Many are called, few are chosen: the role of science in drug development decisions

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Many are called, few are chosen: the role of science in drug development decisions

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Abstract
Pharmaceutical firms are extremely selective in deciding which patented drug candidates are taken up into clinical development, given the high costs and risks involved. We argue that the scientific base of drug candidates, and who was responsible for that scientific research, are key antecedents of take-up into clinical trials and whether the patent owner ('internal take-up') or another firm ('external take-up') leads the clinical development effort. We hypothesize that patented drug candidates that refer to scientific research are more likely to be taken up in development, and that in-house conducted scientific research is predominantly associated with internal take-up due to the ease of knowledge transfer within the firm. Examining 18,360 drug candidates patented by 136 pharmaceutical firms we find support for these hypotheses. In addition, drug candidates referring to in-house scientific research exhibit a higher probability of eventual drug development success. Our findings underline the importance of a 'rational drug design' approach that explicitly builds on scientific research. The benefits of internal scientific research in clinical development highlight the potential downside of pervasive organizational specialization in the life sciences in either scientific research or clinical development.

Keywords R&D · Patents · Science · Drug development · Pharmaceutical industry

JEL Classification O31 · O32

1 Introduction

There is a long-standing interest in the innovation literature to better understand the link between scientific research and technological development in order to justify the large public investments in scientific research (Cockburn and Henderson, 2001; Calderini

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et al., 2007; Baycan & Stough, 2013), to explain private sector investments in scientific research (Arora et al., 2018, 2021; Rosenberg, 1990) and to understand the drivers of technological advancement and economic growth (Pavitt, 1991; Zucker & Darby, 1996; Jones, 1995; Griliches, 1986). At the firm level, past research has devoted a great deal of attention to the relationship between science and firms' technological performance measured through patents, showing a positive relation for scientifically active firms and companies collaborating with academia (e.g. Cockburn & Henderson, 1998; Della Malva et al., 2015; Fabrizio, 2009; Fleming & Sorenson, 2004; Gambardella, 1992).

However, there is still a long way to go from a patented invention to a successful innovation. The pharmaceutical industry is a case in point. To obtain market approval, a patented drug candidate needs to successfully pass efficacy and safety tests during clinical trials on healthy individuals (phase I) and patients (phase II and phase III). This clinical development is not only enormously costly but also very risky, with only 20% of trials being successful and obtaining regulatory approval (PPD, 2017). In the face of this daunting development process, firms are highly selective with respect to the patented drug candidates that are taken up in development. On average, firms single out only five out of 250 discovered drug candidates for further development, of which only one will eventually succeed (Campbell, 2005; PPD, 2017). Despite firms' extreme selectivity at this initial stage of the drug development process, this selection decision has received scant attention in the literature. In this paper, we examine the nature and consequences of this selection decision, and the particular role of the scientific antecedents of patented drug candidates.

When firms decide whether to commence the drug development process, they need to weigh the high costs of developing a drug candidate with the considerable but highly uncertain benefits after market approval (Adams & Brantner, 2006; Arora et al., 2009; DiMasi et al., 2003). Scientific insights are considered to be an important potential input for this decision: to increase the efficiency of the drug development process and to more accurately predict the chances of success before making large investments in clinical trials, practitioners and industry experts have emphasized the importance of science (Schuhmacher et al., 2016, p123). In particular, failed drug development projects often suffer from mismatches between disease, molecular compound, target group and clinical techniques, issues that can potentially be foreseen and even resolved when drug candidates are strongly grounded in scientific research (Kola & Landis, 2004; Barrenho, Miraldo and Smith, 2013; Cook et al., 2014; Hay et al., 2014; Waring et al., 2015; Chiou et al., 2016).

The key premise in this paper is that the origins of a drug candidate in scientific research ("R") may have important consequences for a pharmaceutical firm's decision whether to take it into clinical development ("D"). We hypothesize that drug candidates that have their origins in science have a higher chance to be successful in clinical development and are therefore more likely to be taken up into clinical development. A related and crucial aspect of the scientific research underlying the drug candidate is whether it matters who takes up the drug into development. The developer can be either the firm holding the patent on the drug candidate or another pharmaceutical firm, through a transaction in the market for technology.

Handing over a drug candidate may be grounded in a division-of-labor logic that argues that research and development require distinct resources and capabilities, such that a single firm is unlikely to be well equipped to perform both tasks (Arora & Gambardella, 1994). Conversely, we argue that there are also reasons for vertically integrating research and development activities within the same firm. Integration of "R" and "D" allows for a more efficient transfer of scientific knowledge by facilitating

interactions and exchange between researchers and developers. This is especially the case when the firm's scientists have been directly involved in the generation of a drug candidate's scientific background, resulting into a unique and deep understanding of relevant scientific knowledge, which is likely to be a critical factor in the development success of a drug candidate.

Empirically, we consider 18,360 patented drug candidates of 136 major biopharmaceutical firms and analyze whether or not these were taken up into clinical trials. We also examine which drug candidates entering clinical trials finally were successful and received market approval. In order to explore the factors at play in drug development decisions and the role of scientific research we also conducted eight interviews with senior managers from six pharmaceutical companies, most of whom also had prior hands-on research experience, in September–November 2021. The interviews illustrate the practical relevance of our arguments and helped inform the specification of the empirical model. The interviews were structured into three main parts, addressing the relevant sample of patents, the factors firms take into account when deciding whether to initiate a drug development project, and the overall role of science in drug development.

Our analysis confirms a strongly significant positive relationship between the likelihood of take-up into clinical development — by any firm — and the scientific background of the drug candidate, both for scientific research conducted by the patent owner ('internal science') and for scientific research conducted outside the patenting firm ('external science'). The patent-owning firm is more likely to take the drug candidate into clinical development — relative to another firm doing so —when it has performed the scientific research on which the drug candidate is based itself ('internal science'). We also find that in such circumstances – a drug candidate building on internal scientific research is taken up by the patent-owning firm—clinical development exhibits a higher success rate.

While these findings give a clear indication that vertical integration strategies may work, we also find evidence for a division-of-labor argument: the take-up of drug candidates by external developers is more likely when the patent-owning firm has a weaker track record and has less expertise in clinical development. Moreover, the volume of documented scientific research underlying a patented drug candidate, as indicated by the number of citations to scientific research, is associated with both a greater likelihood of external development and external development success. This exemplifies the importance of documented scientific research for the broader ecosystem of pharmaceutical firms.

Our findings confirm the important role of scientific research in drug development. While previous studies have shown the close relationship between scientific research and firms' patent performance (e.g. Cockburn & Henderson, 1998; Della Malva et al., 2015; Fabrizio, 2009; Fleming & Sorenson, 2004; Leten et al., 2022), our study highlights the important role of scientific research in the crucial decision to take patented drug candidates into clinical development. We also extend prior work on corporate investments in scientific research by showing that internal science does not only strengthens firms' absorptive capacity (Cockburn & Henderson, 1998; Gambardella, 1992) but also increases the likelihood of a successful in-house development trajectory from "R" to "D" and market introduction.

Our study contributes to the debate on the private value of internal investments by companies in scientific research. Arora and colleagues (2018 & 2021) document that firms have reduced their internal investment in scientific research over time. They attribute this 'shift away from science' to a decline in the private value of science due to the growth of technology markets for science-based inventions (Arora et al., 2018) and growing appropriation problems due to increases in product market competition and knowledge spillovers (Arora

et al., 2021). The findings of our study do however show that reducing investments in internal science may come at a cost for firms in terms of a less productive drug development process. While corporate investments in science declined significantly during the period 1980–2010, this decline seem to have stalled during the last decade (Arora et al., 2021), what can be considered as indicative that companies have come to appreciate the value of internal science again. Our findings also contribute new insights to the literature on the organization of corporate science and R&D and informs the recent debate on the increasing specialization in the life sciences industry (Cockburn, 2007; Arora et al., 2018, Arora et al., 2020). We suggest that a 'hard' separation between scientific research and drug development, that is, performing these activities in separate organizations, may increase the risk of foregone drug development opportunities and drug development success.

2 Background literature

2.1 Science-based drug discovery

Most pharmaceutical firms follow a science-based approach in drug discovery. In this approach, firms rely on scientific insights to understand the mechanisms that cause a certain disease, after which they search for drug candidates that inhibit these mechanisms (Pisano, 1997). In analyzing the case histories of the discovery of 21 important drugs, Cockburn and Henderson (1998) found that 14 of those drugs were discovered through 'fundamental scientific advances' or by 'mechanism-based screening'. A recent example of the importance of scientific research in drug discovery concerns the development of the messenger RNA (mRNA) COVID-19 vaccines by Pfizer-BioNTech and Moderna, which was the direct result of breakthrough scientific research by Katalin Karko and Drew Weissmann at the University of Pennsylvania on the functioning of mRNA-based vaccines (Franzoni et al., 2021).

Science-based drug discovery is however not the only possible path to a working drug. There are numerous examples of haphazard discoveries, such as lithium—originally used for the treatment of bladder stones but after John Cades' rather accidental discovery of its sedating effects also applied to treat psychiatric disorders—or the famous example of penicillin, where after a 2-week holiday Alexander Fleming found a mould was effective in wearing off Staphylococcus bacteria (Pharmacy Cormier, 2019; Times, 2016). Another, more deliberate, alternative to science-based drug discovery is the use of big data. An early example is aspirin, originally a simple painkiller. By integrating the information from electronic health records, post-marketing surveillance data, and pharmacological analysis, it was found to have potential as a treatment for colorectal cancer, resulting in a draft recommendation by the US Preventive Services Task Force in September 2015 (Qian et al., 2019). Finally, there are drugs that have been used clinically for many decades but without a clear scientific understanding of the mechanism of action. A well-known example is *acetaminophen*, a pain reliever and fever reducer (also known as *paracetamol*) that sells billions of doses every year. Despite attempts to unravel its mechanism by eminent scientists such as John R. Vane (the Nobel Laureate who cracked the mystery of aspirin's mechanism), it still is not entirely clear how it affects the central nervous system (Drahl, 2014).

2.2 Internal versus external drug development

The pharmaceutical industry has been characterized by an increasing division of labor, with universities and dedicated biotech firms focusing on research, while contract research organizations (CROs) focusing on clinical-trial support, and large pharmaceutical firms specializing increasingly in development. Coinciding with the evolution towards specialization, a flourishing market for technology has emerged, providing firms with the option to hand over patented drug compounds for which they lack the expertise to carry them through the clinical trial process or for which they do not see a strategic fit (Cockburn, 2004, 2007; Stuart et al., 2007; Arora et al., 2009, 2020b; Malik, 2011; Belderbos et al., 2016).

Handing over a patented drug candidate to another firm through the market for technology due to a lack of development expertise is grounded in the division-of-labor theory that argues that research and development require distinct resources and capabilities, such that a single firm is unlikely to be well equipped to perform both tasks (Arora & Gambardella, 1994; Arora et al., 2001). Empirical evidence indeed suggests that technology markets allow firms to capitalize on their respective competitive advantages in either research or development (Chesbrough & Chen, 2013; Gittelman & Kogut, 2003; Laursen et al., 2010; Leone & Reichstein, 2012).

On the other hand, there also appear to be substantial advantages of vertical integration, and in practice, large pharmaceutical firms do not only focus on development but also engage in scientific research (Arora et al., 2018, 2020). A benefit of integrating the development of drug candidates and the supporting scientific research within a single firm is the elimination of transaction costs incurred through transferring drug candidates via markets for technology (Teece, 1988). In particular, vertical integration helps to solve problems of opportunistic behavior when contracts are incomplete (Hart & Moore, 1990). In the pharmaceutical industry, R&D is characterized by long-term, risky projects entailing complex and sticky knowledge, and highly specialized work for which the quality may be difficult to monitor. These conditions call for considerable investments to realize an efficient knowledge transfer to the transaction partner (Agrawal, 2006; Thursby & Thursby, 2011; Ceccagnoli & Jiang, 2013; Klueter, Monteiro and Dunlap, 2017; Reinholt et al., 2011). The imperfections in the market for technology therefore render development of drug candidates by the patent owner a valid alternative (Cockburn, 2004; Arora & Gambardella, 1994; Cockburn, 2007).

3 Hypotheses

3.1 Scientific origins of drug candidates and their take-up in clinical development

Industry experts have called for a *"return and renaissance to scientific depth and scrutiny"* in drug development (Schuhmacher et al., 2016, p 123). They insist on the unique role of scientific research by explicitly acknowledging that it's only through understanding fundamental disease mechanisms that one can develop a novel targeted treatment, lest one "shoots in the dark" (Eichler et al., 2009; Sams-Dodd, 2013; Workman, 2015). This deep understanding originates from scientific research and occurs through theoretical examination and in-vitro or in-vivo research in the lab. By providing a deeper understanding of the mechanisms underlying

a particular disease, scientific research serves as a 'map' to the most fruitful directions in drug discovery (Fleming & Sorenson, 2004; Rosenberg, 1990). While the public sector is the largest producer of scientific research, pharmaceutical firms also invest significant amounts of money in scientific research (Arora et al., 2018). By doing so, pharmaceutical firms build up the necessary knowledge base to absorb externally conducted science and to guide their drug discovery activities towards high potential drug candidates (Leten et al., 2022).

Industry experts have emphasized the guiding role of scientific research, not only for finding a fit between disease, target and drug, but also for designing effective clinical trials that have to establish the best drug candidates for a specific disease (Kola & Landis, 2004; Waring et al., 2015; Barrenho, Miraldo, and Smith 2013; Cook et al., 2014; Chiou et al., 2016; Hay et al., 2014). The scientific research 'map' may not only steer drug discovery to global optima but may also lead to a smoother drug development trajectory for a given discovery (Della Malva et al., 2015; Fleming & Sorenson, 2004; Lim, 2004). Scientific insights can help to avoid problems with efficacy and safety, which explain half of all failures in drug development (Bhogal & Balls, 2008), by providing a better understanding how drugs can be administered effectively and safely. An example is the progressive insight on the important role of drug transport mechanisms, such as how they (fail to) penetrate through biological membranes. While this was long considered to be a merely biophysical problem that could be dealt with later in the development process, there is mounting evidence that scientific knowledge about transport proteins in a drug candidate allows making a much more accurate assessment of its odds of successful development (Dobson & Kell, 2008; Morgan et al., 2012).

Based on the above considerations we expect that scientific research can provide important insights into whether a patented drug candidate can be successful in the clinical development process. Hence, the scientific research origins of a patented drug candidate are likely to increase the probability that it is taken up in clinical development. Our interviews with R&D managers illustrated the importance of pre-clinical research and the associated weight of scientific staff in early-stage drug development decisions: "*Pre-clinical research is quite a long period; a lot happens here. Many questions have been addressed at this point, such as whether the compound is 'druggable', so soluble in fat or water, can the molecule pass through the blood–brain barrier,* etc." *"In terms of governance, decisions up to phase I are taken by people with senior research positions in the relevant therapeutic area."*

We hypothesize:

Hypothesis 1. *The scientific research origins of a patented drug candidate are associated with a higher probability that the drug candidate is taken up in development.*

3.2 Scientific origins of drug candidates and internal versus external take-up in development

Pharmaceutical firms conduct research internally, but also source science that was performed by other companies as well as government labs and universities (Arora et al., 2018; Leten et al., 2022). Our conversations with R&D managers confirmed that firms have no other option than to combine internal with external scientific research due to the extreme specialization that characterizes the industry: "*Specialization these days is enormous, so as a firm you have to set up collaborations. Also, the firm's own discovery activities — where we work with long time horizons — are by themselves typically insufficient to strengthen the patent portfolio."* Or, as another manager phrased it: "*Many large*

pharma firms realized that their internal research capacity was too limited to be productive, which has led to specialization".

While external research has to cross the organizational boundary between a research performing and a drug-developing organization (Rosenkopf & Nerkar, 2001), internal scientific knowledge has to 'travel', from scientific research ("R") to clinical development ("D"). This knowledge transfer presents a number of challenges. Embedding scientific research as well as clinical development in the same organization may help in addressing these challenges. Knowledge has to be transferred from lab researchers ('researchers'), who are involved in scientific research, to clinical developers ('developers'), who are involved in clinical trials. The effective absorption of scientific knowledge for drug development rests on the assimilation of theories on disease mechanisms into animal models and lab practices, and is easily hampered by cognitive distances within the drug development organization (Cook et al., 2014; Mak et al., 2014; McGonigle & Ruggeri, 2014). Codified representations of scientific research often do not represent a comprehensive view of the knowledge, making them susceptible to subjective interpretation (Meyer, 2000), such that effective transfers require close interaction between researchers and developers (de Wit-de Vries et al., 2019).

The proximity of the researchers in whom the scientific knowledge is embedded (Zucker & Darby, 1996) and the possibility for them to interact directly with developers and decision makers (Nonaka, 1994; von Hippel, 1994) facilitates the exchange of knowledge (Klueter et al., 2017; Thursby & Thursby, 2011). It also fosters researchers' and developers' understanding of each other's challenges and the development of a common culture with shared objectives and beliefs (Arrow, 1975). The internal research scientists may also emphasize the significance of their discoveries for drug development to corporate decision makers and advocate that the firm carries through their scientific groundwork into drug development (Peck et al., 2015). Hence, when a firm's scientists have been directly involved in the generation of a drug candidate's scientific background, their comprehensive understanding of the scientific knowledge and the relative ease of transfer of this knowledge within the same organization will favor in-house take-up of the drug candidate in development over take-up by another firm.

The above arguments suggest that patented drug candidates that have their origins in internal scientific research are more likely taken up in internal development by the research-performing firm than by another (external) firm. Our interviews provided illustrations that firms may be best able to leverage internally conducted science in drug development. Conducting science in-house embeds the firm in the ecosystem that is involved in getting the drug successfully developed: *"Take the example of [type of drug developed at the company]: there is a lot of expertise on this in the company; the firm knows this area very well. Not just in terms of scientific expertise, but also—thanks to doing the science—how to develop such drugs: you need to know the relevant people to develop a drug in certain area."*

We hypothesize:

Hypothesis 2. *Patented drug candidates that have their origins in internal scientific research are associated with a higher probability to be taken up into internal rather than external development.*

4 Data and methods

This study focuses on 136 of the largest R&D spending (in absolute terms) pharmaceutical and biotech companies with headquarters in the United States, the EU or Japan. The sample firms have been selected from the '2004 EU Industrial R&D Investment Scoreboard' and a list of largest patentees in biotechnology at the European Patent Office in the year 2005. The EU Industrial R&D Investment Scoreboard lists the top 500 corporate investors in R&D with home base in the EU, and the top 500 companies with their home base outside the EU. We gathered complete patent and publication data for the consolidated firms, accounting for annual changes in group structures. As company structures change regularly within the pharmaceutical industry, we performed a rigorous consolidation of the 140 sample firms for eight consecutive years (1995–2002) using information on subsidiaries listed in firms' annual reports. We linked the firms and their patents to clinical development data of the Pharmaceutical Industry Database (PHID), a database with information on clinical trials and development activities in the global pharmaceutical industry. This dataset tracks clinical development activity until 2013 and contains information on the firms leading the clinical trials and the specific patents underlying the compounds involved in clinical development. We explain the main data sources in more detail below.

4.1 Patented drug candidates and take-up in development

Patent data is extracted from PATSTAT at the DOCDB patent family level. We collected all priority patents by the firms applied for between 1995 and 2002. This early period allows us to track the full history of clinical development after take-up and to examine ultimate development success up to the year 2013.[1] Among the 48,112 patents granted to the sample firms, 18,381 patents (38%) protect a molecular compound and are the subject of our analysis. Patents that are not protecting a molecular entity but e.g. focus on new instruments for research cannot serve as basis for new drug development.[2] We identify patents protecting compounds by considering IPC class A61, in combination with IPC classes C07 or C12. IPC class A61 indicates pharmaceutical applications (A61K) and medical therapies (A61P), while C07 indicates organic chemistry and C12 designates biochemistry (World Health Organization, 2010; Smoch, 2012). Classes A61 and C07 are mentioned, respectively, on 94% and 88% of the patents underlying the clinical development efforts of the firms in the PHID database. Patents in class C12 are less common (21%), indicating the still relatively modest position of biotechnology in pharmaceuticals in the observation period.

We regard a patent as taken up into development when the patent is associated with a clinical development activity in PHID database. The project database reports on the lead company performing the clinical trials, allowing us to distinguish between internal and external take-up, depending on whether the lead company is the patent owner or another firm, respectively. Among the focal patents, 21 patents are included in clinical development trajectories of both the patent owning firm and of other firms. Since we are interested in

[1] Discovering and developing new drugs is a lengthy process. Using data from a group of 13 large pharmaceutical companies covering the period 2000–2007, Paul et al. (2010) reported that the process of discovering and developing new medicines takes on average 12.5 years.

[2] In supplementary analysis we find consistent results if we include patents that are not protecting compounds.

distinguishing internal and external take-up, we excluded these ambiguous cases from the analysis, resulting in a final sample of 18,360 patents.

4.2 Scientific origins of drug candidates

We identify a patented drug candidate's underlying scientific research by examining scientific references in the patent's prior art, i.e. its citations to scientific publications. Studies agree that these scientific references capture the relevant scientific background of the patent (Meyer and Persson 1998; Belderbos et al., 2017; Callaert et al., 2013). Scientific references on patents represent scientific knowledge required for a proper understanding of the invention and may therefore be instrumental in estimating the potential for its successful development during clinical trials. We identify the scientific references mentioned on the patents and link these to Clarivate's Web of Science database to retrieve author information. In-house scientific research ('internal science') is identified if the patent-owning firm (or one of its subsidiaries) is listed among the institutional affiliations of the (co-)authors of the publication.[3] The other cases are labelled as external scientific research ('external science'). To allow estimating the independent effects of internal and external science, we construct two separate dummy variables. The variable *internal science* is a dummy that takes on a value of one if a patented drug candidate cites at least one internal scientific publication. The variable *external science* is a dummy that takes on a value of one if a patented drug candidate cites at least one external scientific publication. If a patented drug candidate cites internal and external science, both dummies take the value one.

The first rows of Table 1 shows the occurrence of scientific references in different groups of drug candidates: all patents protecting drug candidates, and patents taken up in clinical development, the latter distinguished by who leads the development effort. Of the 18,360 patents under investigation, 308 are taken up in development by the patent owner and 211 by other firms. The overall take-up rate (2.8%) is similar to estimations from previous studies (Campbell, 2005; PPD, 2017). The majority (61%) of the patents include external scientific references. Patents are generally more likely to cite external scientific research than scientific research conducted in-house (23%).[4] What stands out is that those patents that are taken up in clinical development exhibit higher incidences of scientific references – 74% for external scientific research and 34% for internal scientific research. Conversely, the tendency to cite scientific research appears not very different for patents taken up by the patent-owning firm versus those taken up by other firms.

4.3 Empirical model and control variables

We test our hypotheses by relating the probability that a patented drug candidate is taken up in clinical development to the presence of internal and external scientific references. We first examine take-up in general as dependent variable and estimate a logit model. We then distinguish take-up by the patent owning firm and take-up by other firms and estimate a multinomial logit model, given that the categorical outcome variable has three possible

[3] In case of take-up by another firm, we additionally examined whether that firm had been responsible for the scientific research, but such cases did not occur.

[4] 20% of patented drug candidates cite both internal and external science while 35.7% cites no science. Only 3% of the patents cites internal but no external science (not shown in Table 1).

Table 1 Descriptive statistics

	Total		Not taken-up		Taken up		Taken up		Taken up	
							By patent owner		By other firm	
Number of observations	18,360		17,841		519		308		211	
Number of patent owning firms	136		136		136		59		77	
Variables	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D
Patent level variables										
Internal science	0.23	0.42	0.23	0.42	0.34	0.47	0.35	0.48	0.32	0.47
External science	0.61	0.49	0.61	0.49	0.74	0.44	0.74	0.44	0.75	0.43
# scientific references	7.58	15.36	7.46	15.09	11.94	22.42	10.01	17.92	14.76	27.51
Technological scope	8.97	6.16	8.84	6.05	13.42	8.12	13.78	7.91	12.89	8.42
Number of inventors	4.46	3.17	4.44	3.15	5.44	3.59	5.6	3.89	5.19	3.09
Number of patent owners	1.12	0.34	1.12	0.34	1.11	0.33	1.09	0.31	1.14	0.36
Firm level variables										
R&D expenditures	5.94	2.2	5.95	2.2	5.68	2.33	5.97	2.21	5.26	2.45
Science intensity	1.62	20.55	1.34	1.37	11.38	121.7	18.13	157.72	1.53	1.92
Size of Pipeline	0.43	26.43	0.21	0.91	8.14	157.05	13.49	203.83	0.35	1.35
Success rate in development	0.03	0.07	0.03	0.07	0.03	0.05	0.04	0.06	0.02	0.04
Firm-therapeutic area level variables										
Other drug candidates in area	17.54	26.76	17.43	26.7	21.28	28.63	23.39	29.05	18.21	27.8
Strength in development	1.06	1.22	1.06	1.22	1.09	1.24	1.38	1.28	0.66	1.04
Other firms active in development	102.77	89.53	103.45	90.09	79.43	63.12	75.29	55.06	85.47	73.04
Core domain	0.23	0.42	0.22	0.00	0.37	0.02	0.4	0.03	0.33	0.03

Internal and external science are dummies taking the value 1 when a patent cites an internal or external publication. # scientific references is the number of scientific references. Technological scope, number of inventors and number of patent owners measure the number of IPC classes, patent inventors and patent owners, respectively. R&D expenditures is expressed as the logarithm of millions of USD. Science intensity and size of pipeline measure the number of firm publications and ongoing development projects, both normalized by R&D expenditures in the patent application year. Success in development is the share of successful prior development projects. Other drug candidates in area is the number of firm patents in the therapeutic area of the focal patent. Strength in development and other firms active in development measure a focal firm's relative share in ongoing development projects in relevant therapeutic classes, and the number of other firms active in those classes. Core domain is a dummy taking the value 1 for patents in a firm's core IPC class

values: no take-up, take-up by the patent owning firm, take-up by another firm. Since our analysis can includes multiple patents per firm, we cluster standard errors at the firm level to control for possible idiosyncratic firm effects in the take-up decision process and to allow valid inference (Cameron & Trivedi, 2010, p. 306). We report exponentiated coefficients that represent the marginal effects in the form of the increase in odds of take–up versus no take-up due to a one-unit change in the explanatory variables. An exponentiated coefficient that is larger (smaller) than one indicates an increase (decrease) in the probability of take-up. For instance, a coefficient of 1.05 (0.95) for a dummy variable signifies that the odds of take up increase (decrease) by 5 percent if the dummy variable takes the value 1 rather than the value 0.

In the empirical models we include controls at the level of the patent, the patent-owning firm and the combined (firm, therapeutic area)-level. Control variables are measured at the moment of patent application if not stated otherwise. Patent-level controls are the technological scope of the patent, the size of the patent inventor team, and the number of firms co-owning the patent. In line with prior work (Lerner, 1994), technological scope is measured by the number of 6-digit IPC classes of a patent. A broad technology scope may provide multiple development opportunities for medical treatment potentially increasing the probability of take-up. Larger teams of patent inventors may generate more valuable patents as they combine a more diverse set of capabilities (Belderbos et al., 2014), or may signal more substantive investments and discoveries. Multiple patent owners may increase the probability that at least one partner firm takes up the patent in clinical development. In addition, we control for the overall number of scientific references to capture potential residual effects of the scientific origins of the drug candidate, beyond the internal or external source.

Firm-level controls are firm size, measured by (the natural logarithm of) the firm's R&D expenditures, and the firm's science intensity, measured by its number of publications in the past four years divided by R&D expenditures (in the patent application year). If multiple firms co-own the patent, these controls reflect the mean across co-applicants. Third, the size of the firm's drug development pipeline is taken into account. On the one hand, if the firm has more current clinical trial experience, it is likely to have stronger capabilities to perform clinical development. On the other hand, it has also been noted that it is rather a sparsely-filled pipeline of development projects that may push firms to take up new drug candidates in development, yet possibly of lower quality and higher risk (Arora et al., 2009; Kola & Landis, 2004). The variable is measured as the number of projects in ongoing clinical trials of which the firm is the lead developer divided by R&D expenditures in the patent application year. Finally, we control for the success rate of the patent-owner's clinical development experiences in the past ten years by including the share of terminated clinical development projects that have been finalized successfully, i.e. registered for market approval. Prior success may increase the firm's confidence in its clinical capabilities and stimulate (internal) take-up.

The models also include control variables that vary by firm and therapeutic area. The number of other drug candidates (patent applications) the firm has within the therapeutic areas of the focal patent (IPC subclasses of A61P) captures the 'internal competition' for take-up. Three other variables may specifically affect the patent-owning firm's decision on

whether to take up the drug candidate into development (internal take-up) as opposed to handing it over to another firm (external take-up). First, we account for the firm's *relative* strength in development, measured as the patent-owning firm's share (in percentage) of overall current development activity in the pharmaceutical industry (i.e. relative to all development activities in the PHID database) that is relevant for the focal drug candidate.[5] To establish relevant development activities for a drug candidate, we determined the probability that patents of a particular IPC class, if taken up in clinical development, are associated with each of the disease categories indicated by ATC classes used in clinical trials.[6] We calculate the share of the focal firm's development activities for a particular patent IPC class weighted by these probabilities.

Second, we control for the number of other firms that are active in the main areas of clinical development for the focal patent and are potential partner firms to license the patented drug candidate to for external development. We take as main areas of development those ATC classes that are linked to the drug candidate's IPC classes with a probability above 0.5. Third, we control for the firm's specialization and long term interest in a particular therapy or type of compound. We constructed a dummy ('core domain') taking the value one if the patented drug candidate has an IPC6 therapeutic or compound class (a subclasses of A61P, C07, or C12] that is among the top ten IPC classes in the patent portfolio of the firm in the past four years.

Finally, in the interviews R&D managers pointed out firms have become increasingly strict in their screening process for candidate drugs.[7] We therefore also include a time trend for the application year of the drug candidate and dummies for the therapeutic areas the drug candidate is targeting, using the subclasses of IPC A61P. The latter helps to account for heterogeneity in the attractiveness of therapeutic areas related to differences in development success and the cost of clinical trials across therapeutic areas (Kola & Landis, 2004; Mullard, 2016) as well as the quality of existing drugs on the market.

Descriptive statistics are presented in Table 1 and the correlation matrix is presented in Table 2. Table 1 shows that drug candidates that are taken up in development have more scientific references ($t=6.57$, $p<0.0001$), a greater technological scope ($t=16.83$, $p<0.0001$), and more inventors ($t=7.09$, $p<0.0001$) than drug candidates that are not taken up. Take-up by patent owners is associated with a greater pipeline of development projects ($t=2.03$, $p=0.04$) and greater patent owner development success ($t=5.11$, $p<0.0001$) compared to take-up by other firms. Drug candidate take-up by other firms is more likely ($t=1.81$, $p=0.07$) than take up by patent owners when there are more firms active in the main areas for clinical development of the patent. The correlation matrix reported in Table 2 shows positive correlations between the scientific reference variables and the take-up of a focal drug candidate in clinical development. The correlations between the explanatory variables are generally low, indicating no direct concerns of multi-collinearity.

[5] One manager pointed out the importance of the strategic fit of the drug candidate as follows: *"Say you have developed an oncology asset, or you believe it may be useful in that domain, but you're not an oncology firm, then it's logical to opt for out-licensing"*.

[6] ATC refers to the Anatomical Therapeutic Chemical system in which drugs are classified into different groups based on their active substances, according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties.

[7] As one interviewed R&D manager put it: *"The norms in the discovery phase for deciding whether to take a drug candidate forward have become stricter in the last years, and the bar that drug candidates have to jump over is now equal across therapeutic areas"*.

Table 2 Correlations

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	Take-up in development																
2	Internal take-up	**0.92**															
3	External take-up	**0.37**	−0.01														
4	Internal science	**0.04**	**0.04**	**0.02**													
5	External science	**0.04**	**0.03**	**0.03**	**0.29**												
6	# Scientific references	**0.04**	**0.02**	**0.05**	**0.41**	**0.39**											
7	Technological scope	**0.12**	**0.10**	**0.07**	**0.05**	**0.15**	**0.15**										
8	Number of inventors	**0.05**	**0.05**	**0.02**	−0.01	**−0.02**	**0.03**	**0.19**									
9	Number of patent owners	−0.01	−0.01	0.01	**0.05**	**−0.02**	**−0.02**	0.01	**0.08**								
10	R&D expenditures	−0.01	0.00	**−0.03**	0.00	**−0.10**	**−0.08**	**0.05**	**0.04**	**0.09**							
11	Science intensity	**0.10**	**0.10**	0.00	0.00	**0.02**	0.01	0.00	−0.01	−0.01	**−0.04**						
12	Size of Pipeline	**0.06**	**0.06**	0.00	0.00	0.01	0.00	0.00	0.00	0.00	**−0.03**	**0.22**					
13	Success rate in development	0.00	0.01	**−0.02**	−0.01	**-0.02**	−0.01	**0.06**	**0.03**	**−0.12**	**0.13**	−0.01	0.00				
14	Other drug candidates in area	**0.03**	**0.03**	0.00	0.01	**−0.02**	**−0.05**	**0.49**	**0.04**	**0.08**	**0.28**	0.00	−0.01	**0.02**			
15	Strenght in development	**0.02**	**0.03**	**−0.04**	−0.01	**−0.14**	**−0.12**	**−0.02**	**−0.04**	**0.02**	**0.33**	−0.01	0.00	**0.09**	**0.28**		
16	Other firms active in development	**−0.05**	**−0.04**	**−0.02**	**−0.07**	**−0.18**	**−0.12**	**−0.43**	**−0.05**	**−0.02**	0.01	0.00	0.00	**−0.02**	**−0.23**	**0.06**	
17	Core domain	**0.06**	**0.05**	**0.03**	**−0.08**	**−0.13**	**−0.13**	**0.19**	**0.13**	**0.08**	**0.06**	0.00	0.00	0.01	**0.14**	**0.06**	**−0.08**

Significant correlations ($p < 0.05$) in bold

5 Empirical results

Table 3 presents the results of (multinomial) logit regressions relating the probability that a patented drug candidate is taken up in development to the types of scientific background. Model 1 contains only the control variables. Patents with more scientific references, a broader scope and a larger inventor team have a higher probability of take-up. Take-up is also more likely if the patent-owning firm has more drugs in the pipeline, pointing to a positive current experience effect of clinical trial activity. When there is larger internal competition for the drug candidate within its therapeutic area, take-up is less likely, and when the patent owning firm is a larger player in the therapeutic area in the industry, take-up probabilities increase. The take-up incidence increases strongly (the odds ratio increases by 63 percent as indicated by the exponentiated coefficient of 1.63) if the drug candidate is in a core therapeutic domain of the firm. Finally, the estimate for the year trend suggests that take-up rates are declining over time (the odds of take-up versus no take-up decrease every year by 15.7 percent).

The second model in Table 3 examines the role of the scientific research origins of patented drug candidates in the take-up probability. Both the internal science and external science dummies have a statistically significant positive coefficient ($p < 0.01$). This confirm the first hypothesis that drug candidates that are grounded in scientific research are more likely to be taken up into clinical development. The exponentiated coefficients shown in Table 3 indicate the marginal effects, which appear relatively large. The odds of take-up rather than no take-up increase by 43 percent if the drug candidate has scientific origins in internal scientific research and by 57 percent if it has origins in external scientific research. This implies that internal and external scientific research antecedents increases the odds of take-up—which is on average 2.9%—to 4.2% and 4.5% respectively, which amounts to approximately an additional 238 and 275 candidate drugs that enter development.

To assess the overall explanatory power of the model, we assessed its predictions relative to the drug development candidates' true fate, using the sample mean take-up rate as the classification threshold. We find that model 1 with only controls strikes a reasonable trade-off between *sensitivity* (64,0%), predicting take-up if the drug candidate indeed entered clinical trials, and *specificity* (70,6%) predicting no take-up when the drug candidate was discarded. After adding internal and external science dummies in model 2, sensitivity increases to 66.9% while specificity takes a similar value of 70.5%.

Model 3 present the results of multinomial logit models distinguishing internal and external take-up, with *no take-up* as reference category. External science is positively and significantly associated with both internal and external take-up, with a roughly similar magnitude (increasing the odds of take-up versus no take-up by 52–59 percent). In contrast, internal science is only positively and significantly associated with internal take-up, and this with a substantial magnitude (an odds increase of 71 percent). This finding confirms our second hypothesis that drug candidates that have their origins in internal scientific research are more likely to be taken up in internal development by the research-performing firm rather than by another (external) firm, both compared to the no take-up reference group. Wald tests show that the internal science coefficients for internal versus external take-up are different at the 10% significance level ($\chi^2 = 2.91$, $p = 0.08$), while the role of external science does not differ significantly for internal versus external take-up.

The estimated coefficients for the control variables suggest that internal take-up is significantly less likely if there are competing drug candidates developed by the firm in the therapeutic area, and more likely if there are multiple inventors. Internal take up increases if

Table 3 Results of (multinomial) logit models of the probability of take-up of a patented drug candidate in clinical development

	Model 1		Model 2		Model 3			
	Take-up		Take-up		Internal take-up		External take-up	
Internal science			1.438**	(0.212)	1.710***	(0.311)	1.145	(0.223)
External science			1.569***	(0.178)	1.590***	(0.206)	1.515**	(0.262)
No. of scientific references	1.010***	(0.003)	1.005	(0.003)	0.997	(0.004)	1.012***	(0.004)
Technological scope	1.067***	(0.007)	1.064***	(0.007)	1.067***	(0.009)	1.058***	(0.011)
Number of inventors	1.046***	(0.012)	1.050***	(0.012)	1.058***	(0.013)	1.036*	(0.019)
Number of patent owners	0.81	(0.236)	0.792	(0.226)	0.624	(0.233)	1.098	(0.356)
R&D expenditures	0.983	(0.024)	0.987	(0.024)	1.019	(0.038)	0.969	(0.039)
Science intensity	1.038	(0.028)	1.017	(0.030)	1.022	(0.063)	1.011	(0.055)
Size of Pipeline	1.037**	(0.017)	1.038**	(0.017)	1.046***	(0.018)	1.035	(0.021)
Success rate in development	0.548	(0.390)	0.479	(0.376)	1.123	(1.020)	0.035**	(0.056)
Other drug candidates in area	0.993**	(0.003)	0.993**	(0.003)	0.990***	(0.003)	0.998	(0.004)
Strength in development	1.116*	(0.063)	1.126**	(0.062)	1.321***	(0.082)	0.769*	(0.112)
Other firms active in development	0.999	(0.001)	1.000	(0.001)	0.999	(0.001)	1.001	(0.001)
Dummy(core domain)	1.634***	(0.206)	1.745***	(0.223)	1.780***	(0.290)	1.746***	(0.329)
Year trend	0.843***	(0.019)	0.838***	(0.020)	0.868***	(0.028)	0.797***	(0.026)
Constant and Therapeutic field dummies	included		included		included		included	
Loglikelihood	− 2,151.17		− 2,135.03		− 2,433.65			
Pseudo R2	0.089		0.096		0.103			
Number of observations	18,360		18,360		18,360			
Number of firms	136		136		136			

Cluster-robust standard errors in parentheses. Coefficients are exponentiated. * $p<0.10$, ** $p<0.05$, *** $p<0.01$

firms have more development experience as measured by their drug development pipeline, a greater development strength in the area, and if the drug candidate is in a core domain of the firm. Take-up by other firms is more likely when the scientific background of the drug candidate is more extensively documented, as measured by the number of scientific references. External development is more likely when the patent-owning firm has been less successful in its past development and when it has a weaker development strength (a smaller share in the pharmaceutical industry's development activity in the domain). These findings are consistent with the notion of division-of-labor whereby firms specialize in those activities where they have a competitive advantage. External take up is also positively associated with the therapeutic field or compound being in the core domain of the patent owning firm. Perhaps this indicates that firms that are specialized in a domain are judged to be more knowledgeable and to have more promising drug candidates, allowing them to be more successful on the market for technologies. The coefficients for the time trend suggest that the decline in the take-up rate of drug candidates has been stronger for out-licensed drug candidates associated with external take-up than for internal development.

5.1 Drug development success

We additionally examined whether clinical development projects culminated in market approval of the drug candidates and whether the drug candidates' scientific origins are associated with development success and not only with the take-up decision. By the year 2013, the last year for which we have information on clinical trials, all projects were terminated, either successfully or unsuccessfully. We exclude projects that list more than one patent for the protection of its drug candidate (16 patents and 32 projects) to allow a proper identification, but include all development projects that are based on the same patent. Firm-level control variables are calculated for the firm leading the clinical trials. Due to missing information on firm characteristics for a number of firms engaging in external take-up, we can analyze a sample of 140 development projects by other firms in addition to 307 projects in internal development.[8]

We estimate separate logit models relating the probability of market approval, conditional on take-up in clinical development, for the same set of explanatory variables as in the take-up model.[9] We allow all coefficients to differ between internal and external development trajectories. An important caveat in this analysis is that we examine development success *conditional on* take-up. Since firms are expected to take up all promising drug candidates in development and base their take-up decisions on the scientific antecedents of these drug candidates, there is a strong selection effect resulting in limited residual variation in the quality of and information on the development projects and their corresponding patented drug candidates. Success or failure will be more related to unexpected events such as unpredicted safety concerns and the market success of competing drugs.

Table 4 shows the results of logit regressions of the success rate of the development projects. If take-up is by the patent owning firm, the success rate is significantly and positively related to internal scientific research. The estimated exponentiated coefficient implies that

[8] Descriptive statistics and correlations for these samples are relegated to the appendix.

[9] The only difference is that we did not include the variables *other drug candidates in area* and *other firms active in development* in the models analyzing drug development success. While these variables may affect take-up decisions, there are no clear reasons why they would affect development success.

Table 4 Results of logit models of the probability of success in development after take-up

	Success Internal take-up	Success External take-up
Internal science	1.796*	0.456
	(0.309)	(0.264)
External science	1.632	2.239
	(0.372)	(1.523)
No. of scientific references	1.008	1.015**
	(0.008)	(0.006)
Technological scope	1.018	0.994
	(0.027)	(0.045)
Number of inventors	0.951	0.926
	(0.043)	(0.081)
Number of patent owners	0.446	1.906
	(0.523)	(1.485)
R&D expenditures	1.354***	0.871
	(0.089)	(0.123)
Science intensity	0.995**	1.002*
	(0.002)	(0.001)
Size of Pipeline	1.001***	0.996**
	(0.000)	(0.001)
Success rate in development	1.498	62.394
	(3.045)	(286.937)
Strength in development	1.086	0.696
	(0.173)	(0.162)
Year trend	1.019	0.874
	(0.069)	(0.131)
Constant and Therapeutic field dummies	included	included
Loglikelihood	− 140.386	− 63.644
Pseudo R2	0.166	0.263
Number of observations	307	140
Number of firms	55	38

Cluster-robust standard errors in parentheses. Coefficients are exponentiated. * $p<0.10$, ** $p<0.05$, *** $p<0.01$

the odds of success versus failure increase by 80 percent if the drug candidate has scientific origins in scientific research conducted by the lead firm. No significant relationship is found between (internal) scientific research underlying patented drug candidates and the success of external development. These results are consistent with our argument for Hypothesis 2 that firms are better equipped to take a drug candidate into development when they have contributed to the underlying scientific research themselves.

Internal development appears more successful for firms with a larger R&D budget combined with a lower scientific intensity, both indicating allocation of resources to clinical development. A larger drug pipeline and hence more clinical development experience is also associated with a higher success rate of internal development. The development success analysis of projects taken up by other firms shows a positive association with the

number of scientific references, a finding that is consistent with its positive association with the external take-up probability in Table 3. External take-up success is also significantly and negatively associated with the size of the pipeline of the external developer. Perhaps in-licensing decisions by firms with a small pipeline are taken more carefully and include, on average, more promising drug candidates. Take-up success increases in the science intensity of the developing firm.

5.2 Supplementary analyses

Extended analysis and robustness tests, which are available upon request, show robustness of the take-up results when examining the take-up decision earlier in the trajectory, i.e. already at the start of pre-clinical research instead of at the start of clinical trials. Results were also consistent when we extended the set of observations to include patents that do not protect drug compounds. A Hausman test did not suggest that the assumption of independence of irrelevant alternatives of the multinomial logit model of Table 3 model 3 had to be rejected, and separate logit models returned near-identical results.

6 Conclusion and discussion

This paper examined whether the scientific background of drug candidates influences the probability of take-up in clinical development projects, either by the patent owner or by other firms through the market for technology. We hypothesized that scientific research underlying a drug candidate is important for take-up, and that internally conducted scientific research would predominantly be associated with internal take-up due to the stronger barriers to knowledge transfer across firm boundaries. Investigating 18,360 drug candidates patented by 136 pharmaceutical and biotech companies, we find support for these hypotheses. While previous studies have shown the importance of scientific research for firm patenting (Della Malva et al., 2015; Fleming & Sorenson, 2004; Gambardella, 1992), our study indicates that scientific research is also highly relevant for firms deciding on their drug development investments. In confirmation of the views of industry experts and life science scientists (Barrenho et al., 2013; Chiou et al., 2016; Cook et al., 2014; Hay et al., 2014; Kola & Landis, 2004; Waring et al., 2015), our findings suggest that pharmaceutical firms consider scientific research when taking development decisions in the restrictive selection process of drug candidates to be taken-up into clinical trials – the first major hurdle in the road from discovery to market introduction.

A salient finding of this study is that involvement in internal scientific research underlying the patented drug candidate leads the patent owner (rather than another firm) to lead clinical development. Additional analysis of the probability of clinical development success furthermore revealed that internal scientific research underlying the drug candidate has a positive effect on the success of clinical development – provided that the development is led by the firm that conducted the scientific research. We argued that scientific knowledge is difficult to transfer and absorb without it being properly embedded in the firm leading the development. Hence, there is evidence of a relationship between in-house scientific research, which if successful leads to an increased likelihood of take-up, and subsequently to an increased probability of drug development success.

On the other hand, the volume of documented scientific research underlying a patented drug candidate, as indicated by the number of citations to scientific research, is associated with both a greater likelihood of external development and external development success. While markets for technology have been regarded a viable alternative to in-house development and exploitation of technologies (Arora et al., 2018), our study shows that the effectiveness of markets for technology and inter-organizational technology transfer depends on the origins of the scientific knowledge underlying technologies.

In addition to providing new insights on the relationship between scientific research and (clinical) development decisions, we contribute to two important discussions in the literature. First, we provide further evidence for the innovative benefits of in-house scientific research. Our findings suggest that internal science may not only increase firms' absorptive capacity (Cockburn & Henderson, 1998; Cohen & Levinthal, 1989; Gambardella, 1992), but may also stimulate innovation by spurring investments in internal development. In this regard, our study contributes to the debate on the private value of corporate investments in scientific research. A reduced corporate investment in scientific research can be observed over time (Arora et al., 2018 & 2021) accompanied by a specialization in development (Leten et al., 2022), attributed to the growth of technology markets for science-based inventions (Arora et al., 2018) and reduced returns on investment due to increased product market competition (Arora et al., 2021). The findings of our study do however show that reducing investments in internal science may come at a cost for firms in terms of a less productive drug development process. Emerging evidence of a recently stalled decline in basic research investments (Arora et al., 2021) could be considered as indicative that companies have come to appreciate the value of internal science again. This concurs with industry experts' claims that science is only increasing in importance for unravelling disease mechanisms (LaMattina, 2011).

Second, our findings reflect on the potential consequences of the structure of the pharmaceutical industry, which has been characterized by an increasing specialization whereby universities and small biotechnology firms focus on scientific research and large pharmaceutical firms conduct most clinical development (Cockburn, 2007; Arora et al, 2018, 2020b). While we do not claim that our results are conclusive, our findings support the idea that conducting both research and development inhouse can have important benefits for a firm. We find that in-house clinical development is more common for drug candidates drawing on internal scientific research, and that the latter is also associated with a higher likelihood of clinical development success. Hence, firms benefit from their scientific research, in particular if they combine scientific research and development in-house.

Our study has a number of limitations. First, we approximated the scientific background of a drug candidate by the scientific references of its protecting patent, and this measure is subject to the usual limitations of patent citations (Callaert et al., 2013). Some references may not be known to the patent owner or corporate decision makers. Surveys of patent inventors (Fleming & Sorenson, 2004; Tijssen, 2001) have however shown that inventors are aware of a significant part of the scientific papers cited in their patents, qualifying scientific references as a proper indicator of a patented drug candidate's underlying scientific research. Moreover, advances in science after the patent application may also contribute to the take-up and development success of a drug candidate. Second, we could only examine patent, firm and firm-therapeutic area characteristics at the time of the patent application, and could not control for actions taken after patent application that may benefit the take-up decision and development success, such as engagement in collaboration (Crispeels et al., 2018; Belderbos et al., 2016; Colen et al., 2022).

Third, we assumed that all patents in our sample have the potential to serve as drug candidates. This may be overly optimistic as patent applications may also be driven by strategic motivations (Thumm, 2004; Blind et al., 2006; Czarnitzki et al., 2020). While we aimed to mitigate this concern by focusing on patents covering molecular compounds and by including technology class controls, it cannot be completely eliminated. Fourth, the molecular compounds investigated refer to patent applications only up to the early years of this century (2002). This time lag has the important advantage that it allowed us to investigate the eventual success of drug development efforts of the firm as well. Studying the take-up relationships in more recent years would be an important contribution that follow-up research could make. Another interesting route for further research would be to examine the role of firms' geographic distance to external scientific research that is cited in patented drug candidates. As geographic distance complicates knowledge transfer (e.g. Belenzon and Shankerman, 2013), it is conceivable that firms will be less likely to take patented drug candidates into development if there is a large geographic distance to the cited scientific research. This might be less the case when firms employ 'boundary spanners' (e.g. de Wit-de Vries et al., 2019; Hilkenmeier et al., 2021) who work in development but interact closely with external scientific researchers and know how to translate scientific insights into a corporate development context.

Finally, although we see our findings as indicating that firms have a knowledge advantage in the development phase if they have contributed to the scientific research background of the patented drug candidate, there may be possible alternative explanations for this finding. Firms may favor internal development of drug candidates because the prior research activity of the firm indicates a strong fit with the firm's core strategic activities. Take-up may therefore also reflect that such research is conducted as part of the firm's high-level strategic agenda encompassing both research and development, e.g. through the use of R&D portfolio management (Ding et al., 2014). Such high-level strategic decisions imply an early commitment of budget and personnel, which may make take-up decisions prone to the sunk-cost fallacy, optimism bias and over-commitment (Peck et al., 2015; Eliëns et al., 2018).[10]

The alternative of not taking up the drug candidate for further internal development but to transfer it to another firm may be seen as a failure of the team that produced the scientific research. Managers may want to avoid such negative signals and give the researchers the chance to work with the clinical trial team in order to show their capabilities, or may otherwise be subject to the *not-sold-here* syndrome (Natalicchio et al., 2014; Peck et al., 2015; Antons and Piller, 2015). While these are all potential reasons for internal clinical development, our findings on clinical trial success show that drug candidates with an internally realized scientific research base have higher success rates. This suggests that the knowledge transfer advantage of the patent-owning firm dominates behavioral explanations of the take-up decision. We encourage future research to investigate internal decision making of firms related to these important and consequential take-up decisions in conjunction with their options on the market for technology in more detail.

7 Appendix

See Table 5

[10] The interviewed R&D managers acknowledged that this could be an issue but dismissed the notion it is a systematic feature of take up decisions: *"Incentive mechanisms, such as being rewarded for milestones, may create an 'artificial pull' [for internal drug candidates] but I don't think this happens systematically.* We control for this alternative explanation by including a variable ('core domain') in the analyses, which indicates whether a drug candidate belongs to a key therapeutic area of the firm.

Table 5 Descriptive statistics for the drug development success analysis

	Mean	SD	1	2	3	4	5	6	7	8	9	10	11
Internal development													
1. successful development	0.24	0.43											
2. Internal science	0.35	0.48	**0.182**										
3. External science	0.74	0.44	0.135	**0.218**									
4. Technological scope	13.87	7.97	0.065	0.058	**0.290**								
5. Number of inventors	5.63	3.91	−0.026	−0.088	0.035	**0.244**							
6. Number of patent owners	1.09	0.31	−0.038	**0.158**	0.062	−0.117	0.001						
7. R&D expenditures	6.01	2.19	**0.191**	0.050	0.083	**0.156**	0.143	0.095					
8. Science intensity	18.2	158	−0.038	−0.072	0.062	−0.067	−0.063	−0.032	**−0.245**				
9. Size of Pipeline	56.22	564	0.066	−0.065	0.052	−0.073	−0.059	−0.028	**−0.229**	**0.539**			
10. Success rate in development	0.04	0.06	0.071	0.017	0.030	**0.175**	0.148	−0.150	**0.238**	−0.021	−0.045		
11. Strenght in development	1.33	1.23	0.094	0.091	−0.049	−0.014	−0.064	−0.013	**0.193**	−0.010	−0.001	0.058	
12. # scientific references	10.07	18.09	**0.158**	**0.423**	**0.324**	**0.304**	0.125	−0.002	0.041	0.006	0.007	0.064	−0.082

Table 5 (continued)

	Mean	SD	1	2	3	4	5	6	7	8	9	10	11
External development													
1. Successful development	0.31	0.46											
2. Internal science	0.39	0.49	−0.013										
3. External science	0.80	0.40	0.057	**0.332**									
4. Technological scope	14.04	8.37	−0.115	0.088	0.154								
5. Number of inventors	5.34	3.04	−0.173	−0.031	−0.117	0.142							
6. Number of patent owners	1.16	0.39	0.003	−0.078	**−0.241**	−0.094	**0.329**						
7. R&D expenditures	5.49	2.73	−0.049	0.083	−0.099	0.106	0.003	−0.088					
8. Science intensity	86.59	271.5	−0.102	0.068	0.051	0.001	0.069	0.141	**−0.529**				
9. Size of Pipeline	172.6	516.4	−0.164	0.052	0.075	0.053	0.129	0.042	**−0.546**	**0.825**			
10. Success rate in development	0.06	0.06	0.041	0.186	−0.081	0.017	0.059	0.028	−0.116	0.087	0.148		
11. Strenght in development	1.77	1.19	−0.089	0.083	0.053	−0.090	−0.133	−0.123	0.173	−0.116	−0.093	0.191	
12. # scientific references	19.71	36.29	−0.023	**0.459**	**0.292**	**0.387**	0.010	−0.057	**0.229**	−0.083	−0.079	−0.003	0.133

Significant correlations ($p < 0.05$) in bold

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Declarations

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