

PROSPECTUS SUPPLEMENT
(To Prospectus dated April 26, 2018)

11,000,000 Shares



Common Stock

We are offering 11,000,000 shares of our common stock. Our common stock is listed on The Nasdaq Global Market under the symbol "PTI." On October 23, 2018, the last reported sale price for our common stock on The Nasdaq Global Market was \$7.40 per share.

We are an "emerging growth company" under applicable Securities and Exchange Commission rules and are subject to reduced public company reporting requirements.

Investing in our common stock involves a high degree of risk. Please read "[Risk Factors](#)" on page S-6 of this prospectus supplement and the documents incorporated by reference into this prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved these securities or determined if this prospectus supplement or the accompanying prospectus is accurate or complete. Any representation to the contrary is a criminal offense.

	Per Share	Total
Public offering price	\$6.750	\$74,250,000
Underwriting discounts and commissions(1)	\$0.405	\$ 4,455,000
Proceeds, before expenses, to us	\$6.345	\$69,795,000

(1) We have agreed to reimburse the underwriters for certain expenses. See "Underwriting."

We have granted the underwriters an option for 30 days from the date of this prospectus supplement to purchase up to 1,650,000 additional shares of our common stock. See "Underwriting" for more information.

The underwriters expect to deliver the shares to the investors on or about October 26, 2018.

Joint Book-Running Managers

Leerink Partners

Piper Jaffray

Cantor

Lead Manager

H.C. Wainwright & Co.

October 23, 2018

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We have not, and the underwriters have not, authorized anyone to provide you with information different than that which is contained in or incorporated by reference in this prospectus supplement, the accompanying prospectus and in any free writing prospectus that we have authorized for use in connection with this offering. We are not, and the underwriters are not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus supplement, the accompanying prospectus, the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, and in any free writing prospectus that we have authorized for use in connection with this offering, is accurate only as of the date of those respective documents. Our business, financial condition, results of operations and prospects may have changed since those dates. You should read this prospectus supplement, the accompanying prospectus, the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, and any free writing prospectus that we have authorized for use in connection with this offering, in their entirety before making an investment decision. You should also read and consider the information in the documents to which we have referred you in the sections of this prospectus supplement entitled “Where You Can Find More Information” and “Incorporation of Certain Information by Reference.”

For investors outside the United States: We have not and the underwriters have not done anything that would permit this offering or possession or distribution of this prospectus in any jurisdiction where action for that purpose is required, other than in the United States. Persons outside the United States who come into possession of this prospectus must inform themselves about, and observe any restrictions relating to, the offering of the shares of common stock and the distribution of this prospectus outside the United States.

ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the terms of this offering of common stock and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus. The second part, the accompanying prospectus dated April 26, 2018, including the documents incorporated by reference therein, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement, on the one hand, and the information contained in the accompanying prospectus or in any document incorporated by reference that was filed with the Securities and Exchange Commission, or SEC, before the date of this prospectus supplement, on the other hand, you should rely on the information in this prospectus supplement. If any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document incorporated by reference in the accompanying prospectus—the statement in the document having the later date modifies or supersedes the earlier statement. You should assume that the information contained in this prospectus supplement is accurate as of the date on the front cover of this prospectus supplement only and that any information we have incorporated by reference or included in the accompanying prospectus is accurate only as of the date given in the document incorporated by reference or as of the date of the prospectus, as applicable, regardless of the time of delivery of this prospectus supplement or the accompanying prospectus or any sale of our common stock. Our business, financial condition, results of operations and prospects may have changed since that date.

Unless the context indicates otherwise, as used in this prospectus supplement, the terms “Proteostasis,” “Company,” “we,” “us” and “our” refer to Proteostasis Therapeutics, Inc.

Market data and certain industry data and forecasts included in this prospectus supplement, the accompanying prospectus and the documents incorporated by reference were obtained from internal company surveys, market research, publicly available information, reports of governmental agencies and industry publications and surveys. We have relied upon industry publications as our primary sources for third-party industry data and forecasts. Industry surveys, publications and forecasts generally state that the information contained therein has been obtained from sources believed to be reliable, but that the accuracy and completeness of such information is not guaranteed. We have not independently verified any of the data from third-party sources, nor have we ascertained the underlying economic assumptions relied upon therein. Similarly, internal surveys, industry forecasts and market research, which we believe to be reliable based upon our management’s knowledge of the industry, have not been independently verified. Forecasts are particularly likely to be inaccurate, especially over long periods of time. In addition, we do not know what assumptions regarding general economic growth were used in preparing the forecasts we cite. Statements as to our market position are based on recently available data. While we are not aware of any misstatements regarding our industry data presented herein and therein, our estimates involve risks and uncertainties and are subject to change based on various factors, including those discussed under “Risk Factors” in this prospectus supplement. While we believe our internal business research is reliable and market definitions are appropriate, neither such research nor definitions have been verified by any independent source. This prospectus may only be used for the purpose for which it has been published.

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights selected information contained elsewhere or incorporated by reference in this prospectus supplement and the accompanying prospectus. This summary does not contain all the information you should consider before investing in our common stock. You should read and consider carefully the more detailed information in this prospectus supplement and the accompanying prospectus, including the factors described under the heading "Risk Factors" in this prospectus supplement and the financial statements, notes to financial statements, financial and other information incorporated by reference in this prospectus supplement and the accompanying prospectus, as well as the information included in any free writing prospectus that we have authorized for use in connection with this offering, before making an investment decision.

Our Company

We are an innovative, clinical stage biopharmaceutical company committed to the discovery and development of novel therapeutics to treat cystic fibrosis, or CF, and other diseases caused by an imbalance in the proteostasis network, a set of pathways that control protein biosynthesis, folding, trafficking and clearance. The Company focuses on identifying therapies that restore protein function. CF is a disease caused by defects in the function or abundance of cystic fibrosis transmembrane conductance regulator, or CFTR. Our CF focused pipeline consists of novel CFTR modulators including correctors, potentiators and amplifiers. Upon discovery of amplifiers, a novel class of CFTR modulators, we have exploited its novel mechanism of action as a drug screening tool and have subsequently identified correctors and potentiators to be developed as part of combination therapies. Investigational agents representative of all three classes of CFTR modulators are currently in clinical development and include PTI-428, an amplifier, and PTI-801 a third generation corrector, and PTI-808, a potentiator. We believe that both PTI-428 and PTI-801 have potential as add-on therapy to current and future standard-of-care CFTR modulator treatments. Additionally, we are pursuing proprietary dual combination of PTI-801 and PTI-808, and triple combination of PTI-801, PTI-808 and PTI-428 as product opportunities. We are developing and, if approved, intend to commercialize our own therapies, including add-on and combination therapies for CF patients who have at least one F508del mutation, representing the majority of the patient population.

Recent Developments

Preliminary Results from PTI-808 and PTI-801 Phase 1 Study

In October 2018, we announced positive preliminary results from three doublet cohorts of the Company's ongoing Phase 1, randomized, double-blind, placebo-controlled studies of the Company's proprietary combination therapy doublet, PTI-808 and PTI-801, and an enrollment update from the triplet, PTI-808, PTI-801, and PTI-428, in subjects with cystic fibrosis.

These studies were designed to assess the safety, tolerability, and pharmacokinetics (PK) of PTI-801, a third-generation cystic fibrosis transmembrane conductance regulator (CFTR) corrector, PTI-808, a novel CFTR potentiator, and PTI-428, a novel CFTR amplifier, compared to placebo over a 14-day dosing period in CF subjects across dose levels of each modulator. Changes in sweat chloride (SC) concentration and in percent predicted FEV₁ (ppFEV₁) were assessed and evaluated as endpoints.

The analysis was based on data from 21 subjects who were randomized to receive investigational drugs or placebo in the first three dose cohorts of the doublet combination: first in patient cohort with 100 mg of PTI-801 and 50 mg of PTI-808, low-dose cohort of 200 mg of PTI-801 and 100 mg PTI-808 and mid-dose cohort of 300 mg of PTI-801 and 300 mg of PTI-808. Preliminary PK results were as expected and supported a once-a-day dosing profile for both PTI-801 and PTI-808. In terms of safety, the compounds were generally well tolerated. No pulmonary exacerbations were reported in the dosing or follow-up period of the study. The dose cohort with

100 mg of PTI-801 and 50 mg of PTI-808 was the first in patient cohort for PTI-808 and PTI-801 combination with an appropriately low dose level in a small number of subjects to collect the initial PK and safety data in CF subjects. The subsequent low-, mid- and high-dose cohorts included or will include higher numbers of subjects sufficient for analysis of efficacy endpoints.

A dose-dependent improvement in ppFEV₁ and sweat chloride concentration was observed in the low-dose (200 mg of PTI-801, 100 mg of PTI-808) and mid-dose (300 mg of PTI-801, 300 mg of PTI-808) cohorts. For ppFEV₁, a statistically significant increase from baseline to day seven of +6.3% and at day 14 of +5.9% was reported in the PTI-801 300mg/PTI-808 300mg dose cohort. A statistically significant increase from placebo was also noted from baseline to day seven of +8.3% and at day 14 of +6.6% in this cohort. A statistically significant decrease in sweat chloride concentration from baseline was also observed at day seven of approximately 11.1 mmol/L and at day 14 of approximately 13 mmol/L in the mid-dose cohort. The fourth, high-dose cohort, patients receiving PTI-801 (400 mg) and PTI-808 (300 mg), is ongoing, with data expected in the first quarter of 2019.

The first dose cohort using the Company's proprietary triplet combination of PTI-801, PTI-808 and PTI-428, a novel CFTR amplifier, is ongoing and we expect preliminary data in the fourth quarter of 2018, with complete data from the doublet and triplet cohorts expected in the first quarter of 2019.

Dual Track Development Strategy in CF

In addition to completed studies of PTI-801 and PTI-428 in patients on background Orkambi® therapy, and the ongoing study of the PTI doublet (PTI-808, PTI-801) and the PTI triplet (PTI-808, PTI-801 and PTI-428), we are conducting separate studies of PTI-801 and PTI-428 in CF subjects on background Symdeko® therapy. Both studies are underway and are expected to read out in the first quarter of 2019.

In its totality, our clinical strategy is expected to inform a Phase 3 development path using our proprietary product candidates either together or as add-ons to current standards of care. Based on the anticipated timing of study readouts across this portfolio of programs, the Company expects to be in a position to initiate Phase 3 studies within the next 12-18 months, subject to completion of manufacturing activities and discussions with regulatory authorities.

At-the-Market Offering Program

In March 2018, we entered into a sales agreement with Leerink Partners LLC, or Leerink, with respect to an at-the-market, or ATM, offering program under which the Company may offer and sell, from time to time at its sole discretion, shares of its common stock, having an aggregate offering price of up to \$50.0 million. Leerink is not required to sell any specific amount but acts as the Company's sales agent on a commercially reasonable efforts basis consistent with its normal trading and sales practices. Common stock will be sold at prevailing market prices at the time of the sale; and as a result, prices may vary. The Company will pay Leerink 3% of the gross proceeds from any common stock sold under the sales agreement. As of October 19, 2018, the Company sold 3,475,166 shares of its common stock for net proceeds of approximately \$21.7 million pursuant to the ATM program including \$11.2 million from sales of 1,364,348 shares in the fourth quarter of 2018. On October 20, 2018, we suspended, and during the duration of this offering and until the expiration of the lock-up period described in the section of this prospectus supplement entitled "Underwriting," we are no longer offering, any shares of our common stock pursuant this ATM program with Leerink.

Financial Update

While we have not finalized our full financial results for the quarter ended September 30, 2018, we expect to report that we had approximately \$46.4 million in cash, cash equivalents and short-term investments as of September 30, 2018. This represents preliminary expectations and is subject to quarter-end and year-end

adjustments in connection with the completion of our customary financial closing procedures, including management’s review and finalization and to accounting review procedures by our independent registered public accounting firm, which have not yet been performed. Consequently, the results should not be viewed as a substitute for our earnings release and Quarterly Report on Form 10-Q. Actual results may differ materially from our preliminary expectations. Additional information and disclosures would be required for a more complete understanding of our financial position and results of operations as of September 30, 2018.

The preliminary financial data included in this prospectus supplement has been prepared by, and is the responsibility of, Proteostasis’s management. PricewaterhouseCoopers LLP has not audited, reviewed, compiled, or applied agreed-upon procedures with respect to the preliminary financial data. Accordingly, PricewaterhouseCoopers LLP does not express an opinion or any other form of assurance with respect thereto.

Corporate Information

We were incorporated in Delaware on December 13, 2006 under the name Proteoguard, Inc. and subsequently changed our name to Proteostasis Therapeutics, Inc. on September 17, 2007. Our principal executive offices are located at 80 Guest Street, Suite 500, Boston, Massachusetts, 02135, and our telephone number is (617) 225-0096. Our website address is www.proteostasis.com. We do not incorporate the information on or accessible through our website into this prospectus supplement, and you should not consider any information on, or that can be accessed through, our website a part of this prospectus supplement.

This prospectus contains references to our trademarks and to trademarks belonging to other entities. Solely for convenience, trademarks and trade names referred to in this prospectus, including logos, artwork, and other visual displays, may appear without the ® or ™ symbols, but such references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or the rights of the applicable licensor to these trademarks and trade names. We do not intend our use or display of other companies’ trade names or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

On February 17, 2016, we completed our initial public offering. 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 \$1.07 billion or more; (ii) December 31, 2021; (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.

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The Offering

Common stock offered by us	11,000,000 shares
Common stock to be outstanding immediately after this offering	47,635,902 shares
Option to purchase additional shares	We have granted the underwriters an option to purchase up to 1,650,000 additional shares of our common stock. This option is exercisable, in whole or in part, for a period of 30 days from the date of this prospectus supplement.
Use of proceeds	We expect to receive net proceeds from this offering, after deducting underwriting discounts and commissions and estimated offering expenses payable by us, of approximately \$69.5 million, or \$80.0 million if the underwriters' option to purchase additional shares is exercised in full. We intend to use the net proceeds from this offering to fund critical path activities for PTI-428 as an add on to standard of care and continue the advancement of PTI-proprietary combination therapies and continue to fund critical path activities toward initiation of Phase 3 as early as 2019, for drug substance (API) for Phase 3 for PTI-428, PTI-801 and PTI-808, including starting material that can be used in registrational studies and for working capital and other general corporate purposes. See "Use of Proceeds."
Risk factors	Investing in our common stock involves a high degree of risk. See the description of risks set forth under "Risk Factors" in this prospectus supplement and otherwise incorporated by reference into this prospectus supplement and the accompanying prospectus for a description of factors to consider before deciding to purchase shares of our common stock.
Nasdaq Global Market Symbol	"PTI"

The number of shares of our common stock to be outstanding immediately after this offering is based on 36,635,902 shares outstanding as of June 30, 2018, and excludes as of that date:

- 3,530,135 shares of common stock issuable upon the exercise of outstanding stock options under our equity incentive plans, with a weighted-average exercise price of \$5.87 per share;
- 925,628 shares of common stock available for issuance under our 2016 Stock Option and Incentive Plan, or 2016 Plan, as well as any future increases in the number of shares of our common stock reserved for issuance under the 2016 Plan pursuant to evergreen provisions;
- 399,328 shares of common stock available for issuance under our 2016 Employee Stock Purchase Plan, or ESPP, as well as any future increases in the number of shares of our common stock reserved for issuance under the ESPP pursuant to evergreen provision; and
- 1,364,348 shares sold pursuant to our ATM program in the fourth quarter of 2018.

Except as otherwise indicated, all information in this prospectus supplement assumes no exercise by the underwriters of their option to purchase additional shares and assumes no exercise of the outstanding stock options described above.

RISK FACTORS

Investing in our common stock involves a high degree of risk. Our business, prospects, financial condition or operating results could be materially adversely affected by the risks identified below, as well as other risks not currently known to us or that we currently consider immaterial. The trading price of our common stock could decline due to any of these risks, and you may lose all or part of your investment. In assessing the risks described below, you should also refer to the information contained in our Annual Report on Form 10-K for the year ended December 31, 2017 and our Quarterly Report on Form 10-Q for the quarter ended June 30, 2018, including the section titled “Risk Factors,” and in the other documents which are incorporated by reference in this prospectus supplement and the accompanying prospectus in their entirety.

Risks Related to this Offering

Our principal stockholders have and will have a controlling influence over our business affairs and may make business decisions with which you disagree and which may adversely affect the value of your investment.

Our executive officers, directors and principal stockholders and their affiliates beneficially own or control, directly or indirectly, a majority of the outstanding shares of our common stock and will continue to do so after this offering. As a result, if some of these persons or entities act together, they will have the ability to exercise significant influence over matters submitted to our stockholders for approval, including the election and removal of directors, amendments to our certificate of incorporation and by-laws and the approval of any business combination. These actions may be taken even if they are opposed by other stockholders. This concentration of ownership may also have the effect of delaying or preventing a change of control of our company or discouraging others from making tender offers for shares of our common stock, which could prevent our stockholders from receiving a premium for their shares. Some of these persons or entities who make up our principal stockholders may have interests different from yours.

Investors purchasing common stock in this offering will experience immediate and substantial dilution.

The offering price of shares of our common stock is higher than the as adjusted net tangible book value per outstanding share of our common stock. You will incur immediate and substantial dilution of \$4.11 per share in the as adjusted net tangible book value of shares of our common stock, based on the public offering price of \$6.75 per share. As a result of the dilution to investors purchasing shares in this offering, investors may receive significantly less than the purchase price paid in this offering, if anything, in the event of liquidation. In addition, we have outstanding options with exercise prices significantly below the offering price. To the extent outstanding options are ultimately exercised, there will be further dilution of the common stock sold in this offering.

We have broad discretion in the use of our existing cash, including the net proceeds we receive from this offering, and may not use them effectively or may use them in a way with respect to which stockholders do not approve.

Although we currently intend to use the net proceeds from this offering in the manner described in “Use of Proceeds” elsewhere in this prospectus, our management will have broad discretion in the application of the net proceeds from this offering and could spend the proceeds in ways that do not improve our results of operations or enhance the value of shares of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the market price of shares of our common stock to decline and delay the development of our product candidates. We may invest the net proceeds from this offering in a manner that does not produce income or that loses value. If we do not invest the net proceeds from this offering in ways that enhance stockholder value, we may fail to achieve expected financial results, which could cause the price of shares of our common stock to decline.

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A significant portion of our total outstanding shares may be sold into the market. This could cause the market price of our common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. If our stockholders sell, or the market believes that our stockholders intend to sell, substantial amounts of our common stock in the public market, the market price of our common stock could decline significantly.

The holders of a significant portion of shares of our common stock, or their transferees, have rights, subject to some conditions, to require us to file one or more registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. If we were to register the resale of these shares, they could be freely sold in the public market. If these additional shares are sold, or if it is believed that they will be sold, in the public market, the trading price of our common stock could decline.

FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus, and the documents incorporated by reference herein and therein contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, that involve a number of risks and uncertainties. Although our forward-looking statements reflect the good faith judgment of our management, these statements can only be based on facts and factors currently known by us. Consequently, these forward-looking statements are inherently subject to risks and uncertainties, and actual results and outcomes may differ materially from results and outcomes discussed in the forward-looking statements.

Words such as “aim,” “may,” “will,” “anticipate,” “estimate,” “expects,” “projects,” “intends,” “plans,” “believes,” “tracking,” “potentially” and words and terms of similar substance used in connection with any discussion of future operating or financial performance, identify forward-looking statements. Forward-looking statements represent management’s present judgment regarding future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially from those described in the forward-looking statements. These risks include, but are not limited to, risks and uncertainties regarding the expected timing of the initiation of, patient enrollment in, data from, and the completion of our preclinical and clinical studies, our ability to conduct clinical trials of our product candidates and the results of such trials, the suitability of our product candidates for their proposed indications as well as risks and uncertainties relating to litigation, government regulation and third-party reimbursement, economic conditions, markets, products, competition, intellectual property, services and prices, key employees, future capital needs and other factors. These statements include but are not limited to statements under the captions “Business,” “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” and in other sections incorporated by reference from our Annual Report on Form 10-K and Quarterly Reports on Form 10-Q, as applicable, as well as our other filings with the SEC. You should be aware that the occurrence of any of the events discussed under the heading “Risk Factors” in this prospectus supplement and any documents incorporated by reference herein or therein could substantially harm our business, operating results and financial condition and that if any of these events occurs, it could adversely affect the value of an investment in our securities.

We qualify all of the forward-looking statements in the foregoing documents by these cautionary statements. Unless required by law, we undertake no obligation to update or revise any forward-looking statements to reflect new information or future events or developments. Thus, you should not assume that our silence over time means that actual events are bearing out as expressed or implied in such forward-looking statements. Before deciding to purchase our common stock, you should carefully consider the risk factors incorporated by reference herein, in addition to the other information set forth in this prospectus supplement, the accompanying prospectus and in the documents incorporated by reference herein.

USE OF PROCEEDS

We estimate that we will receive net proceeds of approximately \$69.5 million (or approximately \$80.0 million if the underwriters' option to purchase additional shares is exercised in full) from the sale of 11,000,000 shares of common stock offered by us in this offering, at the public offering price of \$6.75 per share, and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

We intend to use the net proceeds from this offering:

- to fund critical path activities for PTI-428 as an add on to standard of care and continue the advancement of PTI-proprietary combination therapies and continue to fund critical path activities toward initiation of Phase 3 as early as 2019;
- for drug substance (API) for Phase 3 for PTI-428, PTI-801 and PTI-808, including starting material that can be used in registrational studies; and
- for working capital and other general corporate purposes, including funding for targeted hiring of additional personnel, capital expenditures and costs of operating as a public company.

The amounts and timing of these expenditures will depend on a number of factors, including the factors described under "Risk Factors" in this prospectus supplement. As of the date of this prospectus supplement, we cannot specify with certainty all of the particular uses for the net proceeds to us from this offering. Accordingly, our management will have broad discretion in the application of these proceeds. Pending these uses, we intend to invest the net proceeds in high quality, investment grade instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government, or hold as cash.

PRICE RANGE OF COMMON STOCK

Our common stock began trading on The Nasdaq Global Market under the symbol “PTI” on February 11, 2016. Prior to that time, there was no public market for our common stock. The following table sets forth the high and low sale prices per share of our common stock, as reported on The Nasdaq Global Market, for the periods indicated:

	High	Low
Year ending December 31, 2018		
Fourth quarter (through October 23, 2018)	\$10.38	\$ 1.71
Third quarter	3.02	2.13
Second quarter	5.66	2.68
First quarter	8.61	2.38
Year ended December 31, 2017		
Fourth quarter	6.95	1.41
Third quarter	5.40	1.71
Second quarter	8.12	3.50
First quarter	16.67	7.67
Year ended December 31, 2016		
Fourth quarter	15.81	6.61
Third quarter	20.63	10.03
Second quarter	20.47	8.80
First quarter (from February 11, 2016)	13.99	5.27

On October 23, 2018, the last reported sale price of our common stock as reported on The Nasdaq Global Market was \$7.40 per share. As of October 19, 2018, we had approximately 23 holders of record of our common stock. The actual number of stockholders is greater than this number of record holders and includes stockholders who are beneficial owners but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

DIVIDEND POLICY

We have never declared or paid any dividends on our capital or common stock. We currently intend to retain all available funds and any future earnings, if any, to fund the development and growth of our business and we do not anticipate paying any cash dividends in the foreseeable future. Any future determination to pay dividends will be made at the discretion of our board of directors. Investors should not purchase our common stock with the expectation of receiving cash dividends.

CAPITALIZATION

The following table sets forth our cash and cash equivalents and capitalization as of June 30, 2018:

- on an actual basis; and
- on an as adjusted basis to give effect to our issuance and sale of 11,000,000 shares of our common stock in this offering at the public offering price of \$6.75 per share and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

You should read the following table together with the “Use of Proceeds,” our condensed financial statements and other financial data incorporated by reference in this prospectus supplement from our Annual Report on Form 10-K for the year ended December 31, 2017. All information is in thousands, except share and per share data.

	As of June 30, 2018	
	Actual	As Adjusted(1)
Cash and cash equivalents	<u>\$ 19,930</u>	<u>\$ 89,455</u>
Short-term investments	<u>\$ 40,890</u>	<u>\$ 40,890</u>
Stockholders' equity:		
Preferred stock, \$0.001 par value; 5,000,000 shares authorized, no shares issued or outstanding, actual and as adjusted	—	—
Common stock, \$0.001 par value; 125,000,000 shares authorized, 36,635,902 shares issued and outstanding, actual; 125,000,000 shares authorized, 47,635,902 shares issued and outstanding, as adjusted	37	48
Additional paid-in capital	298,515	368,029
Accumulated other comprehensive loss	(12)	(12)
Accumulated deficit	<u>(242,207)</u>	<u>(242,207)</u>
Total stockholders' equity	<u>56,333</u>	<u>125,858</u>
Total capitalization	<u>\$ 56,333</u>	<u>\$ 125,858</u>

- (1) Does not give effect to \$11.2 million in net proceeds received in the fourth quarter of 2018 from sales of 1,364,348 shares of our common stock pursuant to our at-the-market offering program.

The table above does not include, as of June 30, 2018:

- 3,530,135 shares of common stock issuable upon the exercise of outstanding stock options under our equity incentive plans, with a weighted-average exercise price of \$5.87 per share;
- 925,628 shares of common stock available for issuance under our 2016 Plan, as well as any future increases in the number of shares of our common stock reserved for issuance under the 2016 Plan pursuant to evergreen provisions; and
- 399,328 shares of common stock available for issuance under our ESPP, as well as any future increases in the number of shares of our common stock reserved for issuance under the ESPP pursuant to evergreen provisions.

DILUTION

Investors purchasing shares of our common stock in this offering will experience immediate and substantial dilution in the pro forma net tangible book value of their shares of common stock. Dilution in pro forma net tangible book value represents the difference between the public offering price per share and the pro forma net tangible book value per share of our common stock immediately after the offering.

The historical net tangible book value of our common stock as of June 30, 2018 was \$56.3 million, or \$1.54 per share. Historical net tangible book value per share of our common stock represents our total tangible assets (total assets less intangible assets) less total liabilities, divided by 36,635,902 shares of common stock outstanding as of that date.

After giving effect to (1) the issuance of 11,000,000 shares of common stock in this offering and (2) the receipt of the net proceeds from the sale of 11,000,000 shares of common stock in this offering at the public offering price of \$6.75 per share and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of June 30, 2018 would have been approximately \$125.9 million, or \$2.64 per share of common stock. This represents an immediate increase in net tangible book value of \$1.10 per share to existing stockholders and an immediate dilution of \$4.11 per share in net tangible book value per share to new investors purchasing our common stock in this offering.

The following table illustrates this dilution on a per share basis to new investors:

Public offering price per share	\$6.75
Historical net tangible book value per share as of June 30, 2018	\$1.54
Increase in net tangible book value per share attributable to new investors purchasing shares in this offering	<u>1.10</u>
As adjusted net tangible book value per share after giving effect to this offering	<u>\$2.64</u>
Dilution per share to new investors participating in this offering	<u>\$4.11</u>

If the underwriters exercise their option in full to purchase an additional 1,650,000 shares of common stock in this offering, the as adjusted net tangible book value per share after the offering would be \$2.77 per share, the increase in the net tangible book value per share to existing stockholders would be \$1.23 per share and the dilution to new investors purchasing our common stock in this offering would be \$3.98 per share.

The above discussion does not include, as of June 30, 2018:

- 3,530,135 shares of common stock issuable upon the exercise of outstanding stock options under our equity incentive plans, with a weighted-average exercise price of \$5.87 per share;
- 925,628 shares of common stock available for issuance under our 2016 Plan, as well as any future increases in the number of shares of our common stock reserved for issuance under the 2016 Plan pursuant to evergreen provisions;
- 399,328 shares of common stock available for issuance under our ESPP, as well as any future increases in the number of shares of our common stock reserved for issuance under the ESPP pursuant to evergreen provision; and
- 1,364,348 shares sold pursuant to our ATM program in the fourth quarter of 2018.

The foregoing table and calculations assume no exercise of the outstanding stock options described above. To the extent that outstanding exercisable options are exercised, you may experience further dilution.

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In addition, we may choose to raise additional capital due to market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans. To the extent that we raise additional capital by issuing equity securities or convertible debt, your ownership will be further diluted.

To the extent that new stock options, restricted stock units, warrants or common stock are issued in the future, there will be further dilution to investors participating in this offering.

**MATERIAL UNITED STATES FEDERAL INCOME TAX
CONSIDERATIONS FOR NON-U.S. HOLDERS**

The following is a summary of the material U.S. federal income tax considerations of the ownership and disposition of our common stock to non-U.S. holders (as defined below), but does not purport to be a complete analysis of all the potential tax considerations relating thereto. This summary is based upon the provisions of the Internal Revenue Code of 1986, as amended, or the Code, Treasury regulations promulgated thereunder, administrative rulings and judicial decisions, all as of the date hereof. These authorities may be changed or subject to differing interpretations, possibly with retroactive effect, so as to result in U.S. federal income tax consequences different from those set forth below. We have not sought any ruling from the Internal Revenue Service, or the IRS, with respect to the statements made and the conclusions reached in the following summary, and there can be no assurance that the IRS will agree with such statements and conclusions.

This summary also does not address the tax considerations arising under the laws of any U.S. state or local or any non-U.S. jurisdiction, U.S. federal estate or gift tax laws, the Medicare tax on net investment income or any alternative minimum tax consequences. In addition, this discussion does not address tax considerations applicable to an investor's particular circumstances or to investors that may be subject to special tax rules, including, without limitation:

- banks, insurance companies or other financial institutions;
- tax-exempt or governmental organizations;
- brokers or dealers in securities or currencies;
- traders in securities that elect to use a mark-to-market method of accounting for their securities holdings;
- persons that own, or are deemed to own, more than five percent of our capital stock;
- certain former citizens or long-term residents of the United States;
- persons who hold our common stock as a position in a hedging transaction, "straddle," "conversion transaction" or other risk reduction transaction;
- persons who do not hold our common stock as a capital asset within the meaning of Section 1221 of the Code (generally, for investment purposes);
- S corporations, partnerships, or other entities or arrangements treated as pass-through entities for U.S. federal income tax purposes (or investors in any such entities);
- persons deemed to sell our common stock under the constructive sale provisions of the Code;
- regulated investment companies or real estate investment trusts;
- pension plans;
- controlled foreign corporations;
- passive foreign investment companies; or
- persons that acquire our common stock as compensation for services.

In addition, if a partnership, including any entity or arrangement classified as a partnership for U.S. federal income tax purposes, holds our common stock, the tax treatment of a partner generally will depend on the status of the partner and upon the activities of the partnership. Accordingly, partnerships that hold our common stock, and partners in such partnerships, should consult their tax advisors.

You are urged to consult your tax advisor with respect to the application of the U.S. federal income tax laws to your particular situation, as well as any tax consequences of the purchase, ownership and disposition of our common stock arising under the U.S. federal estate or gift tax rules or under the laws of any U.S. state or local or any non-U.S. or other taxing jurisdiction or under any applicable tax treaty.

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Non-U.S. Holder Defined

For purposes of this discussion, you are a non-U.S. holder if you are a beneficial owner of our common stock that is for U.S. federal income tax purposes (i) a foreign corporation or any other foreign organization taxable as a corporation for U.S. federal income tax purposes, (ii) a nonresident alien individual, or (iii) a foreign estate or trust that in either case is not subject to U.S. federal income tax on a net-income basis on income or gain from a note or share of common stock.

Distributions

As discussed under “Dividend Policy,” above, we do not anticipate paying any dividends on our common stock in the foreseeable future. If we were to make distributions on our common stock, those payments will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. To the extent those distributions exceed both our current and our accumulated earnings and profits, they will constitute a return of capital and will first reduce your basis in our common stock, but not below zero, and then will be treated as gain from the sale of stock, subject to the tax treatment described in the discussion below regarding taxable dispositions of our common stock. Any such distributions would also be subject to the discussions below regarding backup withholding and FATCA.

Subject to the discussion below regarding a dividend received by you that is effectively connected with the conduct of a U.S. trade or business, a dividend paid to you generally will be subject to U.S. withholding tax either at a rate of 30% of the gross amount of the dividend or such lower rate as may be specified by an applicable income tax treaty. In order to receive a reduced treaty rate, you must provide us with an IRS Form W-8BEN (generally including a U.S. taxpayer identification number), IRS Form W-8-BEN-E or another appropriate version of IRS Form W-8 (or a successor form), in each case, certifying qualification for the reduced rate.

Dividends received by you that are effectively connected with the conduct of a U.S. trade or business (and, if required by an applicable income tax treaty, are attributable to a permanent establishment maintained by you in the United States) generally are exempt from such withholding tax. In order to obtain this exemption, you must provide us with an IRS Form W-8ECI or successor form or other applicable IRS Form W-8 properly certifying such exemption. Such effectively connected dividends, although not subject to withholding tax, are taxed at the same graduated rates applicable to U.S. persons, net of certain deductions and credits, subject to an applicable income tax treaty providing otherwise. In addition, if you are a corporate non-U.S. holder, you may also be subject to a branch profits tax at a rate of 30% or such lower rate as may be specified by an applicable income tax treaty on your earnings and profits in respect of such effectively connected dividend income.

If you are eligible for a reduced rate of withholding tax pursuant to a tax treaty, you may be able to obtain a refund of any excess amounts currently withheld if you file an appropriate claim for refund with the IRS.

Gain on Sale or Other Taxable Disposition of Common Stock

Subject to the discussions below regarding backup withholding and FATCA, a non-U.S. holder generally will not be required to pay U.S. federal income tax on any gain realized upon the sale or other taxable disposition of our common stock unless:

- the gain is effectively connected with the conduct of a U.S. trade or business (and, if required by an applicable income tax treaty, the gain is attributable to a permanent establishment maintained by you in the U.S.), in which case you will be required to pay tax on the net gain derived from the sale under regular graduated U.S. federal income tax rates, and for a non-U.S. holder that is a corporation, such non-U.S. holder may be subject to the branch profits tax on any earnings and profits attributable to such gains at a 30% rate or such lower rate as may be specified by an applicable income tax treaty;

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- you are an individual who is present in the United States for a period or periods aggregating 183 days or more during the calendar year in which the sale or disposition occurs and certain other conditions are met, in which case you will be required to pay a flat 30% tax on the gain derived from the sale, which tax may be offset by U.S. source capital losses in the taxable year of disposition (even though you are not considered a resident of the United States) (subject to applicable income tax or other treaties); or
- our common stock constitutes a U.S. real property interest by reason of our status as a “U.S. real property holding corporation” for U.S. federal income tax purposes, a USRPHC, at any time within the shorter of the five-year period preceding the disposition or your holding period for our common stock. Generally, a corporation is a USRPHC only if the fair market value of its U.S. real property interests equals or exceeds 50% of the sum of the fair market value of its worldwide real property interests plus its other assets used or held for use in a trade or business. We believe that we are not currently and will not become a USRPHC. However, because the determination of whether we are a USRPHC depends on the fair market value of our U.S. real property relative to the fair market value of our other business assets, there can be no assurance that we are not currently or will not become a USRPHC in the future. Even if we are or were to become a USRPHC, however, as long as our common stock is regularly traded on an established securities market (as determined under the Code), such common stock will be treated as U.S. real property interests only if you actually or constructively hold more than five percent of such regularly traded common stock at any time during the applicable period that is specified in the Code.

Backup Withholding and Information Reporting

Generally, we must report annually to the IRS the amount of dividends paid to you, your name and address, and the amount of tax withheld, if any. A similar report will generally be sent to you. Pursuant to applicable income tax treaties or other agreements, the IRS may make these reports available to tax authorities in your country of residence.

Payments of dividends or of proceeds on the disposition of stock made to you may be subject to additional information reporting and backup withholding at the then applicable rate unless you establish an exemption, for example by properly certifying your non-U.S. status on an IRS Form W-8BEN, IRS Form W-8BEN-E or another appropriate version of IRS Form W-8 (or a successor form). Notwithstanding the foregoing, backup withholding and information reporting may apply if either we or our paying agent has actual knowledge, or reason to know, that you are a U.S. person.

Backup withholding is not an additional tax; rather, the U.S. federal income tax liability of persons subject to backup withholding will be reduced by the amount of tax withheld. If withholding results in an overpayment of taxes, a refund or credit may generally be obtained from the IRS, provided that the required information is furnished to the IRS in a timely manner.

Foreign Account Tax Compliance Act (FATCA)

Provisions commonly referred to as “FATCA” may impose withholding tax on certain types of payments made to “foreign financial institutions” and certain other non-U.S. entities. The legislation imposes a 30% withholding tax on dividends on, or gross proceeds from the sale or other disposition of, our common stock paid to a foreign financial institution or to certain non-financial foreign entities, unless (i) the foreign financial institution undertakes certain diligence and reporting obligations, (ii) the non-financial foreign entity either certifies it does not have any substantial U.S. owners or furnishes identifying information regarding each substantial U.S. owner and such entity meets certain other specified requirements, or (iii) the foreign financial institution or non-financial foreign entity otherwise qualifies for an exemption from these rules. If the payee is a foreign financial institution and is subject to the requirements in (i) above, it must enter into an agreement with the U.S. Treasury requiring, among other things, that it undertake to identify accounts held by certain U.S. persons or

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U.S.-owned foreign entities, annually report certain information about such accounts, and withhold 30% on payments to account holders whose actions prevent it from complying with these reporting and other requirements. If the country in which a payee is resident has entered into an “intergovernmental agreement” with the United States regarding FATCA, that agreement may permit the payee to report to that country rather than to the U.S. Treasury. Under final Treasury regulations and published guidance, the obligation to withhold from payments made to a foreign financial institution or a foreign non-financial entity under the new legislation with respect to dividends on our common stock are currently in effect, but with respect to the gross proceeds of a sale or other disposition of our common stock will not begin until January 1, 2019. Prospective investors should consult their tax advisors regarding FATCA.

The preceding discussion of U.S. federal income tax considerations is for general information only. It is not tax advice. Each prospective investor should consult its own tax advisor regarding the particular U.S. federal, state and local and non-U.S. tax consequences of purchasing, holding and disposing of our common stock, including the consequences of any proposed change in applicable laws.

UNDERWRITING

Leerink Partners LLC and Piper Jaffray & Co. are acting as representatives of each of the underwriters named below and as joint bookrunning managers for this offering. Subject to the terms and conditions set forth in the underwriting agreement among us and the underwriters, we have agreed to sell to the underwriters, and each of the underwriters has agreed, severally and not jointly, to purchase from us, the number of shares of common stock set forth opposite its name below.

Underwriter	Number of Shares
Leerink Partners LLC	4,400,000
Piper Jaffray & Co.	3,575,000
Cantor Fitzgerald & Co.	1,925,000
H.C. Wainwright & Co., LLC	1,100,000
Total	11,000,000

Subject to the terms and conditions set forth in the underwriting agreement, the underwriters have agreed, severally and not jointly, to purchase all of the shares sold under the underwriting agreement if any of the shares are purchased. If an underwriter defaults, the underwriting agreement provides that the purchase commitments of the non-defaulting underwriters may be increased or the underwriting agreement may be terminated.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act, or to contribute to payments the underwriters may be required to make in respect of those liabilities.

The underwriters are offering the shares, subject to prior sale, when, as and if issued to and accepted by them, subject to approval of legal matters by their counsel, including the validity of the shares, and other conditions contained in the underwriting agreement, such as the receipt by the underwriters of officers' certificates and legal opinions. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part.

Commissions and Discounts

The representatives have advised us that the underwriters propose initially to offer the shares to the public at the public offering price set forth on the cover page of this prospectus and to dealers at that price less a concession not in excess of \$0.243 per share. After the initial offering of the shares, the public offering price, concession or any other term of the offering may be changed by the representatives.

The following table shows the public offering price, underwriting discounts and commissions and proceeds before expenses to us. The information assumes either no exercise or full exercise by the underwriters of their option to purchase additional shares of our common stock.

	Per Share	Total	
		Without Option	With Option
Public offering price	\$6.750	\$74,250,000	\$85,387,500
Underwriting discounts and commissions	\$0.405	\$ 4,455,000	\$ 5,123,250
Proceeds, before expenses, to us	\$6.345	\$69,795,000	\$80,264,250

We estimate expenses payable by us in connection with this offering, other than the underwriting discounts and commissions referred to above, will be approximately \$270,000. We also have agreed to reimburse the underwriters for up to \$20,000 for their FINRA counsel fee. In accordance with FINRA Rule 5110, this reimbursed fee is deemed underwriting compensation for this offering.

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Option to Purchase Additional Shares

We have granted an option to the underwriters, exercisable for 30 days after the date of this prospectus, to purchase up to 1,650,000 additional shares at the public offering price, less the underwriting discounts and commissions. If the underwriters exercise this option, each underwriter will be obligated, subject to conditions contained in the underwriting agreement, to purchase a number of additional shares proportionate to that underwriter's initial amount reflected in the above table.

No Sales of Similar Securities

We have agreed that we will not, without the prior written consent of Leerink Partners LLC and Piper Jaffray & Co. offer, sell, contract to sell, pledge, or otherwise dispose of (or enter into any transaction which is designed to, or might reasonably be expected to, result in the disposition (whether by actual disposition or effective economic disposition due to cash settlement or otherwise) by the Company or any affiliate of the Company or any person in privity with the Company or any affiliate of the Company), directly or indirectly, including the filing (or participation in the filing) of a registration statement with the Commission in respect of, or establish or increase a put equivalent position or liquidate or decrease a call equivalent position within the meaning of Section 16 of the Exchange Act, any shares of common stock other than those issued hereunder, or any securities convertible into, or exercisable, or exchangeable for, shares of common stock, which we refer to collectively as Company Securities, or publicly announce an intention to effect any such transaction, for a period of 90 days after the date of the underwriting agreement among us and the underwriters, provided that we may (i) issue and sell Company Securities pursuant to any employee stock option plan, incentive plan, employee stock purchase plan, stock ownership plan or dividend reinvestment plan of ours disclosed herein and in effect as of the date of such underwriting agreement, (ii) issue common stock issuable upon the conversion of securities outstanding as of the date of such underwriting agreement or (iii) file one or more registration statements on Form S-8.

Our executive officers, directors and certain of our principal stockholders have agreed not to sell or transfer any common stock or securities convertible into or exchangeable or exercisable for common stock, for 90 days after the date of the underwriting agreement among us and the underwriters without first obtaining the written consent of Leerink Partners LLC and Piper Jaffray & Co. on behalf of the underwriters. One of our principal stockholders has agreed not to sell or transfer any common stock or securities convertible into or exchangeable or exercisable for common stock, for 45 days after the date of the underwriting agreement among us and the underwriters without first obtaining the written consent of Leerink Partners LLC and Piper Jaffray & Co. on behalf of the underwriters. This lock-up agreement applies to Company Securities, whether owned now, acquired later by the person executing the agreement, or for which the person executing the agreement later acquires the power of disposition. Specifically, these persons have agreed, with certain limited exceptions, not to directly or indirectly:

- offer, sell, contract to sell or pledge any Company Securities;
- sell any option or contract to purchase any Company Securities;
- purchase any option or contract to sell any Company Securities;
- grant any option, right or warrant to purchase any Company Securities; and
- otherwise dispose of or transfer any Company Securities.

Such persons have also agreed not to enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequence of ownership of Company Securities, or to make any demand for or exercise any right with respect to the registration of any shares of common stock or any other Company Securities. The foregoing transactions are prohibited regardless of whether they are to be settled by delivery of common stock or any other Company Securities. The restrictions described in this paragraph and the paragraph immediately preceding it do not apply to our directors, executive officers or shareholders with respect to:

- transfers (1) as a bona fide gift, (2) to any trust for the direct or indirect benefit of the individual or his or her immediate family, (3) as a distribution to partners, members, other shareholders, other equity holders or beneficiaries of such persons, (4) by will, other testamentary document or intestate succession upon the death of such persons, (5) pursuant to orders of a court or regulatory agency or

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(6) to the person's affiliates or to any investment fund or other entity controlled or managed by, or under common control or management by, or any investment fund or other entity that controls or manages, the person; provided that in each case, the transferee agrees to be bound in writing by the same restrictions, and that, in the cases of transfers described in (1), (2), (3) and (6), such transfers do not trigger any filing or reporting obligation or result in any other voluntary or mandatory public disclosure; and

- the establishment of a trading plan pursuant to Rule 10b5-1 under the Exchange Act for the transfer of shares of common stock, provided that such plan does not provide for the transfer of common stock during the restricted period and no public disclosure of the entry into such a trading plan is required or is voluntarily made by any person during the restricted period.

Nasdaq Global Market Listing

Our common stock is listed on The Nasdaq Global Market under the symbol "PTL."

Price Stabilization, Short Positions and Penalty Bids

Until the distribution of the shares is completed, SEC rules may limit underwriters and selling group members from bidding for and purchasing our common stock. However, the representative may engage in transactions that stabilize the price of the common stock, such as bids or purchases to peg, fix or maintain that price.

In connection with the offering, the underwriters may purchase and sell our common stock in the open market. These transactions may include short sales, purchases on the open market to cover positions created by short sales and stabilizing transactions. Short sales involve the sale by the underwriters of a greater number of shares than they are required to purchase in the offering. "Covered" short sales are sales made in an amount not greater than the underwriters' option described above. The underwriters may close out any covered short position by either exercising their option or purchasing shares in the open market. In determining the source of shares to close out the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the option granted to them. "Naked" short sales are sales in excess of such option. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of our common stock in the open market after pricing that could adversely affect investors who purchase in the offering. Stabilizing transactions consist of various bids for or purchases of shares of common stock made by the underwriters in the open market prior to the closing of the offering.

The underwriters may also impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it because the representative has repurchased shares sold by or for the account of such underwriter in stabilizing or short covering transactions.

Similar to other purchase transactions, the underwriters' purchases to cover the syndicate short sales may have the effect of raising or maintaining the market price of our common stock or preventing or retarding a decline in the market price of our common stock. As a result, the price of our common stock may be higher than the price that might otherwise exist in the open market. The underwriters may conduct these transactions on The Nasdaq Global Market, in the over-the-counter market or otherwise.

Neither we nor any of the underwriters make any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of our common stock. In addition, neither we nor any of the underwriters make any representation that the representative will engage in these transactions or that these transactions, once commenced, will not be discontinued without notice.

The underwriters may also engage in passive market making transactions in our common stock on The Nasdaq Global Market in accordance with Rule 103 of Regulation M during a period before the commencement of offers

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or sales of shares of our common stock in this offering and extending through the completion of distribution. A passive market maker must display its bid at a price not in excess of the highest independent bid of that security. However, if all independent bids are lowered below the passive market maker's bid, that bid must then be lowered when specified purchase limits are exceeded.

Electronic Distribution

In connection with the offering, certain of the underwriters or securities dealers may distribute prospectuses by electronic means, such as e-mail.

Other Relationships

The underwriters and certain of their affiliates are full service financial institutions engaged in various activities, which may include securities trading, commercial and investment banking, financial advisory, investment management, investment research, principal investment, hedging, financing and brokerage activities. Some of the underwriters and certain of their affiliates may in the future engage in investment banking and other commercial dealings in the ordinary course of business with us and our affiliates, for which they may in the future receive customary fees, commissions and expenses.

In addition, in the ordinary course of their business activities, the underwriters and their affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers. Such investments and securities activities may involve securities and/or instruments of ours or our affiliates. The underwriters and their affiliates may also make investment recommendations and/or publish or express independent research views in respect of such securities or financial instruments and may hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

Selling Restrictions

Notice to Prospective Investors in the European Economic Area

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive (each, a "Relevant Member State"), with effect from and including the date on which the Prospectus Directive is implemented in that Relevant Member State, no offer of shares may be made to the public in that Relevant Member State other than:

- A. to any legal entity which is a qualified investor as defined in the Prospectus Directive;
- B. to fewer than 150 natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representatives; or
- C. in any other circumstances falling within Article 3(2) of the Prospectus Directive,

provided that no such offer of shares shall require the Company or the representatives to publish a prospectus pursuant to Article 3 of the Prospectus Directive or supplement a prospectus pursuant to Article 16 of the Prospectus Directive.

Each person in a Relevant Member State who initially acquires any shares or to whom any offer is made will be deemed to have represented, acknowledged and agreed that it is a "qualified investor" within the meaning of the law in that Relevant Member State implementing Article 2(1)(e) of the Prospectus Directive. In the case of any shares being offered to a financial intermediary as that term is used in Article 3(2) of the Prospectus Directive, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the shares acquired by it in the offer have not been acquired on a non-discretionary basis on behalf of, nor have they been

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acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer of any shares to the public other than their offer or resale in a Relevant Member State to qualified investors as so defined or in circumstances in which the prior consent of the representatives has been obtained to each such proposed offer or resale.

We, the representatives and each of our and the representatives' and their affiliates will rely upon the truth and accuracy of the foregoing representations, acknowledgements and agreements.

This prospectus supplement has been prepared on the basis that any offer of shares in any Relevant Member State will be made pursuant to an exemption under the Prospectus Directive from the requirement to publish a prospectus for offers of shares. Accordingly, any person making or intending to make an offer in that Relevant Member State of shares which are the subject of the offering contemplated in this prospectus supplement may only do so in circumstances in which no obligation arises for the company or any of the underwriters to publish a prospectus pursuant to Article 3 of the Prospectus Directive in relation to such offer. Neither the company nor the underwriters have authorized, nor do they authorize, the making of any offer of shares in circumstances in which an obligation arises for the company or the underwriters to publish a prospectus for such offer.

For the purpose of the above provisions, the expression "an offer to the public" in relation to any shares in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the shares to be offered so as to enable an investor to decide to purchase or subscribe the shares, as the same may be varied in the Relevant Member State by any measure implementing the Prospectus Directive in the Relevant Member State and the expression "Prospectus Directive" means Directive 2003/71/EC (including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member States) and includes any relevant implementing measure in the Relevant Member State and the expression "2010 PD Amending Directive" means Directive 2010/73/EU.

MiFID II Product Governance

Any person offering, selling or recommending the shares (a "distributor") should take into consideration the manufacturers' target market assessment; however, a distributor subject to MiFID II is responsible for undertaking its own target market assessment in respect of the shares (by either adopting or refining the manufacturers' target market assessment) and determining appropriate distribution channels.

Notice to Prospective Investors in the United Kingdom

In addition, in the United Kingdom, this document is being distributed only to, and is directed only at, and any offer subsequently made may only be directed at persons who are "qualified investors" (as defined in the Prospectus Directive) (i) who have professional experience in matters relating to investments falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended (the "Order") and/or (ii) who are high net worth companies (or persons to whom it may otherwise be lawfully communicated) falling within Article 49(2)(a) to (d) of the Order (all such persons together being referred to as "relevant persons") or otherwise in circumstances which have not resulted and will not result in an offer to the public of the shares in the United Kingdom within the meaning of the Financial Services and Markets Act 2000.

Any person in the United Kingdom that is not a relevant person should not act or rely on the information included in this document or use it as basis for taking any action. In the United Kingdom, any investment or investment activity that this document relates to may be made or taken exclusively by relevant persons.

Notice to Prospective Investors in Canada

The shares may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of

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the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions and Ongoing Registrant Obligations. Any resale of the shares must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus supplement (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

LEGAL MATTERS

The validity of the shares of common stock being offered by this prospectus supplement will be passed upon for us by Goodwin Procter LLP, Boston, Massachusetts. The underwriters are being represented by Ropes & Gray LLP, Boston, Massachusetts.

EXPERTS

The financial statements incorporated in this prospectus supplement by reference to the Annual Report on Form 10-K for the year ended December 31, 2017 have been so incorporated in reliance on the report (which contains an explanatory paragraph relating to the Company's ability to continue as a going concern as described in Note 1 to the financial statements) of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus supplement and the accompanying prospectus are part of the registration statement on Form S-3 we filed with the SEC under the Securities Act and do not contain all the information set forth in the registration statement. Whenever a reference is made in this prospectus supplement or the accompanying prospectus to any of our contracts, agreements or other documents, the reference may not be complete and you should refer to the exhibits that are a part of the registration statement or the exhibits to the reports or other documents incorporated by reference in this prospectus supplement and the accompanying prospectus for a copy of such contract, agreement or other document. Because we are subject to the information and reporting requirements of the Exchange Act, we file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at <http://www.sec.gov>. You may also read and copy any document we file at the SEC's Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of the Public Reference Room.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to "incorporate by reference" the information we file with it, which means that we can disclose important information to you by referring you to those documents. Information incorporated by reference is part of this prospectus supplement and the accompanying prospectus. Later information filed with the SEC will update and supersede this information.

We incorporate by reference the documents listed below and any future filings made with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus supplement until the termination of the offering of the shares covered by this prospectus supplement (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items):

- our Annual Report on Form 10-K for the fiscal year ended December 31, 2017 filed with the SEC on March 14, 2017;
- our definitive proxy statement on Schedule 14A, filed with the SEC on April 19, 2018 with respect to those portions incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2017 (other than the information furnished rather than filed);
- our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2018 and June 30, 2018 filed with the SEC on May 9, 2018 and August 8, 2018, respectively;

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- our Current Reports on Form 8-K filed with the SEC on February 7, 2018, March 23, 2018, April 4, 2018, April 17, 2018, April 23, 2018, May 7, 2018, June 6, 2018 (other than the information furnished rather than filed), June 19, 2018 and October 17, 2018 (other than the information furnished rather than filed);
- the description of our capital stock contained in our registration statement on Form 8-A filed on February 10, 2016, under the Securities Exchange Act of 1934, as amended, including amendment or reports filed for the purpose of updating such description; and
- all of the filings that we make pursuant to the Exchange Act (1) after the date of the filing of the original registration statement and prior to the effectiveness of the registration statement and (2) until all of the securities to which this prospectus relates have been sold or the offering is otherwise terminated (except in each case for information contained in any such filing where we indicate that such information is being furnished and is not considered “filed” under the Exchange Act), which filings will be deemed to be incorporated by reference in this prospectus and to be a part hereof from the date of filing of such documents.

The SEC file number for each of the documents listed above is 001-37695.

Upon request, we will provide, without charge, to each person, including any beneficial owner, to whom a copy of this prospectus supplement is delivered, a copy of the documents incorporated by reference into this prospectus supplement but not delivered with the prospectus supplement. You may request a copy of these filings, and any exhibits we have specifically incorporated by reference as an exhibit in this prospectus supplement, at no cost by writing or telephoning us at the following address:

Proteostasis Therapeutics, Inc., Attention: Investor Relations, 80 Guest Street, Suite 500, Boston, MA 02135, or by telephone request to (617) 225-0096.

In accordance with Rule 412 of the Securities Act, any statement contained in a document incorporated by reference herein shall be deemed modified or superseded to the extent that a statement contained herein or in any other subsequently filed document which also is or is deemed to be incorporated by reference herein modifies or supersedes such statement.

PROSPECTUS



\$100,000,000

**COMMON STOCK
PREFERRED STOCK
DEBT SECURITIES
WARRANTS
UNITS**

This prospectus will allow us to issue, from time to time at prices and on terms to be determined at or prior to the time of the offering, any combination of the securities in this prospectus, either individually or in units. We may also offer common stock or preferred stock upon conversion of the debt securities, common stock upon conversion of the preferred stock, or common stock, preferred stock or debt securities upon the exercise of warrants. In addition, this prospectus may be used to offer securities for the account of persons other than us. This prospectus provides a general description of the securities we may offer. We will provide you with specific terms of any offering in one or more supplements to this prospectus. This prospectus may not be used to offer or sell our securities unless accompanied by a prospectus supplement. You should read this prospectus and any prospectus supplement, as well as any documents incorporated by reference into this prospectus or any prospectus supplement, carefully before you invest.

Our common stock is listed on The NASDAQ Global Market under the symbol "PTI." On April 2, 2018, the last reported sale price of our common stock was \$4.69 per share. Prospective purchasers of our securities are urged to obtain current information as to the market prices of our securities, where applicable.

Investing in our securities involves a high degree of risk. Before deciding whether to invest in our securities, you should consider carefully the risks that we have described on page 3 of this prospectus under the caption "[Risk Factors](#)." We may include specific risk factors in supplements to this prospectus under the caption "Risk Factors."

Our securities may be sold directly to investors, through agents designated from time to time or to or through underwriters or dealers. For additional information on the methods of sale, you should refer to the section entitled "Plan of Distribution" in this prospectus. If any underwriters or agents are involved in the sale of our securities with respect to which this prospectus is being delivered, the names of such underwriters or agents and any applicable commissions or discounts and over-allotment options will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds that we expect to receive from such sale will also be set forth in a prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is April 26, 2018.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, utilizing a “shelf” registration process. Under this shelf registration process, shares of our common stock and preferred stock, various series of debt securities and/or warrants to purchase any of such securities, either individually or in units, may be offered in one or more offerings. This prospectus provides you with a general description of the securities that may be offered. Each time a type or series of securities is offered under this prospectus, we will provide a prospectus supplement that will contain specific information about the terms of that offering.

This prospectus does not contain all of the information included in the registration statement. For a more complete understanding of the offering of the securities, you should refer to the registration statement, including its exhibits. The prospectus supplement may also add, update or change information contained or incorporated by reference in this prospectus. However, no prospectus supplement will offer a security that is not registered and described in this prospectus at the time of its effectiveness. This prospectus, together with the applicable prospectus supplements and the documents incorporated by reference into this prospectus, includes all material information relating to this offering. You should carefully read this prospectus, the applicable prospectus supplements, the information and documents incorporated herein by reference and the additional information under the heading “Where You Can Find More Information” before making an investment decision.

You should rely only on the information we have provided or incorporated by reference in this prospectus or any prospectus supplement. We have not authorized anyone to provide you with information different from that contained or incorporated by reference in this prospectus. No dealer, salesperson or other person is authorized to give any information or to represent anything not contained or incorporated by reference in this prospectus. You must not rely on any unauthorized information or representation. This prospectus is an offer to sell only the securities offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. You should assume that the information in this prospectus or any prospectus supplement is accurate only as of the date on the front of the document and that any information we have incorporated herein by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus or any sale of a security.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference in the accompanying prospectus were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

This prospectus may not be used to consummate sales of our securities, unless it is accompanied by a prospectus supplement. To the extent there are inconsistencies between any prospectus supplement, this prospectus and any documents incorporated by reference, the document with the most recent date will control.

Unless the context otherwise requires, “Proteostasis,” “the Company,” “we,” “us,” “our” and similar names refer to Proteostasis Therapeutics, Inc.

Our trademarks include, without limitation, our name and corporate logo. Other service marks, trademarks and trade names contained in this prospectus, any prospectus supplement or the documents incorporated by reference herein and therein are the property of their respective owners.

PROTEOSTASIS THERAPEUTICS, INC.

About Proteostasis Therapeutics, Inc.

We are an innovative, clinical stage biopharmaceutical company committed to the discovery and development of novel therapeutics to treat cystic fibrosis, or CF, and other diseases caused by an imbalance in the proteostasis network, a set of pathways that control protein biosynthesis, folding, trafficking and clearance. The Company focuses on identifying therapies that restore protein function. CF is a disease caused by defects in the function or abundance of cystic fibrosis transmembrane conductance regulator, or CFTR. Our CF focused pipeline consists of novel CFTR modulators including correctors, potentiators and amplifiers. Upon discovery of amplifiers, a novel class of CFTR modulators, we have exploited its novel mechanism of action as a drug screening tool and have subsequently identified correctors and potentiators to be developed as part of combination therapies. Investigational agents representative of all three classes of CFTR modulators are currently in clinical development and include PTI-428, an amplifier, and PTI-801 a third generation corrector, both of which we believe are amenable for add-on therapy to standard-of-care CFTR modulator treatment and PTI-808, a potentiator intended to be developed as part of a dual combination with PTI-801 and a triple combination that also includes PTI-428 and PTI-801. We are developing and, if approved, intend to commercialize our own therapies, including add-on and combination therapies for CF patients who have at least one F508del mutation, representing the majority of the patient population.

Employees

As of April 2, 2018, we employed 49 employees, including 36 in research and development and 13 in general and administrative. Forty four of these employees are full-time employees, two are part-time employees and three are seasonal interns. We have never had a work stoppage, and none of our employees is represented by a labor organization or under any collective-bargaining arrangements. We consider our employee relations to be good.

Corporate and Available Information

We were incorporated in Delaware on December 13, 2006 under the name Proteoguard, Inc. and subsequently changed our name to Proteostasis Therapeutics, Inc. on September 17, 2007. Our principal executive offices are located at 200 Technology Square, 4th Floor, Cambridge, Massachusetts 02139, and our telephone number is (617) 225-0096. Our website address is www.proteostasis.com. We make our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, and amendments to those reports, available free of charge at our website as soon as reasonably practicable after they have been filed with the SEC. We do not incorporate the information on or accessible through our website into this report, and you should not consider any information contained in, or that can be accessed through, our website as part of this document.

This report contains references to our trademarks and to trademarks belonging to other entities. Solely for convenience, trademarks and trade names referred to in this report, including logos, artwork, and other visual displays, may appear without the ® or ™ symbols, but such references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or the rights of the applicable licensor to these trademarks and trade names. We do not intend our use or display of other companies' trade names or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other companies. Except where the context requires otherwise, the terms "Company," "Proteostasis," "PTI," "we," "us" and "our" used in this report refer to Proteostasis Therapeutics, Inc.

The public may read and copy any materials we file with the SEC at the SEC's Public Reference Room at 100 F Street, NE, Washington, DC 20549. The public may obtain information of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC maintains a website that contains the materials we file with the SEC at www.sec.gov.

RISK FACTORS

Investing in our securities involves risks. You should carefully consider the risk factors contained in the applicable prospectus supplement and any related free writing prospectus for a specific offering of securities, as well as those incorporated by reference in this prospectus, before making an investment decision. You should also carefully consider other information contained and incorporated by reference in this prospectus and any applicable prospectus supplement, including our financial statements and the related notes thereto incorporated by reference in this prospectus. The risks and uncertainties described in the applicable prospectus supplement and our other filings with the SEC incorporated by reference herein are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently consider immaterial may also adversely affect us. If any of the described risks occur, our business, financial condition or results of operations could be materially harmed. In such case, the value of our securities could decline and you may lose all or part of your investment.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

The SEC encourages companies to disclose forward-looking information so that investors can better understand a company's future prospects and make informed investment decisions. This prospectus and the documents we have filed with the SEC that are incorporated herein by reference contain such "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995.

Words such as "may," "anticipate," "estimate," "expects," "projects," "intends," "plans," "believes," "tracking" and words and terms of similar substance used in connection with any discussion of future operating or financial performance, identify forward-looking statements. Forward-looking statements represent management's present judgment regarding future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially from those described in the forward-looking statements. These risks include, but are not limited to, risks and uncertainties regarding our preclinical and clinical studies, our ability to conduct clinical trials of our product candidates and the results of such trials, as well as risks and uncertainties relating to litigation, government regulation and third-party reimbursement, economic conditions, markets, products, competition, intellectual property, services and prices, key employees, future capital needs and other factors. Please also see the discussion of risks and uncertainties under the caption "Risk Factors" contained in any supplements to this prospectus and in our most recent annual report on Form 10-K, as revised or supplemented by our most recent quarterly report on Form 10-Q, as well as any amendments thereto, as filed with the SEC and which are incorporated herein by reference.

In light of these assumptions, risks and uncertainties, the results and events discussed in the forward-looking statements contained in this prospectus or in any document incorporated herein by reference might not occur. Investors are cautioned not to place undue reliance on the forward-looking statements, which speak only as of the date of this prospectus or the date of the document incorporated by reference in this prospectus. We are not under any obligation, and we expressly disclaim any obligation, to update or alter any forward-looking statements, whether as a result of new information, future events or otherwise. All subsequent forward-looking statements attributable to us or to any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to in this section.

RATIO OF EARNINGS TO FIXED CHARGES

Our ratio of earnings to fixed charges for each of the five most recently completed fiscal years and any required interim periods will each be specified in a prospectus supplement or in a document that we file with the SEC and incorporate by reference pertaining to the issuance, if any, by us of debt securities or preference securities in the future.

USE OF PROCEEDS

We will retain broad discretion over the use of the net proceeds from the sale of the securities offered hereby. Except as provided in the applicable prospectus supplement or any related free writing prospectus that we may authorize to be provided to you, we intend to use the net proceeds from the sale of the securities by us through this prospectus for general corporate purposes, which may include capital expenditures, working capital and general and administrative expenses. We may also use a portion of the net proceeds to acquire or invest in businesses, products and technologies that are complementary to our own, although we have no current plans, commitments or agreements with respect to any acquisitions as of the date of this prospectus. We will set forth in the applicable prospectus supplement or free writing prospectus our intended use for the net proceeds received from the sale of any securities sold pursuant to the prospectus supplement or free writing prospectus. Pending these uses, we intend to invest the net proceeds in short-term obligations of the U.S. treasury securities and U.S. government-sponsored enterprise securities.

DESCRIPTION OF CAPITAL STOCK

We are authorized to issue 125,000,000 shares of common stock, par value \$0.001 per share, and 5,000,000 shares of preferred stock, par value \$0.001 per share. On April 2, 2018, we had 34,482,574 shares of common stock outstanding and approximately 23 shareholders of record.

The following summary of certain provisions of our capital stock does not purport to be complete. You should refer to our amended and restated certificate of incorporation and our amended and restated by-laws, both of which are included as exhibits to the registration statement we have filed with the SEC in connection with this offering. The summary below is also qualified by provisions of applicable law.

Common Stock

We are authorized to issue one class of common stock. Holders of our common stock are entitled to one vote for each share of common stock held of record for the election of directors and on all matters submitted to a vote of stockholders. Holders of our common stock are entitled to receive dividends ratably, if any, as may be declared by our board of directors out of legally available funds, subject to any preferential dividend rights of any preferred stock then outstanding. Upon our dissolution, liquidation or winding up, holders of our common stock are entitled to share ratably in our net assets legally available after the payment of all our debts and other liabilities, subject to the preferential rights of any preferred stock then outstanding. Holders of our common stock have no preemptive, subscription, redemption or conversion rights. The rights, preferences and privileges of holders of common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future. Except as described under “Antitakeover Effects of Delaware Law and Provisions of our Amended and Restated Certificate of Incorporation and Amended and Restated By-laws” below, a majority vote of the holders of common stock is generally required to take action under our amended and restated certificate of incorporation and amended and restated by-laws.

Preferred Stock

Our board of directors are authorized, without action by the stockholders, to designate and issue up to an aggregate of 5,000,000 shares of preferred stock in one or more series. Our board of directors can designate the rights, preferences and privileges of the shares of each series and any of its qualifications, limitations or restrictions. Our board of directors may authorize the issuance of preferred stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of common stock. The issuance of preferred stock, while providing flexibility in connection with possible future financings and acquisitions and other corporate purposes could, under certain circumstances, have the effect of restricting dividends on our common stock, diluting the voting power of our common stock, impairing the liquidation rights of our common stock, or delaying, deferring or preventing a change in control of our company, which might harm the market price of our common stock. See also “Antitakeover Effects of Delaware Law and Provisions of our Amended and Restated Certificate of Incorporation and Amended and Restated By-laws—Provisions of our Amended and Restated Certificate of Incorporation and Amended and Restated By-laws—Undesignated preferred stock” below.

If a specific series of preferred stock is offered under this prospectus, we will describe the terms of the preferred stock in the prospectus supplement for such offering and will file a copy of the certificate establishing the terms of the preferred stock with the SEC. To the extent required, this description will include:

- the title and stated value;
- the number of shares offered, the liquidation preference per share and the purchase price;
- the dividend rate(s), period(s) and/or payment date(s), or method(s) of calculation for such dividends;

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- whether dividends will be cumulative or non-cumulative and, if cumulative, the date from which dividends will accumulate;
- the procedures for any auction and remarketing, if any;
- the provisions for a sinking fund, if any;
- the provisions for redemption, if applicable;
- any listing of the preferred stock on any securities exchange or market;
- whether the preferred stock will be convertible into our common stock, and, if applicable, the conversion price (or how it will be calculated) and conversion period;
- whether the preferred stock will be exchangeable into debt securities, and, if applicable, the exchange price (or how it will be calculated) and exchange period;
- voting rights, if any, of the preferred stock;
- a discussion of any material and/or special United States federal income tax considerations applicable to the preferred stock;
- the relative ranking and preferences of the preferred stock as to dividend rights and rights upon liquidation, dissolution or winding up of the affairs of Proteostasis; and
- any material limitations on issuance of any class or series of preferred stock ranking senior to or on a parity with the series of preferred stock as to dividend rights and rights upon liquidation, dissolution or winding up of Proteostasis.

Registration Rights

The holders of 6,831,803 shares of our common stock, or their permitted transferees, are entitled to rights with respect to the registration of these securities under the Securities Act. These rights are provided under the terms of a stockholders' agreement between us and the holders of our preferred stock. The stockholders' agreement includes demand registration rights, short-form registration rights and piggyback registration rights. All fees, costs and expenses of underwritten registrations under the stockholders' agreement will be borne by us and all selling expenses, including underwriting discounts and selling commissions, will be borne by the holders of the shares being registered.

Demand Registration Rights

The holders of 6,831,803 shares of our common stock, including shares issuable upon the conversion of preferred stock or their permitted transferees, are entitled to demand registration rights. Under the terms of the stockholders' agreement, we will be required, upon the written request of holders of two-thirds of these securities, to use our best efforts to file a registration statement and use reasonable, diligent efforts to effect the registration of all or a portion of these shares for public resale. We are required to effect only two registrations pursuant to this provision of the stockholders' agreement.

Short Form Registration Rights

The holders of 6,831,803 shares of our common stock, or their permitted transferees, are also entitled to short form registration rights. Pursuant to the stockholders' agreement, if we are eligible to file a registration statement on Form S-3, upon the written request of any of these holders to sell registrable securities at an aggregate price of at least \$1,000,000, we will be required to use our best efforts to affect a registration of such shares. We are required to effect only two registrations in any twelve month period pursuant to this provision of the stockholders' agreement.

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Piggyback Registration Rights

The holders of 6,831,803 shares of our common stock, or their permitted transferees, are entitled to piggyback registration rights. If we register any of our securities either for our own account or for the account of other security holders, the holders of these shares are entitled to include their shares in the registration. Subject to certain exceptions contained in the stockholders' agreement, we and the underwriters may limit the number of shares included in the underwritten offering if the underwriters determine in good faith that marketing factors require a limitation of the number of shares to be underwritten.

Indemnification

Our stockholders' agreement contains customary cross-indemnification provisions, under which we are obligated to indemnify holders of registrable securities in the event of material misstatements or omissions in the registration statement attributable to us, and they are obligated to indemnify us for material misstatements or omissions attributable to them.

Expiration of Registration Rights

The registration rights granted under the investor rights agreement will terminate upon the earlier of (i) a deemed liquidation event, as defined in our amended and restated certificate of incorporation or (ii) at such time when all registrable securities could be sold without restriction under Rule 144 of the Securities Act.

Antitakeover Effects of Delaware Law and Provisions of our Amended and Restated Certificate of Incorporation and Amended and Restated By-Laws

Certain provisions of the Delaware General Corporation Law and of our amended and restated certificate of incorporation and amended and restated by-laws could have the effect of delaying, deferring or discouraging another party from acquiring control of us. These provisions, which are summarized below, are expected to discourage certain types of coercive takeover practices and inadequate takeover bids and, as a consequence, they might also inhibit temporary fluctuations in the market price of our common stock that often result from actual or rumored hostile takeover attempts. These provisions are also designed in part to encourage anyone seeking to acquire control of us to first negotiate with our board of directors. These provisions might also have the effect of preventing changes in our management. It is possible that these provisions could make it more difficult to accomplish transactions that stockholders might otherwise deem to be in their best interests. However, we believe that the advantages gained by protecting our ability to negotiate with any unsolicited and potentially unfriendly acquirer outweigh the disadvantages of discouraging such proposals, including those priced above the then-current market value of our common stock, because, among other reasons, the negotiation of such proposals could improve their terms.

Delaware Takeover Statute

We are subject to the provisions of Section 203 of the Delaware General Corporation Law. In general, Section 203 prohibits a publicly held Delaware corporation from engaging in a "business combination" with an "interested stockholder" for a three-year period following the time that this stockholder becomes an interested stockholder, unless the business combination is approved in a prescribed manner. Under Section 203, a business combination between a corporation and an interested stockholder is prohibited unless it satisfies one of the following conditions:

- before the stockholder became interested, our board of directors approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;
- upon consummation of the transaction which resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the voting

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stock outstanding, shares owned by persons who are directors and also officers, and employee stock plans, in some instances, but not the outstanding voting stock owned by the interested stockholder; or

- at or after the time the stockholder became interested, the business combination was approved by our board of directors and authorized at an annual or special meeting of the stockholders by the affirmative vote of at least two-thirds of the outstanding voting stock which is not owned by the interested stockholder.

Section 203 defines a business combination to include:

- any merger or consolidation involving the corporation and the interested stockholder;
- any sale, transfer, lease, pledge or other disposition involving the interested stockholder of 10% or more of the assets of the corporation;
- subject to exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;
- subject to exceptions, any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder; or
- the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

In general, Section 203 defines an interested stockholder as any entity or person beneficially owning 15% or more of the outstanding voting stock of the corporation and any entity or person affiliated with or controlling or controlled by the entity or person.

Provisions of our Amended and Restated Certificate of Incorporation and Amended and Restated By-laws

Our amended and restated certificate of incorporation and amended and restated by-laws include a number of provisions that may have the effect of delaying, deferring or discouraging another party from acquiring control of us and encouraging persons considering unsolicited tender offers or other unilateral takeover proposals to negotiate with our board of directors rather than pursue non-negotiated takeover attempts. These provisions include the items described below.

Board composition and filling vacancies. In accordance with our amended and restated certificate of incorporation, our board is divided into three classes serving staggered three-year terms, with one class being elected each year. Our amended and restated certificate of incorporation also provides that directors may be removed only for cause and then only by the affirmative vote of the holders of 75% or more of the shares then entitled to vote at an election of directors. Furthermore, any vacancy on our board of directors, however occurring, including a vacancy resulting from an increase in the size of our board, may only be filled by the affirmative vote of a majority of our directors then in office even if less than a quorum.

No written consent of stockholders. Our amended and restated certificate of incorporation provides that all stockholder actions are required to be taken by a vote of the stockholders at an annual or special meeting, and that stockholders may not take any action by written consent in lieu of a meeting. This limit may lengthen the amount of time required to take stockholder actions and would prevent the amendment of our by-laws or removal of directors by our stockholder without holding a meeting of stockholders.

Meetings of stockholders. Our amended and restated by-laws provide that only a majority of the members of our board of directors then in office may call special meetings of stockholders and only those matters set forth in the notice of the special meeting may be considered or acted upon at a special meeting of stockholders. Our amended and restated by-laws limit the business that may be conducted at an annual meeting of stockholders to those matters properly brought before the meeting.

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Advance notice requirements. Our amended and restated by-laws establish advance notice procedures with regard to stockholder proposals relating to the nomination of candidates for election as directors or new business to be brought before meetings of our stockholders. These procedures provide that notice of stockholder proposals must be timely given in writing to our corporate secretary prior to the meeting at which the action is to be taken. Generally, to be timely, notice must be received at our principal executive offices not less than 90 days or more than 120 days prior to the first anniversary date of the annual meeting for the preceding year. The notice must contain certain information specified in our amended and restated by-laws.

Amendment to certificate of incorporation and by-laws. As required by the Delaware General Corporation Law, any amendment of our amended and restated certificate of incorporation must first be approved by a majority of our board of directors, and if required by law or our amended and restated certificate of incorporation, must thereafter be approved by a majority of the outstanding shares entitled to vote on the amendment, and a majority of the outstanding shares of each class entitled to vote thereon as a class, except that the amendment of the provisions relating to stockholder action, directors, limitation of liability and the amendment of our amended and restated certificate of incorporation must be approved by not less than 75% of the outstanding shares entitled to vote on the amendment, and not less than 75% of the outstanding shares of each class entitled to vote thereon as a class. Our amended and restated by-laws may be amended by the affirmative vote of a majority vote of the directors then in office, subject to any limitations set forth in the amended and restated by-laws; and may also be amended by the affirmative vote of at least 75% of the outstanding shares entitled to vote on the amendment, or, if the board of directors recommends that the stockholders approve the amendment, by the affirmative vote of the majority of the outstanding shares entitled to vote on the amendment, in each case voting together as a single class.

Undesignated preferred stock. Our amended and restated certificate of incorporation provides for authorized shares of preferred stock. The existence of authorized but unissued shares of preferred stock may enable our board of directors to render more difficult or to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise. For example, if in the due exercise of its fiduciary obligations, our board of directors were to determine that a takeover proposal is not in the best interests of us or our stockholders, our board of directors could cause shares of preferred stock to be issued without stockholder approval in one or more private offerings or other transactions that might dilute the voting or other rights of the proposed acquirer or insurgent stockholder or stockholder group. In this regard, our amended and restated certificate of incorporation grants our board of directors broad power to establish the rights and preferences of authorized and unissued shares of preferred stock. The issuance of shares of preferred stock could decrease the amount of earnings and assets available for distribution to holders of shares of common stock. The issuance may also adversely affect the rights and powers, including voting rights, of these holders and may have the effect of delaying, deterring or preventing a change in control of us.

Choice of forum. Our amended and restated by-laws provide that the Court of Chancery of the State of Delaware is the sole and exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a breach of fiduciary duty, any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our certificate of incorporation or our by-laws, or any action asserting a claim against us that is governed by the internal affairs doctrine. Although our amended and restated by-laws contain the choice of forum provision described above, it is possible that a court could rule that such a provision is inapplicable for a particular claim or action or that such provision is unenforceable.

Limitations on Liability and Indemnification of Officers and Directors. Our amended and restated certificate of incorporation and amended and restated by-laws limit the liability of our officers and directors to the fullest extent permitted by the Delaware General Corporation Law and provides that we will indemnify them to the fullest extent permitted by such law.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company, LLC.

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The NASDAQ Global Market

Our common stock is listed for quotation on The NASDAQ Global Market under the symbol “PTI.” On April 2, 2018 the last reported sale price of our common stock was \$4.69 per share.

DESCRIPTION OF DEBT SECURITIES

The following description, together with the additional information we include in any applicable prospectus supplements, summarizes the material terms and provisions of the debt securities that may be offered under this prospectus. While the terms we have summarized below will apply generally to any future debt securities that may be offered pursuant to this prospectus, we will describe the particular terms of any debt securities that may be offered in more detail in the applicable prospectus supplement. If we so indicate in a prospectus supplement, the terms of any debt securities offered under that prospectus supplement may differ from the terms we describe below, and to the extent the terms set forth in a prospectus supplement differ from the terms described below, the terms set forth in the prospectus supplement shall control.

Under this prospectus, debt securities, which may be senior or subordinated, may be sold from time to time, in one or more offerings. We will issue any such senior debt securities under a senior indenture that we will enter into with a trustee to be named in the senior indenture. We will issue any such subordinated debt securities under a subordinated indenture, which we will enter into with a trustee to be named in the subordinated indenture. We have filed forms of these documents as exhibits to the registration statement, which includes this prospectus. We use the term “indentures” to refer to both the senior indenture and the subordinated indenture. The indentures will be qualified under the Trust Indenture Act of 1939, as in effect on the date of the indenture, or the Trust Indenture Act. We use the term “debenture trustee” to refer to either the trustee under the senior indenture or the trustee under the subordinated indenture, as applicable.

The following summaries of material provisions of the senior debt securities, the subordinated debt securities and the indentures are subject to, and qualified in their entirety by reference to, all the provisions of the indenture applicable to a particular series of debt securities.

General

Each indenture provides that debt securities may be issued from time to time in one or more series and may be denominated and payable in United States dollars or foreign currencies or units based on or relating to United States dollars or foreign currencies, including euros. Neither indenture limits the amount of debt securities that may be issued thereunder, and each indenture provides that the specific terms of any series of debt securities shall be set forth in, or determined pursuant to, an authorizing resolution and/or a supplemental indenture, if any, relating to such series.

We will describe in each prospectus supplement the following terms relating to a series of debt securities:

- the title;
- the aggregate principal amount and any limit on the amount that may be issued;
- the currency or units based on or relating to currencies in which debt securities of such series are denominated and the currency or units in which principal or interest or both will or may be payable;
- whether we will issue the series of debt securities in global form, the terms of any global securities and who the depositary will be;
- the maturity date and the date or dates on which principal will be payable;
- the interest rate, which may be fixed or variable, or the method for determining the rate and the date interest will begin to accrue, the date or dates interest will be payable and the record dates for interest payment dates or the method for determining such dates;
- whether or not the debt securities will be secured or unsecured, and the terms of any secured debt;
- the terms of the subordination of any series of subordinated debt;
- the place or places where payments will be payable;

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- our right, if any, to defer payment of interest and the maximum length of any such deferral period;
- the date, if any, after which, and the price at which, we may, at our option, redeem the series of debt securities pursuant to any optional redemption provisions;
- the date, if any, on which, and the price at which we are obligated, pursuant to any mandatory sinking fund provisions or otherwise, to redeem, or at the holder's option to purchase, the series of debt securities;
- whether the indenture will restrict our ability to pay dividends, or will require us to maintain any asset ratios or reserves;
- whether we will be restricted from incurring any additional indebtedness;
- a discussion on any material or special United States federal income tax considerations applicable to a series of debt securities;
- the denominations in which we will issue the series of debt securities, if other than denominations of \$1,000 and any integral multiple thereof; and
- any other specific terms, preferences, rights or limitations of, or restrictions on, the debt securities.

We may issue debt securities that provide for an amount less than their stated principal amount to be due and payable upon declaration of acceleration of their maturity pursuant to the terms of the indenture. We will provide you with information on the federal income tax considerations and other special considerations applicable to any of these debt securities in the applicable prospectus supplement.

Conversion or Exchange Rights

We will set forth in the prospectus supplement the terms, if any, on which a series of debt securities may be convertible into or exchangeable for our common stock or our other securities. We will include provisions as to whether conversion or exchange is mandatory, at the option of the holder or at our option. We may include provisions pursuant to which the number of shares of our common stock or our other securities that the holders of the series of debt securities receive would be subject to adjustment.

Consolidation, Merger or Sale; No Protection in Event of a Change of Control or Highly Leveraged Transaction

The indentures may not contain any covenant that restricts our ability to merge or consolidate, or sell, convey, transfer or otherwise dispose of all or substantially all of our assets. However, any successor to or acquirer of such assets will be required to assume all of our obligations under the indentures or the debt securities, as appropriate.

Unless we state otherwise in the applicable prospectus supplement, the debt securities will not contain any provisions that may afford holders of the debt securities protection in the event we have a change of control or in the event of a highly leveraged transaction (whether or not such transaction results in a change of control), which could adversely affect holders of debt securities.

Events of Default Under the Indenture

The following will be events of default under the indentures with respect to any series of debt securities that we may issue:

- if we fail to pay interest when due and our failure continues for 90 days and the time for payment has not been extended or deferred;

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- if we fail to pay the principal, or premium, if any, when due and the time for payment has not been extended or delayed;
- if we fail to observe or perform any other covenant relating to such series contained in the debt securities of such series or the applicable indentures, other than a covenant specifically relating to and for the benefit of holders of another series of debt securities, and our failure continues for 90 days after we receive written notice from the debenture trustee or holders of not less than a majority in aggregate principal amount of the outstanding debt securities of the applicable series; and
- if specified events of bankruptcy, insolvency or reorganization occur as to us.

No event of default with respect to a particular series of debt securities (except as to certain events of bankruptcy, insolvency or reorganization) necessarily constitutes an event of default with respect to any other series of debt securities. The occurrence of an event of default may constitute an event of default under any bank credit agreements we may have in existence from time to time. In addition, the occurrence of certain events of default or an acceleration under the indenture may constitute an event of default under certain of our other indebtedness outstanding from time to time.

If an event of default with respect to debt securities of any series at the time outstanding occurs and is continuing, then the trustee or the holders of not less than a majority in principal amount of the outstanding debt securities of that series may, by a notice in writing to us (and to the debenture trustee if given by the holders), declare to be due and payable immediately the principal (or, if the debt securities of that series are discount securities, that portion of the principal amount as may be specified in the terms of that series) of and premium and accrued and unpaid interest, if any, on all debt securities of that series. Before a judgment or decree for payment of the money due has been obtained with respect to debt securities of any series, the holders of a majority in principal amount of the outstanding debt securities of that series (or, at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) may rescind and annul the acceleration if all events of default, other than the non-payment of accelerated principal, premium, if any, and interest, if any, with respect to debt securities of that series, have been cured or waived as provided in the applicable indenture (including payments or deposits in respect of principal, premium or interest that had become due other than as a result of such acceleration). We refer you to the prospectus supplement relating to any series of debt securities that are discount securities for the particular provisions relating to acceleration of a portion of the principal amount of such discount securities upon the occurrence of an event of default.

Subject to the terms of the indentures, if an event of default under an indenture shall occur and be continuing, the debenture trustee will be under no obligation to exercise any of its rights or powers under such indenture at the request or direction of any of the holders of the applicable series of debt securities, unless such holders have offered the debenture trustee reasonable indemnity. The holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the debenture trustee or exercising any trust or power conferred on the debenture trustee, with respect to the debt securities of that series, provided that:

- the direction so given by the holder is not in conflict with any law or the applicable indenture; and
- subject to its duties under the Trust Indenture Act, the debenture trustee need not take any action that might involve it in personal liability or might be unduly prejudicial to the holders not involved in the proceeding.
- A holder of the debt securities of any series will only have the right to institute a proceeding under the indentures or to appoint a receiver or trustee, or to seek other remedies if:
 - the holder previously has given written notice to the debenture trustee of a continuing event of default with respect to that series;

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- the holders of at least a majority in aggregate principal amount of the outstanding debt securities of that series have made written request, and such holders have offered reasonable indemnity to the debenture trustee to institute the proceeding as trustee; and
- the debenture trustee does not institute the proceeding, and does not receive from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series (or at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) other conflicting directions within 60 days after the notice, request and offer.

These limitations will not apply to a suit instituted by a holder of debt securities if we default in the payment of the principal, premium, if any, or interest on, the debt securities.

We will periodically file statements with the applicable debenture trustee regarding our compliance with specified covenants in the applicable indenture.

Modification of Indenture; Waiver

The debenture trustee and we may change the applicable indenture without the consent of any holders with respect to specific matters, including:

- to fix any ambiguity, defect or inconsistency in the indenture; and
- to change anything that does not materially adversely affect the interests of any holder of debt securities of any series issued pursuant to such indenture.

In addition, under the indentures, the rights of holders of a series of debt securities may be changed by us and the debenture trustee with the written consent of the holders of at least a majority in aggregate principal amount of the outstanding debt securities of each series (or, at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) that is affected. However, the debenture trustee and we may make the following changes only with the consent of each holder of any outstanding debt securities affected:

- extending the fixed maturity of the series of debt securities;
- reducing the principal amount, reducing the rate of or extending the time of payment of interest, or a premium payable upon the redemption of any debt securities;
- reducing the principal amount of discount securities payable upon acceleration of maturity;
- making the principal of or premium or interest on any debt security payable in currency other than that stated in the debt security; or
- reducing the percentage of debt securities, the holders of which are required to consent to any amendment or waiver.

Except for certain specified provisions, the holders of at least a majority in principal amount of the outstanding debt securities of any series (or, at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) may on behalf of the holders of all debt securities of that series waive our compliance with provisions of the indenture. The holders of a majority in principal amount of the outstanding debt securities of any series may on behalf of the holders of all the debt securities of such series waive any past default under the indenture with respect to that series and its consequences, except a default in the payment of the principal of, premium or any interest on any debt security of that series or in respect of a covenant or provision, which cannot be modified or amended without the consent of the holder of each outstanding debt security of the series affected; provided, however, that the holders of a majority in principal amount of the outstanding debt securities of any series may rescind an acceleration and its consequences, including any related payment default that resulted from the acceleration.

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Discharge

Each indenture will provide that we can elect to be discharged from our obligations with respect to one or more series of debt securities, except for obligations to:

- register the transfer or exchange of debt securities of the series;
- replace stolen, lost or mutilated debt securities of the series;
- maintain paying agencies;
- hold monies for payment in trust;
- compensate and indemnify the trustee; and
- appoint any successor trustee.

In order to exercise our rights to be discharged with respect to a series, we will have to deposit with the trustee money or government obligations sufficient to pay all the principal of, any premium, if any, and interest on, the debt securities of the series on the dates payments are due.

Form, Exchange, and Transfer

We will issue the debt securities of each series only in fully registered form without coupons and, unless we otherwise specify in the applicable prospectus supplement, in denominations of \$1,000 and any integral multiple thereof. The indentures provide that we may issue debt securities of a series in temporary or permanent global form and as book-entry securities that will be deposited with, or on behalf of, The Depository Trust Company or another depository named by us and identified in a prospectus supplement with respect to that series.

At the option of the holder, subject to the terms of the indentures and the limitations applicable to global securities described in the applicable prospectus supplement, the holder of the debt securities of any series can exchange the debt securities for other debt securities of the same series, in any authorized denomination and of like tenor and aggregate principal amount.

Subject to the terms of the indentures and the limitations applicable to global securities set forth in the applicable prospectus supplement, holders of the debt securities may present the debt securities for exchange or for registration of transfer, duly endorsed or with the form of transfer endorsed thereon duly executed if so required by us or the security registrar, at the office of the security registrar or at the office of any transfer agent designated by us for this purpose. Unless otherwise provided in the debt securities that the holder presents for transfer or exchange or in the applicable indenture, we will make no service charge for any registration of transfer or exchange, but we may require payment of any taxes or other governmental charges.

We will name in the applicable prospectus supplement the security registrar, and any transfer agent in addition to the security registrar, that we initially designate for any debt securities. We may at any time designate additional transfer agents or rescind the designation of any transfer agent or approve a change in the office through which any transfer agent acts, except that we will be required to maintain a transfer agent in each place of payment for the debt securities of each series.

If we elect to redeem the debt securities of any series, we will not be required to:

- issue, register the transfer of, or exchange any debt securities of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption of any debt securities that may be selected for redemption and ending at the close of business on the day of the mailing; or
- register the transfer of or exchange any debt securities so selected for redemption, in whole or in part, except the unredeemed portion of any debt securities we are redeeming in part.

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Information Concerning the Debenture Trustee

The debenture trustee other than during the occurrence and continuance of an event of default under the applicable indenture, will undertake to perform only those duties as are specifically set forth in the applicable indenture. Upon an event of default under an indenture, the debenture trustee under such indenture must use the same degree of care as a prudent person would exercise or use in the conduct of his or her own affairs. Subject to this provision, the debenture trustee is under no obligation to exercise any of the powers given it by the indentures at the request of any holder of debt securities unless it is offered reasonable security and indemnity against the costs, expenses and liabilities that it might incur.

Payment and Paying Agents

Unless we indicate otherwise in the applicable prospectus supplement, on any interest payment date, we will pay the interest on any debt securities to the person in whose name such debt securities, or one or more predecessor securities, are registered at the close of business on the regular record date for the interest.

We will pay principal of and any premium and interest on the debt securities of a particular series at the office of the paying agents designated by us, except that unless we otherwise indicate in the applicable prospectus supplement, we will make interest payments by check which we will mail to the holder. Unless we otherwise indicate in a prospectus supplement, we will designate the corporate trust office of the debenture trustee in the City of New York as our sole paying agent for payments with respect to debt securities of each series. We will name in the applicable prospectus supplement any other paying agents that we initially designate for the debt securities of a particular series. We will maintain a paying agent in each place of payment for the debt securities of a particular series.

All money we pay to a paying agent or the debenture trustee for the payment of the principal of or any premium or interest on any debt securities which remains unclaimed at the end of two years after such principal, premium or interest has become due and payable will be repaid to us, and the holder of the security thereafter may look only to us for payment thereof.

Governing Law

The indentures and the debt securities will be governed by and construed in accordance with the laws of the State of New York, except to the extent that the Trust Indenture Act is applicable.

Subordination of Subordinated Debt Securities

Our obligations pursuant to any subordinated debt securities will be unsecured and will be subordinate and junior in priority of payment to certain of our other indebtedness to the extent described in a prospectus supplement. The subordinated indenture does not limit the amount of senior indebtedness we may incur. It also does not limit us from issuing any other secured or unsecured debt.

DESCRIPTION OF WARRANTS

Warrants to purchase shares of our common stock, preferred stock and/or debt securities in one or more series together with other securities or separately may be offered, as described in the applicable prospectus supplement. Below is a description of certain general terms and provisions of the warrants that may be offered. Particular terms of the warrants will be described in the warrant agreements and the prospectus supplement to the warrants.

The applicable prospectus supplement will contain, where applicable, the following terms of and other information relating to the warrants:

- the specific designation and aggregate number of, and the price at which the warrants will be issued;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- the designation, amount and terms of the securities purchasable upon exercise of the warrants;
- if applicable, the exercise price for shares of our common stock and the number of shares of common stock to be received upon exercise of the warrants;
- if applicable, the exercise price for shares of our preferred stock, the number of shares of preferred stock to be received upon exercise, and a description of that series of our preferred stock;
- if applicable, the exercise price for our debt securities, the amount of debt securities to be received upon exercise, and a description of that series of debt securities;
- the date on which the right to exercise the warrants will begin and the date on which that right will expire or, if you may not continuously exercise the warrants throughout that period, the specific date or dates on which you may exercise the warrants;
- whether the warrants will be issued in fully registered form or bearer form, in definitive or global form or in any combination of these forms, although, in any case, the form of a warrant included in a unit will correspond to the form of the unit and of any security included in that unit;
- any applicable material United States federal income tax consequences;
- if applicable, the identity of the warrant agent for the warrants and of any other depositaries, execution or paying agents, transfer agents, registrars or other agents;
- the proposed listing, if any, of the warrants or any securities purchasable upon exercise of the warrants on any securities exchange;
- if applicable, the date from and after which the warrants and the common stock, preferred stock and/or debt securities will be separately transferable;
- if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;
- information with respect to book-entry procedures, if any;
- the anti-dilution provisions of the warrants, if any;
- any redemption or call provisions;
- whether the warrants are to be sold separately or with other securities as parts of units; and
- any additional terms of the warrants, including terms, procedures and limitations relating to the exchange and exercise of the warrants.

DESCRIPTION OF UNITS

Units consisting of common stock, preferred stock, debt securities and/or warrants for the purchase of common stock, preferred stock and/or debt securities in one or more series may be offered. In this prospectus, we have summarized certain general features of the units. We urge you, however, to read the prospectus supplements related to the series of units being offered, as well as the unit agreements that contain the terms of the units. We will file as exhibits to an amendment to the registration statement of which this prospectus is a part, or will incorporate by reference from a current report on Form 8-K that we file with the SEC, as applicable, the form of unit agreement and any supplemental agreements that describe the terms of the series of units being offered before the issuance of the related series of units.

We may evidence each series of units by unit certificates that would issue under a separate agreement that we may enter into with a unit agent. Each unit agent, if one is appointed, will be a bank or trust company that we select. We will indicate the name and address of the unit agent, if one is appointed, in the applicable prospectus supplement relating to a particular series of units.

PLAN OF DISTRIBUTION

We may sell the securities from time to time pursuant to underwritten public offerings, negotiated transactions, block trades or a combination of these methods. We may sell the securities to or through underwriters or dealers, through agents, or directly to one or more purchasers. The securities may be distributed from time to time in one or more transactions:

- at a fixed price or prices, which may be changed;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

We may also sell equity securities covered by this registration statement in an “at the market offering” as defined in Rule 415 under the Securities Act. Such offering may be made into an existing trading market for such securities in transactions at other than a fixed price, either:

- on or through the facilities of the Nasdaq Global Market or any other securities exchange or quotation or trading service on which such securities may be listed, quoted or traded at the time of sale; and/or
- to or through a market maker other than on the Nasdaq Global Market or such other securities exchanges or quotation or trading services.

Such at-the-market offerings, if any, may be conducted by underwriters acting as principal or agent.

Each time we offer and sell securities hereto, we will provide a prospectus supplement (and any related free writing prospectus that we may authorize to be provided to you) that will set forth the terms of the offering of the securities, including:

- the name or names of the underwriters, if any;
- the purchase price of the securities and the proceeds we will receive from the sale;
- any over-allotment options under which underwriters may purchase additional securities;
- any agency fees or underwriting discounts and other items constituting agents’ or underwriters’ compensation;
- any public offering price;
- any discounts or concessions allowed or re-allowed or paid to dealers; and
- any securities exchange or market on which the securities may be listed.

Only underwriters named in the prospectus supplement are underwriters of the securities offered by the prospectus supplement.

If underwriters are used in the sale, they will acquire the securities for their own account and may resell the securities from time to time in one or more transactions at a fixed public offering price or at varying prices determined at the time of sale. The obligations of the underwriters to purchase the securities will be subject to the conditions set forth in the applicable underwriting agreement. We may offer the securities to the public through underwriting syndicates represented by managing underwriters or by underwriters without a syndicate. Subject to certain conditions, the underwriters will be obligated to purchase all of the securities offered by the prospectus supplement, other than securities covered by any over-allotment option. Any public offering price and any discounts or concessions allowed or re-allowed or paid to dealers may change from time to time. We may use underwriters with whom we have a material relationship. The prospectus supplement, naming the underwriter, will describe the nature of any such relationship.

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We may sell securities directly or through agents we or they designate from time to time. The prospectus supplement will name any agent involved in the offering and sale of securities and any commissions we will pay to them. Unless the prospectus supplement states otherwise, any agent will be acting on a best-efforts basis for the period of its appointment.

We may authorize agents or underwriters to solicit offers by certain purchasers to purchase securities from us at the public offering price set forth in the prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified date in the future. The prospectus supplement will set forth the conditions to these contracts and any commissions we must pay for solicitation of these contracts.

We may provide agents and underwriters with indemnification against civil liabilities, including liabilities under the Securities Act, or contribution with respect to payments that the agents or underwriters may make with respect to these liabilities. Agents and underwriters may engage in transactions with, or perform services for, us in the ordinary course of business.

Any securities we may offer, other than common stock, will be new issues of securities with no established trading market. Any underwriters may make a market in these securities, but will not be obligated to do so and may discontinue any market making at any time without notice. We cannot guarantee the liquidity of the trading markets for any securities.

Any underwriter may engage in over-allotment, stabilizing transactions, short-covering transactions and penalty bids in accordance with Regulation M under the Exchange Act. Over-allotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum price. Syndicate-covering or other short-covering transactions involve purchases of the securities, either through exercise of the over-allotment option or in the open market after the distribution is completed, to cover short positions. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the securities originally sold by the dealer are purchased in a stabilizing or covering transaction to cover short positions. Those activities may cause the price of the securities to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time.

Any underwriters that are qualified market makers on The NASDAQ Global Market may engage in passive market making transactions in the common stock on The NASDAQ Global Market in accordance with Regulation M under the Exchange Act, during the business day prior to the pricing of the offering, before the commencement of offers or sales of the common stock. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security; if all independent bids are lowered below the passive market maker's bid, however, the passive market maker's bid must then be lowered when certain purchase limits are exceeded. Passive market making may stabilize the market price of the securities at a level above that which might otherwise prevail in the open market and, if commenced, may be discontinued at any time.

LEGAL MATTERS

Goodwin Procter LLP, Boston, Massachusetts, will pass upon the validity of the issuance of the securities offered by this prospectus.

EXPERTS

The financial statements incorporated in this prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2017 have been so incorporated in reliance on the report (which contains an explanatory paragraph relating to the Company's ability to continue as a going concern as described in Note 1 to the financial statements) of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

WHERE YOU CAN FIND MORE INFORMATION

We are subject to the reporting requirements of the Securities Exchange Act of 1934, as amended, and file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy these reports, proxy statements and other information at the SEC's public reference facilities at 100 F Street, N.E., Room 1580, Washington, D.C. 20549. You can request copies of these documents by writing to the SEC and paying a fee for the copying cost. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the public reference facilities. SEC filings are also available at the SEC's web site at <http://www.sec.gov>. Our common stock is listed on The NASDAQ Global Market, and you can read and inspect our filings at the offices of the Financial Industry Regulatory Authority at 1735 K Street, Washington, D.C. 20006.

This prospectus is only part of a registration statement on Form S-3 that we have filed with the SEC under the Securities Act and therefore omits certain information contained in the registration statement. We have also filed exhibits and schedules with the registration statement that are excluded from this prospectus, and you should refer to the applicable exhibit or schedule for a complete description of any statement referring to any contract or other document. You may inspect a copy of the registration statement, including the exhibits and schedules, without charge, at the public reference room or obtain a copy from the SEC upon payment of the fees prescribed by the SEC.

We also maintain a website at www.proteostasis.com, through which you can access our SEC filings. The information set forth on our website is not part of this prospectus.

INCORPORATION OF DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" information that we file with them. Incorporation by reference allows us to disclose important information to you by referring you to those other documents. The information incorporated by reference is an important part of this prospectus, and information that we file later with the SEC will automatically update and supersede this information. Statements in this prospectus regarding the provisions of certain documents filed with, or incorporated by reference in, the registration statement are not necessarily complete and each statement is qualified in all respects by that reference. Copies of all or any part of the registration statement, including the documents incorporated by reference or the exhibits, may be obtained upon payment of the prescribed rates at the offices of the SEC listed above in "Where to Find More Information." The documents we are incorporating by reference are:

- our Annual Report on Form 10-K for the year ended December 31, 2017 filed on March 14, 2018;
- our Current Reports on Form 8-K filed on February 7, 2018, March 23, 2018 and April 4, 2018;

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- the portions of our definitive proxy statement on Schedule 14A filed on April 27, 2017 that are specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2016 (other than the information furnished rather than filed) with the SEC under the Securities Exchange Act of 1934, as amended;
- the description of our common stock contained in our registration statement on Form 8-A filed on February 10, 2016, including any amendments or reports filed for the purpose of updating such description; and
- all of the filings that we make pursuant to the Securities Exchange Act of 1934, as amended, (1) after the date of the filing of the original registration statement and prior to the effectiveness of the registration statement and (2) until all of the securities to which this prospectus relates have been sold or the offering is otherwise terminated, except in each case for information contained in any such filing where we indicate that such information is being furnished and is not considered “filed” under the Securities Exchange Act of 1934, as amended, which filings will be deemed to be incorporated by reference in this prospectus and the accompanying prospectus supplement and to be a part hereof from the date of filing of such documents.

The SEC file number for each of the documents listed above is 001-37695.

In addition, all documents subsequently filed by us pursuant to Section 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, before the date any offering under this prospectus is terminated or completed are deemed to be incorporated by reference into, and to be a part of, this prospectus.

Any statement contained in this prospectus or in a document incorporated or deemed to be incorporated by reference into this prospectus will be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus or any other subsequently filed document that is deemed to be incorporated by reference into this prospectus modifies or supersedes the statement. Any statement so modified or superseded will not be deemed, except as so modified or superseded, to constitute a part of this prospectus.

We will provide without charge to each person, including any beneficial owner, to whom a copy of this prospectus is delivered, upon the request of any such person, a copy of any or all of the information incorporated herein by reference (exclusive of exhibits to such documents unless such exhibits are specifically incorporated by reference herein). Requests, whether written or oral, for such copies should be directed to Proteostasis Therapeutics, Inc., Attention: Investor Relations, 200 Technology Square, 4th Floor, Cambridge, MA 02139, (617) 225-0096.

You should rely only on information contained in, or incorporated by reference into, this prospectus and any prospectus supplement. We have not authorized anyone to provide you with information different from that contained in this prospectus or incorporated by reference in this prospectus. We are not making offers to sell the securities in any jurisdiction in which such an offer or solicitation is not authorized or in which the person making such offer or solicitation is not qualified to do so or to anyone to whom it is unlawful to make such offer or solicitation.

11,000,000 Shares



Common Stock

PROSPECTUS SUPPLEMENT

Joint Book-Running Managers

Leerink Partners

Piper Jaffray

Cantor

Lead Manager

H.C. Wainwright & Co.

October 23, 2018
