

PROSPECTUS SUPPLEMENT
(To Prospectus dated July 3, 2017)



Up to \$50,000,000

Common Stock

We have entered into a sales agreement with Leerink Partners LLC, or Leerink, dated March 23, 2018, relating to shares of our common stock offered by this prospectus. In accordance with the terms of the sales agreement, we may offer and sell shares of our common stock having an aggregate offering price of up to \$50 million from time to time through Leerink acting as our agent.

Our common stock is listed on The NASDAQ Global Market under the symbol "PTI." On March 21, 2018, the last reported sale price of our common stock was \$5.47 per share.

Sales of our common stock, if any, under this prospectus may be made in sales deemed to be "at the market offerings" as defined in Rule 415 promulgated under the Securities Act of 1933, as amended, or the Securities Act, including without limitation sales made directly on The NASDAQ Global Market, the existing trading market for our common stock or any other trading market for our common stock or to or through a market maker. Leerink is not required to sell any specific number or dollar amount of securities, but will act as sales agent and use commercially reasonable efforts to sell on our behalf all of the shares of common stock requested to be sold by us, consistent with its normal trading and sales practices, on mutually agreed terms between Leerink and us. There is no arrangement for funds to be received in any escrow, trust or similar arrangement.

Leerink will be entitled to compensation at a fixed commission rate equal to 3.0% of the gross sales price per share sold through it as agent under the Sales Agreement. In connection with the sale of our common stock on our behalf, Leerink will be deemed to be an "underwriter" within the meaning of the Securities Act and the compensation of Leerink will be deemed to be underwriting commissions or discounts. We have also agreed to provide indemnification and contribution to Leerink with respect to certain liabilities, including liabilities under the Securities Act or the Exchange Act of 1934, as amended, or the Exchange Act.

INVESTING IN OUR SECURITIES INVOLVES RISKS. SEE THE "[RISK FACTORS](#)" ON PAGE S-5 OF THIS PROSPECTUS AND IN THE DOCUMENTS INCORPORATED BY REFERENCE IN THIS PROSPECTUS CONCERNING FACTORS YOU SHOULD CONSIDER BEFORE INVESTING IN OUR COMMON STOCK.

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.

Leerink Partners LLC

March 26, 2018.

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ABOUT THIS PROSPECTUS SUPPLEMENT

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, we may from time to time sell shares of our common stock having an aggregate offering price of up to \$50,000,000 under this prospectus at prices and on terms to be determined by market conditions at the time of the offering. This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein. The second part, the accompanying prospectus, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined.

This prospectus includes or incorporates by reference important information about us, our common stock, and other matters you should know before investing. Together with the documents incorporated by reference, this prospectus includes all material information relating to the offering of securities under this prospectus. You should carefully read this prospectus, the information and documents incorporated herein by reference and the additional information under the headings “Where You Can Find More Information” and “Incorporation of Documents by Reference” before making an investment decision.

You should rely only on the information contained in or incorporated by reference in this prospectus. We have not, and Leerink has not, authorized anyone to provide you with information that is in addition to, or 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 shares of our common stock 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 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. Our business, financial condition, liquidity, results of operations, and prospects may have changed since those dates.

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 registration statement to which this prospectus relates 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.

Unless the context otherwise requires, “Proteostasis,” “the Company,” “we,” “us,” “our” and similar names refer to Proteostasis Therapeutics, Inc. When we refer to “you” or “yours” we mean the investors and potential investors in the shares of common stock offered hereby.

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

To the extent there are inconsistencies between this prospectus and any documents incorporated by reference, the document with the most recent date will control.

PROSPECTUS SUPPLEMENT SUMMARY

The following is a summary of what we believe to be the most important aspects of our business and the offering of our securities under this prospectus. We urge you to read this entire prospectus, including the more detailed consolidated financial statements, notes to the consolidated financial statements and other information incorporated by reference from our other filings with the SEC. Investing in our securities involves risks. Therefore, carefully consider the risk factors set forth in this prospectus or incorporated by reference herein, as well as other information in this prospectus and the documents incorporated by reference herein, before purchasing our securities. Each of the risk factors could adversely affect our business, operating results and financial condition, as well as adversely affect the value of an investment in our securities.

About Proteostasis Therapeutics, Inc.

We are a clinical stage biopharmaceutical company developing small molecule therapeutics to treat cystic fibrosis, or CF, and other diseases caused by dysfunctional protein processing. The Company focuses on identifying therapies that restore protein function. CF is a disease caused by defects in the cystic fibrosis transmembrane conductance regulator, or CFTR, protein and insufficient CFTR protein function. Our CF focused pipeline consists of novel CFTR modulators including correctors, potentiators and amplifiers. We have exploited the novel mechanism of action of the amplifiers as a drug screening tool and have identified correctors and potentiators to be developed as part of a combination therapy. We are in clinical development for PTI-428, an amplifier, PTI-801, a corrector, and PTI-808, a potentiator. We are developing and, if approved, intend to commercialize our own therapies, including a double combination of our corrector and potentiator and a triple combination consisting of our corrector, potentiator and amplifier to be indicated for CF patients who have at least one F508del mutation, representing the majority of the patient population.

THE OFFERING

The following summary contains basic information about our common stock and the offering and is not intended to be complete. It does not contain all the information that may be important to you. For a more complete understanding of our common stock, you should read this prospectus and the documents referred to herein.

Issuer	Proteostasis Therapeutics, Inc.
Common stock offered by us	Shares of our common stock having an aggregate offering price of up to \$50 million.
Common stock to be outstanding after this offering	Up to 43,556,855 shares (as more fully described in the notes following this table), assuming sales of 9,140,767 shares of our common stock in this offering at an assumed offering price of \$5.47 per share, which was the last reported sale price of our common stock on The NASDAQ Global Market on March 21, 2018. The actual number of shares issued in connection with this offering will vary depending on how many shares of our common stock we choose to sell and the prices at which such sales occur.
Manner of offering	Sales of shares of our common stock under this prospectus may be made by any method deemed to be an “at the market offering” as defined in Rule 415(a)(4) under the Securities Act of 1933, as amended. Subject to the terms of the sales agreement, Leerink Partners LLC will make all sales using commercially reasonable efforts consistent with its normal trading and sales practices and applicable state and federal laws, rules and regulations and the rules of The NASDAQ Global Market, on mutually agreeable terms between Leerink Partners LLC and us. See “Plan of Distribution” beginning on page S-11 of this prospectus.
Sales agent	Leerink Partners LLC
Use of proceeds	We expect to use the net proceeds from this offering, if any, for working capital and general corporate purposes. See “Use of Proceeds” beginning on page S-8 of this prospectus.
Risk factors	Your investment in shares of our common stock involves substantial risks. You should consider the matters referred to under the heading “Risk Factors” in this prospectus, including the risk factors incorporated by reference herein from our filings with the SEC.
The NASDAQ Global Market symbol	“PTI”
The number of shares of common stock to be outstanding after this offering is based on 34,416,088 shares of common stock outstanding as of December 31, 2017. It does not include:	
	<ul style="list-style-type: none">• 2,838,558 shares of our common stock issuable upon exercise of stock options outstanding as of December 31, 2017 under our stock option plans as of that date, at a weighted average exercise price of \$6.69 per share;

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- 636,008 shares of our common stock available for future issuance under our 2016 Stock Option and Incentive Plan; and
- 266,685 shares of common stock available for future issuance under our 2016 Employee Stock Purchase Plan.

RISK FACTORS

An investment in our common stock involves risks. Before making an investment decision, you should carefully consider the risks described below, as well as the those discussed under section titled “Risk Factors” in our Form 10-K for the year ended December 31, 2017, filed with the SEC on March 14, 2018, and in our subsequent quarterly reports on Form 10-Q and annual reports on Form 10-K, as updated by our subsequent filings under the Exchange Act, each of which is incorporated by reference in this prospectus. In addition, please read “About This Prospectus” in this prospectus and “Special Note Regarding Forward-Looking Statements” in this prospectus, where we describe additional uncertainties associated with our business and the forward-looking statements included or incorporated by reference in this prospectus. Please note that additional risks not currently known to us or that we currently deem immaterial may also impair our business and operations.

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.

You will incur immediate and substantial dilution as a result of this offering.

The assumed offering price per share of our common stock in this offering is substantially higher than the net tangible book value (deficit) per share of our common stock. Therefore, if you purchase shares of our common stock in this offering, you will pay a price per share that substantially exceeds our net tangible book value (deficit) per share after this offering. Assuming the sale of \$50 million of our common stock in this offering, based on the assumed offering price of \$5.47 per share, which was the last reported sale price of our common stock on The NASDAQ Global Market on March 21, 2018, and net tangible book value per share of our common stock of \$2.00 as of December 31, 2017, if you purchase shares in this offering, you will suffer immediate and substantial dilution of \$2.79 per share in the as adjusted net tangible book value (deficit) of common stock purchased. See “Dilution” beginning on page S-9 of this prospectus for a more detailed description of the dilution to new investors 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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You may experience future dilution as a result of future equity offerings.

To raise additional capital, we may in the future offer additional shares of our common stock or other securities convertible into or exchangeable for our common stock at prices that may not be the same as the price per share in this offering. We may sell shares or other securities in any other offering at a price per share that is less than the price per share paid by investors in this offering, and investors purchasing shares or other securities in the future could have rights superior to existing stockholders. The price per share at which we sell additional shares of our common stock, or securities convertible or exchangeable into common stock, in future transactions may be higher or lower than the price per share paid by investors in this offering.

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.

We have not paid dividends in the past and do not expect to pay dividends in the future on our common stock, and any return on investment may be limited to the value of our common stock.

We have never paid cash dividends and we currently intend to retain any future earnings and do not anticipate paying cash dividends in the foreseeable future. The declaration and payment of all future dividends, if any, will be at the sole discretion of our board of directors, which retains the right to change our dividend policy at any time, and may be limited by our debt arrangements in place from time to time. The payment of dividends will depend on our earnings, capital requirements, financial condition, prospects and other factors our board of directors may deem relevant. If we do not pay dividends, our common stock may be less valuable because stockholders must rely on sales of their common stock after price appreciation, which may never occur, to realize any future gains on their investment.

The common stock offered hereby will be sold in “at the market offerings” and investors who buy shares at different times will likely pay different prices.

Investors who purchase shares in this offering at different times will likely pay different prices, and so may experience different outcomes in their investment results. We will have discretion, subject to market demand, to vary the timing, prices, and numbers of shares sold, and there is no minimum or maximum sales price. Investors may experience a decline in the value of their shares as a result of share sales made at prices lower than the prices they paid.

The actual number of shares we will issue under the sales agreement, at any one time or in total, is uncertain.

Subject to certain limitations in the sales agreement and compliance with applicable law, we have the discretion to deliver a placement notice to Leerink at any time throughout the term of the sales agreement. The number of shares that are sold by Leerink after delivering a placement notice will fluctuate based on the market price of the common shares during the sales period and limits we set with Leerink. Because the price per share of each share sold will fluctuate based on the market price of our common stock during the sales period, it is not possible at this stage to predict the number of shares that will be ultimately issued.

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.

Such statements in connection with any discussion of future operations or financial performance are identified by the use of words such as "may," "anticipate," "estimate," "expect," "project," "intend," "plan," "believe," and other words and terms of similar meaning. Such statements are based on management's expectations and are subject to certain factors, risks and uncertainties that may cause actual results, outcomes of events, timing and performance to differ materially from those expressed or implied by such 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 detailed under the heading "Risk Factors" in this prospectus as updated and supplemented by the discussion of risks and uncertainties under "Risk Factors" contained in our most recent Annual Report on Form 10-K, as revised or supplemented by our subsequent Quarterly Reports on Form 10-Q or our Current Reports on Form 8-K, as well as any amendments thereto, as filed with the SEC and which are incorporated herein by reference. The information contained in this document is believed to be current as of the date of this document. We do not intend to update any of the forward-looking statements after the date of this document to conform these statements to actual results or to changes in our expectations, except as required by law.

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.

USE OF PROCEEDS

We may issue and sell shares of our common stock having aggregate gross sales proceeds of up to \$50 million from time to time under this prospectus. Because there is no minimum offering amount required pursuant to the sales agreement with Leerink, the actual total public offering amount, commissions and proceeds to us, if any, are not determinable at this time. Actual net proceeds will depend on the number of shares we sell and the prices at which such sales occur. There can be no assurance that we will sell any shares under or fully utilize the sales agreement with Leerink as a source of financing.

We intend to use the net proceeds, if any, from sales of shares of our common stock covered by this prospectus for working capital and general corporate purposes, which may include capital expenditures, working capital and general and administrative expenses.

Our expected use of net proceeds, if any, from the sale of shares of common stock pursuant to the sales agreement with Leerink represents our intentions based upon our present plans and business conditions, which could change in the future as our plans and business conditions evolve. The amount and timing of our actual expenditures will depend upon numerous factors, including, but not limited to, results of our research and development efforts, the timing and success of preclinical and clinical studies, our ongoing clinical trials or clinical trials we may commence in the future, the timing of regulatory submissions and the feedback from regulatory authorities. As a result, our management will have broad discretion over the use of the net proceeds from this offering, if any.

We may temporarily invest the net proceeds in short-term obligations of the U.S. government and its agencies pending their use for the purposes described above. We have not determined the amount of net proceeds to be used specifically for such purposes and, as a result, management will retain broad discretion over the allocation of net proceeds, if any.

DILUTION

If you invest in this offering, your ownership interest will be diluted to the extent of the difference between the public offering price per share and the as adjusted net tangible book value (deficit) per share after giving effect to this offering. We calculate net tangible book value (deficit) per share by dividing the net tangible book value (deficit), which is tangible assets less total liabilities, by the number of outstanding shares of our common stock. Dilution represents the difference between the amount per share paid by purchasers of shares in this offering and the as adjusted net tangible book value per share of our common stock immediately after giving effect to this offering. Our net tangible book value as of December 31, 2017 was approximately \$68.7 million, or \$2.00 per share.

After giving effect to the sale of our common stock in the aggregate amount of \$50 million at an assumed offering price of \$5.47 per share, which was the last reported sale price of our common stock on The NASDAQ Global Market on March 21, 2018, and after deducting offering commissions and estimated expenses payable by us, our net tangible book value (deficit) as of December 31, 2017 would have been \$116.9 million, or \$2.68 per share of common stock. This represents an immediate increase in the net tangible book value (deficit) of \$0.68 per share to our existing stockholders and an immediate dilution in net tangible book value (deficit) of \$2.79 per share to new investors. The following table illustrates this per share dilution:

Assumed offering price per share		\$5.47
Net tangible book value per share as of December 31, 2017	\$2.00	
Increase per share attributable to this offering	<u>0.68</u>	
As adjusted net tangible book value (deficit) per share as of December 31, 2017 after this offering		<u>2.68</u>
Dilution per share to new investors		\$2.79

The table above assumes for illustrative purposes that an aggregate of 9,140,767 shares of our common stock are sold at a price of \$5.47 per share, which was the last reported sale price of our common stock on The NASDAQ Global Market on March 21, 2018, for aggregate gross proceeds of \$50 million. The shares sold in this offering, if any, will be sold from time to time at various prices. An increase of \$1.00 per share in the price at which the shares are sold from the assumed offering price of \$5.47 per share shown in the table above, assuming all of our common stock in the aggregate amount of \$50 million during the term of the sales agreement with Leerink is sold at that price, would increase our as adjusted net tangible book value (deficit) per share after the offering to \$2.77 per share and would increase the dilution in net tangible book value (deficit) per share to new investors in this offering to \$3.70 per share, after deducting offering commissions and estimated expenses payable by us. A decrease of \$1.00 per share in the price at which the shares are sold from the assumed offering price of \$5.47 per share shown in the table above, assuming all of our common stock in the amount of \$50 million during the term of the sales agreement with Leerink is sold at that price, would decrease our as adjusted net tangible book value (deficit) per share after the offering to \$2.56 per share and would decrease the dilution in net tangible book value (deficit) per share to new investors in this offering to \$1.91 per share, after deducting offering commissions and estimated offering expenses payable by us. This information is supplied for illustrative purposes only and may differ based on the actual offering price and the actual number of shares offered.

The above discussion is based on 34,416,088 shares of common stock outstanding as of December 31, 2017. It does not include:

- 2,838,558 shares of our common stock issuable upon exercise of stock options outstanding as of December 31, 2017 under our stock option plans as of that date, at a weighted average exercise price of \$6.69 per share;
- 636,008 shares of our common stock available for future issuance under our 2016 Stock Option and Incentive Plan; and

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- 266,685 shares of common stock available for future issuance under our 2016 Employee Stock Purchase Plan.

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 additional capital is raised through the sale of equity or equity-based securities, the issuance of these securities could result in further dilution to our stockholders.

PLAN OF DISTRIBUTION

We have entered into a sales agreement with Leerink, under which we may issue and sell from time to time up to \$50 million of our common stock through Leerink as our sales agent. Sales of our common stock, if any, will be made at market prices by any method permitted by law that is deemed to be an “at the market offering” as defined in Rule 415 under the Securities Act, including without limitation sales made directly on The NASDAQ Global Market or any other trading market for our common stock or to or through a market maker. If authorized by us in writing, Leerink may also purchase shares of our common stock as principal.

Each time we wish to issue and sell common stock under the sales agreement, we will notify Leerink of the maximum number of shares to be issued, the time period during which sales are requested to be made, any limitation on the number of shares that may be sold in one trading day and any minimum price below which sales may not be made. Once we have so instructed Leerink, unless Leerink declines to accept the terms of the notice, Leerink has agreed to use its commercially reasonable efforts consistent with its normal trading and sales practices and applicable state and federal laws, rules and regulations and the rules of The NASDAQ Global Market to sell such shares up to the amount specified on such terms. Leerink or we may suspend the offering of our common stock being made through Leerink under the sales agreement upon proper notice to the other party. Leerink and we each have the right, by giving written notice as specified in the sales agreement, to terminate the sales agreement in each party’s sole discretion at any time.

The aggregate compensation payable to Leerink as sales agent is equal to 3.0% of the gross sales price of the shares sold through it pursuant to the sales agreement. We estimate that the total expenses of the offering payable by us, excluding commissions payable to Leerink under the sales agreement, will be approximately \$376 thousand.

The remaining sales proceeds, after deducting any expenses payable by us and any transaction fees imposed by any governmental, regulatory, or self-regulatory organization in connection with the sales, will equal our net proceeds for the sale of such common stock.

Leerink will provide written confirmation to us following the close of trading on The NASDAQ Global Market on each day in which common stock is sold through it as sales agent under the sales agreement. Each confirmation will include the number of shares of common stock sold through it as sales agent on that day, the volume weighted average price of the shares sold and the net proceeds to us.

We will report the number of shares of common stock sold through Leerink under the sales agreement, the net proceeds to us and the compensation paid by us to Leerink in connection with the sales of common stock on or prior to the dates required by the Securities Act.

Settlement for sales of common stock will occur, unless the parties agree otherwise, on the second business day that is also a trading day following the date on which any sales were made in return for payment of the net proceeds to us, or such earlier day as is industry practice or as is required for regular-way trading. There is no arrangement for funds to be received in an escrow, trust or similar arrangement.

In connection with the sales of our common stock on our behalf, Leerink may be deemed to be an “underwriter” within the meaning of the Securities Act, and the compensation paid to Leerink may be deemed to be underwriting commissions or discounts. We have agreed in the sales agreement to provide indemnification and contribution to Leerink against certain liabilities, including liabilities under the Securities Act and the Exchange Act. As sales agent, Leerink will not engage in any transactions that stabilizes our common stock.

Our common stock is listed on The NASDAQ Global Market and trades under the symbol “PTI.” The transfer agent of our common stock is American Stock Transfer & Trust Company, LLC.

Leerink and/or its affiliates have provided, and may in the future provide, various investment banking and other financial services for us for which services they have received and, may in the future receive, customary fees.

LEGAL MATTERS

The validity of the shares of common stock offered hereby will be passed upon for us by Goodwin Procter LLP, Boston, Massachusetts. Leerink is being represented in connection with this offering 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

We are subject to the reporting requirements of the Exchange Act 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

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documents we are incorporating by reference are (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits furnished or filed on such form that are related to such items):

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

In addition, all documents subsequently filed by us pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act 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.

PROSPECTUS

\$125,000,000



**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 June 2, 2017, the last reported sale price of our common stock was \$4.39 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 4 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 July 3, 2017.

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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.

PROSPECTUS SUMMARY

This summary highlights selected information from this prospectus or incorporated by reference in this prospectus, and does not contain all of the information that you need to consider in making your investment decision. You should carefully read the entire prospectus, the applicable prospectus supplement and any related free writing prospectus, including the risks of investing in our securities contained in the applicable prospectus supplement and any related free writing prospectus, and in the other documents that are incorporated by reference into this prospectus. You should also carefully read the information incorporated by reference into this prospectus, including our financial statements, and the exhibits to the registration statement of which this prospectus is a part.

About Proteostasis Therapeutics, Inc.

We are an innovative biopharmaceutical company committed to the discovery and development of novel therapeutics that treat diseases caused by an imbalance in the proteostasis network, a set of pathways that control protein biosynthesis, folding, trafficking and clearance. Leveraging our unique and comprehensive expertise of the proteostasis network, we have developed the Disease Relevant Translation, or DRT, technology platform, a validated drug screening approach for identifying highly translatable therapeutics based on predictive and functionally pertinent phenotypic assays and disease relevant models. Using this proprietary platform, we identified a new class of small molecules, which we call amplifiers, that modulate proteins in the proteostasis network. Our initial therapeutic focus is cystic fibrosis, or CF, which is caused by defects in the cystic fibrosis transmembrane conductance regulator, or CFTR, protein and insufficient CFTR protein function. We continue to grow our CF focused pipeline with novel CFTR modulators including correctors, potentiators, read-through agents and amplifiers. We have exploited the novel mechanism of action of the amplifiers as a drug screening tool in our DRT platform and have identified correctors and potentiators to be developed as part of a combination therapy. We are developing and, if approved, intend to commercialize our own triple combination therapy to be indicated for CF patients who have at least one F508del mutation representing the majority of the patient population.

Employees

As of June 1, 2017, we employed 77 full-time employees, including 61 in research and development and 16 in general and administrative. Two of these employees are part-time employees and five of these employees are seasonal (summer 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,

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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.

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.

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 June 2, 2017, we had 25,044,843 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 12,305,142 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 12,305,142 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 12,305,142 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 12,305,142 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

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outstanding at the time the transaction commenced, excluding for purposes of determining the voting 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 June 2, 2017 the last reported sale price of our common stock was \$4.39 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.

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, 2016 have been so incorporated in reliance on the report, which contains an explanatory paragraph relating to the Company's requirement for additional financing to fund future operations 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, 2016 filed on March 30, 2017;
- our Quarterly Report on Form 10-Q for the quarter ended March 31, 2017 filed on May 12, 2017;
- our Current Reports on Form 8-K filed on February 1, 2017, March 30, 2017 (Item 5.02 only) and June 7, 2017;

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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;
- 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.

Up to \$50,000,000



Common Stock

PROSPECTUS

Leerink Partners LLC

March 26, 2018
