

Financing Medical Innovation

Andrew W. Lo* and Richard T. Thakor†

19 August 2021

Abstract

We review the recent literature on financing medical innovation, with a specific focus on the drug and device development process and how it may be enhanced to improve outcomes. We begin by laying out stylized facts about the structure of the drug development process and its associated costs and risks, and the evidence that the rate of discovery for life-saving treatments has declined over time, while its costs have increased. We make the argument that these structural features require drug development (i.e., biopharmaceutical) firms to rely on external financing, while at the same time amplifying market frictions that may hinder the ability of these firms to obtain financing, especially for treatments that may have large societal value relative to the benefits going to the firms and their investors. We then provide an overview of the evidence for various types of market frictions to which these drug development firms are exposed, and discuss how these frictions affect their incentive to invest in the development of new drugs, thereby generating underinvestment in valuable treatments. In light of this evidence, numerous studies have proposed possible ways to overcome this “funding gap” problem, including the use of financial innovation. We discuss the potential of these approaches to improve outcomes.

* MIT Sloan School of Management, CSAIL, and NBER

† University of Minnesota – Carlson School of Management and MIT LFE

1. Introduction

The healthcare system is essential to the global economy. As the Covid-19 pandemic of 2020-2021 starkly demonstrated, the functioning of the economy is intimately tied to its ability to manage health, as concerns about the treatment of the pandemic led to the partial shutdown of the global economy. Moreover, the healthcare system's effectiveness in meeting its challenges may be the bellwether of the future health of the global economy. For example, healthcare expenditures in the United States have steadily risen over the past few decades to roughly 18% of GDP as of 2019.

The foundation of the healthcare system is the development of new therapeutics that provide societal value. However, the development and delivery of treatments requires funding. This requirement closely connects the expansion of healthcare to finance. A major challenge in the development of new treatments is that the required investments are large, the gestation lags are long, and the payoffs are highly uncertain, with daunting risks that include not only scientific risk but also the regulatory risks of drug approval and financing risks. This has led to what has been called “the funding gap”, the difference between the aggregate amount of capital needed to invest in all welfare-enhancing drug development projects and the amounts actually invested. What gives rise to the funding gap? How can finance help to close this gap?

In this review article, we consider the academic research surrounding these questions. We explain how firms that engage in the development of life-saving therapies may face market frictions related to their need to finance their investments. These

frictions can potentially alter their investment decisions, resulting in fewer therapies that reach patients, and profound implications for society.

We begin by describing the types of firms that engage in drug development¹—biotechnology and pharmaceutical firms—collectively referred to as biopharmaceutical (biopharma) firms. We then describe the regulatory process that these firms must go through in order to successfully develop a new drug. We lay out certain stylized facts about the costs and risks associated with the drug development process—specifically, that it is lengthy, risky, and expensive—and describe the evidence that these costs and risks have increased over time. In stark comparison, \$1 billion of (real) investment was able to produce dozens of drugs in 1950, an amount that would be insufficient to develop even a single drug on average from start to finish today.

We argue that the institutional features, costs and risks associated with drug development lead to four important conclusions. First, the large costs of drug development faced by biopharma firms necessitate reliance on external financing. Second, this requirement creates a strong link between the prospects of biopharma firms and financial markets, exposing these firms to external financing frictions and capital market imperfections. Third, the institutional features of drug development that are relatively unique to biopharma end up amplifying these external financing frictions, leading to underinvestment in R&D and in therapies that are potentially valuable from a societal perspective. Fourth, financial innovations offer the promise of overcoming these

¹ For expositional simplicity, when we use the term “drug development,” we are implicitly including the development of medical devices, diagnostics, and health-related technologies unless otherwise specified.

impediments to enhance aggregate investment in drug development, making a strong case for more *normative research* into contracting innovations.

We then provide an overview of the body of evidence in support of these conclusions. We describe how biopharma firms use financing sources, and how frictions such as asymmetric information may alter the ability of these firms to use financing and make optimal investment decisions. Among other topics, we delve into the use of equity markets by biopharma firms, the competitive structure of the industry, the effects of the regulatory environment, and the markets for technology and venture capital/private equity. When put together, there is strong evidence that the investment incentives of drug development firms are influenced by the various frictions to which they are exposed, and that these incentives impinge on their financing decisions.

Given the importance of developing new therapeutics and the documented difficulties faced by biopharma firms, a number of studies have proposed contracting and other solutions to overcome these impediments. We survey these solutions, which include financial innovation coupled with changes to the therapeutic development process.

Finally, we note that beyond the social value of improving outcomes in the biopharma industry, the R&D-intensive nature of biopharma means that it also offers more generalized insights into the R&D and innovation investment process, as well as its

associated corporate financial decisions and regulatory policy (e.g. Lakdawalla (2018)).² A particular advantage of focusing on biopharma in this regard comes from data availability; there are detailed, granular data about clinical trials that are available to researchers examining drug development. The innovation literature typically uses patents in order to measure innovation activity, but it has been noted that patents have a number of shortcomings as an innovation proxy (e.g. Williams (2017), Freilich (2019)). By allowing researchers to view actual project-level decisions through the clinical trials process—for example, firms beginning clinical trials to treat rare diseases—drug development affords new measures of innovation that do not rely on patents. Furthermore, measures have been developed that estimate the *novelty* of new compounds in the drug development process (Krieger, Li, and Papanikolaou (forthcoming)). From a broader corporate finance perspective, the ability to track individual project decisions for both public and private firms offers a view into corporate decision-making not usually offered in other contexts. For example, much of the extant literature on mergers and acquisitions (M&A) focuses on acquisitions of entire firms; data on drug development allows researchers to examine both whole-firm acquisitions as well as acquisitions of individual projects.

In Section 2, we describe the drug development process, including the types of firms involved in drug development and the regulatory approval process for new drugs.

² Empirical patterns that have been broadly documented for R&D and productivity may also be driven by the biopharma industry. For example, Benmelech, Eberly, Papanikolaou, and Krieger (2021) show that the stylized fact of increased investment in intangible capital but sluggish productivity growth since the 1990s can be attributed to pharmaceutical firms, but that improvements in treatments may not be accurately reflected in aggregate productivity measures.

In Section 3 we connect these institutional features to the financing of projects, and makes the argument for why the prospects of biopharma firms are strongly linked to financial markets, and how this may lead to underinvestment in drug development. Section 4 contains a survey of the empirical evidence for the exposure of biopharma firms to market frictions, how they connect to financing, and their effect on investment incentives. We discuss potential solutions to the problem of underinvestment in drug development in Section 5, including financial innovation, and conclude in Section 6.

2. The Drug Development Process

To understand how frictions in financing may affect investment incentives in drug development, it is important to understand the process that firms must undergo to bring a new therapeutic to market. In this section, we first describe the types of firms which undertake drug development. We then detail the regulatory process for developing a drug, and provide stylized facts about the risk and cost of this process. This lays the foundation to explain why drug development firms are more exposed to financial markets.

2.1 Types of Drug Development Firms

Firms that engage in drug development are often separated into two main categories: biotechnology (biotech) and pharmaceutical (pharma) companies. Biotech companies are often differentiated from pharma companies by their production process: biotech firms derive their products from living material, while pharmaceutical companies derive their products from chemicals. However, some firms may use both types of

production methods, making a clean separation between pharma and biotech firms challenging (e.g. Carlson (2016)).

Does the distinction between pharma and biotech firms matter? While general features of the drug development process may apply to both types of firm, in practice, the characteristics of firms that typify pharma can be significantly different from those of biotech. Biotech companies tend to be smaller and more numerous than pharma firms, due to the confluence of several trends: breakthroughs in our understanding of the biology of human diseases and how to intervene, technological improvements in chemical, biological, and drug manufacturing processes and bioinformatics, and the ease of entry in the development of biological drugs. As a result, pharma firms tend to have more developed portfolios of drugs (and more approved drugs), while biotech companies tend to have more early-stage drug candidates in their development portfolios.

These differences can greatly affect the conclusions of economic analyses that focus on these industries. For example, Thakor, Anaya, Zhang, Vilanilam, Siah, Wong, and Lo (2017) show that the profitability of biotech firms tends to be significantly lower than that of pharma firms, in line with the tendency of pharma firms having more approved drugs, and therefore more positive cash flows. Thakor et al. (2017) also show that the assessment of the attractiveness of an investment in the pharma industry relative to the biotech industry is dependent on the classification method used, with some classification methods suggesting a heavy underperformance for biotech investments, and others coming to a different conclusion. Thakor et al. (2017) make the broad point

that both inclusion criteria and weighting schemes can affect these conclusions due to the differences between pharma and biotech firms. For example, in a sample that includes both pharma and biotech firms, one might conclude that investment performance in the biopharma industry is strong, when in fact the positive performance is coming from a handful of pharma firms, which are more heavily weighted in the analysis because they are larger, while the majority of biotech firms are performing poorly.

Special attention should therefore be paid to firm classifications when conducting research on drug development firms using company databases such as CRSP and Compustat. A researcher may be interested in analyzing the drug development industry as a whole, or either the pharma or biotech sectors specifically. First, when analyzing the drug development industry as a whole, a researcher often must query firm information using formalized industry classification codes (i.e. the Standard Industry Classification (SIC) and North American Industry Classification System (NAICS)). However, there may be multiple industry codes that correspond to pharma or biotech. For example, there are at least five 4-digit SIC codes and at least six 6-digit NAICS codes that reasonably correspond to pharma or biotech, but some biopharma firms may be classified by codes that are shared by non-biopharma firms (e.g. Thakor et al. (2017)). This introduces the possibility of omitting biopharma firms or including non-biopharma firms in one's analysis. Second, when focusing on either pharma or biotech firms, standard classification systems like SIC and NAICS codes do not always offer a clean distinction between pharma and biotech companies. For example, one classification method may designate a firm as pharma while another designates it as biotech. Furthermore, a firm

may start out as a small biotech firm, but then expand operations to be more like a pharma firm, but most traditional classification systems are not dynamic and cannot account for this.

New alternative classification methods offer promising ways to identify pharma and biotech companies using various data sources. For example, Thakor et al. (2017) use machine learning techniques with financial and accounting data to classify pharma and biotech companies. Hoberg and Phillips (2010, 2016) use textual analysis methods and 10-K filings to classify firms in terms of their product similarity.

In the rest of this article, while we will refer to drug development firms generally as “biopharma” firms for convenience, we will be careful to make a distinction between pharma and biotech when it is needed for clarity.

2.2 The FDA Drug Approval Process

The development of drugs in the United States and other countries is highly regulated, as governments require a demonstration of both the efficacy and safety of treatments before they are allowed to reach consumers. In the U.S., the Food and Drug Administration (FDA) is responsible for the regulation and oversight of any firm developing a drug.

The FDA approval process for a new drug is provided in Figure 1.³ The beginning of the process is a more informal preclinical phase, which consists of the discovery or

³ The approval process for medical devices is significantly shorter than that for drugs, but there is evidence that uncertainty and other institutional features of the device approval process affects the innovation incentives of device manufacturers. See, for example, Stern (2017).

identification of new types of treatments, such as new molecular compounds or new mechanisms of delivery of existing compounds to treat specific diseases. An important part of this phase is determining if a drug has the potential to cause harm before it is tested on humans, and thus the developing biopharma firm must conduct laboratory testing to determine this.



Figure 1: FDA Approval Process for a New Drug

After preclinical testing comes the clinical trial testing of the drug compound, which consists of three phases, denoted phase 1, phase 2, and phase 3. These clinical trials involve testing of the treatment on human subjects, with the smallest number of subjects (20 to 100) in phase 1 trials, and the largest number of subjects (hundreds or thousands) in phase 3 trials. In order to “pass” a phase of the clinical trials—i.e., advance from one phase to the next—the firm conducting the trials must demonstrate the efficacy and safety of the drug to the FDA. Once clinical trials are successfully completed, the drug undergoes a final review by the FDA after submitting a “new drug application” (NDA) or “biologic license application” (BLA), depending on whether the compound is chemical or biological in nature. Upon a successful review, the drug is approved for consumer use after the labeling and prescription information is determined. After approval, the FDA

also conducts post-market drug safety monitoring to discover if there are potentially harmful effects of the drug that were not detected during the approval process, and it may take measures to limit the use of the drug by consumers if new safety and/or efficacy concerns arise.

The rigorous requirements of the drug approval process help to protect the end consumers of a drug by ensuring that drugs have the necessary levels of safety and efficacy for consumption and treatment. However, this also creates challenges for the firms developing the drugs given that the process is lengthy, expensive, and risky.

For a typical drug candidate, the development process takes several years from start to finish. The FDA estimates the length of phase 1 trials as “several months”, phase 2 trials as “several months to 2 years”, and phase 3 trials as “1 to 4 years”.⁴ This is consistent with the evidence provided by DiMasi and Grabowski (2007), which shows that phase 1 trials take an average of 1.3 years to complete, phase 2 trials an average of 2.3 years, phase 3 an average of 2.8 years, and the NDA or BLA approval takes an average of 1.4 years. In total, the average development time of a drug from start to finish was 8.1 years for biotech firms, and 7.5 years for pharma firms.⁵

⁴ <https://www.fda.gov/patients/drug-development-process/step-3-clinical-research>

⁵ This development time can be reduced in some special cases. First, a biopharma firm developing a generic drug—that is, an equivalent drug to a marketed drug that enters after the marketed drug’s exclusivity period—can file an Abbreviated New Drug Application (ANDA) and bypass the majority of the drug development process, so long as the generic manufacturer can prove bioequivalence to the marketed drug. Second, recent FDA initiatives such as the Breakthrough Therapy, Fast Track, and Accelerated Approval designations seek to expedite the development and review process if a drug meets certain criteria (such as being the first available treatment, or having a distinct advantage over existing treatments).

The empirical evidence suggests that the cost of developing a drug is high and rising over time. Using a sample of 93 drugs from 12 pharmaceutical firms, DiMasi, Hansen, Grabowski, and Lasagna (1991) estimated the average cost of developing a drug to be \$231 million (in 1987 dollars), including capitalized costs over the entire length of development. However, DiMasi, Hansen, and Grabowski (2003) estimated this cost to be \$802 million (in 2000 dollars), and the most recent estimate by DiMasi, Grabowski, and Hansen (2016) is \$2.558 billion (in 2013 dollars).

This trend of increasing development costs over time was laid out starkly by Scannell, Blanckley, Boldon, and Warrington (2012), who demonstrated the declining R&D efficiency of the industry by showing how \$1 billion (inflation-adjusted) of R&D spending could produce dozens of drugs in the 1950s, but by 2010 could not even produce a single drug (see Figure 2).

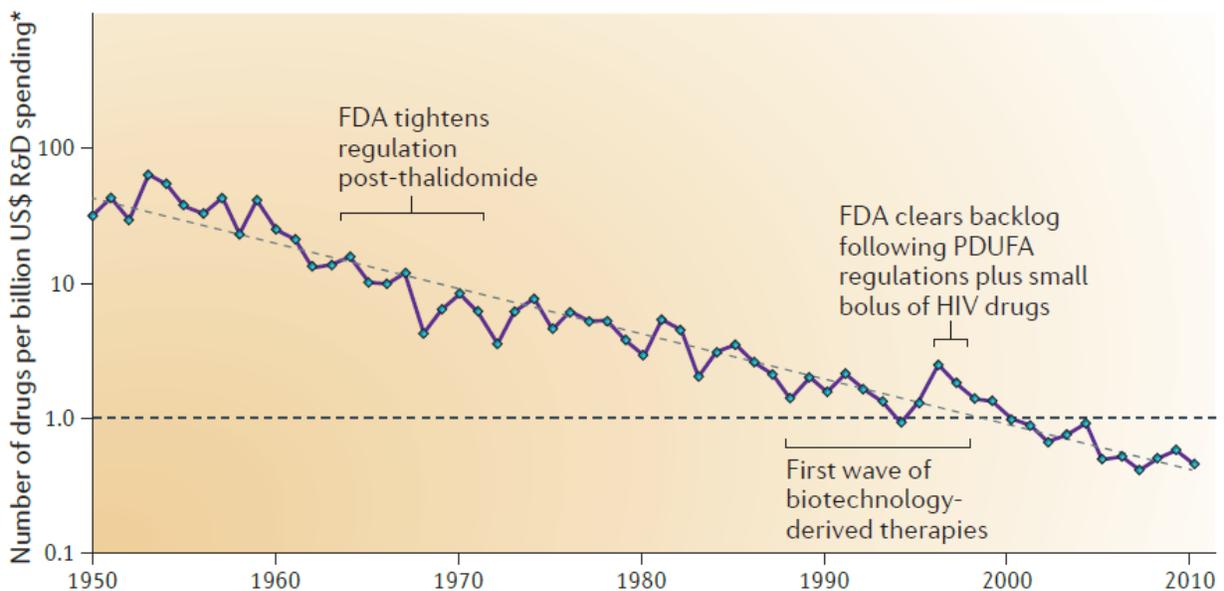


Figure 2: Declining R&D Efficiency in Biopharma, from Scannell et al. (2012)

Finally, the evidence on the risks of drug development clearly shows that the development process has a substantial scientific risk of failure; in other words, drugs going through the development process have a high rate of failing to meet clinical standards of efficacy or safety. Using a sample of 1,316 drugs from 50 pharma companies, DiMasi, Feldman, Seckler, and Wilson (2010) found an average clinical approval success rate from phase 1 to approval of 19%. Using detailed data from a much broader sample of clinical trial outcomes from 2003 to 2011, Hay et al. (2014) report an average probability of successful approval from phase 1 across all indications of 10.4%. Thomas et al. (2016) use a similarly broad sample from 2006 to 2015, and report an average probability of successful approval from phase 1 of 9.6%.⁶ In the most comprehensive sample to date of over 400,000 clinical trial registrations from 2000 to 2015, Wong, Siah, and Lo (2019) estimate an average probability of successful approval from phase 1 of 6.9%. However, approval probabilities vary by the disease category of a particular drug as well as its phase in the clinical trial process. For example, according to Wong, Siah, and Lo (2019), an average drug in oncology has a 0.021 probability of successful development to approval, while an average drug in ophthalmology has a probability of success of 0.135.

⁶ Assessing the risk of drug development has been made easier with the mandated reporting of clinical trial outcomes for many drugs, which was put into place following the Food and Drug Administration Amendments Act of 2007. Trial information and summary results are required to be posted to the FDA's website, clinicaltrials.gov, within a certain time period after completion (see Hsu, Lee, Moon, and Oh (2019)). This data availability has also enhanced the ability of researchers to view the actual project-level investment decisions of these companies, as we discuss in more detail later.

What about the benefits to a firm that succeeds in developing an approved drug? Approval by the FDA allows the drug maker to enjoy a “marketing exclusivity” period for the drug, typically lasting from 3 to 7 years, over which the FDA will not approve any competing drugs during this period. Thus, all else being equal, a firm that successfully has a product approved will enjoy monopoly profits on that drug for a significant amount of time, but afterwards faces potential competition.⁷ However, Grabowski and Vernon (1990) show that firms with approved drugs face a skewed distribution of returns for drugs in the marketplace, with “blockbuster” drugs achieving much higher returns than other drugs. Thus, given the large investment costs of drug development, a very successful commercial result is often needed to justify the high initial investment in the project. This observation is consistent with the evidence provided by Kyle (2018) that measures of market reward are often weakly related to measures of therapeutic value for new drugs, and is also consistent with the empirical evidence that the majority of biopharma firms have negative profitability, and that profitability in the industry has been consistently declining on average, as shown in Thakor et al. (2017) (see Figure 3). However, as the figure shows, there is still marked heterogeneity in the prospects of firms within the industry, with some earning substantially high profits.

⁷ Note that marketing exclusivity is distinct from patent protection; patents for drugs are typically granted early on in the development process, and offer weaker protection than marketing exclusivity (see, e.g., Grabowski and Kyle (2007) and Li, Lo, and Thakor (2021)). Consistent with this, Duggan, Garthwaite, and Goyal (2016) find only small price impacts and little impact on quantities of drugs when patents on them were granted internationally following an expansion of the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreements.

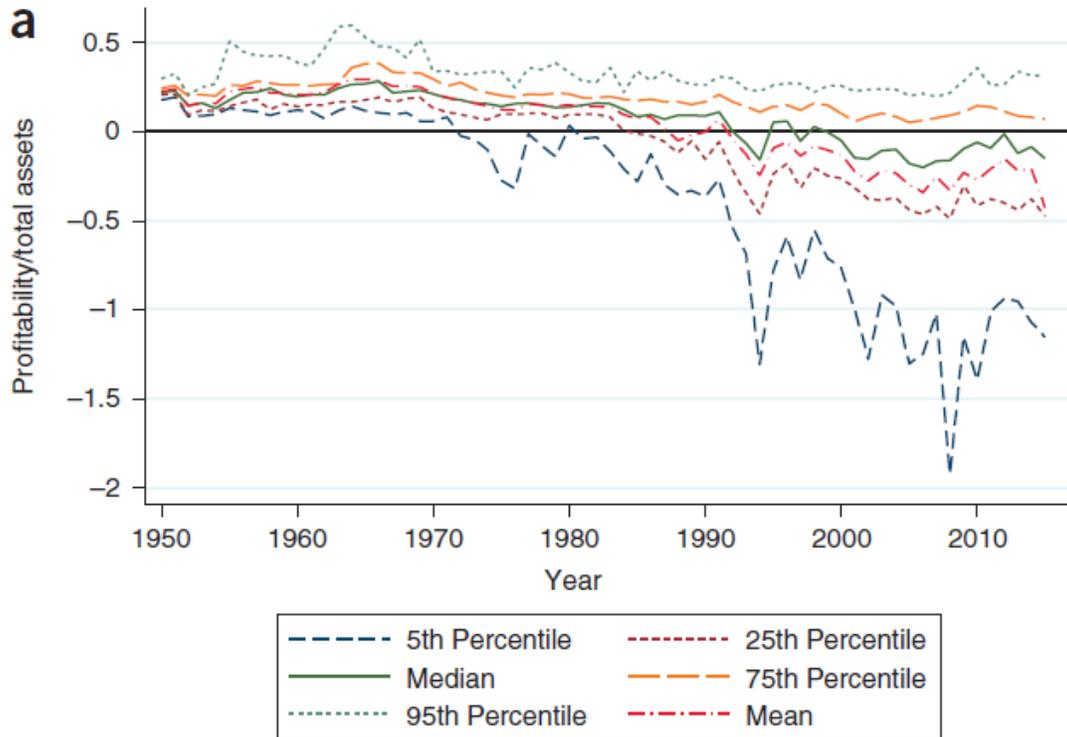


Figure 3: Declining Profitability in Biopharma, from Thakor et al. (2017)

Developing a drug also produces the benefit of knowledge capital, such as scientific expertise, understanding of research and production methods, connections with physicians, and so forth, that can potentially be deployed for subsequent drugs under development to improve their odds of success. For example, a biopharma firm that has spent the money to successfully develop a vaccine can use the knowledge and resources it gained through the development process on subsequent vaccine candidates. However, one caveat is that this knowledge capital is not easily redeployable *across* therapeutic areas. For example, knowledge capital built up in vaccine development may not be applicable to cancer drugs. Krieger, Li, and Thakor (forthcoming) develop a model that

includes knowledge capital as a feature and provide evidence that it creates path dependencies in drug development, which can affect *ex ante* investment incentives.

3. Drug Development, Financing, and Investment

When considered together, the institutional features of the drug development process lead to a number of financial implications for biopharma firms.

First, the high development costs associated with drug development imply that *drug development firms are forced to rely on external financing to fund their investments*, given the inadequacy of internal funds in fully satisfying their investment needs. This is partly because many firms in the industry without an approved product have few sources of revenue (Thakor et al. (2017)). Biopharma firms tend to rely largely on *equity* financing, limiting the use of debt for the most part (Thakor et al. (2017), Giambona, Golec, and Lopez-de-Silanes (2021), Thakor and Lo (forthcoming)). Biopharma firms in particular are able to tap public equity markets through initial public offerings (IPOs) even if they only have preclinical projects (Aghamolla and Thakor (forthcoming)).

This reliance on equity financing is similar to that of many other R&D-intensive firms (Brown, Fazzari, and Petersen (2009)). The traditional explanation for why such firms do not utilize substantial amounts of debt is that they lack sufficient tangible assets to offer as collateral, their low profitability and uncertain cash flows amplifying the agency frictions that impede debt financing.⁸ Myers and Howe (1997) create a model in

⁸ See, e.g., Besanko and Thakor (1987a,b) and Rampini and Viswanathan (2013) for theoretical models of these effects.

which large pharma investment costs create “R&D leverage,” – a commitment to continue spending funds in order to continue development in later phases – that pushes out financial leverage. However, recent evidence suggest that biopharma firms have the ability to use patents as collateral in lieu of “traditional” hard assets, which enhances their ability to take on more debt (see Deshpande and Nagendra (2017) and Mann (2018)).

Second, the reliance on external financing means that the *prospects of biopharma firms will be strongly linked to the state of the market*. During bull equity markets, external financing will generally be plentiful, but during market downturns, it will typically be harder for biopharma firms to acquire the financing to continue investing in drug development. Thus, R&D funding that is market based will have a significant systematic risk component. This insight is in line with earlier finance literature that has documented a significant link between the supply of equity financing and R&D more generally (e.g. Brown, Fazzari, and Petersen (2009)).

Third, the institutional features of biopharma, including the regulatory approval process and the difficulty for investors to assess the financial ramifications of technical details involved in drug development, mean that the frictions associated with the financing-investment link are amplified. This leads to *underinvestment in R&D and therapies that are potentially valuable from a societal perspective*. Put differently, the difficulties faced by biopharma firms in procuring financing for some projects may lead to an

underprovision of therapies relative to the social optimum.⁹ Hall and Lerner (2010) refer to this problem as a “funding gap” for R&D investment by innovative firms (see also Kerr and Nanda (2015)).

A variety of financial frictions may contribute to this funding gap. One classic financing friction is asymmetric information, which leads to adverse selection costs in raising financing (e.g. Myers and Majluf (1984)). Thakor and Lo (2021) make the theoretical argument that low probabilities of success combined with the specialized expertise needed to assess project prospects—particularly in the case of biopharma investments—lead to adverse selection that distorts investment away from the first-best choice, because firms are unable to raise financing for those investments. In particular, there may be investments that are both positive NPV for the firm and valuable for society, but in which firms are unable to invest. Thakor and Lo (2017) also observe that the technical nature of R&D and low probabilities of success make agency problems and moral hazard harder to detect, which further exacerbates the problem. This is because outsiders may lack the technical knowledge to distinguish between good and bad projects. Furthermore, it becomes difficult to ascertain ex post whether project failure is due to the inherent low chance of success or because it was a bad project from the beginning. Thakor and Lo (forthcoming) and Jørring et al. (2021) make similar points theoretically.

⁹ A number of studies have provided evidence from a variety of perspectives that investment in societally-beneficial treatments is lower than optimal. For example, Krieger, Li, and Papanikolaou (forthcoming) provide evidence that novel drugs have higher ex-ante economic value ex-ante, but that firms underinvest in them. Kyle (2018) uses a French government assessment of therapeutic value, and finds evidence suggesting that countries are over-investing in drugs with less therapeutic value.

The underprovision of socially valuable treatments represents an inefficient equilibrium from a social welfare standpoint. In order to find potential solutions to this problem, it is essential to understand the particular frictions that cause it to arise. We do so in the next section.

4. Evidence of Market Frictions and Investment Incentives

The main conclusion from the previous section is that the amplified frictions faced by biopharma firms can cause underinvestment in valuable R&D. In this section, we survey the empirical evidence on how market frictions affect biopharma investments, and the role that financial markets play in this relationship.

4.1 Equity Markets and Investment

A body of empirical evidence has demonstrated a link between equity markets and biopharma investment. There is substantial evidence documenting that biopharma firms have a high degree of market-related risk. Using data on publicly traded biopharma firms, Harrington (2012), Thakor et al. (2017), and Lo and Thakor (2019) all document positive and relatively high betas, often significantly above 1.0, for biopharma firms. This high level of market risk is particularly salient since the *scientific* risk inherent in R&D is idiosyncratic, as Jørring, Philipson, Lo, Singh, and Thakor (2021) demonstrate using project-level data. A consequence of this high level of market risk is a high cost of capital for biopharma firms (e.g. Harrington (2012), Cockburn and Lerner (2009)), which adds further challenge to the prospect of evaluating drug projects as positive NPV.

Papers using clinical trial data have shown how the link between biopharma firms and equity markets can cause suboptimal investment. Lerner, Shane, and Tsai (2003) provide empirical evidence that due to their reliance on financing via stock issues, biotech firms are more likely to fund their R&D through inefficient (i.e., significantly less successful) alliances during periods of limited public equity market financing.¹⁰ Mace (2020) provides evidence that even short-term declines in equity markets can cause biopharma companies to abandon early-stage drugs, which can be attributed to financing constraints and changes in discount rates. Krieger, Li, and Papanikolaou (forthcoming) use detailed clinical trial data and a new method for identifying novel drugs using chemical similarity. They show that novel drugs have lower success rates but higher economic value ex-ante. They provide evidence that firms underinvest in novel drugs, possibly due to external financing frictions: firms experiencing a positive net worth shock generated by an expansion of Medicare Part D develop more novel drugs in response.

Raising financing through equity markets may also cause firms to reduce their investment due to other frictions. For example, Ferreira, Manso, and Silva (2014) and Boot and Vladimirov (2019) theoretically predict that private firms will innovate more than public firms, due to agency and informational frictions causing external shareholders to be less tolerant of failure than insiders. This is consistent with the empirical evidence by

¹⁰ As evidence of suboptimal *overinvestment*, Guedj and Scharfstein (2004) use a sample of 235 cancer drug trials, and show that younger, earlier-stage firms are more likely to advance unpromising drug candidates through clinical trials, in contrast to larger and more mature firms. The pattern is strongest for firms with larger cash reserves. The authors interpret the evidence as consistent with agency problems between managers and shareholders, in which managers are reluctant to drop poor projects when they have no other promising drugs in the pipeline, and are able to use excess cash to continue them (e.g. Jensen (1986)).

Bernstein (2015) that innovation (as measured by patents) declines when private firms go public. Aghamolla and Thakor (forthcoming) show that this is the case for biopharma firms as well; firms conduct fewer drug trials and focus on less risky indications (i.e., those with a higher success rate) when they go public.

While there is evidence that innovative firms in general do employ some debt financing (see Kerr and Nanda (2015) for a review), and that biopharma firms are able to use limited amounts of debt, there has been little empirical work examining whether debt hinders or enhances drug investment. Recent advances on this front suggest that, when faced with the need to increase investment, biopharma firms shy away from debt. Thakor and Lo (forthcoming) provide evidence that biopharma firms reduce their debt when faced with increased competition that drives additional R&D investment. Giambona, Golec, and Lopez-de-Silanes (2021) use the Biologics Price Competition and Innovation Act as a shock to investment opportunities, and show that affected firms financed new assets primarily through equity, and furthermore decreased their leverage and sought less-restrictive debt covenants. The use of debt financing in drug development represents an important and underexplored area that is ripe for future work, and opens the possibility of finding a link between credit markets and the supply of new therapies.

4.2 The Competitive Structure of the Industry

A key feature that affects the innovation incentives of biopharma firms is the set of frictions related to competition in the industry which, as a number of studies have documented, has increased over time. A fuller understanding of the ways in which investment can be affected by competition opens up the possibility of spurring beneficial

drug investment by changing the level of competition; for example, legislation has often aimed to increase competition in the industry with the dual goals of promoting additional innovation and offering more choices to consumers.¹¹ However, as noted in the innovation literature by Aghion, Bloom, Blundell, Griffith, and Howitt (2005), among others, the theoretical relationship between competition and innovation is not clear-cut. Increased competition may either encourage or dampen innovative incentives.

A salient source of competition in the industry comes from the regulatory environment in which drug development firms operate. For example, Budish, Roin, and Williams (2014) argue that the patent system enhances short-term incentives, pushing firms towards more late-stage research. Garfinkel and Hammoudeh (2021) show that regulatory breakthrough therapy designations (BTDs) for drugs, which allow the expedited development and review of drugs intended to treat serious conditions, can lead rivals to either increase or decrease their development activities, depending on two perspectives on competition: the overall competitiveness of the disease treatment area, and the rival's competitive position within that area.

The marketing exclusivity period awarded to approved drugs is a critical regulatory feature influencing competition between firms, since generic versions of an approved drug from other producers can enter the marketplace when the exclusivity period expires, charging substantially lower prices than the existing "brand-name" drug (e.g. Danzon and Chao, 2000). While it has been argued that the ability of generic drugs

¹¹ See Grabowski and Vernon (1986, 1992), Caves, Whinston, and Hurwitz (1991), Grabowski and Vernon (1990, 1992), Grabowski and Kyle (2007), and Thakor and Lo (forthcoming)). Garthwaite (2018) provides an overview of the welfare implications of this tension.

to enter the marketplace may enhance consumer welfare (e.g. Branstetter, Chatterjee, and Higgins (2016)), the effect of generic entry on the innovation incentives of *incumbent firms* has been the subject of numerous studies. Branstetter, Chatterjee, and Higgins (2014) estimate a negative relationship between generic entry and early-stage research in the affected therapeutic area. Thakor and Lo (forthcoming) examine the economic effects of the implementation of the Hatch-Waxman Act of 1984, which eased the ability of generic drugs to enter into markets by allowing generic producers to bypass portions of the FDA approval process if bioequivalence has been established. They find that the increase in competition brought about by the Hatch-Waxman Act led to incumbent firms “focusing” their R&D effort, increasing their R&D investment but reducing the number of patents produced. Li, Lo, and Thakor (2021) highlight the ability of the legal environment to affect investment incentives, showing that the negative relationship between innovation and generic entry can be reversed when incumbents are restricted in their ability to enter into contracts to delay generic entry.

The competitive environment that biopharma firms operate in, combined with their need for external financing, creates an *interaction* between competition, investment, and financing that recent studies have begun to explore. One of the key conceptual points is that high levels of competition combined with the knowledge-intensive nature of the industry means that informational effects are particularly important. Competitors learn from the outcomes experienced by any firm. Recent studies have been able to use detailed clinical trial data to demonstrate the salience of these informational effects between competitors. Krieger (2021) and Krieger, Li, and Thakor (forthcoming) show how

negative news about a firm (through either trial failures or safety warnings on marketed products) can alter the investments of a firm's competitors when they learn about the information. Hsu, Lee, Moon, and Oh (2019) examine an increase in disclosure requirements and show that peer firms learn from the disclosed information through increased trial suspensions.

Informational effects are strongly linked to external financing because firms need to disclose information to investors in order to secure financing in public markets, but this information may also fall into the hands of competitors. This has been referred to in the literature as the "two-audience signaling" problem; see Kamien and Schwartz (1978), Bhattacharya and Ritter (1983), Bhattacharya and Chiesa (1995), and Gibbons, Gertner, and Scharfstein (1988). Thus, a firm needing external financing faces a tradeoff between the lower cost of external finance due to the information it discloses to investors in order to lessen adverse selection costs and the damage to real cash flows due to the inadvertent leakage of this information to competitors. This "two-audience signaling" problem can be particularly damaging given the winner-take-all feature of the patent and market exclusivity system.

As evidence of this link between information and financing, Aghamolla and Thakor (forthcoming) examine how disclosure requirements affect the propensity of private firms to undertake an IPO and enter public equity markets. They use the Food and Drug Administration Amendments Act (FDAAA) of 2007 as an exogenous shock to disclosure requirements, following which all biopharma firms have been mandated to publicly post clinical trial registrations and summary results for phase 2 and above trials.

Their results show that private biopharma firms were significantly more likely to tap into public equity markets following the increase in disclosure requirements, consistent with the *marginal* cost of disclosure through IPOs going down, since firms already had to disclose more information. Along similar lines, Dambra et al. (2015) and Lewis and White (2020) show that IPOs by biotech firms increased substantially following a reduction in compliance costs brought about by the Jumpstart Our Business Startups (JOBS) Act of 2012.

The link between disclosure and financing represents an important channel through which biopharma firms may choose a financing source, and thus becoming exposed to different financing risks, since different securities involved in financing involve different information sensitivities. For example, Boot and Thakor (1993) and DeMarzo and Duffie (1999) argue on theoretical grounds that equity is more informationally sensitive than debt; Bhattacharya and Chiesa (1995) point out that the use of bank financing permits firms to avoid revealing their proprietary information to competitors, unlike external financing. Additional empirical work is needed to show how informational effects may affect the choice by biopharma firms of financing sources such as equity, public debt, bank debt, and venture capital, and the subsequent impact of this choice on drug investment.

Apart from information disclosure, increased competition in and of itself can move firms towards different sources of financing because of the need to stay competitive with peers. Aghamolla and Thakor (2021) exploit similarities across firms' development portfolios to demonstrate that there are peer effects in the propensity of private

biopharma firms to tap public equity markets through an IPO. They provide evidence that firms are more likely to undertake an IPO following their peers due to competitive pressures; an IPO and the large influx of capital it brings provides a competitive advantage to a firm, causing its peers to follow suit to maintain a more level playing field. Aghamolla and Thakor (2021) also show similar effects for other sources of funding, such as venture capital. Thakor and Lo (forthcoming) show that an increase in competition induces biopharma firms to hold less debt. They argue that the need for firms to invest in new R&D rather than in existing assets to escape competitive pressures reduces the fixed asset base that can be used as collateral, while the potential for inefficient liquidation due to debt is more damaging with greater R&D investment. More research on competitive effects related to other sources of financing for biopharma firms is needed.

4.3 Markets for Technology

Markets for technology generally entail significant merger and acquisition (M&A) and licensing activity (e.g., Gans and Stern (2003)). These activities offer biopharma firms an important alternative means to develop drugs. Firms have the choice of developing new drugs in-house, entering into licensing agreements to co-develop with other firms, or acquiring projects (such as late-stage research) from other firms to develop them further towards commercialization. A small firm without access to enough capital to develop a drug through to approval also may opt to sell the drug (e.g. patents, rights, equipment) to a capital-rich firm like a large pharma company. A stylized fact has emerged that many biotech firms engage in early-stage research with the intention of selling the research to larger pharma firms when it has progressed to a certain point of

clinical development. Detailed project-level data from clinical trials allows researchers to closely track these sorts of agreements, which also allows broader insights into acquisition markets not offered in other contexts, for example, the ability to observe acquisitions of individual projects rather than acquisitions of entire firms.

The empirical evidence supports the notion of markets for technology being an important source to which biopharma firms can turn, particularly given the institutional details of the drug development process (see, e.g., Grabowski and Kyle (2012)). Additionally, it supports the idea that these markets may help to guide drug projects to their first-best developers. Hermosilla and Wu (2018) show how cooperation via technological licensing can lead to improved outcomes because it pools the complementary capabilities of firms; these gains are especially salient in larger markets. Danzon, Epstein, and Nicholson (2007) examine biopharma M&A activity from 1988 to 2001, and find that mergers and acquisitions are typically a response to financial trouble or gaps in a firm's pipeline. Along similar lines, Higgins and Rodriguez (2006) and Krieger, Li, and Thakor (forthcoming) show that biopharma firms with weaker internal pipelines are likely to engage in acquisitions in order to replenish their pipelines, rather than initiating new drug trials or continuing to develop their existing projects. Part of the reason for this strategy is developing new products internally are too time-consuming and expensive for firms experiencing a negative shock or declining productivity, whereas acquiring projects offer a quick and efficient way to replace lagging products. Furthermore, firms with accumulated knowledge capital in a particular therapeutic area may reap the benefits of redeploying that capital on newly-acquired projects, thus

enabling an efficient reallocation of drug projects to their first-best users (e.g. Krieger, Li, and Thakor (forthcoming)).

However, frictions related to control rights have the potential to limit the effectiveness of markets for technology. Cunningham, Ederer, and Ma (2021) provide evidence that incumbent pharma firms may use acquisitions as a means to consolidate their market power by shutting down competing projects. Hermosilla (2021) shows that firms rush to acquire replacement products after phase 3 failures, but these acquisitions subsequently underperform due to the contract negotiations in the acquisition process. The allocation of control rights between partners in pharmaceutical alliances can affect the efficiency of drug development conducted by those alliances (Lerner, Shane, and Tsai (2004) and Higgins (2007)). Overall, these papers paint a picture in which markets for technology –through acquisitions and alliances– may introduce either efficiencies or inefficiencies into the drug development process. More research is needed to understand whether the net effects reflect efficiencies or inefficiencies, and the circumstances in which they arise. Furthermore, acquiring a project or company requires financing, and licensing requires a contribution of financial resources from participating firms; this financing connection and how it contributes to the efficiency of markets for technology is also an area that needs further exploration.

Related to this link, a recent development (particularly since 2020) is the growing popularity of acquisitions as an avenue for firms to go public and tap external equity markets. Special Purpose Acquisition Companies (SPACs) are financing “shell” companies that contain no assets, but which go public through an IPO with the intention

of later acquiring a firm. Once the acquisition is done, the SPAC itself dissolves, leaving the acquired company as a publicly traded entity. SPACs have been touted as an alternative to a traditional IPO, as a firm is able to become publicly traded without having to file a prospectus or go through the regulatory IPO process. Several biopharma companies have gone public via SPAC acquisitions. The consequences of SPACs for the drug development process are still unexplored, and constitute a new and exciting area for research.

4.4 Venture Capital and Private Equity

Venture capital (VC) and private equity (PE) are other avenues of financing available to biopharma firms. The extant VC and PE finance literature has shown that these are important sources of funding that foster innovation (e.g. Kortum and Lerner (2000)). VC and PE funding is particularly important for earlier-stage biotech firms that require startup capital, but lack the means to access broader public financing markets.

The nature of VC and PE investment creates a large degree of risk and uncertainty for drug development. VC investments are highly cyclical, which can cause difficulty for capital-intensive, high-risk, and long-duration projects—even the most successful biopharma firms are sometimes unable to secure capital when they need it. Furthermore, scale matters, since VC investment rounds are typically smaller, with an average biopharma VC funding round of \$8 million (Aghamolla and Thakor (2021)). With high and rising development costs for drug projects, venture capitalists now need a much larger fund and are less able to diversify. Over the course of the past few years, PE funds have become more involved in financing biopharma investments. Large PE firms have

launched funds, but have tended to focus on investments in later-stage assets rather than preclinical drugs.

The possibility of hold-up problems in VC and PE firm investment contracts has been shown to introduce inefficiencies in such arrangements (e.g., Kaplan and Stromberg (2004)). Recent evidence suggests that these types of problems can affect investments by biopharma firms. Li, Tong, and Taylor (2021) provide evidence that common ownership of drug projects across firms by venture capitalists can lead them to shut down some drug development projects to reduce competition across portfolios. The role of VC and PE firms in the drug development process remains an understudied area with important consequences.

5. Solutions to Underinvestment

The previous sections have laid out the case that the features of drug development cause many frictions for biopharma firms, leading to underinvestment. This may particularly be the case for drugs that are valuable to society, as the risks of development outweigh the potential economic benefits to firms. For example, cancer drugs tend to have the lowest probability of success (less than 5% on average), and thus firms may shy away from developing potentially valuable cancer treatments. Researchers have offered a number of potential solutions to this problem. In this section, we survey these insights.

5.1 The Drug Development Process

A variety of solutions have been proposed on the regulatory front, from changes to patent policy and competition to public funding mandates. In some cases, initiatives have promoted further research into diseases by biopharma firms, but in other cases the efficacy of policy initiatives has been limited. For example, as discussed in the previous sections, policies such as enhanced patent protection may improve or hinder innovation incentives. Similarly, public funding allocations may be sub-optimal; see Kyle (2020) for a review and discussion of these initiatives.

One potential policy solution that has been offered is to change the FDA approval process itself. Some recent initiatives by the FDA offer a faster review and approval process for certain qualifying drugs (such as the Breakthrough Therapy Designation), while the 21st Century Cures Act has allowed the introduction of "real world evidence" such as observational studies and patient input to complement the FDA clinical trial process in order to expedite approvals (Lo, Philipson, and von Eschenbach (2016), Lo (2017)).

Other proposals include the use of adaptive platform trials (APTs) to advance the clinical trial process. These trials are new designs of randomized controlled trials (RCTs) that are able to study multiple interventions in a disease or condition on an ongoing basis, with interventions entering and leaving the platform on the basis of a predefined algorithm (Angus, Alexander, Berry et al. (2019)). The most established APT is I-SPY 2, a phase 2 trial investigating neoadjuvant (preliminary) therapies for breast cancer in conjunction with standard chemotherapy compared to standard chemotherapy for women diagnosed with local metastatic breast cancer before surgical resection (Das and

Lo (2017)). A framework for modeling the accrual of information in an adaptive clinical trial as a sequence of real options is developed in Chaudhuri and Lo (2020), following the example of Royalty Pharma's financing of Sunesis Pharmaceuticals' phase 3 adaptive clinical trial of its leukemia drug, Vosaroxin (Lo and Narahariseti (2014)). Berry et al. (2020) determine that an adaptive trial provides the maximal net benefit for trials of COVID-19 vaccine candidates in number of averted infections and deaths, short of the deliberate infection of volunteers in "human challenge" trials.

Another approach involves the use of Bayesian decision-making to improve the criteria of the clinical trial process. Current clinical trial design attempts to minimize the probability of ineffective treatment caused by a false positive (type 1) result. However, the threshold for the probability of type 1 error, α , may not be appropriate to the preferences of the patient (Chaudhuri et al. (2018), Chaudhuri and Lo (2021)). For example, a 2.5% threshold for α may not be appropriate for patients with terminal illnesses that have no effective therapies. Montazerhodjat, Chaudhuri, Sargent and Lo (2017) find that the optimal alphas determined by Bayesian decision analysis (BDA) were often much larger than 2.5% for terminal cancers with short survival times and no effective therapies, such as pancreatic cancer, and smaller than 2.5% for less serious cancers with long survival times and multiple effective therapies. Isakov, Lo, and Montazerhodjat (2019) generalize this finding to the 25 most lethal diseases in the United States. Chaudhuri, Lo, Xiao, and Xu (2020) apply Bayesian patient-centered models to anti-infective therapeutics, incorporating epidemiological models to determine the optimal α during outbreaks of epidemic disease. Most recently, a survey of over 2700

Parkinson's disease (PD) patients by Hauber et al. (2021) finds that risk thresholds in a BDA framework for new neurostimulative devices in the treatment of PD increase markedly with the perceived benefit of the device to the patient.

A crucial part of de-risking the drug development process is an accurate determination of the probabilities of success of the consecutive phases of drug approval (Wong, Siah, and Lo (2019)), clinical trial outcomes, and clinical outcomes in individual patients (Siah, Khozin, Wong, and Lo (2019)), while the analogous probabilities of vaccine development success are estimated in Lo, Siah, and Wong (2020). Machine learning techniques have significant power in predicting approvals not only among later-phase drug candidates, (Lo, Siah, and Wong (2019)), but with extensive feature engineering augmented by domain expertise in drug development, outperforming this recent baseline (Siah et al. (2021)).

5.2 Financial Innovation

A key difficulty that biopharma firms face is that the drug development process is risky and expensive. Fagnan, Fernandez, Lo, and Stein (2013) point out that a potential solution can be found through financial innovation, which can be used to transfer risks to market participants that are more willing to bear them. As a result, more funding can be channeled towards drug development, particularly in areas that there may be greater societal need but higher risks for firms.

Fagnan, Fernandez, Lo, and Stein (2013) proposed the idea of a “megafund” which pools together a number of different projects. The idea relies on basic finance portfolio theory and the notion of diversification, that some of the individual risks associated with

drug projects will cancel each other out, reducing the overall risk of the fund. The megafund is then able to issue tranches of debt as well as equity because of its lower risk. This in turn provides a more attractive risk-return profile to large investors, thus allowing additional funds to flow to the investments. This approach is generalizable to any large investment project with low probabilities of success, a long gestation lag, large required up-front investment, and very large payoffs relative to the investment, provided that the basic assumptions of diversification hold for the individual projects within the portfolio (Hull, Lo, and Stein (2019)). The degree of correlation of success or failure between portfolio development projects is critical to the success or failure of the megafund, with statistically independent projects favoring its success; however, the basic "vanilla" structure is able to maintain promising returns even with a moderate degree of correlation using the most recent drug development project data (Lo and Siah (2021)). Dynamic leverage applied to the megafund, maintaining a constant level of default risk as the financing moves from an all-equity capital structure to a mixed one with an increasing amount of debt, can boost equity returns and add significant value to the fund (Montazerhodjat, Frishkopf, and Lo (2016)).

Drug development for orphan diseases, defined in the United States as those conditions which affect fewer than 200 thousand people nationwide, is particularly amenable to the megafund approach, due to lower capital requirements, legislative incentives, and a lower correlation of failures among disease targets (Fagnan, Gromatzky, Stein, Fernandez, and Lo (2014), Fagnan, Yang, McKew, and Lo (2015), and Lo and Thakor (2019)). Drug development for glioblastoma can also be substantially financially

de-risked with the assistance of domain experts to choose the portfolio (Siah et al. (2021)). A portfolio approach within a public-private partnership including government guarantees is more suitable for ovarian cancer therapeutics, reducing tail risk while increasing expected returns to investors (Chaudhuri et al. (2019)), while a portfolio approach with government guarantees and philanthropic support for pediatric oncology therapeutics has the potential to eliminate significant downside risk while maximizing expected returns (Das, Rousseau, Adamson, and Lo (2018)). However, simulations based on clinical data show that a megafund portfolio of therapeutics for Alzheimer's Disease (AD) is unlikely to generate returns sufficient to attract private sector capital by itself (Lo, Ho, Cummings, and Kosik (2014)), as are megafund portfolios of vaccine candidates (Vu, Kaplan, Chaudhuri, Mansoura, and Lo (2020)).

Financial innovation has also been proposed in other forms. Jørring et al. (2021) propose the idea of “FDA Hedges”, which are insurance contracts that pay drug developing firms upon the failure of individual drug projects to gain FDA approval. Jørring et al. (2021) develop a theoretical model to highlight the informational frictions that allow these contracts to reduce underinvestment in R&D and enhance welfare. They also provide evidence that these contracts have little systematic risk, so if they were to be freely traded on exchanges, investors would not demand a systematic risk premium, making the pricing attractive for firms. They also provide a discussion of the feasibility of introducing these contracts.

5.3 Organizational Innovation

Changes in organizational structure of the firm may also enhance biopharma funding. For example, the business development company (BDC), a closed-end investment fund with relaxed requirements that allow it to raise money in the public equity and debt markets, can be used to fund multiple early-stage ventures for long-term investors in biomedical innovation (Forman, Lo, Shilling and Sweeney (2015)). Likewise, the project-focused organization (PFO), analogous to movie project development within the Hollywood studio system, undertaken with the sole purpose of conducting a specific R&D project, may be a useful alternative to the traditional venture capital or entrepreneurial startup model (Lo and Pisano (2016)).

Academic and philanthropic institutions play an increasing role in the financing of biopharma firms, but few data are yet available on their performance or the magnitude of their impact. Huang et al. (2021) make a systematic study of technology licensing by the Massachusetts Institute of Technology (MIT). They find that 4 approved small-molecule drugs cite MIT patents, but another 31 FDA-approved drugs have some involvement of MIT licensees, of which 55% are a new molecular or biological entity, and 55% were granted priority review by the FDA, an indication that they address an unmet medical need.

Venture philanthropy, a funding model in which nonprofit, mission-driven organizations fund initiatives to advance their objectives while achieving returns to be reinvested toward their goal, has been increasing in popularity since the notable financial success of the Cystic Fibrosis Foundation's funding of the development of Kalydeco, the first disease-modifying therapy approved to treat cystic fibrosis (Kim and Lo (2019)). In

addition, these philanthropic organizations can provide scientific assistance to de-risk the drug development process, as with the National Brain Tumor Society and the development of a portfolio of assets to treat glioblastoma (Siah et al. (2021)).

6. Concluding Remarks

In this paper, we have surveyed the literature on drug development financing, providing stylized facts that the drug development process is lengthy, risky, and expensive, and these costs and risks have increased over time. The institutional features, costs, and risks associated with drug development result in biopharma firms relying more heavily on external financing to fund their investments, creating a strong link between drug development and financial markets. This link—when combined with the institutional features of drug development—creates challenges in funding certain potentially valuable R&D efforts, leading to an underprovision of social-welfare-enhancing therapies.

We surveyed the body of empirical evidence that demonstrates how market frictions and financial markets interact with and affect the investment incentives of biopharma firms. We concluded by surveying research that proposes solutions to the underinvestment problem, including changes to the drug development process and financial innovation. Throughout, we have highlighted areas that are understudied and have the potential for impactful future research.

In addition to its implications for improving the drug development process, financial research on the biopharma industry also offers valuable insights into the processes of R&D and innovation investment, as well as general corporate financial decisions. This setting offers granular data about clinical trials, providing researchers with alternative measures of innovation and the ability to track individual project decisions for both public and private firms. This opens up the possibility for a variety of new insights to be extracted about firms outside of the biopharma industry.

Our focus in this article has been on financing issues related to the drug development side of healthcare. Drug development is of course a part of the larger healthcare system. After a new therapy has been developed, it must be delivered to patients, which brings to the surface a host of issues related to how patients can finance their care (see Gruber (2021) for a review). Another area at the intersection of finance and healthcare is the financing of hospitals, clinics, and nursing homes that directly deliver healthcare to patients. These are entities whose goals both overlap with and differ from those of firms in other industries. Their differences make them interesting to study in terms of their financing and investment decisions in response to informational and other frictions. There is a nascent emerging literature studying these issues, which is ripe for additional contributions.¹²

¹² The literature includes papers that have examined how hospitals respond to shocks to their financial assets in terms of investments and shifts in treatment (Adelino, Lewellen, and Sundaram (2015), Adelino, Lewellen, and McCartney (forthcoming)); how credit market frictions can lead to hospitals providing worse quality of care and increased mortality (Aghamolla, Karaca-Mandic, Li, and Thakor (2021)); and how private equity investment into nursing homes can result in worse care outcomes (Gupta, Howell, Yannelis, and Gupta (2021)).

References

1. Adelino, Manuel, Katharina Lewellen, and W. Ben McCartney. "Hospital financial health and clinical choices: evidence from the financial crisis." *Management Science*, forthcoming.
2. Adelino, Manuel, Katharina Lewellen, and Anant Sundaram. "Investment decisions of nonprofit firms: Evidence from hospitals." *The Journal of Finance* 70, no. 4 (2015): 1583-1628.
3. Aghamolla, Cyrus, Pinar Karaca-Mandic, Xuelin Li, and Richard T. Thakor. "Merchants of death: The effect of credit supply shocks on hospital outcomes." No. w28709. National Bureau of Economic Research, 2021.
4. Aghamolla, Cyrus, and Richard T. Thakor. "Do mandatory disclosure requirements for private firms increase the propensity of going public?." *Journal of Accounting Research* (forthcoming)
5. Aghamolla, Cyrus, and Richard T. Thakor. "IPO peer effects." *Journal of Financial Economics* (2021).
6. Angus, Derek C., Brian M. Alexander, Scott Berry, et. al. "Adaptive Platform Trials: Definition, Design, Conduct and Reporting Considerations." *Nature Reviews Drug Discovery* 18, no. 10, (2019): 797-807.
7. Benmelech, Efraim, Janice Eberly, Dimitris Papanikolaou, and Joshua Krieger. "Private and Social Returns to R&D: Drug Development and Demographics." In *AEA Papers and Proceedings*, vol. 111, pp. 336-40. 2021.
8. Bernstein, Shai. "Does going public affect innovation?." *The Journal of Finance* 70, no. 4 (2015): 1365-1403.
9. Berry, Donald, Scott Berry, Peter Hale, Leah Isakov, Andrew W. Lo, Kien Wei Siah, Chi Heem Wong. "A Cost/Benefit Analysis of Clinical Trial Designs for COVID-19 Vaccine Candidates." *PLoS ONE* 15, no. 12 (2020): e0244418. <https://doi.org/10.1371/journal.pone.0244418> .
10. Besanko, David, and Anjan V. Thakor. "Collateral and rationing: sorting equilibria in monopolistic and competitive credit markets." *International Economic Review* (1987): 671-689.
11. Besanko, David, and Anjan V. Thakor. "Competitive equilibrium in the credit market under asymmetric information." *Journal of Economic Theory* 42, no. 1 (1987): 167-182.
12. Bhattacharya, Sudipto, and Gabriella Chiesa. "Proprietary information, financial intermediation, and research incentives." *Journal of Financial Intermediation* 4, no. 4 (1995): 328-357.
13. Bhattacharya, Sudipto, and Jay R. Ritter. "Innovation and communication: Signalling with partial disclosure." *The Review of Economic Studies* 50, no. 2 (1983): 331-346.
14. Boot, Arnoud WA, and Vladimir Vladimirov. "'Collusion' with Public and Private Ownership and Innovation." Available at SSRN 3057555 (2019).
15. Boot, Arnoud WA, and Anjan V. Thakor. "Security design." *The Journal of Finance* 48, no. 4 (1993): 1349-1378.

16. Branstetter, Lee, Chirantan Chatterjee, and Matthew J. Higgins. Starving (or fattening) the golden goose?: Generic entry and the incentives for early-stage pharmaceutical innovation. No. w20532. National Bureau of Economic Research, 2014.
17. Branstetter, Lee, Chirantan Chatterjee, and Matthew J. Higgins. "Regulation and welfare: evidence from paragraph IV generic entry in the pharmaceutical industry." *The RAND Journal of Economics* 47, no. 4 (2016): 857-890.
18. Budish, Eric, Benjamin N. Roin, and Heidi Williams. "Do firms underinvest in long-term research? Evidence from cancer clinical trials." *American Economic Review* 105, no. 7 (2015): 2044-85.
19. Carlson, Robert. "Estimating the biotech sector's contribution to the US economy." *Nature Biotechnology* 34, no. 3 (2016): 247-255.
20. Caves, Richard E., Whinston, Michael D., and Mark A. Hurwitz, 1991, "Patent Expiration, Entry, and Competition in the U.S. Pharmaceutical Industry". *Brookings Papers on Economic Activity: Microeconomics* Vol. 1991, 1-66.
21. Chaudhuri, Shomesh E., Katherine Cheng, Andrew W. Lo, Shirley Pepke, Sergio Rinaudo, Lynda Roman, and Ryan Spencer. "A Portfolio Approach to Accelerate Therapeutic Innovation in Ovarian Cancer." *Journal of Investment Management* 17, No. 2 (2019), 5-16.
22. Chaudhuri, Shomesh E., Martin P. Ho, Telba Irony, Murray Sheldon, and Andrew W. Lo. "Patient-Centered Clinical Trials." *Drug Discovery Today* 23, no. 2 (2018): 395-401.
23. Chaudhuri, Shomesh E. and Andrew W. Lo. "Financially adaptive clinical trials via option pricing analysis." *Journal of Econometrics* (2020): 1-11.
24. Chaudhuri, Shomesh E. and Andrew W. Lo. "Incorporating Patient Preferences via Bayesian Decision Analysis." *Clinical Journal of the American Society of Nephrology* 16, no. 1 (2021): 639-641.
25. Chaudhuri, Shomesh, Andrew W. Lo, Xiao, Danyang, and Xu, Qingyang. "Bayesian Adaptive Clinical Trials for Anti- Infective Therapeutics During Epidemic Outbreaks." *Harvard Data Science Review* (2020).
26. Cockburn, Iain, and Josh Lerner. "The Cost of Capital for Early-Stage Biotechnology Ventures." (2006).
27. Cunningham, Colleen, Florian Ederer, and Song Ma. "Killer acquisitions." *Journal of Political Economy* 129, no. 3 (2021): 649-702.
28. Dambra, Michael, Laura Casares Field, and Matthew T. Gustafson. "The JOBS Act and IPO volume: Evidence that disclosure costs affect the IPO decision." *Journal of Financial Economics* 116, no. 1 (2015): 121-143.
29. Danzon, Patricia M., and Li-Wei Chao. "Does regulation drive out competition in pharmaceutical markets?." *The Journal of Law and Economics* 43, no. 2 (2000): 311-358.
30. Danzon, Patricia M., Andrew Epstein, and Sean Nicholson. "Mergers and acquisitions in the pharmaceutical and biotech industries." *Managerial and Decision Economics* 28, no. 4-5 (2007): 307-328.
31. Das, Sonya, and Andrew W. Lo. "Re-Inventing Drug Development: A Case Study of the I-SPY 2 Breast Cancer Clinical Trials Program." *Contemporary Clinical Trials* 62 (2017): 168-174.

32. Das, Sonya, Raphaël Rousseau, Peter C. Adamson, and Andrew W. Lo. "New Business Models to Accelerate Innovation in Pediatric Oncology Therapeutics: A Review." *JAMA Oncology* 4, no. 9 (2018), 1274-1280.
33. DeMarzo, Peter, and Darrell Duffie. "A liquidity- based model of security design." *Econometrica* 67, no. 1 (1999): 65-99.
34. Deshpande, Nishad, and Asha Nagendra. "Patents as collateral for securitization." *Nature Biotechnology* 35, no. 6 (2017): 514-516.
35. DiMasi, Joseph A., and Henry G. Grabowski. "The cost of biopharmaceutical R&D: is biotech different?." *Managerial and Decision Economics* 28, no. 4- 5 (2007): 469-479.
36. DiMasi, Joseph A., Ronald W. Hansen, Henry G. Grabowski, and Louis Lasagna. "Cost of innovation in the pharmaceutical industry." *Journal of Health Economics* 10, no. 2 (1991): 107-142.
37. DiMasi, Joseph A., Henry G. Grabowski, and Ronald W. Hansen. "Innovation in the pharmaceutical industry: new estimates of R&D costs." *Journal of Health Economics* 47 (2016): 20-33.
38. DiMasi, Joseph A., Ronald W. Hansen, and Henry G. Grabowski. "The price of innovation: new estimates of drug development costs." *Journal of Health Economics* 22, no. 2 (2003): 151-185.
39. Duggan, Mark, Craig Garthwaite, and Aparajita Goyal. "The market impacts of pharmaceutical product patents in developing countries: Evidence from India." *American Economic Review* 106, no. 1 (2016): 99-135.
40. Fagnan, David E., Jose-Maria Fernandez, Andrew W. Lo, and Roger M. Stein. "Can Financial Engineering Cure Cancer?" *American Economic Review* 103, no. 3 (2013): 406-411.
41. Fagnan, David E., Austin A. Gromatzky, Roger M. Stein, Jose-Maria Fernandez, and Andrew W. Lo. "Financing Drug Discovery for Orphan Diseases." *Drug Discovery Today* 19, no. 5 (2014): 533-538.
42. Fagnan, David E., N. Nora Yang, John C. McKew, and Andrew W. Lo. "Financing Translation: Analysis of the NCATS Rare-Diseases Portfolio." *Science Translational Medicine* 7 (276) (2015): 276ps3.
43. Ferreira, Daniel, Gustavo Manso, and André C. Silva. "Incentives to innovate and the decision to go public or private." *The Review of Financial Studies* 27, no. 1 (2014): 256-300.
44. Forman, Sandra M., Andrew W. Lo, Monica Shilling, and Grace K. Sweeney. "Funding Translational Medicine via Public Markets: The Business Development Company." *Journal of Investment Management* 13, no. 4 (2015): 9-32.
45. Freilich, Janet. "Prophetic patents." *UC Davis L. Rev.* 53 (2019): 663.
46. Gans, Joshua S., and Scott Stern. "The product market and the market for "ideas": commercialization strategies for technology entrepreneurs." *Research Policy* 32, no. 2 (2003): 333-350.
47. Garfinkel, Jon A., and Mosab Hammoudeh. "Competition Threats and Rival Innovation Responses: Evidence from Breakthrough Therapies." Available at SSRN 3684095 (2020).

48. Garthwaite, Craig. "The economics of drug development: Pricing and innovation in a changing market." *NBER Reporter* 3 (2018): 19-24.
49. Giambona, Erasmo, Joseph Golec, and Florencio Lopez-de-Silanes. "Do firms purposefully change capital structure? Evidence from an investment-opportunity shock to drug firms." *Journal of Financial and Quantitative Analysis* 56, no. 3 (2021): 915-944.
50. Grabowski, Henry G., and Margaret Kyle. "Generic competition and market exclusivity periods in pharmaceuticals." *Managerial and Decision Economics* 28, no. 4-5 (2007): 491-502.
51. Grabowski, Henry G., and Margaret Kyle. "Mergers, Acquisitions, and Alliances" with Henry Grabowski, Chapter 18 in *Handbook of the Economics of the BioPharmaceutical Industry* (edited by Patricia Danzon and Sean Nicholson), 2012.
52. Grabowski, Henry, and John Vernon. "Longer Patents for Lower Imitation Barriers: The 1984 Drug Act." *American Economic Review* 76, no. 2 (1986): 195-98.
53. Grabowski, Henry, and John Vernon. "A new look at the returns and risks to pharmaceutical R&D." *Management Science* 36, no. 7 (1990): 804-821.
54. Grabowski, Henry G., and John M. Vernon. "Brand Loyalty, Entry, and Price Competition in Pharmaceuticals after the 1984 Drug Act." *Journal of Law and Economics* 35, no. 2 (1992): 331-50.
55. Gruber, Jonathan. "Financing Healthcare Delivery."
56. Guedj, Ilan, and David Scharfstein. "Organizational Scope and Investment: Evidence from the Drug Development Strategies and Performance of Biopharmaceutical Firms." No. 10933. National Bureau of Economic Research, Inc, 2004.
57. Gupta, Atul, Sabrina T. Howell, Constantine Yannelis, and Abhinav Gupta. "Does private equity investment in healthcare benefit patients? evidence from nursing homes." No. w28474. National Bureau of Economic Research, 2021.
58. Hall, Bronwyn H., and Josh Lerner. "The financing of R&D and innovation." In *Handbook of the Economics of Innovation*, vol. 1, pp. 609-639. North-Holland, 2010.
59. Harrington, Scott E. "Cost of capital for pharmaceutical, biotechnology, and medical device firms." *The Oxford handbook of the economics of the biopharmaceuticals industry* (2012): 75-99.
60. Hauber, Brett, Brennan Mange, Mo Zhou, Shomesh Chaudhuri, Heather L Benz, Brittany Caldwell, John P Ruiz, Anindita Saha, Martin Ho, Stephanie Christopher, Dawn Bardot, Margaret Sheehan, Anne Donnelly, Lauren McLaughlin, Katrina Gwinn, Andrew W. Lo, and Murray Sheldon. "Parkinson's Patients' Tolerance for Risk and Willingness to Wait for Potential Benefits of Novel Neurostimulation Devices: A Patient-Centered Threshold Technique Study." *MDM Policy & Practice* (2021): 1-13.
61. Hermosilla, Manuel. "Rushed innovation: Evidence from drug licensing." *Management Science* 67, no. 1 (2021): 257-278.
62. Hermosilla, Manuel, and Yufei Wu. "Market size and innovation: The intermediary role of technology licensing." *Research Policy* 47, no. 5 (2018): 980-991.
63. Higgins, Matthew J. "The allocation of control rights in pharmaceutical alliances." *Journal of Corporate Finance* 13, no. 1 (2007): 58-75.

64. Higgins, Matthew J., and Daniel Rodriguez. "The outsourcing of R&D through acquisitions in the pharmaceutical industry." *Journal of Financial Economics* 80, no. 2 (2006): 351-383.
65. Hoberg, Gerard, and Gordon Phillips. "Product market synergies and competition in mergers and acquisitions: A text-based analysis." *The Review of Financial Studies* 23, no. 10 (2010): 3773-3811.
66. Hoberg, Gerard, and Gordon Phillips. "Text-based network industries and endogenous product differentiation." *Journal of Political Economy* 124, no. 5 (2016): 1423-1465.
67. Hsu, Po-Hsuan, Kyungran Lee, S. Katie Moon, and Seungjoon Oh. "Information Transparency in Drug Development: Evidence from Mandatory Disclosure of Clinical Trials." Available at SSRN 3459511 (2019).
68. Huang, Samuel, Kien Wei Siah, Detelina Vasileva, Shirley Chen, Lita Nelsen and Andrew W. Lo. "Life sciences intellectual property licensing at the Massachusetts Institute of Technology." *Nature Biotechnology* 39 (2021): 293-301.
69. Hull, John, Andrew W. Lo, and Roger M. Stein. "Funding Long Shots." *Journal of Investment Management* 17, no. 4 (2019): 1-33.
70. Isakov, Leah, Andrew W. Lo, and Vahid Montazerhodjat. "Is the FDA Too Conservative or Too Aggressive?: A Bayesian Decision Analysis of Clinical Trial Design." *Journal of Econometrics* 211, no. 1 (2019): 117-136.
71. Jensen, Michael C. "Agency costs of free cash flow, corporate finance, and takeovers." *The American Economic Review* 76, no. 2 (1986): 323-329.
72. Jørring, Adam, Andrew W. Lo, Tomas J. Philipson, Manita Singh, and Richard T. Thakor. Sharing R&D risk in healthcare via FDA hedges. No. w23344. National Bureau of Economic Research, 2017.
73. Kaplan, Steven N., and Per ER Strömberg. "Characteristics, contracts, and actions: Evidence from venture capitalist analyses." *The Journal of Finance* 59, no. 5 (2004): 2177-2210.
74. Kerr, William R., and Ramana Nanda. "Financing innovation." *Annual Review of Financial Economics* 7 (2015): 445-462.
75. Kim, Esther, and Andrew W. Lo. "Venture Philanthropy: A Case Study of the Cystic Fibrosis Foundation." April 23 (2019).
76. Kortum, Samuel, and Josh Lerner. "Assessing the contribution of venture capital to innovation." *RAND Journal of Economics* 31, no. 4 (2000): 674-692.
77. Krieger, Joshua L. "Trials and terminations: Learning from competitors' R&D failures." *Management Science* (2021)
78. Krieger, Joshua, Danielle Li, and Dimitris Papanikolaou. "Missing Novelty in Drug Development." *The Review of Financial Studies*, forthcoming.
79. Krieger, Joshua, Xuelin Li, and Richard T. Thakor. "Find and replace: R&D investment following the erosion of existing products." *Management Science*, forthcoming.
80. Kyle, Margaret K. "Are important innovations rewarded? Evidence from pharmaceutical markets." *Review of Industrial Organization* 53, no. 1 (2018): 211-234.

81. Kyle, Margaret K. "The Alignment of Innovation Policy and Social Welfare: Evidence from Pharmaceuticals." *Innovation Policy and the Economy* 20, no. 1 (2020): 95-123.
82. Lakdawalla, Darius N. "Economics of the pharmaceutical industry." *Journal of Economic Literature* 56, no. 2 (2018): 397-449.
83. Lerner, Josh, Hilary Shane, and Alexander Tsai. "Do equity financing cycles matter? Evidence from biotechnology alliances." *Journal of Financial Economics* 67, no. 3 (2003): 411-446.
84. Lewis, Craig M., and Joshua T. White. "Deregulating Innovation Capital: The Effects of the JOBS Act on Biotech Startups." Available at SSRN 3640852 (2020).
85. Li, Xuelin, Tong Liu, and Lucian A. Taylor. "Common Ownership and Innovation Efficiency." (2021).
86. Li, Xuelin, Andrew W. Lo, and Richard T. Thakor. Paying off the Competition: Market Power and Innovation Incentives. No. w28964. National Bureau of Economic Research, 2021.
87. Lo, Andrew W. "Discussion: New Directions for the FDA in the 21st Century." *Biostatistics* 18, no. 3 (2017): 404-407.
88. Lo, Andrew W., Carole Ho, Jayna Cummings, and Kenneth S. Kosik. "Parallel Discovery of Alzheimer's Therapeutics." *Science Translational Medicine* 6 (241) (2014): 241cm5.
89. Lo, Andrew W., and Sourya V. Naraharisetti. "New Financing Methods in the Biopharma Industry: A Case Study of Royalty Pharma, Inc." *Journal of Investment Management* 12, no. 1 (2014): 4-19.
90. Lo, Andrew W., Tomas J. Philipson, and Andrew C. von Eschenbach. "Health, Wealth, and the 21st Century Cures Act." *JAMA Oncology* 2, no. 1 (2016): 17-18.
91. Lo, Andrew W., and Gary Pisano. "Lessons From Hollywood: A New Approach to Funding R&D." *Sloan Management Review* 57, no. 2 (2016): 47-57.
92. Lo, Andrew W., and Kien Wei Siah. "Financing Correlated Drug Development Projects." *Journal of Structured Finance* (2021). <https://doi.org/10.3905/jsf.2020.1.114>.
93. Lo, Andrew W., Kien Wei Siah, and Chi Heem Wong. "Machine Learning with Statistical Imputation for Predicting Drug Approval." *Harvard Data Science Review* 1, no. 1 (2019).
94. Lo, Andrew W., Kien Wei Siah, and Chi Heem Wong. "Estimating Probabilities of Success of Clinical Trials for Vaccines and Other Anti- Infective Therapeutics." *Harvard Data Science Review* (2020).
95. Lo, Andrew W., and Richard T. Thakor. "Risk and Reward in the Orphan Drug Industry." *The Journal of Portfolio Management* 45, no. 5 (2019): 30-45.
96. Mace, Chris. "The Real Effects of Secondary Markets on Innovation." Available at SSRN 3348102 (2020).
97. Mann, William. "Creditor rights and innovation: Evidence from patent collateral." *Journal of Financial Economics* 130, no. 1 (2018): 25-47.
98. Montazerhodjat, Vahid, Shomesh E. Chaudhuri, Daniel J. Sargent, and Andrew W. Lo. "Use of Bayesian Decision Analysis to Minimize Harm in Patient-Centered Randomized Clinical Trials in Oncology." *JAMA Oncology* 3, no. 9 (2017): e170123.

99. Montazerhodjat, Vahid, John J. Frishkopf, and Andrew W. Lo. "Financing Drug Discovery via Dynamic Leverage." *Drug Discovery Today* 21, no. 3 (2016): 410-414.
100. Myers, Stewart C., and Christopher Dwight Howe. "A Life-cycle Financial Model of Pharmaceutical R & D." Program on the Pharmaceutical Industry, Sloan School of Management, Massachusetts Institute of Technology, 1997.
101. Myers, Stewart C., and Nicholas S. Majluf. "Corporate financing and investment decisions when firms have information that investors do not have." *Journal of Financial Economics* 13, no. 2 (1984): 187-221.
102. Rampini, Adriano A., and S. Viswanathan. "Collateral and capital structure." *Journal of Financial Economics* 109, no. 2 (2013): 466-492.
103. Scannell, Jack W., Alex Blanckley, Helen Boldon, and Brian Warrington. "Diagnosing the decline in pharmaceutical R&D efficiency." *Nature Reviews Drug Discovery* 11, no. 3 (2012): 191-200.
104. Siah, Kien Wei, Nicholas W. Kelley, Steffen Ballerstedt, Björn Holzhauer, Tianmeng Lyu, David Mettler, Sophie Sun, Simon Wandel, Yang Zhong, Bin Zhou, Shifeng Pan, Yingyao Zhou, and Andrew W. Lo. "Predicting drug approvals: The Novartis data science and artificial intelligence challenge." *Patterns* (2021), <https://doi.org/10.1016/j.patter.2021.100312>
105. Siah, Kien Wei, Sean Khozin, Chi Heem Wong, and Andrew W. Lo. "Machine-Learning and Stochastic Tumor Growth Models for Predicting Outcomes in Patients With Advanced Non-Small-Cell Lung Cancer." *JCO Clinical Cancer Informatics* 3 (2019): 1-11.
106. Siah, Kien Wei, Qingyang Xu, Kirk Tanner, Olga Futer, John J. Frishkopf, and Andrew W. Lo. "Accelerating glioblastoma therapeutics via venture philanthropy." *Drug Discovery Today*, In Press (2021), <https://doi.org/10.1016/j.drudis.2021.03.020>.
107. Stern, Ariel Dora. "Innovation under regulatory uncertainty: Evidence from medical technology." *Journal of public economics* 145 (2017): 181-200.
108. Thakor, Richard T., Nicholas Anaya, Yuwei Zhang, Christian Vilanilam, Kien Wei Siah, Chi Heem Wong, and Andrew W. Lo. "Just how good an investment is the biopharmaceutical sector?." *Nature Biotechnology* 35, no. 12 (2017): 1149-1157.
109. Thakor, Richard T., and Andrew W. Lo. Optimal Financing for R&D-intensive firms. No. w23831. National Bureau of Economic Research, 2017.
110. Thakor, Richard T., and Andrew W. Lo. "Competition and R&D financing: Evidence from the biopharmaceutical industry." *Journal of Financial and Quantitative Analysis* (2019): 1-69.
111. Thomas, David W., Burns, Justin, Audette, John, Carroll, Adam, Dow-Hygelund, Corey, and Hay, Michael. "Clinical Development Success Rates". Biotechnology Innovation Organization (BIO), 2016.
112. Vu, Jonathan, Ben Kaplan, Shomesh E. Chaudhuri, Monique Mansoura, and Andrew W. Lo. "The Challenging Economics of Vaccine Development in the Age of COVID-19, and What Can Be Done About It." *DIA Global Forum* 12 (5) (2020).
113. Williams, Heidi L. "How do patents affect research investments?." *Annual Review of Economics* 9 (2017): 441-469.

114. Wong, Chi Heem, Kien Wei Siah, and Andrew W. Lo. "Estimation of Clinical Trial Success Rates and Related Parameters." *Biostatistics* 20, no. 2 (2019): 273–286. <https://doi.org/10.1093/biostatistics/kxx069>.