be entitled to receive standard medical, life and dental insurance benefits for yourself and your dependents in accordance with Company policy. Company reserves the right to change or eliminate these benefits on a prospective basis at any time.
401(k) Plan:	You will be eligible to participate in the aTyr Pharma, Inc. 401(k) Savings Plan immediately following the start of your employment.
Vacation & Sick Time:	You will be entitled to accrue 15 days of vacation per year. You will have 6 days of sick time available each year.
Holidays:	You will be eligible for aTyr's paid holidays. The schedule is published prior to the beginning of each calendar year.
Employment at Will:	Your employment will be at will, which means it may be terminated at any time by you or the Company with or without cause and that your employment is not for any specific period of time. Any change to the at-will employment relationship must be by a specific, written agreement signed by you and the Company's Chief Executive Officer.
Start Date:	June 15, 2013 or a mutually agreed upon date.

As a condition of your employment, you will be required to sign and abide by our Employee Nondisclosure and Assignment Agreement when you begin your employment. A copy is attached for your reference. In addition, in order to comply with the Immigration Reform and Control Act of 1986, within three (3) days of your Start Date you will be required to provide sufficient documentation to verify your identity and legal authorization to work in the United States. Please bring with you on your Start Date, the original of one of the documents noted in List A or one document from List B and one document from List C as itemized in the enclosed "Lists of Acceptable Documents". If you do not have the originals of any of these documents, please contact me immediately.

In the event of any dispute or claim relating to or arising out of your employment relationship with the Company, this agreement, or the termination of your employment with the Company for any reason (including, but not limited to, any claims of breach of contract, defamation, wrongful Ms.

termination or age, sex, sexual orientation, race, color, national origin, ancestry, marital status, religious creed, physical or mental disability or medical condition or other discrimination, retaliation or harassment), you and the Company agree that all such disputes shall be fully resolved by confidential, binding arbitration conducted by a single arbitrator through the American Arbitration Association ("AAA") under the AAA's National Rules for the Resolution of Employment Disputes then in effect, which are available online at the AAA's website at www.adr.org. The arbitrator shall permit adequate discovery and is empowered to award all remedies otherwise available in a court of competent jurisdiction and any judgment rendered by the arbitrator may be entered by any court of competent jurisdiction. By executing this letter, you and the Company are both waiving the right to a jury trial with respect to any such disputes. Company shall bear the costs of the arbitrator, forum and filing fees. Each party shall bear its own respective attorney fees and all other costs, unless otherwise provided by law and awarded by the arbitrator.

It is aTyr's policy to respect fully the rights of your previous employers in their proprietary or confidential information. No employee is expected to disclose, or is allowed to use for aTyr's purposes, any confidential or proprietary information he or she may have acquired as a result of previous employment.

I am pleased to extend this offer to you and look forward to your acceptance. Please sign and return the enclosed copy of this offer letter as soon as possible to indicate your agreement with the terms of this offer. This offer will lapse if not signed and returned by Thursday, April 25, 2013.

Once signed by you, this letter will constitute the complete agreement between you and aTyr Pharma, Inc. regarding employment matters and will supersede all prior written or oral agreements or understandings on these matter.

Our mission is to discover life-changing therapies with relentless determination for people with grave maladies where others fall short. I believe you will be able to make an immediate

contribution to this mission and I think you will enjoy the rewards of working for an innovative, fast-paced company. One of the keys to our success is top people. We hope you accept our offer to be one of those people.

Yours sincerely,

/s/ John D. Mendlein
John Mendlein, Ph.D.
Executive Chairman and Chief Executive Officer

Enclosures

I accept the terms of employment as described in this offer letter dated 25 April 2013 ***and will start my employment on*** 8 July 2013***. I confirm that by my start date at aTyr Pharma, Inc. I will be under no contract or agreement with any other entity which would in any way restrict my ability to work at aTyr Pharma, Inc. or perform the functions of my job for aTyr, including, but not limited to, any employment agreement and/or non-compete agreement.***

/s/ Kelly Blackburn *Date* 25 April 2013
Ms. Kelly Blackburn

aTyr Pharma, Inc.
3565 General Atomics Court Suite 103 San Diego CA 92121
Phone 858 731 8389 Fax 858 731 8394

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm (EY to provide changes)

We consent to the incorporation by reference in the Registration Statements (Form S-8 No. 333-203955) of aTyr Pharma Inc. and in the related Prospectus of our report dated May 6, 2015, with respect to the financial statements of aTyr Pharma Inc. included in this Annual Report (Form 10-K) for the year ended December 31, 2015.

/s/ Ernst & Young LLP

San Diego, California
March 30, 2016

Exhibit 31.1

CERTIFICATION OF PRINCIPAL EXECUTIVE OFFICER
PURSUANT TO RULE 13a-14(a) AND 15d-14(a) OF THE SECURITIES EXCHANGE ACT,
AS ADOPTED PURSUANT TO SECTION 302
OF THE SARBANES-OXLEY ACT OF 2002

I, John D. Mendlein, certify that:

1. I have reviewed this Annual Report on Form 10-K of aTyr Pharma, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the consolidated financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

c) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 30, 2016

/s/ John D. Mendlein
John D. Mendlein, Ph.D.
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION OF THE PRINCIPAL FINANCIAL OFFICER
PURSUANT TO RULE 13a-14(a) AND 15d-14(a) OF THE SECURITIES EXCHANGE ACT,
AS ADOPTED PURSUANT TO SECTION 302
OF THE SARBANES-OXLEY ACT OF 2002

I, John T. Blake, certify that:

1. I have reviewed this Annual Report on Form 10-K of aTyr Pharma, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the consolidated financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

c) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 30, 2016

/s/ John T. Blake
John T. Blake
(Principal Financial and Accounting Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of aTyr Pharma, Inc. (the "Company") for the period ended December 31, 2015, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, John D. Mendlein, Chief Executive Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to my knowledge:

1. The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

2. The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 30, 2016

/s/ John D. Mendlein
John D. Mendlein, Ph.D.
Chief Executive Officer

The foregoing certification is being furnished solely to accompany the Report pursuant to 18 U.S.C. § 1350, and is not being filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, and is not to be incorporated by reference into any filing of the Company, whether made before or after the date hereof, regardless of any general incorporation language in such filing. A signed original of this written statement required by Section 906 has been provided to the Company and will be retained by the Company and furnished to the Securities and Exchange Commission or its staff upon request.

Exhibit 32.2

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002)

In connection with the Annual Report on Form 10-K of aTyr Pharma, Inc. (the "Company") for the period ended December 31, 2015, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, John T. Blake, Principal Financial and Accounting Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to my knowledge:

1. The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

2. The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 30, 2016

/s/ John T. Blake
John T. Blake
Principal Financial and Accounting Officer

The foregoing certification is being furnished solely to accompany the Report pursuant to 18 U.S.C. § 1350, and is not being filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, and is not to be incorporated by reference into any filing of the Company, whether made before or after the date hereof, regardless of any general incorporation language in such filing. A signed original of this written statement required by Section 906 has been provided to the Company and will be retained by the Company and furnished to the Securities and Exchange Commission or its staff upon request.