Evaluation and Learning in R&D Investment*

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Abstract

We investigate the role of knowledge spillovers in determining firms' incentives to invest in exploratory versus incremental R&D. We identify spillovers by linking drug candidates to molecularly similar drugs that are subsequently developed. We find that novel drug candidates generate greater knowledge spillovers: they are more likely to inspire the development of subsequent successful drugs than incremental candidates. Building on this empirical finding, we develop a model of R&D in which firms face a trade-off: incremental drug candidates are easier to evaluate because they are based on more established science, while novel drugs present more opportunities for future learning. Consistent with our model, we show empirically that firms are more willing to engage in exploration when they expect to appropriate a greater fraction of spillover knowledge, when they expect drugs to generate many follow on innovations, and when they face lower discount rates. Interpreting the data through the lens of the model implies that firms place less value on learning and under-invest in developing novel drugs.

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Knowledge spillovers lie at the heart of models of innovation and economic growth (Romer, 1990; Scotchmer, 1991). However, measuring these spillovers is inherently challenging for two key reasons. First, identifying the set of subsequent innovations that build on a focal innovation is not always possible. Second, and more fundamentally, much if not most R&D effort is directed toward ideas that never lead to a publication, patent, or product, even though many of these "failures" offer researchers valuable insights. Our work fills this gap by providing a new measure of knowledge spillovers in the pharmaceutical industry that overcomes both of these challenges.

In this paper, we provide new evidence that both successful and failed R&D projects regularly generate substantial value by paving the way for successful follow-on research. Using drug development as a setting, we introduce a new measure of spillovers—revenues from *future* related drugs—and show that spillover revenue is increasing in project novelty. Using this measure, we generate two new facts. First, we provide the first accounting of the value of failed drugs, showing that they generate the *majority* of all spillover revenues in our data. Second, we show that novel drug candidates generate more successor revenue than incremental ones, despite being significantly less likely to reach the market. The benefits of novel projects are therefore more backloaded, so that standard project metrics will systematically understate their value.

To understand the tradeoffs between investing in novel and incremental R&D projects, we introduce a two-period model of investment in novel and incremental projects that builds on elements of the classic explore-exploit tradeoff. In the first period, a firm chooses between a novel or incremental drug candidate, facing uncertainty about both approval likelihood and potential revenue. Incremental and novel ideas are distinguished not by their inherent (unobserved) quality, but by the information that is available to the firm making the investment decision: firms know more about the potential of ideas that build on prior work. Specifically, incremental drugs, which build on established science, provide an early signal of success, allowing firms to screen out likely failures. For those that pass, the firm learns about expected revenues and decides whether to invest in development. Successful drugs that reach the market generate revenue.

Importantly, drug development decisions are linked inter-temporally. In the second period, either the same firm or a competitor may pursue drug candidates related to the first-period project. If the initial project was incremental—or if it was a novel drug that the firm chose not to develop—then no new information is gained, and the second period replicates the first. But if a novel drug was developed in the first period, it generates a signal about the viability of related drugs, effectively converting future related projects into incremental ones with more predictable outcomes. This information spillover occurs regardless of success and is available to other firms. Thus, our model highlights the tradeoff between *evaluation* versus *learning*: while incremental drugs are easier to screen today, novel projects generate information that improves the screening of related ideas tomorrow.

Our model allows us to *infer* the value firms place on these future knowledge spillovers based on data about the drugs they invest in, and their observed revenues if approved. In particular, a key feature of our model is that it endogenizes the set of drugs that we observe in development because firms in our model can set different criterion for investing in developing novel and incremental drugs. When the private value of learning is high, firms are willing to develop novel drugs even when their direct expected revenues low. This lower threshold means that novel drugs should be more likely to enter development and they should generate lower revenues if approved. By contrast, if firms prioritize drugs that are easier to evaluate, novel drugs should be less likely to go into development, and those that are approved will have higher revenues, reflecting a more selective standard—echoing arguments on the labor discrimination literature. Our model therefore delivers an empirical diagnostic for the relative value that firms place on learning. Crucially, this diagnostic uses only quantities that are observable in our data: the development rate of novel and incremental drugs and their revenues conditional on approval.

In the final part of the paper we examine some of our model's testable predictions in the data. We begin by providing evidence consistent with the view that firms prioritize evaluation over learning. Comparing pre-clinical candidates assessed in the same year for the same disease, we show that firms are significantly less likely to advance more novel candidates into clinical trials. Yet, among drugs that receive regulatory approval, novel candidates generate substantially higher direct revenues than incremental ones. Taken together, these results suggest that firms are more *selective* in developing novel drugs, favoring incremental drugs instead.

In addition, we explore the reasons behind firms' reluctance to develop novel drugs by investigating the three main frictions from our model. Our model highlights three factors that increase the value of learning: 1) greater ability to appropriate revenues from successor drugs, 2) more follow-on opportunities per candidate, and 3) a lower discount rate. We find evidence consistent with each of these predictions. Firms appear more selective in developing novel drugs in therapeutic areas where competitor research activity is high: fewer novel drugs enter development, and those that are approved generate more revenue. In therapeutic areas where focal drugs tend to yield more follow-ons, we find the opposite pattern: more novel drugs enter development and their revenues on approval are lower. Finally, using firm-specific discount rates from Gormsen and Huber (2023), we show that firms with higher discount rates are also more selective in developing novel drugs. Together, these results show how any one of these factors can make or break the learning component of R&D project value.

In sum, our paper highlights, both theoretically and empirically, a dynamic channel through which the choice to explore or exploit impacts the knowledge available to all firms in the future. We offer a unified explanation for three key facts: 1) novel drugs generate more successor revenue; 2) firms are less likely to develop novel drugs, but those that are approved yield higher revenues; and 3) this pattern is exacerbated by more competition, fewer follow-on opportunities, and a higher

discount rate. While we recognize that these findings can be explained by a combination of other factors, our goal is to highlight the explanatory power the simple tension between evaluation in the present and learning the future. In doing so, we present a new way to estimate the value of learning spillovers in exploration. Beyond drug development, this general approach is relevant in any R&D industries where both successful and failed novel projects generate insights that can improve the ability to select future winners.

Our analysis connects several strands of research. First, we extend a rich literature on cumulative innovation. Existing work in this area has developed new ways of tracing knowledge flows across academic and private sector while focusing on how disclosure mechanisms, intellectual property, geography and funding shape the rate and direction of follow-on innovation (Jaffe et al., 1993; Furman and Stern, 2011; Murray and Stern, 2007; Williams, 2013; Murray et al., 2016; Sampat and Williams, 2019; Azoulay et al., 2018). Our paper complements this literature by exploring a new set of questions linking the anticipated value of follow-on innovation to the initial decision of whether to engage in exploration. While our model's intuition bears similarity to the advantages of *firm-specific* expertise or absorptive capacity (Cohen et al., 1990; Henderson and Cockburn, 1996), our focus is on non-excludable aspects of improved evaluation for follow-on activity. In that sense, our paper draws on the literature on how scientific knowledge provides a "map" useful for recombination (Fleming, 2001; Fleming and Sorenson, 2004; Uzzi et al., 2013; Nagaraj and Stern, 2020; Kao, 2021; Hoelzemann et al., 2024; Tranchero, 2024).

Prior studies of the economics of drug development have focused on how broader or longer intellectual property rights affect incentives for follow-on entry into a drug class (Gilchrist, 2016; Gaessler and Wagner, 2022; Wagner et al., 2022). The findings in this paper reinforce the importance of appropriability rights in R&D investments, while introducing a new channel—the ability to capture the future learning benefits associated with *both* successful and failed projects—by which those rights shape the composition of drug development Methodologically, we contribute a new measure of knowledge spillovers that is based on a product's inherent physical properties, rather than on socially contingent patent citations. In this regard, our measures of novelty and spillovers are related to Kelly et al. (2021) who use the textual similarity across patents to identify novel and impactful patents.

Our paper builds on earlier work by a subset of the same authors (Krieger et al., 2022). The key similarity is our use of the molecular similarity measure to identify follow-on innovation. Importantly, however, the two papers have a very different focus: Krieger et al. (2022) focuses on the impact of financial frictions on firms' decisions to invest in novel vs. incremental drug candidates while taking the features of these drugs as given. This paper focuses on measuring, and quantifying, the differential spillovers generated by novel vs. incremental drugs and features a model that endogenizes the observed joint distribution of success probability and revenues in the data.

Second, our work expands on the factors governing the decision to explore or exploit. In a bandit model, agents repeatedly choose between actions with different and potentially uncertain payoff distributions (Slivkins et al., 2019). Bandit models are a natural fit for R&D investment decisions, where managers evaluate projects with varying degrees of uncertainty about scientific maturity, technology performance, and market demand, then update beliefs in response to observed outcomes (Manso, 2011). A typical assumption in these models, as in Keller et al. (2005), is that the payoffs of these technologies or actions are independent. However, this assumption does not apply in many R&D-driven industries, where investing in a new technology applied to a particular problem or market reveals information about other similar technologies and commercialization paths. Including these learning spillovers makes our model closer to the Brownian policy model of Callander (2011) and related papers such as Garfagnini and Strulovici (2016), Callander and Matouschek (2019), and Callander et al. (2022). In those models, however, learning occurs because the outcomes of related projects are close to one another. In our model, it is possible to learn from the failure of one project that a related project is likely to be successful.

Our work also relates to the literature on competition and innovation. The idea that when firms do not fully appropriate the knowledge spillovers from their R&D investments then there will be underinvestment in research is not new (Romer, 1990). However, in addition to providing direct empirical evidence that this is indeed the case, our work also reveals a novel link between firms' research decisions and the degree of competition. In canonical models such as Dixit and Stiglitz (1977); Aghion et al. (2005), firms' incentives to invest in novel R&D are shaped by product market competition for the *focal* innovation, which reduces direct revenues. Our model considers a complementary dynamic mechanism: competition reduces firms' ability to appropriate the value of *future* learning from the most novel R&D. This mechanism relates other models with free-riding in R&D learning (Choi, 1997), but emphasizes a distinct type of learning: improved evaluation ability due to greater experience.

Finally, our work contributes to a growing literature that highlights the value of tolerating (or even embracing) failure to achieve innovative outcomes (Aghion and Tirole, 1994; Azoulay et al., 2011a; Tian and Wang, 2011; Hvide and Panos, 2014; Krieger, 2021). Prior work in the management literature has sought to examine how organizations learn from failures (for a review of this literature, see Desai et al. (2020)). For example, studies have asked how airlines, railroad companies, and NASA have altered their performance and safety records following accidents and wrecks (Haunschild and Sullivan, 2002; Baum and Dahlin, 2007; Madsen and Desai, 2010). However, empirical challenges usually prevent researchers from reliably attributing learning benefits to specific failures (Bennett and Snyder, 2017). Closer to our setting, Magazzini et al. (2012) and Chiou et al. (2016) find that patents associated with successful drugs are cited more often than those associated with failed drugs. Using a novel measure of follow-on innovation, we provide concrete empirical evidence that failed

projects generate substantial spillover knowledge and sometimes lead to quite valuable successor projects.

1 Setting and Data

1.1 Institutional Background

The drug development process is typically divided into three stages: discovery, pre-clinical research, and human clinical trials. In the discovery stage, firms consider potential compounds, many of which may only exist as a concept. Firms may then create computer models of how a particular compound is predicted to behave, or they may synthesize the compound and examine whether it has any effect on the biological target of interest. At the end of the discovery stage, firms apply for patents on promising candidates. In the pre-clinical stage, researchers focus on understanding how the drug impacts the body (pharmacodynamics) and, in turn, how the body impacts the drug (pharmacokinetics). These tests are conducted in test tube cell cultures and in animal models. Finally, if a drug performs well in pre-clinical testing, firms may choose to develop the drug and file an application to begin human clinical trials. Clinical trials have three phases. Phase 1 clinical trials focus primarily on establishing a drug's safety, usually in a healthy population; Phase 2 trials provide preliminary information on a drug's efficacy among patients; and Phase 3 trials are large trials that become the basis of a regulator's decision as to whether or not to approve the drug.

Successful drug development can be quite lucrative. Recent estimates from Aryal et al. (2023) report a mean expected value for approved drugs of $1.63 billion. However, investments in drug development are expensive and risky: DiMasi et al. (2016) estimate that the direct cost of developing a single approved drug is over $1.4 billion.[1] This cost is spread unevenly across the stages of drug development, with clinical (that is, Phase 1 and beyond) trials accounting for the bulk of development expenses. In addition, failure is common, with over 90% of drugs entering clinical trials never making it to market (DiMasi et al., 2016).

When firms develop a drug, they learn about a variety of issues—efficacy against disease, toxicity at different levels of dosing, unintended and "off target" benefits and side effects, interactions with other drugs, and differences in drug metabolism across patient groups—that are also informative about how related drugs will function. And because pharmaceutical firms disclose their research via scientific articles, patents, and other mandated filings, much of this information is accessible to other firms. Indeed, in a cross-industry study, Qiu and Wan (2015) show that pharmaceutical firms rank at the top in terms of generating and benefiting from knowledge spillovers.

[1] The authors in fact estimate combined direct and indirect costs of $2.6 billion, but others have argued that these numbers are too high. See, for instance, http://www.nytimes.com/2014/11/19/upshot/calculating-the-real-costs-of-developing-a-new-drug.html.

Anecdotally, pharmaceutical firms routinely build on insights obtained from *failed* projects. For example, the first cholesterol-reducing statin drug tested in animals was compactin, developed by the Japanese firm Sankyo in the late 1970s (Endo, 2010a). While compactin was found to reduce cholesterol in animals, its development was discontinued because of adverse effects. Merck, however, remained inspired by the drug's potential and worked to develop its own chemical analog to compactin. That compound, lovastatin (Mevacor), went on to be the first approved statin in 1987. Lovastatin then paved the way for a series of chemically similar statins, including Merck's simvastatin (Zocor) and Pfizer's atorvastatin (Lipitor).

1.2 Data and Sample

Our sample of drug candidates comes from Clarivate Analytics' Cortellis Investigational Drugs database (Cortellis), a business-intelligence database that focuses on tracking the progression of candidates from pre-clinical investigation, to clinical development, to approval.

Drugs enter Cortellis when they appear in public documents such as patent filings or shareholder reports. Because patents are typically taken out at the end of the discovery stage, we observe most drugs in pre-clinical investigation, but not in the earlier discovery stage.[2] We think of these pre-clinical candidates as a sample of "potential projects," which we observe regardless of whether a firm ultimately develops them further.

Our main analyses are performed at the drug candidate level. This level of aggregation collapses several types of innovation: use of the same compound for different disease indications and different dosage versions. In our analyses, we say that a drug has reached a particular phase of development if any of these variants reach that phase. In our data, new formulations or new routes of administration for existing drug active ingredients (e.g., extended-release, nasal spray) are generally included as distinct drugs. In robustness checks, we identify these new formulations and exclude them from our analyses in order to focus on more substantive forms of successor innovation (see Section 2.3).

We obtain information on revenues for approved drugs from Evaluate Pharma, a commercial provider of drug sales data. We use a combination of exact matching, fuzzy matching, and manual confirmation to match Evaluate data to Cortellis, relying on drug name and company sponsor. Our data allow us to observe year-by-year sales associated with marketed drugs. This revenue data is necessarily censored: we observe only sales that have occurred, not the full stream of lifetime revenues. Because drugs that have been marketed for a longer period of time will naturally have greater total sales, we focus on a drug's *average annual revenue* for the years in which it appears in our sample.

[2] Drugs in the discovery stage of research are often too nascent to be observable by Cortellis. In many cases, they have not yet been named, do not yet have publicly disclosed patent applications, and may not even be generally known within the firm that is developing them (Hughes et al., 2011). We note that Cortellis's coverage for drugs in pre-clinical trials may be incomplete, especially for drugs in the earliest stages of investigation: the subset that we observe should be thought of as relatively serious contenders in pre-clinical development.

In summary, we are able to track individual drug candidates from preclinical development onward. For each candidate, we observe whether it is developed (e.g., enters clinical trials), whether it is approved, and its revenues conditional on approval.

We make two types of sample restrictions throughout our analysis. Because our measures of novelty and follow-on activity are based on analyses of chemical similarity that only work for so-called "small molecule" drugs, we restrict our analysis to the 80% of drugs in our data that fit this criterion. Our analysis therefore excludes biologic drug candidates such as monoclonal antibodies and vaccines. We also restrict our sample to drug candidates investigated in the United States, where our data coverage is more complete. Panel A of Table 1 shows that our main sample consists of 17,630 pre-clinical drug candidates, 7,938 of which we observe in human clinical trials, and 1,379 of which reach FDA approval. These drugs represent research efforts by over 3,000 firms into 375 distinct lead disease areas (categorized by ICD-9 disease codes).

Finally, we supplement this main data with information on the discount rates that firms they apply to their investment decisions. Our data come from Gormsen and Huber (2023), who infer firms' discount rates using textual analysis of firms' quarterly earnings call transcripts. Gormsen and Huber (2023) parse conference call transcripts for 22 keywords related to discount rates, then manually evaluated the surrounding paragraphs for statements about the firm's discount rate that is applicable to their investment decisions. We are able to merge this information for a small subset of our firms. The low overlap rate is due to the fact that Gormsen and Huber (2023) covers only a subset of large public firms, while drug developers in our sample include many smaller public firms, as well as foreign-listed and private firms.

1.3 Variable Construction

1.3.1 Drug novelty

We focus on a firm's decision to engage in incremental versus exploratory innovation. To measure this, we follow Krieger et al. (2022) and define an individual drug candidate's novelty in terms of its molecular distance from previously developed drugs. Our measure is based on a notion of molecular similarity known as a "Tanimoto" score. Tanimoto scores are widely used in pharmaceutical chemistry to identify relatedness among molecular compounds. A score of 0 indicates that two molecules do not share any common chemical substructures while a score of 1 indicates that the two molecules are identical in their atoms and bonding, up to stereosymmetry.[3]

We compute pairwise similarity scores between an initial drug candidate i and all other drug candidates j that entered human clinical trials prior to the focal candidate i's earliest development

[3]See Wawer et al. (2014), Bickerton et al. (2012), and Maggiora et al. (2014) for a discussion of Tanimoto scores in chemistry. In economics, Krieger et al. (2022), validate this measure by showing that drugs that target the same patient populations or share the same biological mechanism of action (MOA) have significantly higher average similarity scores than pairs unrelated through disease or MOAs.

date. We define candidate i's *novelty* as one minus its maximum pairwise Tanimoto score with prior drugs j, T_{ij}:

$$\text{Novelty}_i \equiv 1 - \max_{j \text{ prior to } i} T_{ij}. \tag{1}$$

By this measure, drug candidates are novel if they have molecular differences from previously developed drugs. In our sample, the mean (backwards-looking) novelty score is 0.48, with an inter-quartile range of 0.36–0.65 (see Table 1, Panel B). For additional discussion and validation, see Krieger et al. (2022).

1.3.2 Successor Drugs and Successor Revenues

To measure the spillover value of drug investments, we link drug candidates to subsequent drug candidates. Specifically, we define a drug candidate j as a *successor* to a focal drug candidate i if the following conditions are met: 1) the two drugs are molecularly similar, defined as having a Tanimoto score greater than 0.75; 2) the successor drug j entered pre-clinical development after the focal drug i entered Phase 1 clinical trials; and 3) drug i is the earliest molecularly similar drug to drug j.

We note that our definition considers only successors that are distinct products, requiring their own development and clinical testing prior to regulatory approval. This excludes generic entrants, but includes closely related products such as extended release formulations or combination therapies.

Figure 1 presents an example of a focal and successor drug. Telapristone acetate (Proellex) entered development for the treatment of uterine fibroids in 2004 but its clinical trial was put on hold due to safety concerns. Despite never reaching the market, Proellex inspired five successor candidates. One of these candidates, ulipristal acetate (Ella), ultimately reached the market and is currently is on the World Health Organization's List of Essential Medicines. Ella is pictured alongside Proellex in Figure 1: the two drugs have a Tanimoto score of 0.81.

Before continuing, we discuss each of the three conditions we use to identify successors.

The first condition ensures that we only consider successor drugs which are indeed molecularly related to the focal drug. As can be seen from Figure 1, drugs with a Tanimoto score of greater than 0.75 indicates a level of similarity that is apparent even to a layperson's eye. The biochemistry literature has shown that these similarities in molecular structure are tied in the to similarity in function (Maggiora et al., 2014).

Second, we restrict to potential successors that are developed after the focal drug has entered clinical trials. Because clinical trial reporting is mandated and public, this restriction ensures that the structures of focal drugs were publicly known at the time a potential successor enters pre-clinical development, reducing the possibly that we mistakenly credit a drug as being a success when in fact it was simultaneously and independently developed. This means that our successor counts

are conservative and may miss some cases where a follow-on firm invests and enters quickly after observing a pioneer's early patenting or preclinical experimentation.

Third, we focus on a drug's earliest molecular antecedent because a single drug often reveals critical information about whether follow-on activity is worthwhile. If the pioneering drug inspires many follow-on drugs, those successors will reach development at various times (sometimes concurrently), rather than each drug inspiring the next in sequence. This dynamic is similar to a single "wildcat" oil well revealing a wealth of valuable information about drilling in a particular geography (Covert and Sweeney, 2022).

Having defined the notion of a successor drug, we define *successor revenue* to a drug i as total revenues across all of its successor drugs j:

$$\text{Successor Revenue}_i \equiv \sum_{j \text{ successor to } i} \text{Revenue}_j \tag{2}$$

In Equation (2), Revenue_j is the average annual revenue associated with successor drug j. Unsuccessful successor drugs are included as having zero revenues.

Before continuing, we highlight several limitations. First, our data are truncated: more recently developed drugs are less likely to be linked to successor drugs simply because they had less time to generate successors. In addition, our measure of average annual revenues does not account for differences in earnings over the lifecycle of a drug. More recently approved drugs will have annual sales measured during a period the drug is on patent whereas older drugs will have some of their revenue years come after the drug faces generic competition. As a result, our main analyses will always control for development-year-quarter fixed effects, so that we are comparing drugs within the same cohort of development. Finally, we note that while we can measure revenue, we cannot measure profitability because we do not observe information on costs.[4]

Despite these limitations, our approach to identifying successor drugs has several advantages relative to patent-based measures of relatedness, e.g., based on citations or text. Foremost, our measure is based on a concrete product characteristic, molecular structure, which uniquely determines a drug. Pharmaceutical patents, by contrast, represent a wide range of intellectual protections (active ingredients, methods of delivery or manufacture) that cannot necessarily be cleanly associated with a specific drug (Gupta, 2023).[5] Second, our similarity measure is based on objective chemical properties and does not rely on a patent examiner's discretion in determining which cita-

[4]The majority of drug development costs are determined by the cost of clinical trials. Trial costs can vary substantially based on the number of patients in a trial, how long the trial is run, and the difficulty of enrolling these patients. These factors can vary greatly across disease types—trials for non-lethal cancers, for instance, require larger sample sizes and longer trials to achieve statistical significance relative to trials for very lethal cancers—but tend to be similar within disease type (our analysis will include disease level fixed effects).

[5]Even in the cases where it is possible to identify a drug's active ingredient patent, these patents often cover molecular classes that include tens of thousands of specific molecules, only one of which may represent the ingredient in question.

tions are relevant. Lei and Wright (2017), for instance, questions the reliability of patent citations as measures of intellectual relatedness by identifying many cases in which citations appear to be unrelated to the original patent.[6] Last, recent studies have also used patent-text based methods to measure similarity (Kelly et al., 2021; Kuhn and Thompson, 2019). Text-based measures may miss differences in design that are only be represented in schematics/diagrams or technical formulas, an important consideration in the context of patents for chemical molecules.

2 Motivating Facts

Panel B of Table 1 describes the distributions for our measures of direct revenue, number of successors, and successor revenue. Unsurprisingly, given their early nature, we find that these measures are all highly skewed, with the vast majority of pre-clinical drugs failing to eventually generate either direct revenue or successor revenue. Panel B also reports the distribution of novelty scores in our sample, where we see a greater variety of more and less novel drugs. We next document a set of stylized facts regarding the spillovers from novel and incremental drug candidates.

2.1 Quantifying Spillovers

Panel A of Figure 2 plots the average number of successor candidates associated with focal drug candidates, by the highest phase of development they reached. While successful drugs (those that have been approved by the FDA) generate substantially more successors on average, failed drugs (those that have not been approved) still generate follow-on activity.[7] For example, the average drug that does not make it past Phase 1 trials is linked to 0.1 successor drugs.

Panels B and C consider successor revenues. In Panel B, we find that the successors associated with approved focal drugs generate a substantially higher amount of revenue, on average, compared to failed focal drugs (almost $30 million per year versus about $6 million). Yet, because there are so many more failed than successful drugs, the total value of spillovers generated by failed drugs is still large. This point is illustrated in Panel C, where we present total successor revenues associated with successful and failed focal drug candidates, aggregated across our sample. Total successor revenues attributed to successful focal drugs is approximately $10 billion per year, whereas this figure is over $16 billion among failed drugs. Due to their sheer number, failed drug candidates make up the largest source of ideas that are linked to commercially successful follow-on innovation.

[6] Consider patent 6,368,227 for "Method of swinging on a swing", issued to Steven Olson (aged 5) on April 2002. The patent has 20 patent citations as of 2022; it is cited, among others, by patent 8,420,782 for "Modular DNA-binding domains and methods of use" and patent 8,586,526 for "DNA-binding proteins and uses thereof." Many of these citations were added by the patent examiner.

[7] Our use of the term "failed" is somewhat imprecise. Because our data do not always have termination dates, we cannot always definitively identify whether a drug has failed, so this set of drugs should be thought of as those that have either failed in development or ones whose ultimate outcome has not yet been realized. For brevity, we will use the terms "not approved" and "failed" interchangeably, although the former is more accurate.

We note that a comparison of the raw differences in number of successors or successor revenues among approved and non approved drugs is likely to understate spillovers to failed drugs. This is because our definition of "failed" drugs includes both drugs that were abandoned during development and those that are simply to developed too recently to have reached approval. These recent drugs (which we may incorrectly classify as failed), will also have had less time to accrue successors or successor revenues. In our analysis going forward, we will include drug development year-quarter fixed effects to control for cohort-level differences in outcomes.

2.2 Novelty and Spillovers

Next, we consider how spillover value varies by drug novelty using the following specification:

$$\text{Outcome}_i = a_0 + a_1\text{Novelty}_i + \delta_t + \delta_d + \varepsilon_i \tag{3}$$

Equation (3) is estimated at the drug level, and includes all candidates that enter human clinical trials in the United States. The main explanatory variable of interest is Novelty_i which represents a drug candidate's molecular novelty (0 being molecularly identical to a prior drug candidate and 1 being completely novel). In our primary specifications, we include controls for cohort fixed effects (development-year-quarter) δ_t as well as fixed effects δ_d for a drug candidate's lead disease indication (ICD-9).

Overall, we find that more novel drug candidates are associated with greater successor revenues. Figure 3 plots the results and Table 2 presents the accompanying regression results. Panel A of Figure 3 shows that more molecularly novel drug candidates generate more successor attempts. Column 2 of Table 2 provides the accompanying magnitude: among drugs developed at the same time for the same condition, a one standard deviation (0.23) increase in a drug's Tanimoto novelty score is associated with $0.43 \times 0.23 = 0.10$ more successor drug candidates, or a 29% increase from a baseline mean of 0.35.

Panel B of Figure 3 also shows that novel drugs generate more successor revenue. In terms of magnitudes, Column 4 of Table 2 indicates that a one standard deviation increase in novelty correlates with increased successor revenues of $\$9.7 \times 0.23 = \$2.2$ million annually, a 32% increase from a mean of \$6.8 million.

Panels C and D provide additional context for these results. In Panel C, we plot the relationship between a drug candidate's novelty and its expected direct revenues (unsuccessful drugs are included as having zero revenues). Here, we find that novel drugs tend to generate a similar amount of direct revenue (the slope is positive but our estimates in Columns 5 and 6 of Table 2 lose significance in some specifications). Panel D finally combines insights from Panels B and C to show that, among novel drugs, successor revenue makes up a greater share of total attributed revenues (direct plus successor). This result can be explained by the fact that novel drug candidates are substantially

more likely to fail in the development process, thereby generating no direct revenues. Given this, successor revenues are a relatively more important part of the total value of novel drug candidates. In Appendix Figure A.1, we show that these findings are robust to the inclusion of firm fixed effects. This suggests that our findings are not exclusively driven by firm-level differences in their orientation towards particular styles of R&D or new product entry.

2.3 Discussion

Our attribution method credits a successor drug candidate to its *earliest* derivative predecessor. This approach raises the possibility that novel focal drugs may be more likely to be credited with generating successors than focal incremental drugs—i.e., a highly incremental focal drug is less likely to be the earliest molecularly similar predecessor of a successor drug because its own molecular predecessor may claim this credit. Three important points are worth noting about these attribution dynamics. First, pairwise similarity is not generally transitive, meaning that even drugs that are molecularly incremental themselves can be linked to successors: an incremental drug's predecessor and its potential successor need not be pairwise similar to each other. In Figure 3, we do indeed see that even highly incremental drugs are associated with successors.

Second, and more importantly, we view our definition as reflective of what it means to inspire new research. As discussed in Section 1.3.2, it is often the case that a single novel drug inspires a series of successors, rather than each successor successively inspiring the next one. For example, the discovery of mevastatin by the pharmacuetical firm Sankyo in 1976 demonstrated that HMG-CoA reductase inhibitors could effectively lower cholesterol levels, directly inspiring the parallel development of lovastatin and simvastatin by its competitor Merck, as well as pravastatin, Sankyo's own follow-on. Rather than each new statin building on its immediate predecessor, these drugs were all developed in research programs that traced their inspiration back to mevastatin's breakthrough demonstration of this therapeutic mechanism (Endo, 2010b). Similarly, the discovery of fluoxetine by Eli Lilly established selective serotonin reuptake inhibition as a viable treatment for depression, inspiring the parallel development of other SSRIs like sertraline and paroxetine.

Third, it is also quite possible for novel drugs to generate few successors. The positive relationship between novelty and successor attempts that we document is far from obvious because uncharted exploration may also simply be more useless. Highly novel drug candidates are less likely to target diseases and (validated) biological mechanisms of action where competing developers are already working Krieger (2021), e.g. those that are more scientifically and commercially viable. For example, a low novelty or moderately novel new GLP-1 receptor agonist drug might be expected to generate many successors because GLP-1's have generated blockbuster profits in the treatment of obesity and diabetes, and dozens of companies are developing new variants of GLP-1 targeting drugs for the same diseases and new uses. With such clustered activity, one could reasonably expect

that a moderately novel GLP-1 drug would be more likely to generate successors, relative to a more novel compound aimed at an unvalidated mechanism of action for diabetes. The positive linear relationship we document is both non-obvious (a priori), and reveals that even marginal increases in novelty may unlock greater cumulative innovation.

Finally, we present three additional empirical analyses to show that our descriptive findings in Figure 3 are not an artifact of our measurement approach. In Appendix Figure A.2, we vary the way we measure successor drugs to assign "partial credit" to all prior drugs that are similar to a given drug candidate, rather than fully crediting the earliest candidate. In Appendix Table A.1, we use alternative novelty measures that are not based on molecular similarity. Specifically, we define a focal drug as novel if it either focuses on a new "target" (e.g., it attempts to impact a new biological pathway such as a protein), or if it focuses on an existing target with a new mechanism of action (e.g., if it is the first to seek to impact that target in a new way).

Finally, we repeat the analysis in Figure 3, but remove all drug candidates associated with new formulations or new routes of administration of the same drug candidate. Cortellis sometimes includes new drug entries for these new forms of delivering an existing active ingredient (e.g., extended/controlled release, oral formulations, subcutaneous or sublingual delivery, etc.). In our main analysis, we treat those new forms as successor drugs since they usually require additional clinical trials and new regulatory approval. In Figure A.3 we reclassify their their revenues as part of their predecessors' direct revenues, and drop them from our sets of focal drugs and successors.[8] The resulting graphs in Figure A.3 are very similar to Figure 3. In all of these alternative analyses, we find that more novel drugs generate more successors and more successor revenue, and that a greater share of their total revenue comes from spillover channels.

3 A model of drug development

Our empirical evidence suggests that novel projects generate more successor revenue than incremental projects, and successor revenues comprise a greater share of the total revenues associated with novel projects. Taken together, this suggests a potential trade off: firms may be less able to evaluate the prospects of novel drugs, but the process of developing such drugs generates greater opportunities for future learning. In this section, we build this tradeoff into a model of R&D.

[8] We exclude combination drugs (multiple active ingredients) from potential reclassification. In total, we flag 23% of our successor sample as potentially new formulations or new route versions of prior drugs based on their exact match to prior active ingredients and the presence of terms in their name that indicate new formulations or new routes of administration. We use an extensive list of exact match terms to flag potential new formalizations and new routes, and also use ChatGPT (4o) to compare Cortellis drug names and classify whether pairs are distinct, combination drugs or new forms. Notably, less than half of those (8% of total successors) that were flagged as potential new forms were also assigned to the same firm as their predecessor—suggesting that most of the potential new versions are indeed competitor follow-ons and likely enter post-patent expiration or market exclusivity periods.

We present a two-period model with one *firm* and the *rest of the market*. In the first period, the firm is given the opportunity to develop a drug, which can either be *novel* or *incremental*. Incremental drugs are easier to screen: the firm is better able to predict which drugs will or will not succeed. Firms know less about novel drugs, but developing them generates information about the success of related drug candidates that this firm or the rest of the market may consider developing in the second period. Essentially, we think of incremental drugs as ones that are related to—and thus informed by—previously-developed novel drugs.

3.1 The model

There are two periods. Period 2 revenues and costs are discounted at factor $\beta \in (0, 1]$ relative to period 1.

Period 1. In period 1, the firm considers whether to develop an initial drug. This drug has *novelty* $N \in \{0, 1\}$, with $N = 0$ indicating an incremental drug and $N = 1$ indicating a novel drug; *success* if developed of $S \in \{0, 1\}$; and expected *revenue* if successful of R. We assume that the probability of success if developed is $Pr(S = 1) = \pi \in (0, 1)$ and that revenue R is drawn according to a distribution F_R on $\mathbb{R}_+$, with the same distributions of success and revenue regardless of drug novelty.[9] (Unless otherwise specified, all random variables are taken to be independent of one another.) The timeline of period 1 is then as follows.

Stage (i): Discovery.

(a) Awareness. The firm is made aware of the initial drug and observes whether the drug is novel or incremental.

(b) Screening incremental drugs. If the drug is incremental, the firm observes a signal σ^0 of whether the drug would be successful if developed. Specifically, drugs that would be successful ($S = 1$) always generate a good signal $\sigma^0 = g$. Drugs that would fail ($S = 0$) generate a bad signal $\sigma^0 = b$ with probability $q^0 \in (0, 1)$ and a good signal $\sigma^0 = g$ with probability $1 - q^0$. That is, if an incremental drug is low quality, the firm learns this fact with probability q^0.

If the drug is incremental and $\sigma^0 = b$, then the firm screens the drug out ($P = 0$) and the period is over. Otherwise—if $\sigma^0 = g$, or if the drug is novel—then the firm proceeds to *pre-clinical testing* ($P = 1$), Stage (ii).[10]

[9] We interpret R as the firm's expected revenue, rather than the drug's realized revenue, if the drug were to be successfully developed. The role of this expectation is to account for the noise that we will observe when we bring this model to data. In particular, in the data, there may be drugs that are successfully developed and yet yield negligible revenue. In the model, these would be drugs whose realized revenue underperformed relative to expectations.

[10] An incremental drug with $\sigma^0 = b$ does not enter pre-clinical testing because it will fail with certainty. Implicitly, one can think of there as being a small cost of proceeding to the next stage.

Stage (ii): Pre-clinical testing. The firm observes the drug's revenue R. The firm then decides whether to pay a cost $C^1 > 0$ to bring the drug into *development* ($D^1 = 1$), Stage (iii). If not ($D^1 = 0$), the period is over.

Stage (iii): Development. Development proceeds in $M \geqslant 1$ phases, corresponding to phases of human clinical trials.

In each development phase $t \in \{1, ..., M-1\}$: The firm observes a signal σ^t of success S. If $S = 1$, the firm observes a good signal $\sigma^t = g$ with certainty. If $S = 0$, the firm observes a bad signal $\sigma^t = b$ with probability $q^t \in (0, 1)$ and a good signal $\sigma^t = g$ with probability $1 - q^t$. Then the firm decides whether to pay a cost $C^{t+1} > 0$ to bring the drug into phase $t + 1$ of development ($D^{t+1} = 1$). If not ($D^{t+1} = 0$), the period is over.[11]

In the final development phase $t = M$: Success S is revealed. If $S = 1$, the firm brings the drug to *market*, Stage (iv). Otherwise the period is over.

Stage (iv): Market. The drug realizes revenue for the firm, equal in expectation to R.

Period 2. If the initial drug is incremental, then there is no second period decision. In this case we normalize the firm's second-period payoff to 0.

If the initial drug is novel, some number of related drugs may arrive. Each related drug j has success if developed of $S_j \in \{0, 1\}$ and revenue if successful of R_j. Assume that $Pr(S_j = 1) = \pi_2 \in (0, 1)$ and $R_j \sim F_{2R}$. If the initial drug was brought to development, i.e., if $D^1 = 1$, then these related drugs are essentially rendered incremental, and we call them *successor drugs*. For each related drug that arrives, the second period proceeds similarly to the first, where there will now be additional information about successor drugs.

Stage (i): Discovery.

(a) Awareness. A non-negative number Q of related drugs arrives, with Q drawn from F_Q and having mean $\mu_Q > 0$. For each related drug $j \in \{1, ..., Q\}$, either the focal firm ($A_j = 1$) or the rest of the market ($A_j = 0$) is made aware of the drug, meaning that this player has the exclusive opportunity to investigate and develop it. The probability that the focal firm is made aware of any given related drug is $Pr(A_j = 1) = \alpha \in (0, 1]$.

(b) Screening successor drugs. If the initial drug was developed ($D^1 = 1$), then the player who is made aware of successor drug j observes a signal σ_j^0 of S_j. Specifically, drugs that would succeed ($S_j = 1$) generate a good signal $\sigma_j^0 = g$ with certainty, while drugs that would fail ($S_j = 0$) generate a bad signal $\sigma_j^0 = b$ with probability $q^0 \in (0, 1)$ and a good signal $\sigma_j^0 = g$ with probability $1 - q^0$.

[11] If the drug does not make it to development phase t, then we take $D^{t+1} = 0$: the drug is also not brought to development phase $t + 1$.

If drug j is a successor drug and $\sigma_j^0 = b$, then the relevant player screens the drug out. Otherwise—if $\sigma_j^0 = g$, or if the initial drug was not developed—then the drug proceeds to pre-clinical testing, Stage (ii).

Stages (ii) – (iv). These stages proceed exactly as in period 1, separately for each drug that enters pre-clinical testing, for the player who is made aware of that drug.[12]

We assume that all parameters and distributions that were not specified to be drawn from a distribution are commonly known at the start of the game: success probabilities π and π_2, revenue distributions F_R and F_{2R}, costs C^t, signal precision q^t, the expected number of successor drugs μ_Q, and the probability α that the firm has the opportunity to develop a given successor drug.

Putting all the payoffs together, the firm's realized profit over the two periods can be written out fully as

$$\underbrace{SD^M R - \left(\sum_{t=1}^{M} D^t C^t\right)}_{\text{Period-1 profit from initial drug}} + \underbrace{N\beta \sum_{j\in\{1,\ldots Q\}} A_j \left(S_j D_j^M R_j - \left(\sum_{t=1}^{M} D_j^t C^t\right)\right)}_{\text{If novel: Period-2 profit from related drugs}}. \tag{4}$$

The first expression is the direct term benefit of investing in the drug, which is the benefit captured by a standard NPV calculation. If the firm is forward-looking ($\beta > 0$) it should also take into account the potential indirect benefits of its investment decisions.[13]

If the initial drug is novel, the rest of the market also realizes a payoff from developing related drugs (those with $A_j = 0$), given by

$$\underbrace{N\beta \sum_{j\in\{1,\ldots Q\}} (1 - A_j) \left(S_j D_j^M R_j - \left(\sum_{t=1}^{M} D_j^t C^t\right)\right)}_{\text{If novel: Period-2 profit to others from related drugs}}. \tag{5}$$

As discussed below, after being made aware of a drug, the firm will develop that drug if its revenue (R or R_j) is large enough. To guarantee that revenue can in fact be large enough so that a drug is developed, assume that the support of the revenue distribution F_R extends above $\sum_{t=1}^{M} C^t/\pi$, and likewise the support of F_{2R} extends above $\sum_{t=1}^{M} C^t/\pi_2$.[14] To guarantee that first-period revenue can be low enough so that direct profits alone are not enough to justify development, assume that the support of the revenue distribution F_R extends below C^1.

[12] For related drug j, we now replace R, S, D^t, and σ^t with R_j, S_j, D_j^t, and σ_j^t.

[13] Properly speaking, the direct revenue from the drug accrues over time and so the firm's value of this will also depend on discounting.

[14] In period 1, if a novel drug has $R > \sum_{t=1}^{M} C^t/\pi$, then committing to pay the cost of all development phases in advance would be more profitable in the first period than choosing not to develop the drug; an incremental drug with a positive signal $\sigma^0 = g$ would yield even higher profit. So for these drugs, the firm would choose $D^1 = 1$. Similarly in the second period if $R_j > \sum_{t=1}^{M} C^t/\pi_2$, both for drugs following a developed and an undeveloped first-period novel drug.

3.2 Preliminary Analysis

We are primarily interested in the firm's first-period decision to invest in developing the initial drug, i.e., the choice of D^1. Recall that this decision is taken after the firm has already screened out some share of incremental drugs that would not have been successful (those with $\sigma^0 = b$), and after the firm learns the expected revenue R for the drug.

To better understand this initial development decision, let us start by decomposing the firm's expected profit as a function of the choice to develop a drug, D^1. This profit is

$$\underbrace{D^1 \cdot (V_1^N(R) - C^1)}_{\text{Direct profits from focal drug}} + \beta\big(W_2^N + \underbrace{ND^1\mu_Q\alpha \cdot \Delta_2^{N=1}}_{\substack{\text{Expected future profits} \\ \text{due to learning spillovers}}}\big) \tag{6}$$

for some terms $V_1^N(R)$, W_2^N, and $\Delta_2^{N=1}$. (See Appendix A.1 for the full expansion of each term, along with a discussion of their properties.)[15] The first term $V_1^N(R)$ is the expected direct profit conditional on having begun development of the drug, which depends both on novelty and revenue. Prior to the development decision D^1 and the initial development cost C^1, we therefore have expected direct profit of $D^1 \cdot (V_1^N(R) - C^1)$. The second term W_2^N is the portion of the firm's second-period profit that doesn't depend on the first-period development decision. Multiplying by the discount factor β gives us these profits in net present value. The third term $\Delta_2^{N=1}$ is the amount that second-period profit increases if a novel first-period drug is developed, for each related drug that the firm sees. That incremental future profit is the result of more informative signals at the evaluation stage for these successor drugs. The firm's net present value from this information is then multiplied by the discount factor β, the expected number of successors μ_Q, and the share of successors whose value this firm can appropriate α.

The key tradeoff in the model is captured by the two observations.

First, the following inequality holds:

$$V_1^{N=0}(R) - V_1^{N=1}(R) \geqslant 0 \text{ for every } R. \tag{7}$$

Equation (7) states that the firm has higher first-period profits from incremental drugs, for any revenue level.[16] This occurs because incremental drugs are easier to evaluate: the additional signal the firm receives allows it to screen out a subset of weak candidates. This "evaluation benefit" accrues entirely to the firm that makes the investment.

[15] Importantly, none of the three terms depends on D^1; the parameters β, μ_Q, and α do not appear in the decision-relevant terms $V_1^N(R)$ or $\Delta_2^{N=1}$; and expected revenue R does not appear in $\Delta_2^{N=1}$. That is, all of the decision-relevant dependence of expression (3.2) on D^1, β, μ_Q, α, and R is made explicit.

[16] The inequality is strict when there is a positive value of developing incremental drugs, i.e., when $V_1^{N=0}(R) > 0$.

Second, we have:

$$\Delta_2^{N=1} > 0. \tag{8}$$

Equation (8) states that developing a novel drug gives a payoff bonus in the second-period. This holds because the development of novel drugs today improves the evaluation of successor drugs in the future. This benefits the firm in two distinct ways. First, by screening out successors that generate bad initial signals, the firm avoids making costly investments in drugs that are likely to fail. Second, the remaining successors that the firm develops will be positively selected and bring higher profits on average. However, unlike the direct evaluation benefit of developing incremental drugs, this "learning benefit" of developing novel drugs is shared by the firm and the rest of the market, both of whom may have the opportunity to develop successors.

Before proceeding, we add the following maintained assumption.

Assumption 1. *The expected discounted increase in second-period profit from developing a novel drug is less than the cost of bringing such a drug to development:* $\beta\mu_Q\alpha\Delta_2^{N=1} < C^1$.

If this assumption were violated, the firm would get so much informational benefit from developing novel drugs that it would want to bring every novel drug into development—even if the drug had low enough revenue that the firm planned on "pulling the plug" in phase 2 (setting $D^2 = 0$). Imposing this assumption, the firm will only develop a novel drug that it plans on taking to market if it continues to receive positive signals about the drug's success.

3.3 Model implications

We can now describe the firm's strategy in the first period of the game. For each type of drug N, incremental or novel, the firm will choose a revenue threshold $\overline{R}^N$. Drugs of type N with expected revenue R above the threshold $\overline{R}^N$ will be developed ($D^1 = 1$), and drugs with revenue below the threshold will not be. Conditional on arriving at development phase t, the firm proceeds to development phase $t+1$ ($D^{t+1} = 1$) if and only if it receives a positive signal ($\sigma^t = g$). See Appendix A.2 for a formalization.

Our model makes an unambiguous prediction that, conditional on having begun development, incremental drugs are more likely to progress at every phase. (All proofs are in Appendix A.3.)

Proposition 3.1. *The probability that a drug passes any given phase of development is higher for incremental drugs. That is, for* $t \in \{1, ..., M-1\}$*, it holds that* $Pr(D^{t+1} = 1|D^t = 1, N = 0) > Pr(D^{t+1} = 1|D^t = 1, N = 1)$*. In addition, incremental drugs have a higher probability of success conditional on reaching the final phase of development:* $Pr(S = 1|D^M = 1, N = 0) > Pr(S = 1|D^M = 1, N = 1)$.

This result arises from the fact that incremental drugs begin with an informational advantage: the firm screens out a subset of incremental drugs that generate a bad signal $\sigma^0 = b$ at the discovery stage. The remaining set of incremental drugs is positively selected to have a higher probability of success. Hence, conditional on arriving at any phase t of development, incremental drugs are more likely to receive a positive signal $\sigma^t = g$, with the firm progressing to the next phase exactly when it sees such a signal.

Proposition 3.1 establishes that incremental drugs are more likely to progress at each stage of development. However, it is theoretically ambiguous whether incremental drugs are more likely to enter development in the first place. This occurs if the firm chooses to set a lower revenue threshold for developing incremental drugs than for novel drugs ($\overline{R}^{N=0} < \overline{R}^{N=1}$). $\overline{R}^{N=0}$ may be lower because the firm is able to screen out a subset of weak incremental candidates so that the remaining candidates are safer bets. Alternatively, $\overline{R}^{N=1}$ may be lower because developing novel drugs generates knowledge spillovers in addition to direct revenue.

Our model yields a diagnostic test for determining the relative thresholds for development. In particular, we connect a firms' thresholds for developing novel and incremental drugs to observable quantities: the likelihood of development conditional on entering pre-clinical testing, and revenue conditional on development.

Proposition 3.2. *One of the following two cases obtains:*[17]

1. ***High evaluation benefit.*** *If $\overline{R}^{N=1} \geqslant \overline{R}^{N=0}$, then novel drugs are less likely to be developed conditional on entering pre-clinical testing but have higher average revenues conditional on being successfully developed. That is, $Pr(D^1 = 1|P = 1, N = 1) \leqslant Pr(D^1 = 1|P = 1, N = 0)$ and $\mathbb{E}[R|S \cdot D^M = 1, N = 1] \geqslant \mathbb{E}[R|S \cdot D^M = 1, N = 0]$.*

2. ***High learning benefit.*** *If $\overline{R}^{N=1} \leqslant \overline{R}^{N=0}$, then novel drugs are more likely to be developed conditional on entering pre-clinical testing but have lower average revenues conditional on being successfully developed. That is, $Pr(D^1 = 1|P = 1, N = 1) \geqslant Pr(D^1 = 1|P = 1, N = 0)$ and $\mathbb{E}[R|S \cdot D^M = 1, N = 1] \leqslant \mathbb{E}[R|S \cdot D^M = 1, N = 0]$.*

Proposition 3.2 provides a diagnostic to help reveal firms' priorities. It states that one of two cases is possible. In the first, firms place a high value on evaluation today: because incremental projects are easier to screen, firms are more confident that the incremental drugs they bring into development will reach FDA approval. The lower risk of failure allows them to profitably invest in an incremental drug idea even when its projected revenue on approval is relatively low. This case implies that incremental projects will be more likely to enter development and will have lower revenues conditional on success. Alternatively, firms may place a high value on learning that will improve their ability to evaluate tomorrow: because firms value the knowledge spillovers when they

[17] In the knife-edge case that $\overline{R}^{N=1} = \overline{R}^{N=0}$, both cases obtain.

explore new areas, they may be willing to invest in novel drugs even when their direct revenues are likely to be low. Here, firms should be more willing to develop novel drug candidates and, conditional on approval, novel drugs will have lower revenues.

We also consider how the firm's development strategy varies with market characteristics.

Proposition 3.3.

1. Incremental drugs: *The revenue threshold for development, $\overline{R}^{N=0}$, is constant in α, μ_Q, and β. Thus, the probability of development conditional on entering pre-clinical testing ($Pr(D^1 = 1|P = 1, N = 0)$) and the expected revenue conditional on successful development ($\mathbb{E}[R|S \cdot D^M = 1, N = 0]$) are constant in these parameters.*

2. Novel drugs: *The revenue threshold for development, $\overline{R}^{N=1}$, strictly decreases in α, μ_Q, and β. So the probability of development conditional on entering pre-clinical testing ($Pr(D^1 = 1|P = 1, N = 1)$) weakly increases in α, μ_Q, and β; and the expected revenue conditional on successful development ($\mathbb{E}[R|S \cdot D^M = 1, N = 0]$) weakly decreases in α, μ_Q, and β .*

Intuitively, factors that reduce the spillover value of novel drugs lead firms to be more selective in the novel drugs that they pursue, resulting in the development of fewer novel relative to incremental drugs.

3.4 Model Discussion

3.4.1 Empirical Content

Each Proposition generates predictions that are testable in our data. We note that while novelty in our model is binary, our empirical measure of novelty, defined in Equation (1), is a continuous measure ranging from 0 to 1.

Proposition 3.1 predicts that, among drugs that enter human clinical trials, drugs that are less novel are more likely to progress at each stage: from Phase 1 development to Phase 2, Phase 2 to Phase 3, and Phase 3 to approval. These quantities are observable in the Cortellis data.[18] We find evidence consistent with this prediction in Section 4.1.

Proposition 3.2 uses observable quantities to infer the value that firms place on learning relative to evaluation. This is important because the value of information about a drug's success—the evaluation benefit in the present, and the learning benefit in the future—is difficult to measure directly. We can think of two distinct sources of value: spurring additional development of promising drugs, and shutting down research that would fail. While we can proxy for the former (a drug's direct revenue as well as successor counts and revenue), we have no way of directly measuring the

[18] Using a similar dataset, Krieger et al. (2022) show that novel drugs are less likely to be approved, conditional on entering Phase 1.

value of avoiding bad projects, which never show up in our data. Proposition 3.2 allows us to infer the net value from both sources using information in our data: development decisions (which we define as progressing past pre-clinical testing to enter human clinical trials) and revenues conditional on success. In particular, it first makes the testable prediction that if novel drugs are more likely to be developed than incremental drugs, then they will also have lower average revenue conditional on success, and vice versa. It then tells us that whichever type of drug has a higher development probability (and lower average revenue) is the one favored by the firm. We find evidence that firms prefer incremental drugs in Section 4.2.

Finally, Proposition 3.3 provides comparative statics about three model parameters: the appropriability of revenues from successor drugs (α), the number of expected successors to a novel drug (μ_Q), and the weight that firms place on future profits (β). An increase in any of these parameters makes firms more willing to invest in novel drugs. This has two testable empirical implications. First, we expect firms to bring more novel drugs into development under higher parameters: the average novelty of drugs in development should be increasing in α, μ_Q, and β. Second, we expect that the correlation between novelty and revenue (given approval) will be less positive when α, μ_Q, or β is higher.

Empirically, we proxy for these parameters in the following ways. To obtain variation in appropriability, we examine research areas with different numbers of firms actively competing to develop drugs. Similarly, we use information on a drug's therapeutic area, biological target, and development history to obtain variation in its number of expected successors. Finally, we adopt Gormsen and Huber (2023)'s measures of firm-level discount rates (measured from analysis of earnings call text) to get variation in the weight that firms place on future profits.

3.4.2 Model Assumptions

Our model makes a number of simplifying assumptions. For instance, we assume that the arrival of different types of drugs is exogenous and undirected, i.e., the firm does not specifically seek out novel or incremental drugs. In addition, we assume that the knowledge generated by developing a novel drug accrues to all firms in the market, so that the developing firm does not have any specific advantage. These simplifications allow us to reduce the number of parameters and assumptions in our model, so that we can focus on its central tradeoff of evaluation versus learning.

We also wish to highlight a key substantive assumption, that the underlying distributions of success likelihoods and revenues are the same for novel and incremental drugs. The motivating premise is that these drugs are distinguished only by a researcher's information. The same physical molecule, with the same underlying biological action, is novel if no similar molecule has been developed in the past, but would be incremental otherwise. Because any molecule could be novel or incremental depending on the state of prior research, we view both types of drug candidates as

being drawn from the same distribution of project fundamentals. Unfortunately this assumption is not directly testable because the initial distribution of quality for nascent ideas is fundamentally unobserved: beyond the fact that datasets such as Cortellis do not capture all drugs in discovery stages, many ideas occur to a researcher but are never recorded.

Assuming that the underlying distribution of returns is the same for novel and incremental projects allows us to highlight the role that selection plays in shaping the *observed* traits of drugs in development. In our model, differences in the risk and returns associated with novel and incremental drugs in development emerge endogenously from differences in the criteria that firms apply when deciding which projects to pursue. Our goal is to highlight how this simple mechanism can generate many of the empirical patterns we observe. In Section 4.4 we provide a more detailed discussion of alternative explanations for these patterns.

Relatedly, while our model is of a single firm developing a single drug, we will test the model by studying outcomes across firms and drugs. This means that we will be aggregating across decisions that have different underlying parameters. For instance, one could imagine that larger firms with more resources than small firms are better equipped to generate follow-on drugs. In the context of the model, that would correspond to these firms having a larger appropriability parameter α. Alternatively, large public firms might face stronger pressure to generate short-term returns. That would mean that they have a lower discount factor β. Given these conflicting factors, our model does not make unambiguous predictions about how firm size—or other dimensions of firm heterogeneity such as incumbency, prior research experience, or product portfolio—influence how firms value learning versus evaluation. We focus our empirical analysis on the parameters highlighted in Proposition 3.3, for which we can make clearer predictions.

4 Empirical Results

4.1 Trial Progression

Our first empirical results focus on the progression of drugs through clinical trials and FDA approval. Proposition 3.1 predicts that incremental drugs are more likely to progress at every stage. This is because better information allows firms to more accurately identify incremental projects that are likely to be successful. To test this, we estimate regressions of the following form:

$$\text{Progression}_i = a_0 + a_1\text{Novelty}_i + \delta_t + \delta_d + \varepsilon_i \tag{9}$$

As with our earlier analysis, Equation (9) is estimated at the drug level. Our main outcomes of interest, Progression_i, are indicators for whether drug i reaches Phase 2, 3, and approval. The sample used in each regression is the set of drugs that made it to prior stage in the United States. For example, when examining whether drugs enter Phase 3 of clinical trials, we restrict to drugs that

have entered Phase 2. The main outcome of interest is explanatory variable of interest is Novelty_i, with 0 indicating no molecular overlap with prior drug candidates and 1 indicating identical atoms and bonding. In our primary specifications, we include controls for cohort fixed effects (development-year-quarter) δ_t as well as fixed effects δ_d for a drug candidate's lead disease indication (ICD-9).

Figure 4 presents the corresponding binned scatterplots associated with Equation (9), with corresponding regression coefficients reported in Table 3. Panel A considers the relationship between a focal drug's novelty (one minus its maximum pairwise Tanimoto similarity score) and its likelihood of progressing from the first stage of clinical trials (Phase 1) into the second (Phase 2). Our specification compares drug candidates that are developed at the same time, for the same disease, but which differ in their novelty. We find statistically significant associations between a drug's novelty and its likelihood of progression through each stage of clinical trials. Column 2 of Table 3 provides the analogous regression specification. The coefficient on novelty of -0.089 indicates that a one standard deviation increase in novelty (0.26), is associated with a $0.26 \times -0.089 = 0.023$ or 2.3 percentage point decrease in the likelihood of entering Phase 2 trials, conditional on entering Phase 1. This translates into a relatively modest 3.2 percent decrease from the mean. In Panels B and C (corresponding to Columns 4 and 6 of Table 3), we see larger negative relations between novelty and progression: one standard deviation increase in novelty is associated with a 13.7% decrease in progression from Phase 2 to Phase 3 and a 9.2% decrease in progression from Phase 3 to launch.

4.2 Evaluation vs. Learning

Our next section presents our main empirical exercise. Here, we evaluate whether firms prioritize the ability to better assess incremental drugs or the opportunity to learn from developing novel drugs. Proposition 3.2 states that if firms care more about evaluation, they will set a lower threshold for developing incremental drugs. In that case, incremental drugs will be more likely to be developed and their revenues will be lower on approval. If firms instead care more about learning, we would find the opposite pattern. To examine this, we estimate two separate specifications.

$$\text{Enter Development}_i = a_0 + a_1 \text{Novelty}_i + \delta_t + \delta_d + \varepsilon_i \tag{10}$$

$$\text{Revenue}_i = a_0 + a_1 \text{Novelty}_i + \delta_t + \delta_d + \varepsilon_i \tag{11}$$

Equation (10) asks whether novel drugs are more likely to be developed. The regression is estimated at the drug level but unlike our previous samples, contains all drug candidates observed in *pre-clinical* development in the United States. Because pharmaceutical firms tend to patent drug candidates very early in the research process, datasets like Cortellis are able to capture many drug candidates that have only been through some lab and animal testing. In our primary specifications,

we include controls for cohort fixed effects (pre-clinical entry year-quarter) δ_t as well as fixed effects δ_d for a drug candidate's lead disease indication (ICD-9).

Equation (11) tests whether novel drugs generate higher direct revenues, upon approval. For this analysis, we restrict to the set of candidates that reach approval in the United States. Again, our specifications include cohort and disease fixed effects.

Figure 5 presents our analysis and provides evidence that firms care more about evaluation: that is, we are in Case 1 of Proposition 3.2. First, Panel A shows the binned scatterplot corresponding to Equation (10). We find that, among drugs that enter pre-clinical investigation at the same time, for the same disease, novel drug candidates are substantially less likely to enter clinical development. The accompanying magnitudes, reported in Column 2 of Table 6, indicate that a one standard deviation increase in novelty (0.21 in the pre-clinical sample), is associated with a $0.21 \times 0.27 = 5.7$ percentage point decrease in the likelihood of entering development, or an approximately 15% decrease from our baseline development rate.

Second, Panel B shows the binned scatterplot corresponding to Equation (11). We find that novel drugs generate more revenue conditional on approval. As reported in Column 4 of Table 6, a one standard deviation increase in novelty is associated with an increased annual revenue of just over $0.21 \times \$515 = \$108$ million, or an over 25% increase from the overall mean among launched drugs. This pattern is consistent with firms using a traditional NPV calculation (as if $\beta \approx 0$ in our model): if firms view novel drugs as riskier to develop, then they will only invest if they anticipate higher revenues on approval.

Before continuing, we note that in Panel C of Figure 3, we showed that novel drugs have higher expected direct revenues when compared to more incremental drugs. Without the context of a model, one might conclude that novel drugs are unambiguously better: they generate as much direct revenue, and they also provide knowledge spillovers for the future. Our model, however, highlights the role of selection. Firms apply a higher revenue threshold for developing novel drugs and, as such, the set of novel projects we observe in development will appear to be drawn from a better distribution. We move on to our next proposition below, but discuss alternative explanations for this main result in Section 4.4.

4.3 Comparative Statics

Proposition 3.3 highlights three key parameters that increase the value that firms place on learning: appropriability (α), the expected number of successors for novel drugs (μ_Q), and the firm's discount factor (β). In all cases, our model predicts that increases in these parameters will lead firms to invest in more novel drugs. Empirically, this translates into two predictions.

First, the average novelty of drugs in development should be higher when the parameters α, μ_Q or β are higher. This reflects the fact that if firms value exploration, they should invest in a higher

share of the novel drug candidates they encounter. We examine this by estimating the following regression:

$$\text{Novelty}_i = a_0 + a_1\text{Param}_i + X\beta + \delta_t + \varepsilon_i \tag{12}$$

Here, the explanatory variable of interest, Param_i is a proxy for α, μ_Q, or β. The sample size will vary depending on the number of drug candidates for which we can obtain measures of Param_i. For example, our analysis of firm discounting involves using data gathered from public firms' earnings calls by Gormsen and Huber (2023) and therefore only includes drugs i that are put into clinical trials by public firms included in Gormsen and Huber (2023)'s data. In all specifications we control for drug cohort fixed effects and depending on our parameter of interest, we include additional controls $X\beta$, discussed later in this section.

Second, we predict lower revenues for approved novel drugs when α, μ_Q or β are higher, reflecting a lower revenue threshold for making these investments. Because our measure of novelty is continuous, we operationalize this prediction by examining the relationship between novelty and revenues, in settings where α, μ_Q or β is high versus low. Specifically we run the following regression:

$$\begin{aligned}\text{Revenue}_{it} &= a_0 + a_1\text{Novelty}_{it} \times \mathbb{I}(\text{Param} > \text{Median}) \\ &\quad + a_2\text{Novelty}_{it} \times \mathbb{I}(\text{Param} < \text{Median}) + X_{it} + X\beta + \delta_t + \varepsilon_i\end{aligned} \tag{13}$$

Equation (13) is similar to Equation (11) but instead of examining the overall relation between novelty and revenues among approved drugs, we compare this correlation in settings with high and low parameter values. Specifically, recall that there is a positive correlation between drug novelty and revenues on approval in our overall data (Figure 5 Panel B). Interpreted in light of Proposition 3.2, this suggests that firms apply a higher revenue threshold for developing novel rather than incremental drugs. Proposition 3.3 predicts that when α, μ_Q or β are low (e.g. firms value learning less), then the correlation between novelty and revenues should be even higher—because firms would require higher direct returns in order to justify investments in novel drugs.

Before continuing, we note that even though our model has the same sign on the comparative statics for α, μ_Q, and β (higher means greater value of learning), the signs in our empirical analysis will sometimes be flipped. This is because we run our analyses in terms of the natural units for the measured proxies for these variables. In particular, we proxy for appropriability, α, through the number of competitors, where more competitors corresponds to lower appropriability. And we proxy for discount *factor* β using a measure of yearly firm discount *rates*, where a higher discount rate means a lower discount factor.

Finally, we emphasize our analysis will be based on correlations and, particularly in the case of discount rates, limited by small sample sizes. While we include controls for potential cofounders

where we can, the goal of this analysis is to provide empirical evidence that is *consistent* with the predictions of Proposition 3.3, rather than to exclude all other potential explanations.

4.3.1 Competition

A firm that develops an innovative drug with many eventual successors only values the revenue from those successors that it develops itself. Figure 6 shows the amount of a focal drug's successor revenue that accrues to the same firm versus the amount that accrues to the rest of the market. We find that, at any stage of development, approximately half of a drug's future successor revenues accrue to rival firms. Proposition 3.3 predicts that when firms expect to capture less of the future revenues (lower α), they will apply a higher bar for investing in novel drugs.

To test this prediction, we link focal drugs to their primary "research area," which we define as the nexus of their disease target (ICD-9) and mechanism of action (MOA) (for example, statins are designed to treat heart disease by inhibiting the HMG-CoA reductase enzyme). We define a notion of research area competitiveness by examining the number of pre-clinical drug candidates in this area that have been developed by other firms over the previous five years. Firms working in research areas with more active competitors may be less able to appropriate spillovers from their own investments.

In Panel A of Figure 7, we present the binned scatterplot corresponding to Equation (12). We see evidence of a strong negative relationship: in more competitive areas (lower α), the average drug that enters development tends to be less novel. Column 1 of Table 4 indicates that a 10 percent increase in competition is related to an 0.75 percent decline in average novelty.

Next, Panel B of Figure 7 plots the coefficients estimated in Equation (13). In settings where competition is high, we see a more positive relation between novelty and revenues. The coefficient estimates presented in Column 1 of Table 5. We find that a one standard deviation increase in novelty in above median competitive research areas increases revenues on approval by twice as much as in below median competitive areas. Taken together, the results in Figure 7 provide evidence consistent with the idea that firms become more selective in developing novel drugs when appropriability concerns diminish the private value of successor revenue.

One may be concerned that more competitive areas are more crowded and may simply have fewer novel drugs left to discover. To address this, our analysis above controls for the total amount of research being conducted in an area defined in several ways: the total number of drug candidates (irrespective of the originating firm) that have ever entered pre-clinical development in the focal drug's ICD9-MOA to date, as well as total entry for the entire disease area or mechanism of action. As such, our results should be interpreted as saying that the average novelty of drugs is lower in more competitive research areas, holding constant the overall amount of research activity that has occurred in these areas to date.

Further, we note that if there were an unobservable factor that simply increases the number of novel drug candidates that are available for firms to develop, we would expect the average novelty of developed drugs to be higher, but their average revenues on approval to remain the same. Rather, the joint pattern presented in Panels A and B is most parsimoniously explained by firms lowering the revenue threshold used to assess whether or not to develop a novel drug candidate.

4.3.2 Expected Successors

Proposition 3.3 also predicts that firms will be more interested in developing novel drugs when they expect such drugs to yield more successors (higher μ_Q). The expected number of successor candidates can vary systematically across drugs due to differences in market attractiveness or scientific potential. For example, drug candidates that identify a promising new biological pathway are more likely to influence subsequent chemical structures than drugs that explore well-known pathways.

We construct the expected number of successors for a given drug candidate using fitted values from a regression of a drug's actual number of chemical successors (using the measure we develop in Section 2.2) on fixed effects for its year of entry, disease market (ICD-9), as well as entry order into its biological target area.[19] This is all information that a firm would be aware of at the time it makes its investment decision.

Figure 8 repeats the exercise described in the previous section, but with Param_i corresponding to predicted successors. In Panel A, we show that the average novelty of drug candidates that firms invest in developing is higher in settings where firms expect focal drugs to generate more successors. Column 2 of Table 4 indicates that a 10 percent increase in the expected number of successors corresponds to a 1 percent increase in average novelty.

Again, this correlation could reflect other factors. For example, research areas with more expected successors may separately have more novel drug candidates that have yet to be discovered. While we cannot control for all observed aspects of research potential, our analysis here again includes detailed controls for the number of prior drug candidates that have been developed in these research areas, as described earlier. We are thus comparing the novelty of drugs being developed in areas with a similar stock of existing innovation.

Next, Panel B of Figure 8 shows that when the expected number of successors is higher, the direct revenues that novel drugs generate tends to be lower. Indeed, the overall positive relation between novelty and revenue documented in Panel B of Figure 5 is driven almost entirely by settings in which firms expect investments to generate relatively few successors. When successors are likely, firms do not appear to hold novel drugs to a higher revenue threshold. The accompanying regression

[19] Specifically, we use the focal drug candidate's entry order across three different "levels" in the Cortellis biological target "tree", an ontology where each level represents a different amount of granularity of describing a biological target or target-action (e.g., g-coupled receptors vs. "angiotensin II type 1 receptor agonist").

coefficients are presented in Column 2 of Table 5. Appendix Figure A.5 presents alternative versions of Figure 8 using different definitions of successors. The results are consistent across all versions.

4.3.3 Firm Discount Rates

Finally, Proposition 3.3 predicts that firms with higher discount rates (lower β) will be more reluctant to develop novel drugs. To test this, we match our sample to Gormsen and Huber (2023)'s measures of self-reported measures of discount rates that firms apply to their investment decisions, as described in Section 1.2. Due to the small sample size of matched firms, we stress that this analysis is meant to be suggestive.

Figure 9 examines the relationship between a firm's self-reported discount rate and its decisions to invest in novel drugs. Panel A shows that the average novelty of drugs developed by firms with a high discount rate tends to be lower. Column 3 of Table 4 indicates that a 10 percent increase in a firm's discount rate is associated with a 2.9 percent decrease in average novelty. Column 3 of Table 5, meanwhile, shows that among approved drugs, novelty is only positively correlated with revenues when discount rates are high.

Taken together, our findings across Sections 4.3.1, 4.3.2, and 4.3.3 provide consistent evidence that factors which decrease the value of future learning lead firms to become more selective when investing in novel drugs in the present.

4.4 Alternative explanations

The underlying tension in our model is that novel drugs have both an advantage and a disadvantage relative to incremental drugs. On one side of the ledger, firms have less information about whether a novel drug will advance to the market if developed. On the other side, the process of developing a novel drug generates information about future, as-yet-undeveloped drugs. With both advantages and disadvantages of novelty, it is unclear which type of drug a firm would prefer to develop. The diagnostic test proposed in Proposition 3.2 highlights how firms that prioritize learning will apply a lower revenue bar when deciding whether to develop a novel drug candidate. As a result, novel drugs will be more likely to be developed, and their revenues conditional on approval should be lower. Alternatively, firms that prioritize evaluation will develop more incremental drugs, and those drugs should have lower revenues on approval. Our evidence in Section 4.2 and Figure 5 finds that firms prioritize more reliable evaluation over learning. In Section 4.3, we show that three different features—more appropriability, more successors of novel drugs, and higher weight on the future—all suggest firms placing more value on learning, and thus shifting development toward novel drugs.

This interpretation relies on a key assumption in our model: that novel and incremental drugs are initially drawn from the same distribution of success probabilities and revenues. This assumption allows us to attribute differences among novel and incremental drugs observed in development to

differences in firms' selection decisions. In practice, however, differences in development rates or revenues between novel and incremental drugs could arise for reasons unrelated to those our model focuses on. For example, it may simply be the case that novel drugs are drawn from a distribution with fatter tails: there are more novel drugs that are likely to fail, and more novel drugs that are likely to be blockbusters. In this case, fewer novel drugs would enter development but their average revenues would be higher—even if firms were applying the same development thresholds for novel and incremental drugs.

Because we cannot observe the universe of potential drug ideas, novel or incremental, we cannot rule out the possibility that our main results are driven by fundamental differences in distributions. However, in this section, we provide additional discussion and analysis aimed at highlighting why the explanation provided by our paper is plausible.

First, suppose that it is indeed the case that the distribution of novel drug ideas is fatter tailed. While this would explain our main results in Figure 5, it would not explain how our results differ across different parameters for appropriability, number of expected successors, and firm discount rates. To explain all of those results, we would need to further assume that the primitive distribution of novel drug ideas is fatter tailed in more competitive research areas *and* in more active research areas *and* for firms who face higher discount rates. While there may be explanations for each of these possibilities, we believe that our model provides a more parsimonious explanation, driven by a very plausible assumption: that novel and incremental drugs differ primarily in how much we information we have about them.

Second, many alternative explanations for why incremental drugs may be more likely to be approved or have lower revenues implicitly focus on drugs that are derivative of *successful* prior drugs. For example, firms may be more likely to develop incremental drugs related to previously approved drugs because they have received a positive signal about that entire class of drugs. Similarly, such incremental drugs, once approved, may have lower revenues because they are more similar to existing treatment options. Our model, however, predicts that even incremental drugs related to *failed* predecessors can be more likely to be approved and have lower average revenues. This is because our model highlights *information* as the primary distinguisher of novel and incremental drugs: as long as firms learn from developing related drugs, incremental drugs related to failed predecessors will still be easier to evaluate.

To examine this, Tables 7 and 8, we test the predictions of Propositions 3.1 and 3.2 after excluding follow-on drugs linked to predecessor drugs that are FDA approved. That is, we compare molecularly novel drugs to molecularly incremental drugs that are derivative of failed predecessors. Consistent with Proposition 3.1, our results in Table 7 show that incremental drugs based on failed predecessors are still more likely to progress through development. In Table 8, we look once again at firms' thresholds for developing novel versus incremental drugs. In Columns 1 and 2, we show that novel drugs are still less likely to enter development and, in Columns 3 and 4,

that they continue to have higher revenues on approval. In all these regressions, our estimated magnitudes are similar. This suggests that the process of developing a drug generates information about future drugs, regardless of whether the focal drug succeeds or fails. Firms, it appears, value the evaluation benefits of developing any type of incremental drug and gain valuable information from novel exploration regardless of the initial project's outcomes.

4.5 Discussion: welfare and policy

While it need not be inefficient for firms to prioritize the development incremental drugs over novel ones, our model and empirical results do highlight a specific case in which firms appear to underinvest in novelty: when competition between firms leads to imperfect appropriability. Developing novel drugs generates learning spillovers that benefit society. When the focal firm cannot capture the full benefits of these spillovers, it will underinvest in developing novel drugs relative to an efficient benchmark. Even if we had found that firms prioritized novel drugs over incremental ones, firms would still underinvest without perfect appropriability. Empirically, we provide evidence consistent with this inefficiency: firms facing less competition tend to invest in more novel drugs.

In highly competitive markets, our results suggest that there may be gains to policies that provide incentives for R&D organizations to internalize the social value of spillovers from exploratory projects. One can imagine several broad aims of policy interventions: 1) limiting follow on competition (e.g., broader patents, regulatory protections against "me-too" products); 2) improving contracting related to follow on work (e.g., reach-through rights, standardized licensing); 3) shifting high-spillover work toward parties that internalize future social spillovers (e.g., public funding, government sponsored trials); or 4) those aimed directly subsidizing novel innovations (e.g., breakthrough regulatory designations, special tax credits for novel R&D).

Many pharmaceutical patents focus not just on a single drug compound or molecule, but on broader families of molecules, denoted by so-called "Markush structures." A firm's original patent for a focal drug may therefore also give it IP rights over chemically similar follow-on drugs. There has been an active debate among policymakers regarding how broad pharmaceutical patents should be (Wagner et al., 2022). Our paper highlights a distinct mechanism: allowing firms to patent broader families of molecular compounds may change not just their incentives to invest in R&D overall, but also impact the *composition* of their investments, favoring greater exploration.[20]

The downside of broader patent rights, of course, is that such rights may be too blunt and may reduce follow-on innovation by others (Shapiro and Gilbert, 1990; Hegde et al., 2022; Wagner et al., 2022). Policy-makers may alternatively focus on improving contracting between firms that create a

[20] One way in which lawmakers have navigated the tension between wider protections and allowing follow-on work by other firms is the notion of a "selection patent." Even if a specific compound is contained within a Markush structure on an existing patent, the initial inventor or other firms may still apply for a separate patent, as long as it can demonstrate unexpected or advantageous properties of the selected compound(s).

focal innovation and those interested pursuing follow-on innovation. One possible policy remedy is to grant the original patent holder a standardized level of "reach-through" rights (i.e., compulsorily licensing, standardized deal terms, fixed royalty rates) to exercise over other firms that file follow-on patents within a highly similar family of compounds. Such a policy would give the original inventor an advantage in capturing the follow-on learning benefits, without granting the innovator the right to block all follow-on development efforts.

Changes to IP regimes are likely to generate a trade-off between improving incentives for ex-ante exploration (by giving focal firms greater rights to downstream learning spillovers), and limiting follow-on innovation by other firms. A different approach would be for more high-spillover research to be performed by parties who value the future social benefits of learning spillovers. This view would support more participation by public funding agencies in the development of foundational research, or more applied research into particularly novel classes of drugs. Government involvement might take a range of formats: government-run trials (via NIH programs); actively managing novel research programs (e.g., DARPA, ARPA-H); or providing low cost testing infrastructure to the private-sector (e.g., animal testing facilities, clinical trial support).

Finally, policymakers could incentivize private investments in novel drugs by using "pull" incentives that directly target more exploratory research programs. For example, investments in clinical trials or publishing research on structurally novel drugs could confer special eligibility for additional R&D tax credits or trade-able priority review "fast lane" vouchers similar to the FDA's breakthrough and orphan drug designations Ridley et al. (2006); Gans and Ridley (2013); Ridley and Régnier (2016). In terms of policy, this prescription differs from that of the typical endogenous growth model, which advocates for general R&D tax credits. In our case, general subsidies would not necessarily increase surplus because firms choose the direction of innovation. Instead, tax credits would need to be tied to the observable characteristics of specific investments, such as their novelty or some assessment of their potential to generate spillovers. Our model provides a potential framework for judging which projects and competitive environments are likely to have the largest wedge between private and social value of novel exploration. Policymakers should then evaluate the success of such programs with a longer term time horizon, using data that consider spillover outcomes, such as the number of drug successors.

5 Conclusion

If past R&D investments inform future decisions, then firms face a choice: is it more valuable to explore new areas to gain fresh insights, or to exploit the information revealed by past work?

In this paper, we show that although novel drug candidates generate more knowledge spillovers, firms prefer to invest in incremental candidates, which are easier to evaluate. This presents a dynamic tension: while firms value the scientific knowledge that allows them to more accurately

discard incremental drugs that are unlikely to succeed, they are reluctant to make the types of exploratory R&D investments that improve future screening decisions. Our empirical results show that, on average, firms place less emphasis on learning, which leads them to invest in fewer novel drugs. Further, we provide evidence that firms' reluctance to invest in novel drugs is especially pronounced when firms expect to appropriate a smaller fraction of follow-on opportunities, when they expect a drug to generate fewer such opportunities, or when future profits are heavily discounted. In demonstrating these results, our paper makes several contributions that may inform future research.

First, we propose an alternative perspective on firms' R&D investment decisions. In workhorse models of innovation (e.g., Manso (2011) or Akcigit and Kerr (2018)), as well as empirical studies measuring the exploration-exploration tradeoff under different conditions (e.g., Azoulay et al. (2011b), Zhuo (2023), Hoelzemann et al. (2024)), firms must decide between R&D projects that differ in their inherent risk and rewards: novel R&D projects are modelled as higher risk and higher reward, while incremental projects are modelled as safer, more modest bets. In this framing, novel innovations generate value because of either their direct revenue potential, or the cumulative rewards unlocked by early success (Callander, 2011).

By contrast, our paper treats novel and incremental projects as distinguished by the amount of information firms possess about their likelihoods of success, rather than by any inherent differences in risk. We show how differences in observed risk can emerge endogenously as a result of differences in firm's R&D choices which reflect the information they have about projects. Viewed through this lens, the fact that novel projects are thought of as "high risk, high return" may simply reflect firms' reluctance to invest in exploration, rather than some fundamental feature of novel projects. Indeed, our model highlights how the very categories of "novel" or "incremental" are themselves shaped by firms' decisions. Projects are only incremental if some firm has chosen to invest in a related project in the past. If this prior investment had not occurred, then the drug candidate in question today would still be novel.

Second, we present a new mechanism by which competition can lead firms to underinvest in innovation. In the existing literature, too much competition can reduce innovation by lowering the profitability of the focal product. Our paper shows that even when profitability of novel products remains high, competition can also reduce innovation by diminishing the private benefits of future learning. Since novel projects generate more learning than incremental ones, this mechanism disproportionately discourages investment in more radical innovations. This dynamic helps explain why we see so much crowding in certain well-understood therapeutic classes (Mancuso et al., 2025), rather than differentiation through exploring new disease targets. Our findings underscore the need for policies that incentivize firms to internalize the learning opportunities inherent in novel R&D, while still allowing competitors to benefit from knowledge spillovers.

Third, we develop a concrete measure of knowledge spillovers that applies to projects regardless of outcome. Our approach measures spillovers with structural properties to link projects to their successors. Beyond drug development, similar chemical informatics methods can quantify learning in related settings like industrial chemicals and materials science. More broadly, analyzing structural elements of hardware prototypes—through design images, patents, engineering plans, or regulatory filings—could bring this approach for quantifying R&D spillovers to other critical industries.

Finally, we emphasize the practical importance of valuing failed R&D efforts. By allowing for learning from adjacent projects, even when the initial projects fail, the model translates abstract concepts of learning from failure into more precise estimates based on project characteristics and historical data. Our descriptive analysis reveals that drugs generate significant value through successor spillovers, many of which originate from unsuccessful trials. This finding reinforces our modeling approach, where firms internalize such spillovers. However, in practice, modern project valuation tools—from simple net present value (NPV) calculations, to more sophisticated real options analysis, Monte Carlo simulations, and machine learning techniques to quantify R&D risk—all neglect the value of future learning opportunities (Nichols, 1994; Cassimon et al., 2004; Hartmann and Hassan, 2006; Gunther McGrath and Nerkar, 2004; Siah et al., 2021; Scannell et al., 2022). Our analysis demonstrates that, by neglecting spillovers in their valuation criteria, firms risk under-investing in novel R&D, ultimately leading to fewer breakthroughs and less cumulative learning. Therefore, incorporating the learning benefits of exploratory R&D investments poses both a measurement and a communication challenge.

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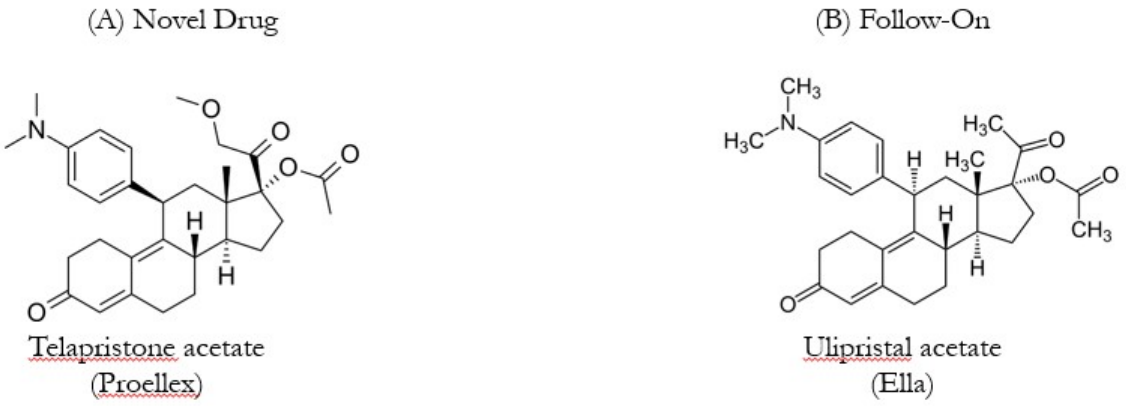
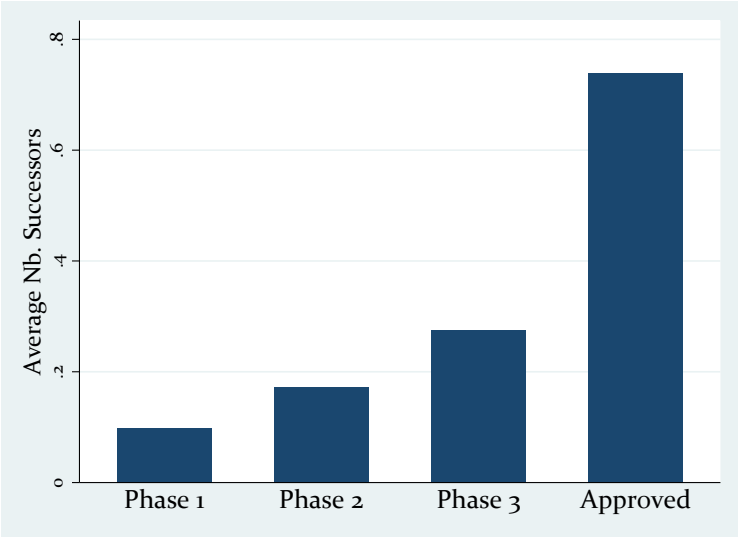
Figure 1: Example of Novel Drug and Follow-On



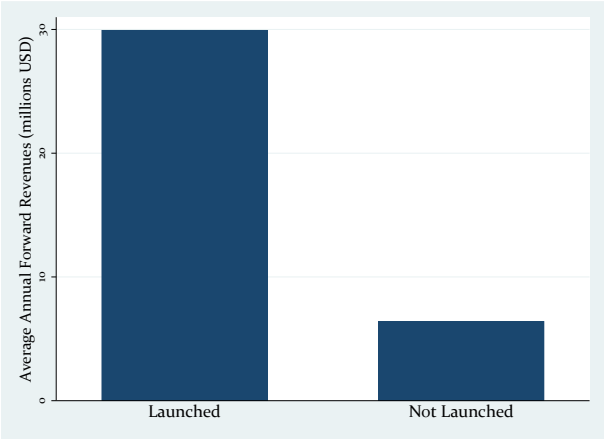
Notes: This figure displays the molecular structure of two drugs that are linked in the data. The drug on the left (Panel A), telapristone acetate (Proellex), is a molecularly novel compound that entered clinical trials for the treatment of uterine fibriods in 2004, sponsored by the biotech company Repros Therapeutics. Several years later, during Phase 3 trials, development was halted due to patients experiencing liver toxicity issues. Despite this, Proellex inspired the development of 5 successor drugs. One of those drugs, ulipristal acetate (Ella) is pictured in Panel B, and has a Tanimoto similarity of 0.81 to Proellex. Ella was developed by a different drug company, HRA Pharma and was approved in 2010. It is currently on the World Health Organization's list of essential medicines.

Figure 2: Successor Revenue, by Development Outcomes

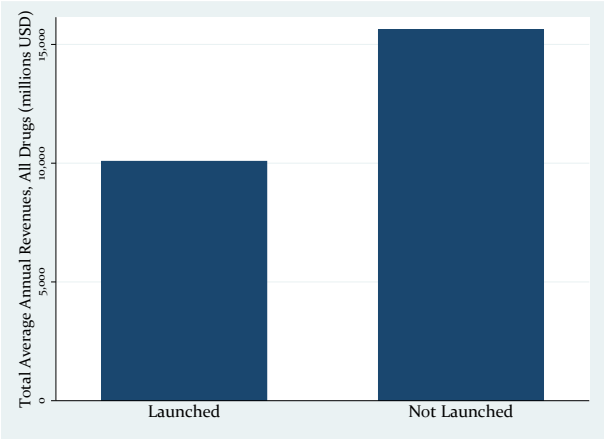
A. # Successors, by Focal Drug's Highest Development Phase



B. Average Successor Revenues

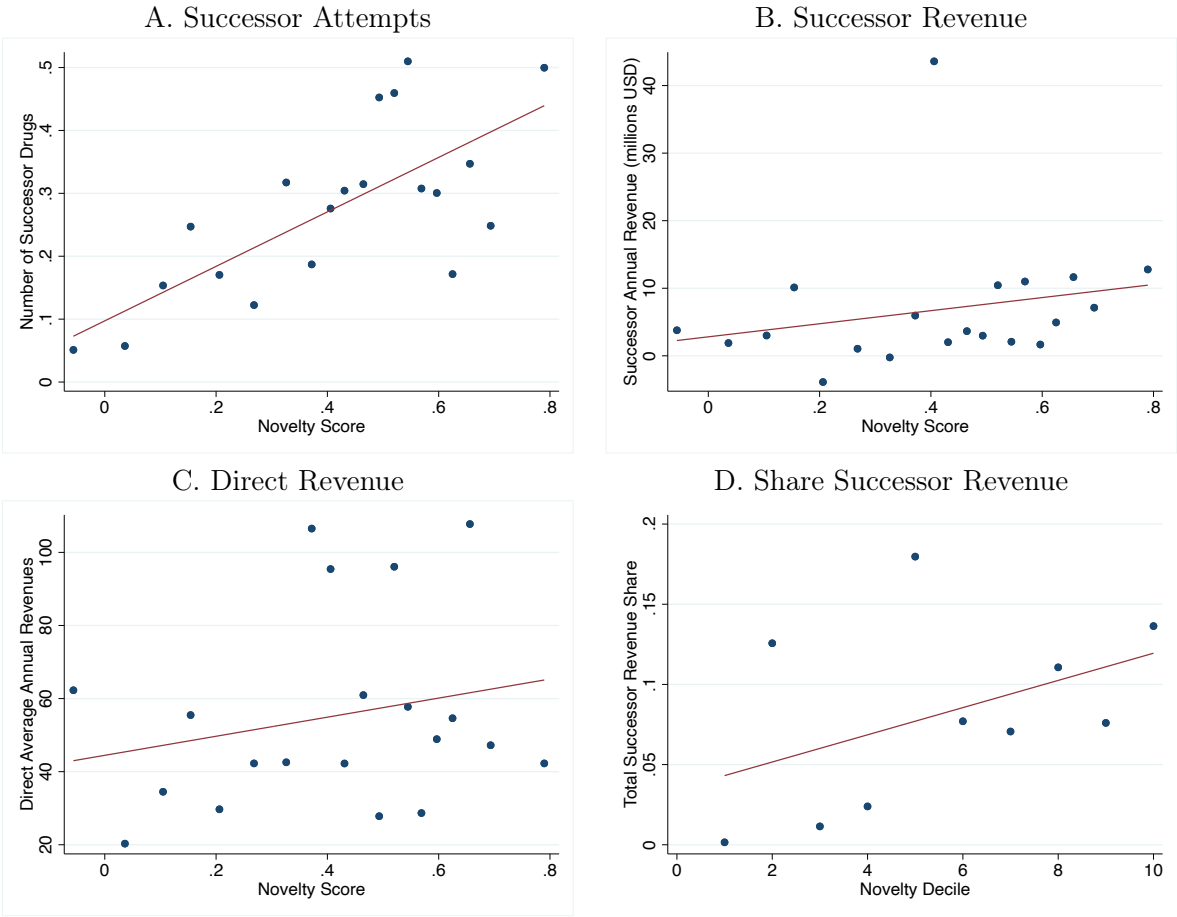


C. Aggregate Successor Revenues



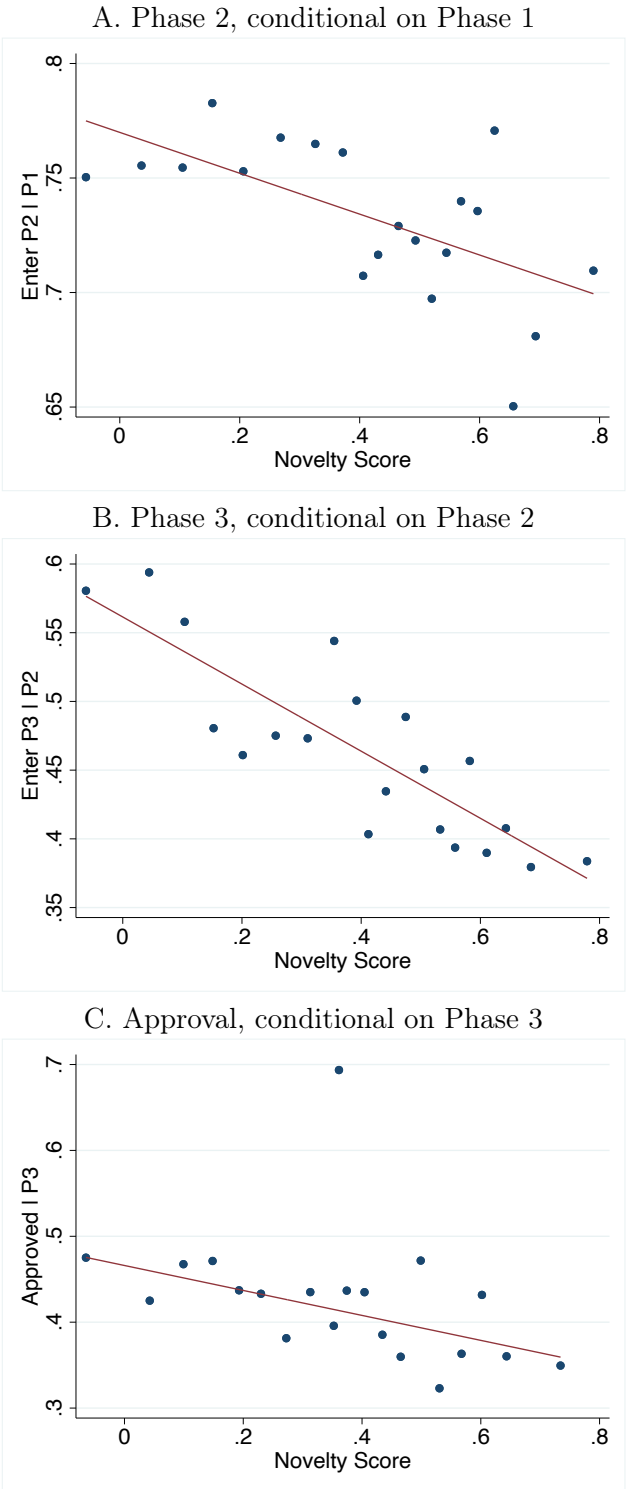
Notes: Figure 2 plots information on successor drugs and successor revenues for drug candidates in our data. Panel A shows the average number of successor drug attempts for drugs by their highest stage of development reached (e.g., phase 1 drugs are those that never graduated to phase 2 and beyond). Panel B plots average successor revenues per drug. Panel C provides the same information, except aggregated over all drugs in our sample. Successor revenues are defined as the sum of average annual revenues across all successor drugs to a given focal drug. Panels B and C present raw drug and revenue counts, and have not been adjusted for cohort differences. The sample includes drugs that enter clinical development in the United States.

Figure 3: Successor Revenues, by Novelty



Notes: Panels A-C of Figure 3 presents binned scatterplots of the relationship between a drug candidate's novelty and measures of successor activity and revenues, at the individual drug level. All specifications include controls for a focal drug's quarter of development and lead disease indication. The sample includes drugs that enter clinical development in the United States. To account for the fact that many drugs have no direct or successor revenues (so that their successor revenue share would be undefined), Panel D plots successor revenue shares aggregated by deciles of novelty. To compute this, we first residualize novelty by fixed effects for the drug's quarter of development and lead disease indication and then calculate the ratio of successor to successor plus direct revenues across all drugs that fall in each novelty decile. Table 2 presents accompanying regressions for Panels A-C, as well as for drug-level shares of successor revenues.

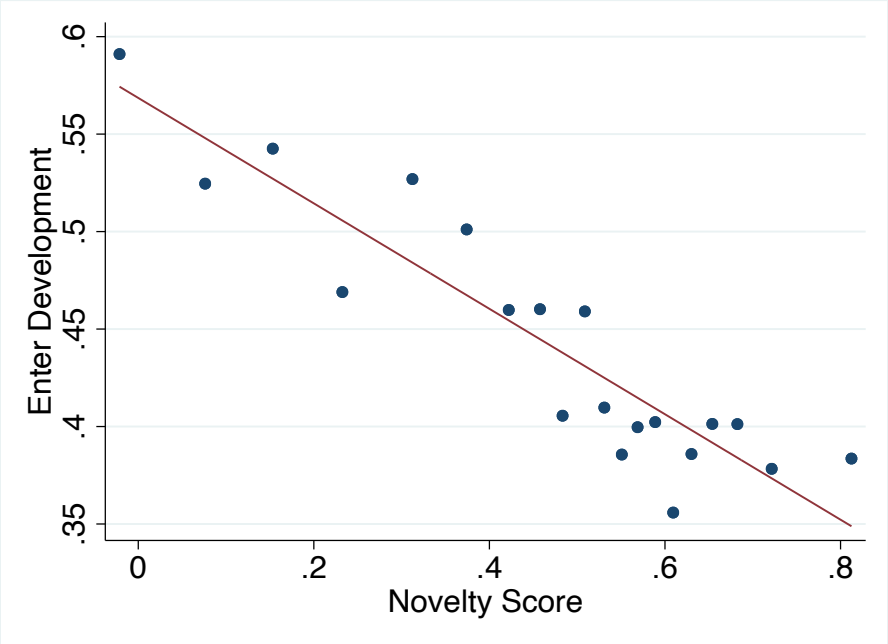
Figure 4: Progression through Development, by Novelty



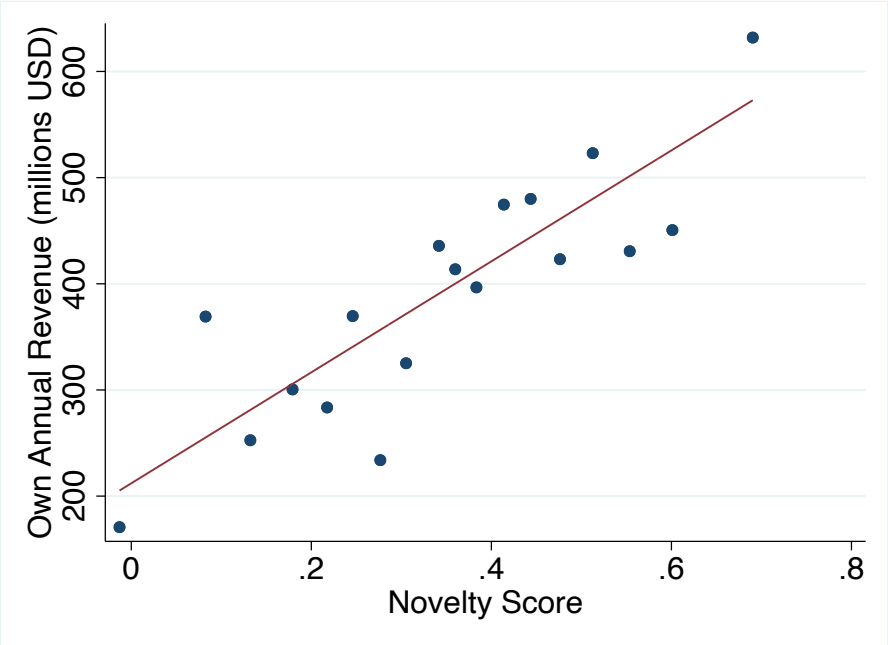
Notes: Figure 4 present a test of Proposition 3.1. Each panel presents a binned scatter plot of the relationship between a drug candidate's molecular novelty and measures of its progression in clinical trials. All specifications include controls for quarter of development and disease indication. The sample includes drugs that enter clinical development in the United States. Accompanying regression estimates are presented in Table 3.

Figure 5: Entry into Development and Revenues on Success, by Project Novelty

A. Development Probability (Likelihood of Clinical Trial Entry)

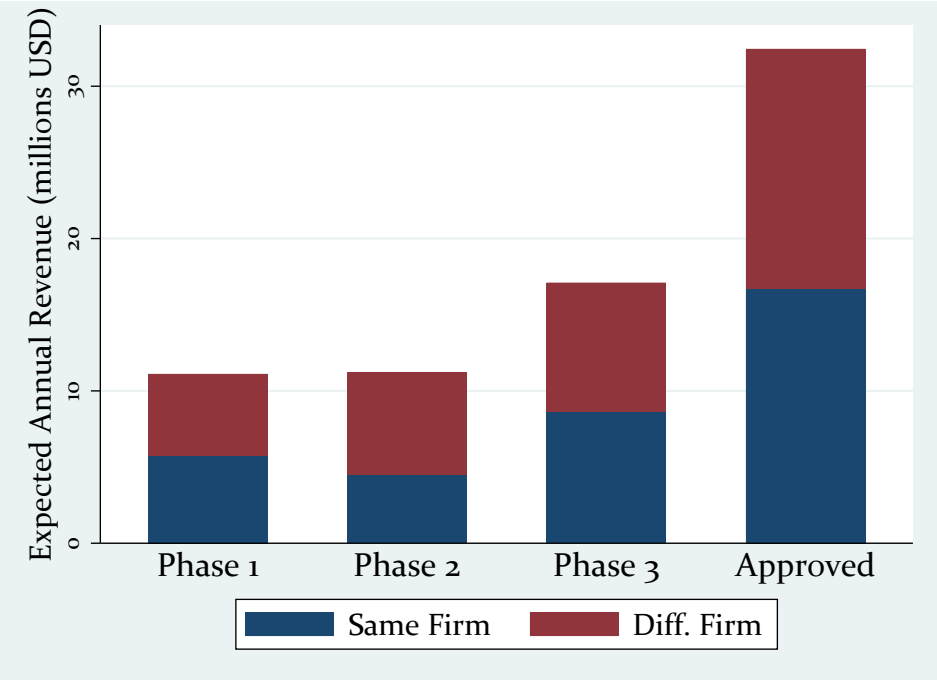


B. Revenue Conditional on Approval



Notes: Figure 5 provides an empirical analysis of Proposition 3.2. Panel A presents binned scatterplots of the relationship between a focal drug's novelty and a firm's decision to invest in clinical drug development. Here, the sample is all drugs that are observed in Cortellis data for US pre-clinical development. In Panel B, we present binned scatterplots of the relation between novelty and average annual direct revenues, for the set of drugs that are approved in the US. All specifications include controls for quarter of development as well as for disease area FEs. The corresponding regression estimates are presented in Columns 2 and 4 of Table 6.

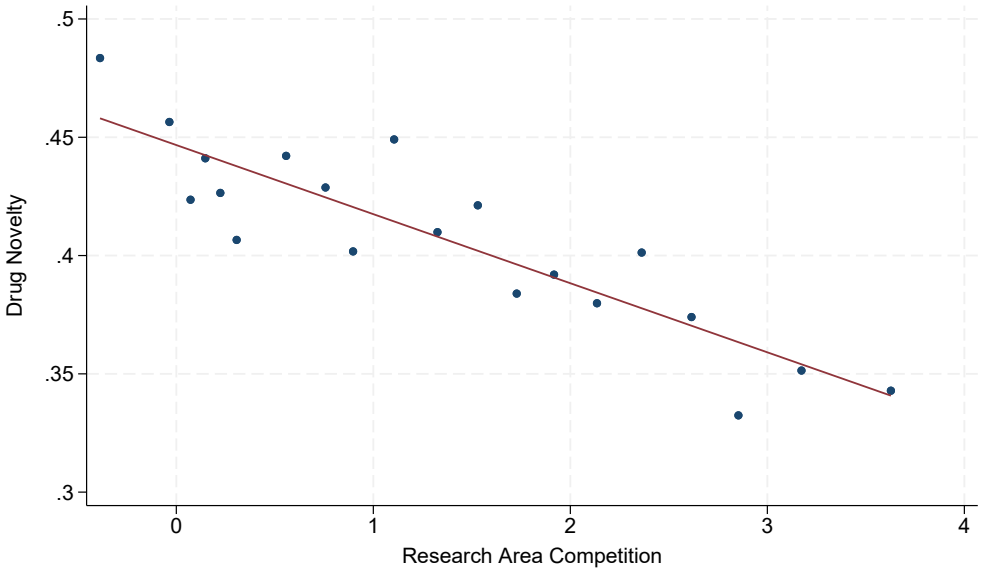
Figure 6: Appropriability of Successor Revenues



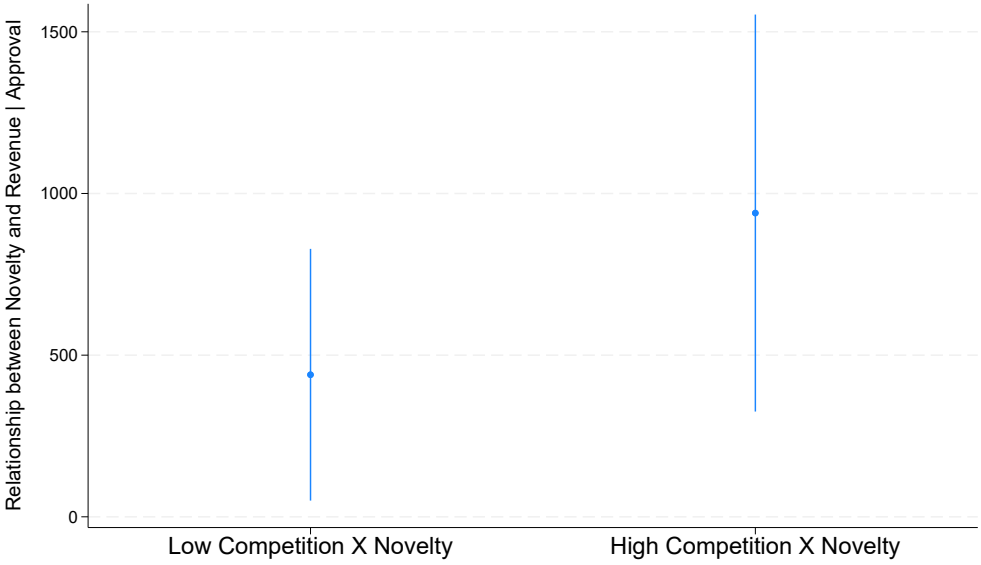
Notes: Figure 6 plots the expected annual successor revenues, by their highest stage of development reached. The blue portion of each bar represents the average annual successor revenues for drugs developed by the same firm as the focal drug, while the red portion reflects successor drugs developed by different firms. Successor revenues are defined as the sum of average annual revenues across all successor drugs to a given focal drug. These graphs present raw drug and revenue counts, and have not been adjusted for cohort differences. The sample includes drugs that enter clinical development in the United States.

Figure 7: Competition and Investments in Novelty Drugs

A. Average Drug Novelty, By Research Area Competition



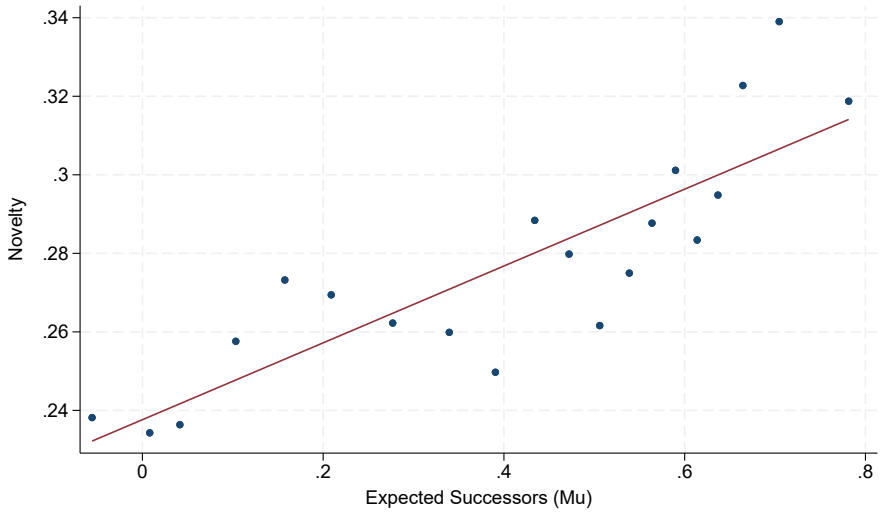
B. Revenue if Approved and Drug Novelty, By Competition



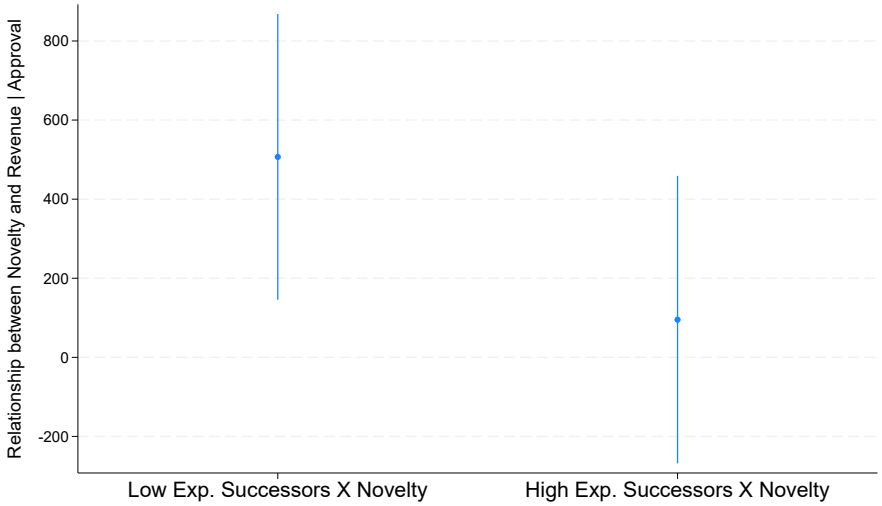
Notes: Panel A presents a binned scatterplot of a focal drug's novelty and the extent of research competition in the focal drug's area. Panel B plots the estimated relationship between novelty and revenues for approved drugs, separately for drugs in therapeutic areas with high research competition and those with low research competition. Research area competition is measured by the number of new drugs developed by competitor firms over the previous 5 years. To ensure that we are not identifying differences driven by the overall amount of research in an area, we control for various measures of total research activity in a research area. All specifications include controls for quarter of development and disease area FEs. Panel B corresponds to Column 1 of Table 5.

Figure 8: Expected Successors and Investments in Novelty Drugs

A. Average Drug Novelty, By Expected Successors



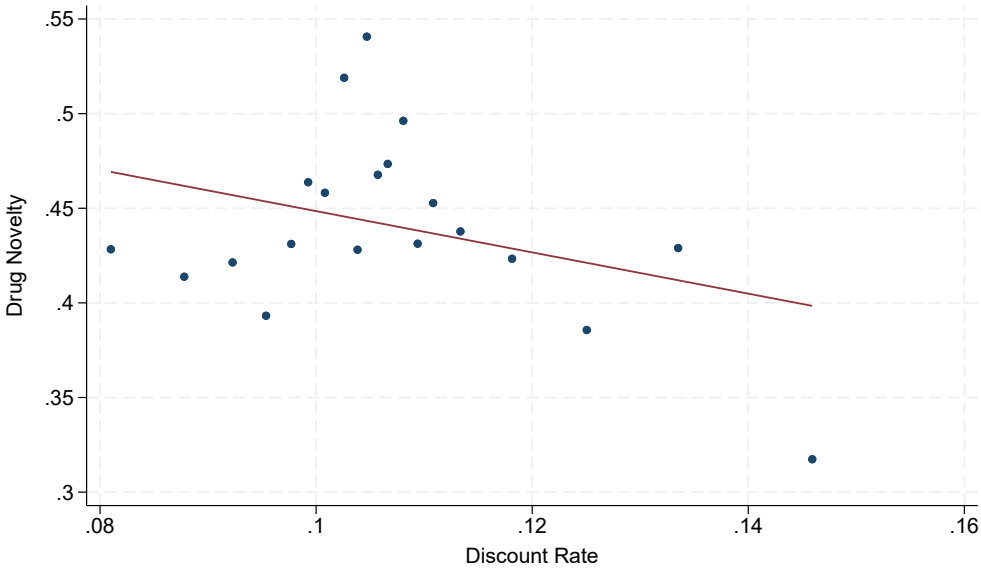
B. Revenue if Approved and Drug Novelty, by Expected Successors



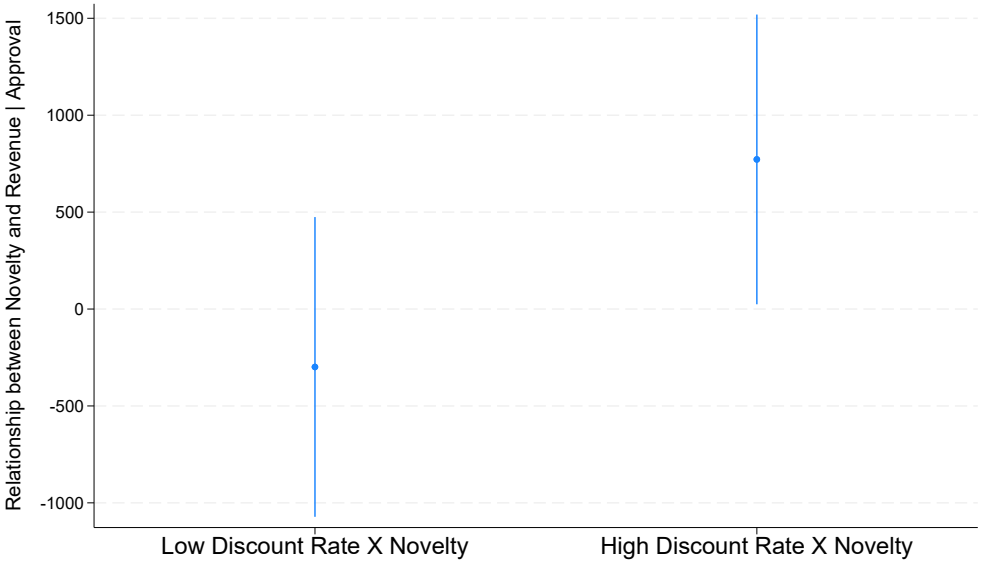
Notes: Panel A shows the relationship between novelty and the expected number of chemically similar successor drugs (μ_Q) in 20 equal sized bins. Panel B shows the relationship between chemical novelty and focal drug revenue for FDA approved drugs in the sample, split by the median level of expected successors. The expected successors values are predicted based on a regression of number of observed successors on the development entry order into a biological target area, as well as fixed effects for clinical entry year and disease market. Panel B corresponds to Column 2 of Table 5. Appendix Figure A.4 shows the distribution of expected successors and provides more detail about the estimation procedure.

Figure 9: Discount Rates and Investments in Novelty Drugs

A. Average Drug Novelty, By Discount Rate



B. Revenue if Approved and Drug Novelty, by Discount Rate



Notes: Panel A shows the relationship between chemical novelty and discount rates of the developing firm in 20 equal sized bins. The binscatter controls for the quarter in which the drug candidates entered phase 1 clinical trials. Panel A corresponds to Column 3 in Table 4. Panel B shows the relationship between drug candidates novelty and revenue (for approved drugs), split by the median discount rate in our sample. The regression controls for drug approval year. Discount rate measures come from Gormsen and Huber (2023). Revenue data comes from Evaluate Pharma. Panel B corresponds to Column 3 of Table 5.

Table 1: Drug Candidate Analysis Sample

Panel A: Full Sample (Counts)

Drugs	17,630
Companies	3,019
Lead Disease Indications (ICD-9s)	375
Drugs (phase 1 and above)	7,098
Drugs (approved)	1,379

Panel B: Drug Candidate Characteristics

	Mean	p25	p50	p75	p99
Novelty Score	0.48	0.36	0.57	0.65	0.80
Direct Revenue	16.10	0.00	0.00	0.00	439.79
# Successors	0.18	0.00	0.00	0.00	3.00
Successor Revenue	4.12	0.00	0.00	0.00	7.21

Notes: Table 1 presents descriptive statistics for the analysis data set of drug candidates. Panel A shows the number of drug candidates, number of companies, number of lead disease indications, number of drug candidates that reached clinical trials, and number of drug candidates that are approved during our analysis time frame. Panel B shows characteristics of drugs. The novelty score is equal to a 1 minus the focal drug candidate's maximum similarity to drugs that had previously reached phase 1 trials at the time the focal drug entered initial development. Direct revenue is the annual revenue associated with the focal drug. Number of successors is the number of follow on drugs attributed to the focal drug. And successor revenue is the sum of the future annual revenue for all successor drugs associated with a given focal drug. Revenues values reported in $millions.

Table 2: Drug Novelty: Successors (Number and Annual Revenue)

makebox[]

VARIABLES	(1) # Successors	(2) # Successors	(3) Successor Revenue	(4) Successor Revenue	(5) Direct Revenue.	(6) Direct Revenue.	(7) Successor Rev. Share	(8) Successor Rev. Share
Novelty Score	0.360***	0.433***	9.938*	9.683*	32.54**	26.10	0.106***	0.128***
	(0.0721)	(0.0955)	(5.948)	(5.734)	(15.38)	(17.09)	(0.0287)	(0.0375)
Observations	3,913	3,844	3,913	3,844	3,913	3,844	843	781
R-squared	0.077	0.117	0.037	0.056	0.069	0.143	0.210	0.379
Drug Cohort Year-Qtr FE	YES	YES	YES	YES	YES	YES	YES	YES
Lead Indication FE		YES		YES		YES		YES

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Notes: Table 2 presents the relationship between a drug candidate's novelty and the number of follow-on successors, successor revenue, direct revenue, and share of direct revenue. All revenue figures, both direct and successor, are defined as average annual revenues for the time that the approved drug appears in Evaluate Pharma. The sample consists of all drug candidates that enter Phase 1 development in the United States.

Table 3: Drug Novelty: Progression by Phase

VARIABLES	(1) Phase 1–2	(2) Phase 1–2	(3) Phase 2–3	(4) Phase 2–3	(5) P3–Launched	(6) P3–Launched
Novelty Score	-0.137***	-0.0892***	-0.302***	-0.244***	-0.178***	-0.145**
	(0.0271)	(0.0296)	(0.0360)	(0.0391)	(0.0549)	(0.0623)
Observations	3,913	3,844	2,871	2,802	1,329	1,266
R-squared	0.111	0.181	0.120	0.226	0.161	0.331
Drug Cohort Year-Qtr FE	YES	YES	YES	YES	YES	YES
Lead Indication FE		YES		YES		YES

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Notes: Table 3 presents the relationship between a drug candidate's novelty and its probability of progressing through clinical trials (Phase 1 to Phase 2; Phase 2 to Phase 3; Phase 3 to approval). The sample consists of all drug candidates that enter Phase 1 development in the United States. All regressions include drug year-quarter of development fixed effects. Columns 2, 4, and 6 additionally include fixed effects for the first indication (ICD-9) for which the drug entered development.

Table 4: Relation Between Future Value Parameters and Average Drug Novelty

	(1) Novelty	(2) Novelty	(3) Novelty
Competition	-0.0292***		
	(0.00305)		
Exp. Successors		0.148***	
		(0.0223)	
Discount Rate			-1.090**
			(0.547)
Observations	4,987	3,081	912
R-squared	0.123	0.125	0.076
Dev. Entry Qtr FE	YES	YES	YES

Notes: This table shows the correlation between each of the three future value measures—expected successors, competition, and discount rate—and the chemical novelty of those drugs. Each regression has fixed effects for the year of clinical development entry. Columns 1 and 2 additionally control for the stock of entry (to-date) in the disease indication. Expected successors is calculated based on the entry year, disease indication (ICD-9), and project entry order into the biological pathway for a given development project. Competition is estimated as the log of recent entry (last five years) by competing firms into a given indication and mechanism of action (MOA). Discount rate is estimated quarterly by Gormsen and Huber (2023) for public firms that disclose information about the discount rate they apply in their investment decisions in earnings calls with analysts. Our sample includes all drugs that enter Phase 1 clinical development. Robust standard errors are in parentheses, and *** p<0.01, ** p<0.05, * p<0.1.

Table 5: Relation Between Revenue and Novelty, for High and Low Future Value Parameters

	(1) Revenue	(2) Revenue	(3) Revenue
Low Competition × Novelty	439.4*		
	(235.8)		
High Competition × Novelty	939.4**		
	(371.9)		
Low Exp. Successors × Novelty		506.9**	
		(218.9)	
High Exp. Successors × Novelty		95.35	
		(220.2)	
Low Discount Rate × Novelty			-298.8
			(463.8)
High Discount Rate × Novelty			771.9*
			(448.3)
Observations	352	352	82
R-squared	0.335	0.321	0.255
Launch Year FE	YES	YES	YES
Indication FE	YES	YES	

Notes: Table 5 shows the relationship between novelty and the focal drug's average annual revenue, interacting novelty with the median splits (low vs. high) of each measure of future value. Expected successors is calculated based on the entry year, disease indication (ICD-9), and project entry order into the biological pathway for a given development project. Competition is estimated as the log of recent entry (last five years) by competing firms into a given indication and mechanism of action (MOA). Discount rate is estimated quarterly by Gormsen and Huber (2023) for public firms that disclose information about the discount rate they apply in their investment decisions in earnings calls with analysts. Columns 1 and 2 in Panel B control for the stock of total entry to-date in the given drug class (indication-MOA) and novelty × that level of entry. Column 2 further controls for the count of entry by other firms into that drug class to-date. The sample size varies in each column based on the number of drugs we are able to match to the given measure, but focuses on the sample of FDA approved drugs. We exclude disease indication fixed effects in Column 3 of Panel B due to power limitations. Robust standard errors are in parentheses, and *** p<0.01, ** p<0.05, * p<0.1.

Table 6: Development Thresholds, by Novelty

VARIABLES	(1) Entered Phase 1	(2) Entered Phase 1	(3) Revenue if Approved	(4) Revenue if Approved
Novelty Score	-0.363***	-0.270***	692.7***	515.2***
	(0.0208)	(0.0221)	(117.3)	(149.5)
Observations	9,451	9,384	551	490
R-squared	0.103	0.186	0.195	0.379
Drug Cohort Year-Qtr FE	YES	YES	YES	YES
Lead Indication FE		YES		YES

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Notes: Columns 1 and 2 show the relationship between drug novelty and the firm's development decision, as defined by the drug entering Phase 1 clinical trials. The sample in Columns 1 and 2 consists of all drugs that are observed in Cortellis data for US pre-clinical development. In Panel B, we present binned scatterplots of the relation between novelty and average annual direct revenues, for the subset of drugs that are approved in the US. All specifications include drug development cohort fixed effects, and Columns 2 and 4 additionally include fixed effects for the lead indication (first disease ICD-9 for which the drug was developed).

Table 7: Drug Novelty: Progression by Phase—excluding successors of launched drugs

VARIABLES	(1) Phase 1–2	(2) Phase 1–2	(3) Phase 2–3	(4) Phase 2–3	(5) P3–Launched	(6) P3–Launched
Novelty Score	-0.116***	-0.0679	-0.154***	-0.120**	-0.0749	-0.0869
	(0.0412)	(0.0449)	(0.0541)	(0.0584)	(0.0870)	(0.0970)
Observations	3,094	3,028	2,219	2,150	929	866
R-squared	0.117	0.190	0.119	0.229	0.201	0.385
Drug Cohort Year-Qtr FE	YES	YES	YES	YES	YES	YES
Lead Indication FE		YES		YES		YES

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Notes: Table 7 presents the relationship between a drug candidate's novelty and its probability of progressing through clinical trials (Phase 1 to Phase 2; Phase 2 to Phase 3; Phase 3 to approval). The sample consists of all drug candidates that enter Phase 1 development in the United States, excluding incremental drugs that are associated with approved prior drugs. All regressions include drug year-quarter of development fixed effects. Columns 2, 4, and 6 additionally include fixed effects for the first indication (ICD-9) for which the drug entered development.

Table 8: Development Thresholds by Novelty—excluding successors of launched drugs

VARIABLES	(1) Entered Phase 1	(2) Entered Phase 1	(3) Revenue if Approved	(4) Revenue if Approved
Novelty Score	-0.335***	-0.237***	709.8***	231.9
	(0.0304)	(0.0315)	(245.4)	(375.8)
Observations	8,070	7,998	360	293
R-squared	0.084	0.172	0.199	0.469
Drug Cohort Year-Qtr FE	YES	YES	YES	YES
Lead Indication FE		YES		YES

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Notes: Appendix Table 8 is analogous to Table 6, but excluding outcomes for incremental drugs associated with successfully marketed predecessors. Columns 1 and 2 show the relationship between drug novelty and the firm's development decision, as defined by the drug entering Phase 1 clinical trials. In Panel B, we present binned scatterplots of the relation between novelty and average annual direct revenues, for the subset of drugs that are approved in the US. All specifications include drug development cohort fixed effects, and Columns 2 and 4 additionally include fixed effects for the lead indication (first disease ICD-9 for which the drug was developed).

APPENDIX

A Additional details on model

A.1 Decomposition of firm's expected profits in Expression (3.2)

Consider a drug (in the first or second period) that has been revealed to have revenue $\tilde{R}$ (R or R_j), and for which the firm believes that the probability of success (S or S_j) is $\tilde{\pi}$. Let the direct payoff within that period from making the initial development decision $\tilde{D}^1$ (D^1 or D_j^1), gross of the development cost C^1, be given by $V(\tilde{R}, \tilde{\pi})$.

If there are $M = 1$ development phases, then the firm makes no further decisions about whether to develop the drug before the success or failure is revealed. In this case, $V(\tilde{R}, \tilde{\pi}) = \tilde{\pi}\tilde{R}$.

If there are $M \geqslant 2$ development phases, then the firm makes additional decisions of whether to proceed. In particular, the firm optimally proceeds with the next round of development, choosing $\tilde{D}^2$ (D^2 or D_j^2) equal to 1 after observing signal $\tilde{\sigma}^1$ (σ^1 or σ_j^1) equal to g, if and only if it plans on proceeding with every other development phase conditional on continued positive signals g. So there is essentially only a single decision to make, over $\tilde{D}^2$ conditional on $\tilde{\sigma}^1 = g$. We can therefore write V (for $M = 1$ or $M \geqslant 2$) as

$$V(\tilde{R}, \tilde{\pi}) \equiv \max_{\tilde{D}^2 \in \{0,1\}} \tilde{D}^2 \cdot \left(\tilde{\pi}(\tilde{R} - \sum_{t=1}^{M-1} C^{t+1}) - (1 - \tilde{\pi}) \sum_{t=1}^{M-1} \left(\prod_{s=1}^{t} (1 - q^t) \right) C^{t+1} \right). \tag{14}$$

Lemma A.1. *V satisfies the following properties.*

1. *For any $\tilde{\pi} \in (0, 1)$ and $\tilde{R} \geqslant 0$, it holds that $V(\tilde{R}, \tilde{\pi}) \leqslant \tilde{R}$.*
2. *For any $\tilde{\pi} \in (0, 1)$ and $\tilde{R} \geqslant 0$, it holds that $V(\tilde{R}, \tilde{\pi}) > C^1$ if $\tilde{R} > \sum_{t=1}^{M} C^t / \tilde{\pi}$.*
3. *For any $\tilde{\pi} \in (0, 1)$, it holds that $V(\tilde{R}, \tilde{\pi})$ is weakly increasing in $\tilde{R}$, with $V(\tilde{R}, \tilde{\pi})$ strictly increasing in $\tilde{R}$ if $V(\tilde{R}, \tilde{\pi}) > 0$.*
4. *For any $\tilde{R} \in (0, 1)$, it holds that $V(\tilde{R}, \tilde{\pi})$ is convex and weakly increasing in $\tilde{\pi}$, with $V(\tilde{R}, \tilde{\pi})$ strictly increasing in $\tilde{\pi}$ if $V(\tilde{R}, \tilde{\pi}) > 0$.*

Proof of Lemma A.1. When $M = 1$ and $V_1^N = \pi^N R$, all of these properties are immediate. So, suppose that $M \geqslant 2$, in which V_1^N is given by (14). We now show the desired properties.

1. Immediate from (14).
2. V_1^N is bounded below by the expression in (14) with the max over $\tilde{D}^2$ replaced by $\tilde{D}^2 = 1$. The expression with $\tilde{D}^2 = 1$ is in turn bounded below by $\tilde{\pi}R - \sum_{t=1}^{M-1} C^{t+1}$.
3. The maximand of (14) is weakly increasing in $\tilde{R}$ for each $\tilde{D}^2$, and is strictly increasing if $\tilde{D}^2 = 1$. Moreover, if $V(\tilde{R}, \tilde{\pi}) > 0$, it must be that the expression is maximized by $D^2 = 1$.

4. The maximand of (14) is constant in $\tilde{\pi}$ if $\tilde{D}^2 = 0$. If this expression is maximized by $\tilde{D}^2 = 1$, then it must be that $\tilde{R} - \sum_{t=1}^{M-1} C^{t+1} > 0$, in which case the expression is strictly increasing, and linear, in $\tilde{\pi}$. The maximized expression is convex because it is a maximum over a constant function and a linear function. □

We next observe that $V(\tilde{R}, \tilde{\pi})$ can be used to derive the terms in decomposition (3.2) of $V_1^N(R)$, W_2^N, and $\Delta_2^{N=1}$.

For the decision in period 1, let π_1^N be the belief on success at the time the firm faces the initial development choice D^1. We have that $\pi_1^{N=1} = \pi$ and $\pi_1^{N=0} = \pi/(\pi + (1-\pi)(1-q^0))$, with $\pi_1^{N=0} > \pi_1^{N=1}$. With this notation, we can now write

$$V_1^N(R) = V(R, \pi_1^N). \tag{15}$$

Note that part 1 of Lemma A.1 implies that, for each N, there are values of R in the support of F_R for which $V_1^N < C^1$. Part 2 implies that, for each N, there are values of R in the support of F_R for which $V_1^N > C^1$. Part 4 confirms the claim in the body of the paper that $V_1^N(R)$ is higher for $N = 0$ (recalling that $\pi_1^{N=0} > \pi_1^{N=1}$).

Continuing on, we have $W_2^{N=0} = 0$, as the second-period payoff conditional on $N = 0$ was normalized to 0. The term $W_2^{N=1}$ then gives the expected discounted second-period payoff for $N = 1$ when $D^1 = 0$:

$$W_2^{N=1} = \mu_Q \alpha \mathbb{E}_{\tilde{R} \sim F_{2R}} \max\{V(\tilde{R}, \pi_2) - C^1, 0\} \tag{16}$$

Finally, to determine the payoff for $N = 1$ when $D^1 = 1$, observe that for each successor drug that arrives, the initial signal takes the probability of success from π_2 to either $\tilde{\pi} = 0$ with probability $(1-\pi_2)q^0$, or $\tilde{\pi} = \pi_2/(\pi_2 + (1-\pi_2)(1-q^0)) > \pi_2$ with probability $(\pi_2 + (1-\pi_2)(1-q^0))$. In the former case, the payoff for that successor drug will be 0; in the latter case, it may be positive. So the expected payoff at the second period when $N = 1$ and $D^1 = 1$ is

$$\beta \mu_Q \alpha (\pi_2 + (1-\pi_2)(1-q^0)) \mathbb{E}_{\tilde{R} \sim F_{2R}} \max\{V(\tilde{R}, \pi_2/(\pi_2 + (1-\pi_2)(1-q^0))) - C^1, 0\}. \tag{17}$$

Hence, $\Delta_2^{N=1}$ is equal to expression (17) minus $W_2^{N=1}$, all divided by coefficient $\beta \mu_Q \alpha$. We have that $\Delta_2^{N=1}$ is positive because better information – a mean-preserving spread of the belief $\tilde{\pi}$ – improves decisionmaking; this can be seen in the convexity of $V(\tilde{R}, \tilde{\pi})$ in π from Lemma A.1 part 4. The payoff is strictly positive because F_{2R} has large enough support that $V(\tilde{R}, \pi_2/(\pi_2 + (1-\pi_2)(1-q^0)))$ is above C^1 with positive probability, and therefore the expectation of the maximand in (17) is positive; and because, for each $\tilde{R}$, it holds that $V(\tilde{R}, 0) = 0 < C^1$. Those facts imply that $\mathbb{E}_{\tilde{R} \sim F_{2R}} \max\{V(\tilde{R}, \tilde{\pi}) - C^1, 0\}$ is convex and is not linear over $\tilde{\pi} \in [0, \pi_2/(\pi_2 + (1-\pi_2)(1-q^0))]$, so the mean-preserving spread of beliefs from an interior point π_2 to these edges has strictly positive value.

A.2 The firm's strategy in period 1

The following result confirms that – thanks to Assumption 1 – the firm's optimal strategy in the first period is as described in the body of the paper: on the equilibrium path, once development has begun, the firm proceeds with development when it sees a positive signal. By the equilibrium path, we mean at histories that the firm reaches with positive probability (conditioning on N and R) given its strategy. Note that this lemma is only relevant if $M > 1$, since there are no development choices at $t \geqslant 1$ if $M = 1$.

Lemma:. *Fix some revenue R and novelty N. If the firm enters development phase $t \in \{1, ..., M-1\}$ on path during the first period, then the firm optimally chooses $D^{t+1} = 1$ if and only if $\sigma^t = g$.*

Given this lemma, we can summarize the firm's strategy in the first period through the single number of a revenue cutoff, $\overline{R}^N$, at each novelty value N. When revenue R is weakly above the cutoff, the firm develops the drug conditional on pre-clinical testing ($D^1 = 1$); when R is below the cutoff, the firm does not.

Proof of Lemma A.2. Fix N and R, and some $t \in \{1, ..., M-1\}$ that the firm may reach on path.

If $\sigma^t = b$, it is clear that the firm optimally chooses $D^{t+1} = 0$: there is a positive cost C^{t+1} of proceeding with the drug development, and no possible benefit.

Let us now show that the firm does proceed when $\sigma^t = g$. First note that the firm has no benefit from mixing; there will always be a pure strategy that is optimal. So, we restrict attention to pure strategies. We now show the result by contradiction. Suppose that, after arriving to this history on the equilibrium path, the firm chooses $D^{t+1} = 0$ even if $\sigma^t = g$. That means that the firm never successfully develops a drug with this realization of N and R, as the firm also chooses $D^{t+1} = 0$ when $\sigma^t = b$. Hence, the cost of choosing $D^1 = 1$ is equal to $C^1 > 0$, and the lifetime benefit is at most equal to second-period benefit from development of $N\beta\mu_Q\alpha\Delta_2^N$ (the benefit can be less than this value if the firm pays additional development costs in periods prior to t). That is, if $N = 0$, then the benefit is zero, and if $N = 1$, the benefit is $\beta\mu_Q\alpha\Delta_2^N$. Applying Assumption 1, the benefit is less than the cost even if $N = 1$, and so the firm chooses $D^1 = 0$. Therefore this history is in fact not on path, yielding the desired contradiction. □

A.3 Proofs

Proof of Proposition 3.1. Recall that the prior probability of $S = 1$ is π, regardless of drug novelty; the probability of $\sigma^t = g$ conditional on $S = 1$ is 1; and the probability of $\sigma^t = g$ conditional on $S = 0$ is $1 - q^t$.

For novel drugs ($N = 1$), Bayes' Rule tells us that the probability of $S = 1$ given the arrival at development phase t (supposing that the firm follows a strategy consistent with Lemma A.2) is

$$Pr(S = 1|D^t = 1, N = 1)\frac{\pi}{\pi + (1-\pi)\prod_{s=1}^{t-1}(1-q^t)} \tag{18}$$

For incremental drugs ($N = 0$), there is an additional signal σ^0, and so the corresponding probability of $S = 1$ given the arrival at development phase t is

$$Pr(S = 1|D^t = 1, N = 0) = \frac{\pi}{\pi + (1-\pi)\prod_{s=0}^{t-1}(1-q^t)}. \tag{19}$$

We can see that $Pr(S = 1|D^t = 1, N)$ is larger for $N = 0$ than $N = 1$. Plugging in $t = M$ implies the second statement of the Proposition.

Furthermore, under the strategy described by Lemma A.2, the probability of proceeding to development phase $t + 1$ when $t < M$ – that is, $Pr(D^{t+1} = 1|D^t = 1, N)$ – is the probability that $\sigma^t = g$:

$$Pr(D^{t+1} = 1|D^t = 1, N) = Pr(S = 1|D^t = 1, N) + (1 - Pr(S = 1|D^t = 1, N))(1 - q^t). \tag{20}$$

This expression is increasing in $Pr(S = 1|D^t = 1, N)$, implying the first statement of the proposition. □

Proof of Proposition 3.2. The likelihood of developing a drug of type N conditional on entering pre-clinical testing is $Pr(D^1 = 1|P = 1, Y) = 1 - F_R(\overline{R}^N)$, which is weakly decreasing in $\overline{R}_N$. The revenue conditional on successful development for a drug of type N is $\mathbb{E}_{R\sim F_R}[R|R \geqslant \overline{R}^N]$, which is weakly increasing in $\overline{R}^N$. □

Proof of Proposition 3.3. In equilibrium, a drug of type N is developed conditional on entering pre-clinical testing if and only if $R \geqslant \overline{R}^N$; this probability weakly decreases in $\overline{R}^N$. Moreover, the distribution of revenues conditional on success is the truncation of $R \sim F_R$ to values for which $R \geqslant \overline{R}^N$; the expectation $\mathbb{E}_{R\sim F_R}[R|R \geqslant \overline{R}^N]$ is weakly increasing in $\overline{R}^N$. So, for both parts of the Proposition, the results on probability of development conditional on entering pre-clinical testing and on expected revenue conditional on successful development will follow from the comparative static on $\overline{R}^N$.[21]

Recall the decomposition (3.2) of the firm's expected profit as a function of the choice D^1, where the three parameters do not appear in $V_1^N(R)$ or $\Delta_2^{N=1}$. The threshold $\overline{R}^N$ is the value of R at

[21] If $\overline{R}^N$ is above or below the support of the distribution, or is in a "hole" in the distribution, then the comparative statics on this probability and expected revenue hold weakly rather than strictly.

which the expression (3.2) is constant over $D^1 \in \{0, 1\}$. Hence, $\overline{R}^N$ is defined by

$$V_1^N(\overline{R}^N) - C^1 + N\beta\mu_Q\alpha \cdot \Delta_2^{N=1} = 0. \tag{21}$$

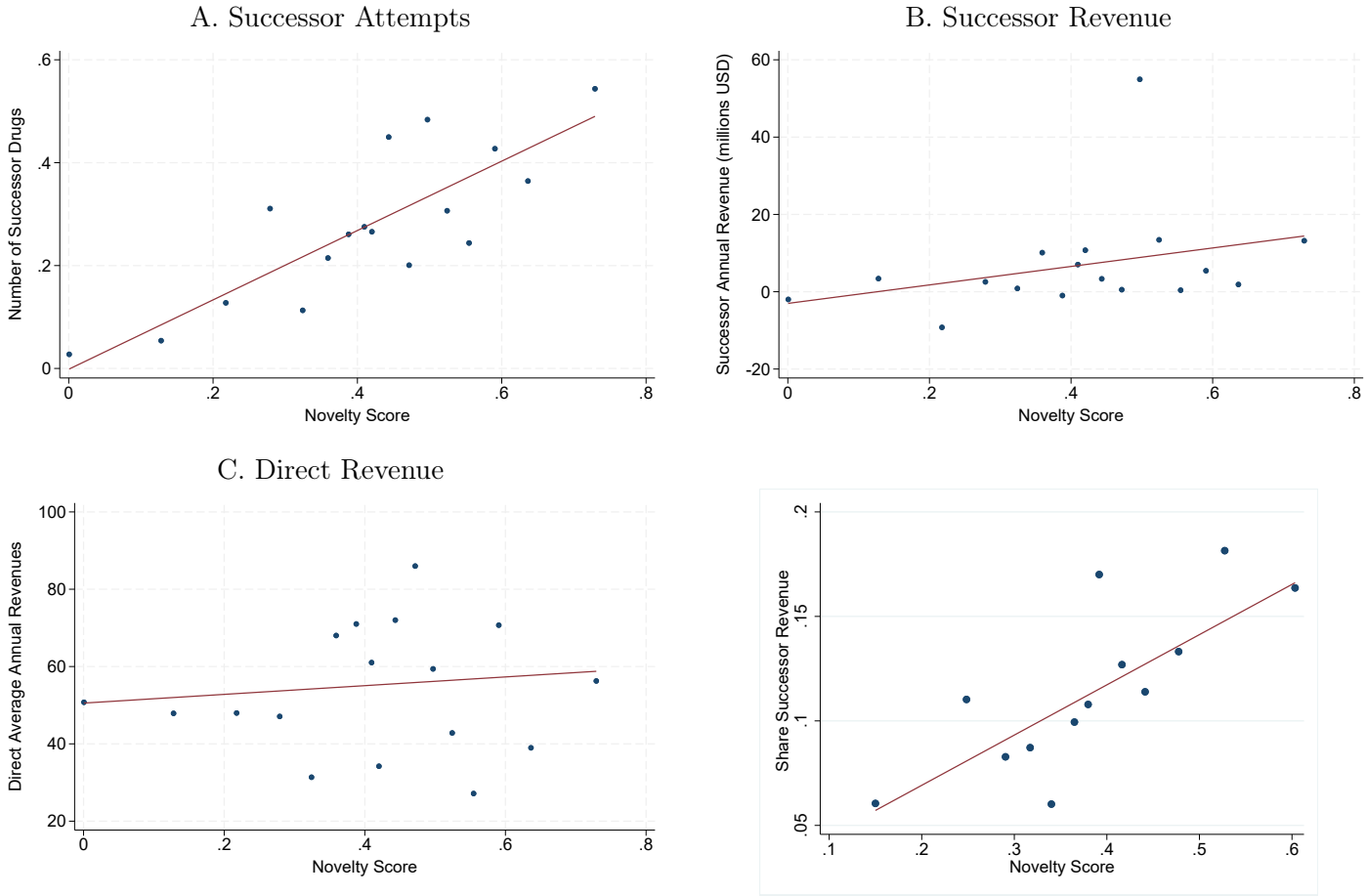
Moreover, recall that for each N, it holds that $V_1^N(R)$ is continuous, and is strictly increasing in R when $V_1^N(R) > 0$; $V_1^N(0) = 0$; the range of $V_1^N(R)$ given $R \sim F_R$ extends to strictly above C^1; and $\Delta_2^{N=1} > 0$. Assumption 1 further states that $C^1 + N\beta\mu_Q\alpha \cdot \Delta_2^{N=1} < 0$. So for each N, there exists a unique $\overline{R}^N > 0$ satisfying the above equation.

1. For $N = 0$, Equation (21) is independent of β, μ_Q, and α, and thus there is a unique solution in $\mathbb{R}_{++}$ that is independent of these parameters.

2. For $N = 1$, the equation (21) depends on β, μ_Q, and α only through the product $\beta\mu_Q\alpha$. Because the LHS is strictly increasing in $\beta\mu_Q\alpha$, it holds that $\overline{R}^N$ must strictly decrease in this term in order to maintain (21). □

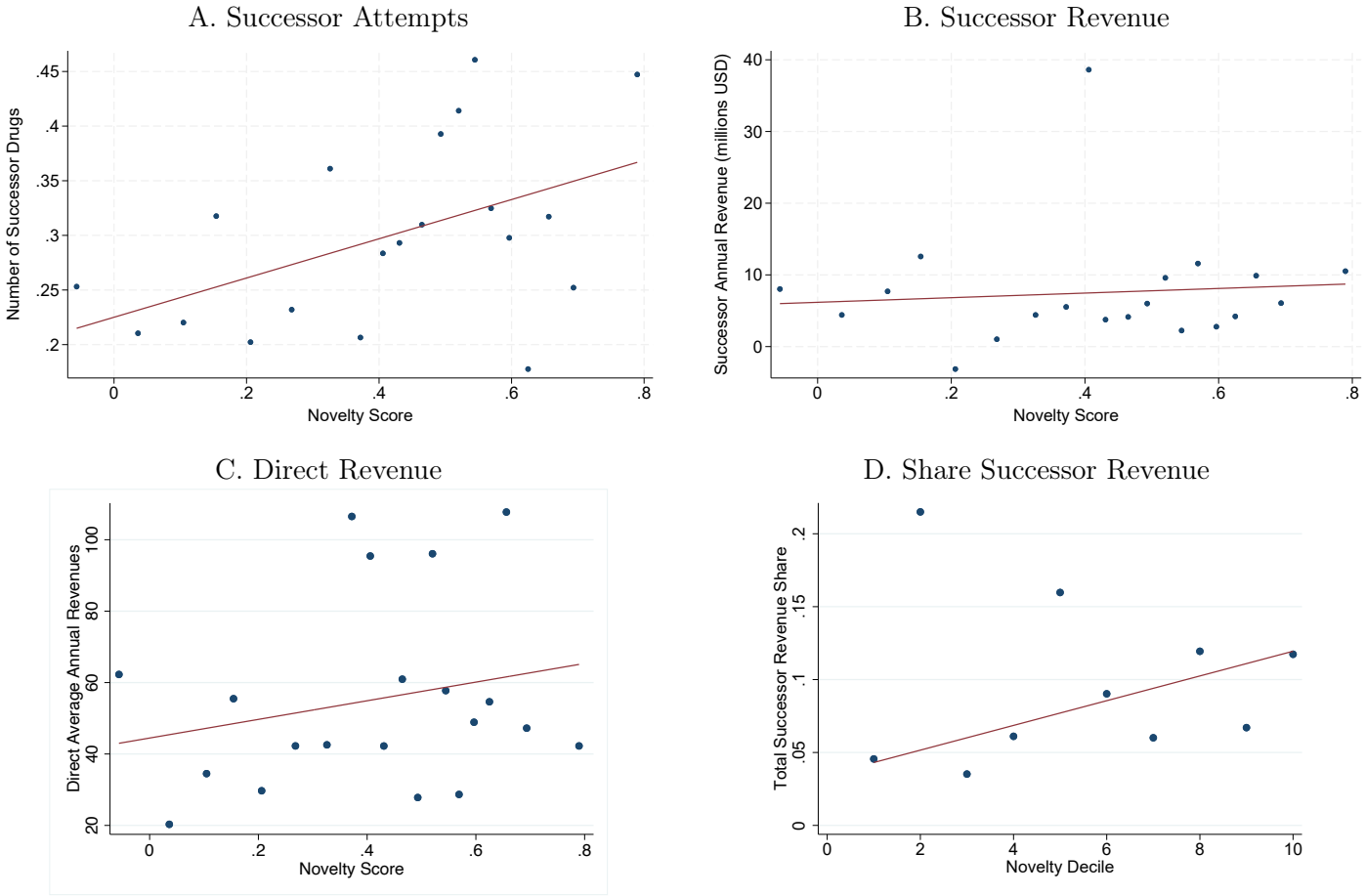
B Appendix Figures

Figure A.1: Successor Revenues, by Novelty (w/Firm Fixed Effects)



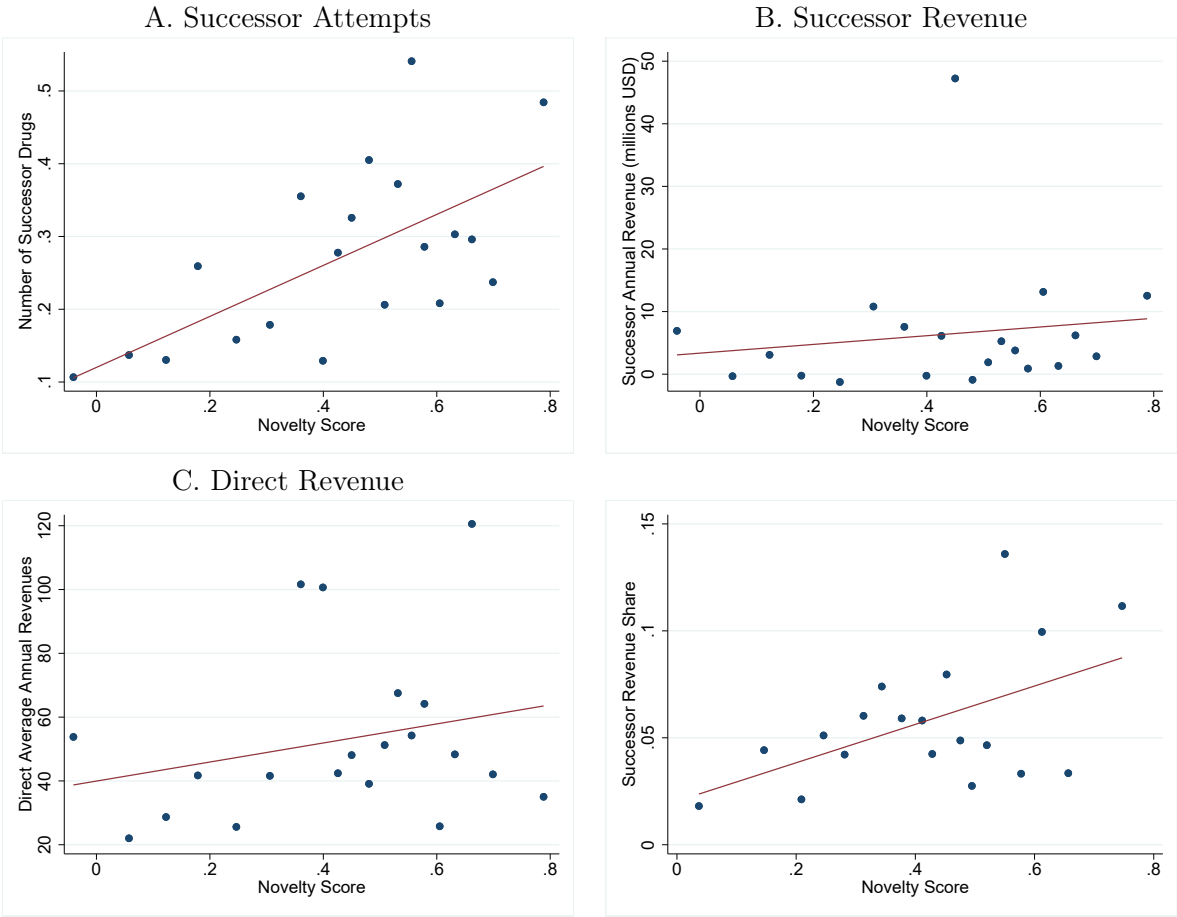
Notes: Figure A.1 presents binned scatterplots of the relationship between a drug candidate's novelty and measures of successor activity and revenues, at the individual drug level. All specifications include controls for a focal drug's quarter of development, lead disease indication, and developer firm fixed effects. The sample includes drugs that enter clinical development in the United States.

Figure A.2: Successor Revenues, by Novelty, Partial Credit Approach



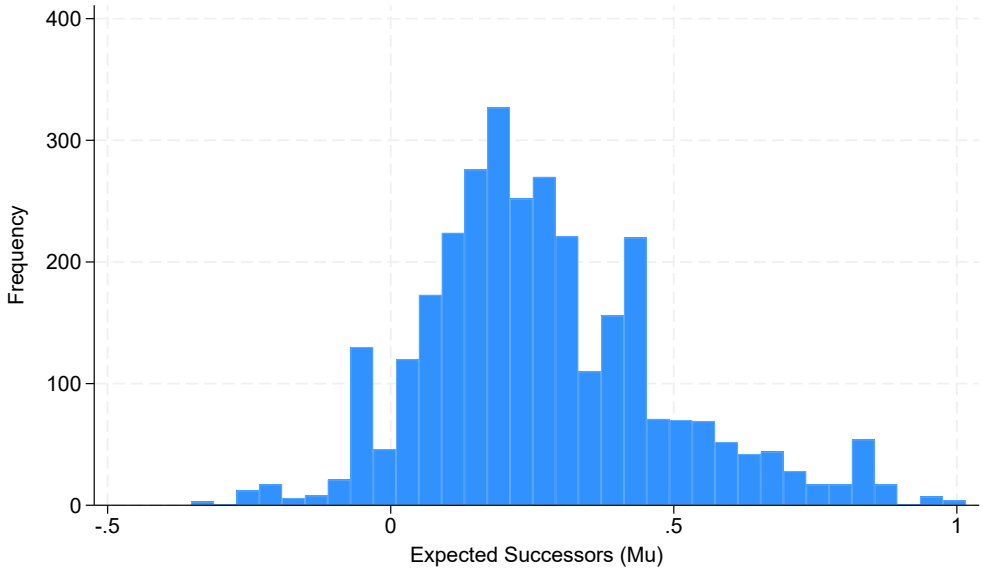
Notes: Figure A.2 replicates Figure 3, but using a partial credit attribution method. This approach gives partial credit to highly similar (Tanimoto score > 0.75) predecessors, with greater partial credit going to earlier predecessors. Panel C is the same as in Figure 3 because it graphs direct revenue and does not depend on successor credit allocation.

Figure A.3: Successor Revenues, by Novelty (without new formulations/routes)



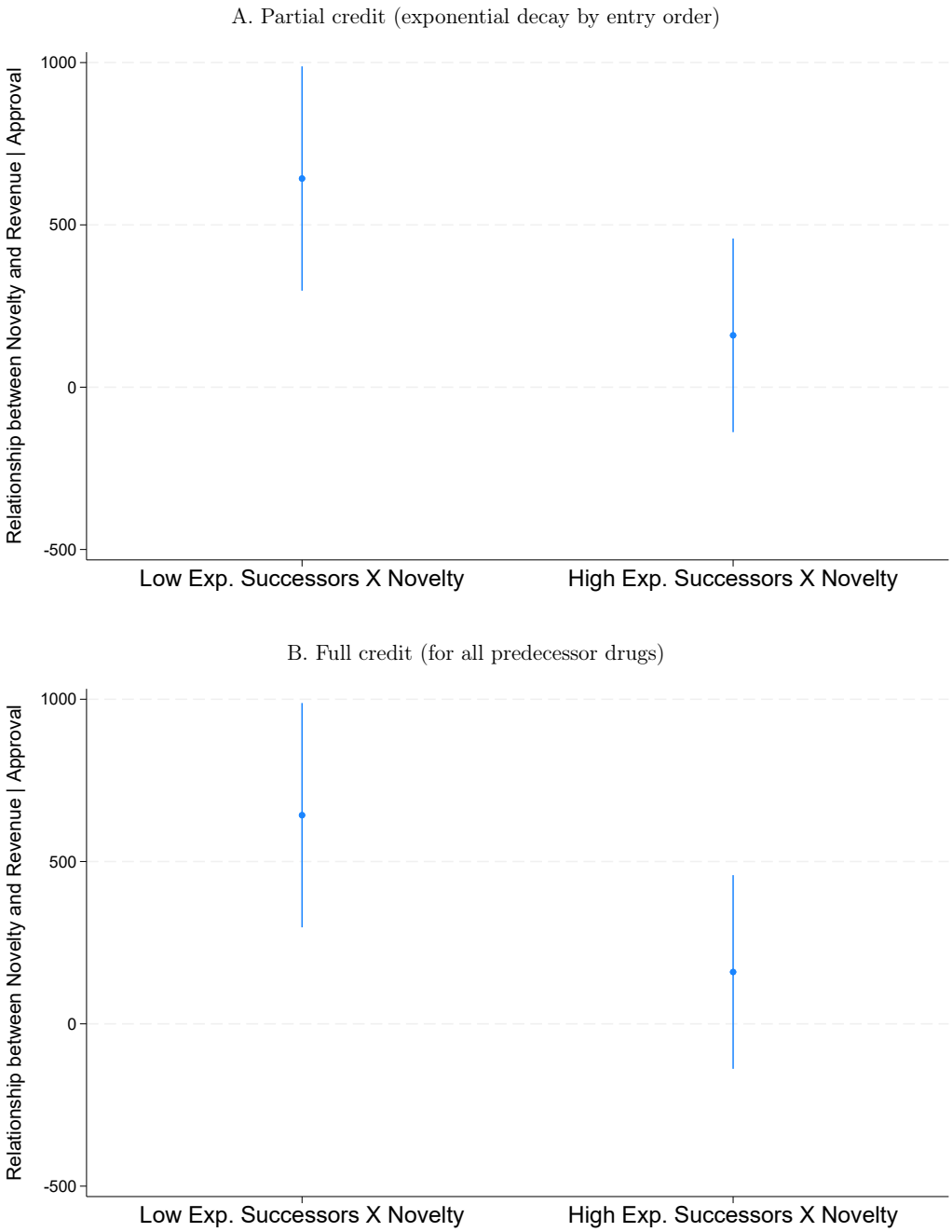
Notes: Figure A.3 presents binned scatterplots of the relationship between a drug candidate's novelty and measures of successor activity and revenues, at the individual drug level. All specifications include controls for a focal drug's quarter of development, and lead disease indication. The sample includes drugs that enter clinical development in the United States. In this version, we remove from the set of drugs that appear to be new formulations or new route of administration versions of existing drugs developed by the same firm. We classify 23% of our successor sample as potentially new formulations or new route versions of prior drugs. Our classification method blends text-matching a long-list of terms in Cortellis's drug names like "extended release," "controlled release," "gel patch," "transdermal," "sublingual," "oral formulation," etc., combined with categorization from ChatGPT (4o) in which we asked the LLM to compare the successor and predecessor's names and classify them as distinct, new formulations, or new routes of administration. We do not code particular drugs as potential new routes or new formulations if we also code that successor drug as a combination therapy (more than one active ingredient). Notably, less than half of the potential new formulation/route drugs (8% of total successors) were also assigned to the same firm as their predecessor—suggesting that most of the potential new route/formulation drugs are indeed distinct competitor follow-ons and likely enter post-patent expiration or market exclusivity periods.

Figure A.4: Distribution of Expected Successors



Notes: Appendix Figure A.4 shows the distribution of our measured of expected successors (μ_Q). We estimate μ_Q for all drugs entering clinical development by first regressing the number of total observed successors (for which the focal drug was the earliest novel predecessor) on the the development entry order for the associated biological target, and fixed effects for the disease market (ICD-9 code) and phase 1 entry year. We use three variables to capture entry order, each of which is the earliest development entry order for a different "level" of the Cortellis Investigational Drugs target ontology. For example, the drug losartan was first developed for high blood pressure. Losartan biological mechanism of action is blocking the angiotensin II type 1 receptor. The Cortellis targets ontology represents that target on a pathway "tree," where each branch represents increasing granularity of classification. Here, the code would be PTG-REC-GPR-00A-PEP-ANG-002-ANT-001, representing that the target is a protein, receptor, g-protein coupled receptor, Class A, activated by a peptide, of the angiotensin II family, and type 1 (since there are two types of angiotensin II receptors). We use entry order into the 5th, 6th and 7th levels of the ontology in our estimation. Losartan was the first angiotensin and angiotensin II targeting drug in our development data (6th and 7th level), but the 22nd g-protein coupled receptor class A peptide-activated targeting drug in our data (5th level)—suggesting that the specific mechanism of action was novel, but the general class of targets was likely established as a fruitful area for drug development. We convert entry order for each level into deciles, and use indicator variables for each decile and level in our prediction regression.

Figure A.5: Novelty and Revenue, by Alternative Expected Successors Measures



Notes: Figure A.5 recreates Figure 8 with alternatives measures of expected successors. Panel A assigns credit for successors decreasing exponentially based on how many chemically similar drugs (to the successor) entered prior to the focal drug. Panel B gives full credit to each focal drug for all successors, regardless of whether prior drugs were chemically similar.

C Appendix Tables

Appendix Table A.1: Novelty and Successor Value, Alternative Definitions of Novelty

VARIABLES	(1) # Successors	(2) Successor Revenue	(3) Successor Rev. Share	(4) # Successors	(5) Successor Revenue	(6) Successor Rev. Share
Pioneer Drug in Target	0.901***	92.12**	0.0943**			
	(0.256)	(41.94)	(0.0422)			
Pioneer Drug in Target-Action				0.388***	31.57**	0.0577**
				(0.109)	(16.01)	(0.0267)
Observations	3,321	3,321	781	3,321	3,321	781
R-squared	0.166	0.132	0.381	0.160	0.127	0.379
Drug Cohort Year-Qtr FE	YES	YES	YES	YES	YES	YES
Phase I Year-Qtr FE	YES	YES	YES	YES	YES	YES
Lead Indication FE	YES	YES	YES	YES	YES	YES

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Notes: Appendix Table A.1 presents the relationship between a drug candidate's novelty (defined in two alternative ways) and the number of follow-on successors, successor revenue, and share of direct revenue. All revenue figures, both direct and successor, are defined as average annual revenues for the time that the approved drug appears in Evaluate Pharma. The sample consists of all drug candidates that enter Phase 1 development in the United States. Pioneer Drug in Target is an indicator for whether a drug attempts to impact a new biological object (e.g. a protein) while Pioneer Drug in Target-Action is an indicator for whether a drug is the first to attempt to impact a biological object in a particular way (e.g. inhibit the expression of a protein).