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in Pharmaceutical R&D

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The Value of Failures in Pharmaceutical R&D

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Abstract

We build a cumulative innovation model in which both success and failure provide valuable information for future research. To test this learning mechanism, we use a dataset covering outcomes of world-wide R&D projects in the pharmaceutical industry, and proxy knowledge flows with forward citations received by patents associated with each project. Empirical results confirm theoretical predictions that patents associated with successfully completed projects (i.e., leading to drug launch on the market) receive more citations than those associated to failed (terminated) projects, which in turn are cited more often than patents lacking clinical or preclinical information. We therefore offer evidence of the value of failures as research inputs in (pharmaceutical) innovation.

Keywords: R&D competition, patent policy, pharmaceutical industry
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1 Introduction

Innovation is a cumulative process (Scotchmer, 2004), where researchers learn from past results and adjust their behaviour on the basis of previous experience (Herriot *et al.*, 1985, Cyert and March, 1992). Successes (e.g., successful achievement of some milestones, or an invention) are widely recognized to be the cornerstones of scientific and technological progress. Inventors tend to privilege learning from successes, also driven by the strong emphasis on positive outcomes in scientific journals and the business press (Denrell, 2003). However, theoretical and empirical contributions highlight the essential role of failures in learning, even though individuals and organizations do not always openly share knowledge about their mistakes (Levitt and March, 1988, Levinthal and March, 1993, Desai, 2010). In addition to its own experience, a research organization can learn by vicariously observing other players in the same field, in particular others' failures (Teerlak and Gong, 2008, Francis and Zheng, 2010). Empirical works have provided evidence of the benefit of learning from failures via both direct and vicarious experiences and feedbacks (Ingram and Baum, 1997, Haunschild and Miner, 1997, Baum and Ingram, 1998, Chuang and Baum, 2003, Baum and Dahlin, 2007, Kim and Miner, 2007, Madsen, 2009, Madsen and Desai, 2010, Francis and Zheng, 2010).

Against this background, in this paper we analyse the learning process in the pharmaceutical industry, exploring how firms build on own and others' failures and successes. The pharmaceutical industry is a domain characterized by high development costs, radical uncertainty and delayed feedbacks. Failures to let compounds advance in clinical trials entail large losses: pre-approval costs per approved drug have been recently estimated to be over 1 billion US dollars (DiMasi *et al.*, 2003, Adams and Brantner, 2006, Paul *et al.*, 2010). The growing number of R&D failures is one of the main causes of the upsurge of the estimated R&D costs per new molecular entity, leading scholars to ask whether the pharmaceutical industry is now facing an R&D productivity crisis (Cockburn, 2006, Pammolli *et al.*, 2011).

In this paper we study to which extent firms learn from past failures and successes in pharmaceutical R&D. We show that the learning process in pharmaceuticals builds both on R&D successes and failures, analogously to the economic value of findings and non-findings spanning from basic research (David *et al.*,

1992). However, since open science is strongly biased toward the publication of positive results, patents and clinical trials play a fundamental role in pharmaceuticals to disclose R&D failures information (Pammolli and Rossi, 2005, Magazzini *et al.*, 2009).[1] Under conditions of uncertainty, patent disclosure may contribute to generate knowledge spillovers, promoting multiple parallel research efforts on plausible targets and stimulating private investment and competition. Moreover, we maintain that the disclosure of failed drug development attempts should be further enhanced by providing full access to the information concerning discontinued clinical trials.

The paper proceeds as follows. In the next section we outline a simple model of pharmaceutical R&D. We consider the case of multiple candidate approaches, as emphasized by recent economic theory of innovation (e.g., Aghion *et al.*, 2008). We assume that, among several approaches, at most one is the right approach that can lead to a final invention (i.e., a marketable drug). In this environment, a piece of "positive" information that raises the success likelihood of one approach will simultaneously reduce that of the other approaches. Similarly, "negative" information, e.g., when a research project based on some approach fails, will reduce the success probability of the experimented approach, and at the same time raise the prospects of other approaches. In a simple way, this captures the idea that both success and failure convey useful information for subsequent innovation.

In section 3 we exploit a comprehensive dataset which covers innovative activities of world-wide pharmaceutical and biotechnology firms as well as public research organizations.[2] The dataset covers more than 200,000 patents in the pharmaceutical field, and provides history records about more than 22,000 drug development projects. Exploiting this information, we link each compound that entered preclinical or clinical development to its patent(s). For every investigational drug our database reports detailed information of development history, from patent application to project termination (when and at which stage) or marketing. This provides us with a unique opportunity to trace an R&D project from patent filing to clinical development outcome. According to the outcome of asso-

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[1] More in general, dedicated incentive schemes such as a "market for R&D failures" (Shalem and Trajtenberg, 2009) has been put forward to enhance the transmission of the information regarding failures among competitors.

[2] This dataset is maintained at IMT Institute for Advanced Studies, Lucca, Italy.

ciated R&D projects, we classify patents into three categories. A patent is called (i) a success, when it is matched to a R&D project which leads to a drug being marketed, (ii) a failure, when the associated R&D project is terminated during preclinical or clinical trials (due to, for instance, toxicological effects or lack of effectiveness), and (iii) inconclusive (or no information), when we have no information about entry into clinical trials. We emphasize that, by a "successful" or "failed" patent, we do not mean that the patent itself is a success or failure. A patent is granted for its technological or scientific contribution, and thus represents some "success" in advancing knowledge. These modifiers refer to the subsequent experimental outcome of R&D projects associated with the patent. Since all new drug candidates are patented well before entering into clinical trials and all companies must successfully pass through clinical trials to launch innovative drugs, the pharmaceutical industry provides an ideal setting to investigate the value of failed R&D attempts.

Following the literature, we use the forward citation a patent receives from other research entities to measure knowledge flows, and compare the citation numbers of success, failure, and uninformative projects. A higher citation number implies a broader dissemination of knowledge contained in the patent (Trajtenberg, 1990, Lanjouw and Schankerman, 1999, Harhoff *et al.*, 1999, Jaffe *et al.*, 2000, Trajtenberg *et al.*, 1997, Jaffe and Trajtenberg, 2002). We find that successful patents do receive more citations than failed ones, which in turn are cited more often than inconclusive ones. Consistent with our theory, there is learning from both success and failure. In addition, we also find that learning from success persists longer – that is, knowledge generated from failure decays faster than that from success.

Section 4 discusses our main findings and provides some conclusions.

2   Learning in Pharmaceutical R&D

The pharmaceutical industry is a textbook example of a "science-based" sector (Pavitt, 1984, Orsenigo *et al.*, 2001). Scientific progress and drug development are deeply intertwined: innovations of both new therapeutic products and improvements of existing ones (in terms of better delivery, reduced side-effects, or improved efficacy) are driven by new discoveries in bacterial, animal, and human

processes by scientific communities. As Science advances, firms dissect and analyse an increasing number of research methods and R&D trajectories (Orsenigo *et al.*, 2001). Furthermore, biopharmaceutical firms are also involved in basic research, with important effects on research productivity (Cockburn and Henderson, 1998).

We therefore consider scientific research in this field as a cumulative process which consists of a series of experiments to discover the "right" or successful approach for product development (e.g., drugs). Within each technology space, such as a disease area, $J > 1$ alternative candidate approaches or trajectories coexist (e.g. different research hypothesis on biological targets and chemically related families of compounds).[3] For the sake of simplicity we consider the case in which at most one approach can lead to success (e.g., a treatment for a medical condition), and it is possible that no approaches succeed. However, our results hold also in the case in which more than one approach can be successful. The true state of nature is described by which approach, if any, is the successful one.

Three outcomes may arise for each approach j, $\tau^j \in \{s, f, n\}$. A result $\tau^j = s$ indicates "success," namely, positive evidence of the tested approach; $\tau^j = f$ and n represent "failure" (negative evidence) and "no result," respectively.[4] With probability β, the experimental result coincides with the true state: the outcome is a good sign $\tau^j = s$ if approach j succeeds, and a bad sign $\tau^j = f$ if it fails. With probability γ, no useful result is generated: the occurrence of the sign $\tau^j = n$ does not depend on the true state. And, with the remaining probability $1 - \beta - \gamma$, the experiment delivers the wrong result. We impose the following assumption, so that a result $\tau^j \in \{s, f\}$ remains informative.

Assumption 1. *(Informative experiments)* $\beta > 1 - \beta - \gamma > 0$.

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[3]Sutton (2001) takes a similar approach to analyse the R&D competition in pharmaceuticals by considering different chemically related families as independent R&D trajectories.

[4]A success validates an approach and a new drug is launched in the market. However, other drugs can follow if they demonstrate in clinical trials to be more effective than the best available treatment. In the cancer field, chemiotherapic agents such as camptothecin (CPT), were first discovered in the Sixties. However drug development of CPT was early discontinued due to severe side effects. New attention was raised over the compound in 1985 when researchers discovered that DNA topoisomerase I is the molecular target of CPT. However, the lactone ring of CPT, necessary for a proper fit into the active site of Topo I exhibit very unstable properties. Following this discovery different approaches have been considered to find more stable and soluble CPT analogues and a set of more effective products has been launched.

A lower γ raises the likelihood that the experiment delivers some outcome (success or failure), and a higher β ensures that this outcome provides more information, that is, it is more aligned with the true state of nature. These parameters capture the "quality" of the experiment and determine how informative its outcome is.[5]

After t experiments have been conducted, let $\{\hat{\alpha}_t^j\}_{j=1,2,\ldots,J}$ be the profile of the success probability of each approach, with $0 \leq \sum_{j=1}^{J} \hat{\alpha}_t^j \leq 1$, due to the mutually exclusive success of each approach. Let us assume that the $t+1$th experiment is run on approach j. We use Bayes' rule to update success probabilities according to the new experiment outcome.

Experiment $t+1$ delivers a positive sign for approach j, $\tau_{t+1}^j = s$, with probability $\hat{\alpha}_t^j \beta + (1 - \hat{\alpha}_t^j)(1 - \beta - \gamma)$. With probability $\hat{\alpha}_t^j$, this approach is the successful one and the experiment gives the right outcome with probability β. With probability $1 - \hat{\alpha}_t^j$, approach j cannot lead to success but the experiment mistakenly delivers the opposite result, with probability $1 - \beta - \gamma$. The updated success probabilities are

$$\hat{\alpha}_{t+1}^j = \frac{\hat{\alpha}_t^j \beta}{\hat{\alpha}_t^j \beta + (1 - \hat{\alpha}_t^j)(1 - \beta - \gamma)} > \hat{\alpha}_t^j \tag{1}$$

for approach j, and

$$\hat{\alpha}_{t+1}^k = \frac{\hat{\alpha}_t^k(1 - \beta - \gamma)}{\hat{\alpha}_t^j \beta + (1 - \hat{\alpha}_t^j)(1 - \beta - \gamma)} < \hat{\alpha}_t^k \tag{2}$$

for all other approaches $k \in \{1, 2, \ldots, J\}$, $k \neq j$. Similarly, the experiment gives a negative result, $\tau_{t+1}^j = f$, with probability $\hat{\alpha}_t^j(1 - \beta - \gamma) + (1 - \hat{\alpha}_t^j)\beta$, and the

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[5]This type of research is "applied" in the sense that the experiment is conducted only on one approach, despite its informational externality to be shown below. Instead, "basic" or "fundamental" research may be viewed as experiments delivering direct results about several approaches. This distinction between basic and applied research stresses not the timing of invention, but the contribution to the knowledge accumulation process. Another type of research is that of research tools, which may be modeled as an invention which increases the precision of applied research, i.e., a better research tool increases β.

updated probabilities are

$$\hat{\alpha}_{t+1}^{j} = \frac{\hat{\alpha}_t^j(1-\beta-\gamma)}{\hat{\alpha}_t^j(1-\beta-\gamma)+(1-\hat{\alpha}_t^j)\beta} < \hat{\alpha}_t^j \qquad (3)$$

for approach j, and

$$\hat{\alpha}_{t+1}^{k} = \frac{\hat{\alpha}_t^k\beta}{\hat{\alpha}_t^j(1-\beta-\gamma)+(1-\hat{\alpha}_t^j)\beta} > \hat{\alpha}_t^k \qquad (4)$$

for other approaches. Lastly, the experiment generates an uninformative outcome, $\tau_{t+1}^j = n$, with probability $\hat{\alpha}_t^j\gamma + (1-\hat{\alpha}_t^j)\gamma = \gamma$, and assessment of success probability remains unchanged:

$$\hat{\alpha}_{t+1}^{j} = \frac{\hat{\alpha}_t^j\gamma}{\hat{\alpha}_t^j\gamma+(1-\hat{\alpha}_t^j)\gamma} = \hat{\alpha}_t^j, \quad \hat{\alpha}_{t+1}^{k} = \frac{\hat{\alpha}_t^k\gamma}{\hat{\alpha}_t^j\gamma+(1-\hat{\alpha}_t^j)\gamma} = \hat{\alpha}_t^k. \qquad (5)$$

By mutual exclusivity, a positive outcome for one approach "crowds out" the prospects of other approaches. More interestingly, a failed experiment reduces the success probability of that approach (and of the whole field), but at the same time it *increases* the probability that the successful route may be concealed in other approaches. In other words, both successful and failed experiments are informative.

To test this insight empirically, we use forward citations to assess the knowledge contribution of a patented technology. We consider a very simple R&D decision and patent citation generation process.[6] Once a new approach is pursued (i.e. a new patent is applied for claiming the new trajectory), let us assume that all the previous patents in the same fields are cited, i.e., there is no strategic citation.[7]

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[6]Strategic interactions at both the final market and R&D competition stages can be introduced to enrich the model, but as a first step, we leave these concerns aside in order to focus on the learning mechanism described above.

[7]The importance of pharmaceutical patents as an incentive to innovation is unquestionable. Survey evidence on the nature and the strength of appropriability conditions in the US and Europe show that the biopharmaceutical industry is the one where patents received the highest score as an effective mechanism for protecting intellectual property rights as well as the one with the highest propensity to patent (Cohen *et al.*, 2000, Arundel and Kabla, 1998). As a result, when analyzing the pharmaceutical industry, patents can be considered a good proxy for innovations.

The number of forward citations a patent receives is thus positively correlated with subsequent inventors' incentives to enter the field. Denote $\hat{\alpha}_t^* \equiv \max\{\hat{\alpha}_t^j\}$ as the highest success probability in the field after t experiments, and let the corresponding approach be j^*. For the sake of simplicity, we assume that a firm's incentive to enter and start a research project increases in probability $\hat{\alpha}_t^*$. Post-entry, the firm, with knowledge $\{\hat{\alpha}_t^j\}$, conducts experiments on the most promising approach j^*. In sum, these assumptions imply that a patent will receive more forward citations if its outcome raises the highest success probability in the field by a larger magnitude.

We now derive our hypothesis. First, consider the firm's experiment on approach j^*. An uninformative result $(\tau_{t+1}^{j^*} = n)$ does not change the knowledge stock or the entry incentives, $\{\hat{\alpha}_{t+1}^j\} = \{\hat{\alpha}_t^j\}$. But a positive sign $(\tau_{t+1}^{j^*} = s)$ raises the highest success probability. A positive experimental result maintains the status of j^* as the most promising approach, and raises its success probability, $\hat{\alpha}_{t+1}^{j^*} > \hat{\alpha}_t^{j^*}$. Therefore, a patent associated with a successful experiment should receive more forward citations than one with no informative outcome.

If the experiment outcome is negative, $(\tau_{t+1}^{j^*} = f)$, then the success probability of approach j^* becomes lower. But the information brought by a failed experiment may sufficiently boost the success probability of other approaches, so that, after incorporating the new information, the highest success probability in the field is larger than $\hat{\alpha}_t^{j^*}$. That is, there may exist $k \neq j^*$ so that:

$$\hat{\alpha}_{t+1}^k = \frac{\hat{\alpha}_t^k \beta}{\hat{\alpha}_t^{j^*}(1 - \beta - \gamma) + (1 - \hat{\alpha}_t^{j^*})\beta} > \hat{\alpha}_t^{j^*} \Leftrightarrow \beta\left(\hat{\alpha}_t^{j^*} - \frac{\hat{\alpha}_t^{j^*} - \hat{\alpha}_t^k}{\hat{\alpha}_t^{j^*}}\right) > (1 - \beta - \gamma)\hat{\alpha}_t^{j^*}.$$

(6)

When this condition holds, a patent associated with a failed outcome will also receive more forward citations than one with uninformative outcomes.[8] In general, this condition requires the difference in success probability between the most promising and the second most promising approach to be not too large. For instance, if at the initial state, i.e., before any experiments are run, the prior belief

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[8]If we assume that patents with informative outcomes receive more forward citations than those with uninformative outcomes, then this relationship holds directly from the information spillover of failed experiments.

is characterized by uniform distribution, $\hat{\alpha}_0^j$ is the same for all j, then the condition holds for the first experiment. Alternatively, under the assumption of uniform prior, if all past experiments are failures and there is still some "untested" approach k, then the success probability of approach k is the same as $\hat{\alpha}_t^{j^*}$; the condition also holds.[9] These two scenarios seem to fit the pharmaceutical context well, where most patents either have no informative results in their backward citations, or only cite past failures. In our data, the vast majority of patents (80.34%) do not contain any informative outcomes in their backward citations. By summing patents that cite only uninformative or negative results, we obtain that 88.12% of total pharmaceutical patents cite no successful patent.

Second, we compare positive and negative experimental outcomes. Fixing $\hat{\alpha}_t^{j^*}$, compare the highest success probability after an experiment is conducted on approach j^*. For $k \neq j^*$,

$$\frac{\hat{\alpha}_t^{j^*}\beta}{\hat{\alpha}_t^{j^*}\beta + (1-\hat{\alpha}_t^{j^*})(1-\beta-\gamma)} > \frac{\hat{\alpha}_t^k\beta}{\hat{\alpha}_t^{j^*}(1-\beta-\gamma) + (1-\hat{\alpha}_t^{j^*})\beta} \quad (7)$$

$$\Leftrightarrow \quad \hat{\alpha}_t^{j^*}[(1-\hat{\alpha}_t^{j^*}) - \hat{\alpha}_t^k]\beta > [\hat{\alpha}_t^k(1-\hat{\alpha}_t^{j^*}) - \hat{\alpha}_t^{j^*2}](1-\beta-\gamma), \quad (8)$$

because $\beta > 1 - \beta - \gamma$, and because

$$\hat{\alpha}_t^{j^*}[(1-\hat{\alpha}_t^{j^*}) - \hat{\alpha}_t^k] > \hat{\alpha}_t^k(1-\hat{\alpha}_t^{j^*}) - \hat{\alpha}_t^{j^*2} \quad \Leftrightarrow \quad \hat{\alpha}_t^{j^*} > \hat{\alpha}_t^k, \quad (9)$$

where $\hat{\alpha}_t^{j^*} + \hat{\alpha}_t^k \leq 1$. A positive result must raise the highest success probability by a larger amount than a negative result, and so must receive more forward citations. Note that this is robust to the history of research, as summarized in $\{\hat{\alpha}_t^j\}$.

To summarize, we test the hypothesis that a patent associated with a successful project receives more citations than one associated with a failed project or a patent whose project is inconclusive. When condition (6) holds, a patent corresponding to a failed project also receives more forward citations than one corresponding to a project which is inconclusive.

Lastly, note that we do not rule out the possibility that none of the candidate approaches are correct. Therefore, if more and more failures are accumulated,

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[9]As for assumption 1, $\beta > 1-\beta-\gamma$, condition (6) certainly holds if $\hat{\alpha}_t^{j^*} - [(\hat{\alpha}_t^{j^*} - \hat{\alpha}_t^k)/\hat{\alpha}_t^{j^*}] = \hat{\alpha}_t^{j^*}$, i.e. when $\hat{\alpha}_t^{j^*} = \hat{\alpha}_t^k$. More generally, it holds when the two probabilities are not too far apart.

eventually an extra failed experiment only indicates that the whole research field is an impasse. We may observe fewer entries, and thus fewer forward citations, for a failed project as more knowledge is accumulated. This is in contrast with previous works such as those of Fershtman and Rubinstein (1997), Haller and Pavlopoulos (2002), Shalem and Trajtenberg (2009), in which one (and only one) right research always exists, and failure in one approach always brings good news in the form of narrowing the range of future exploration.

To help the reader thinking about the process we have in mind, consider, as an example, the case of p38 mitogen-activating protein kinase, a serine-threonine kinase that regulates the inflammatory processes.[10] The biological target was first exploited in two patents by GlaxoSmithKline (GSK) in the early 1980s. Since then, various companies have entered the field and different approaches have been considered. Some companies have patented compounds with structural homology to the original GSK lead compound (that was discontinued in 1998 due to the emergence of toxicological problems), and cited the GSK patent. Others have explored alternative approaches based on the same target but chemically unrelated families of drug candidates. After more than thirty years of research and multiple failures no p38 inhibitor has been commercialized yet. As a result, despite the patent covering the GSK leading compound has received several citations it has been recently questioned whether this inhibitors have still to be considered as viable therapeutic opportunities (Gaestel *et al.*, 2009).

3 Empirical Strategy

3.1 Data and measures

The Pharmaceutical Industry Database (PhID) maintained at IMT Institute for Advanced Studies in Lucca (Italy) contains comprehensive information on innovative activity within the pharmaceutical industry, including R&D project level data, patents and their citations, and collaborations and sales data. It has two broad categories of information, pharmaceutical patents and drug development projects.

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[10]The example presented here are drawn from Magazzini *et al.* (2009). Please refer to the original paper for additional details.

The database covers all pharmaceutical and biotechnology patents granted by the United States Patent and Trademark Office (henceforth, USPTO) since 1965, with information such as numbers of backward citations and forward citations (up to May 2004), application dates, and names of assignees. It also includes worldwide R&D projects for the past 30 years, with more than 22,000 drug development projects in total. The database tracks the development history of each compound, from patent application, preclinical and clinical trials, to final marketing. If a research project (chemical compound) was aborted, information about when termination was announced is also reported.

Our empirical strategy is to compare the patterns of forward citation among patents with different project outcomes. We focus on the pharmaceutical industry and consider only citations from other pharmaceutical patents.[11] We distinguish self-citations from citations by other organizations. It is interesting to compare the dynamics of the two groups as self-citations and citations by other organizations are considered as characterizing of different patterns in knowledge diffusion. On the one side, citations by other inventors have been proved to be good proxies for knowledge flows in the literature (Jaffe *et al.*, 2000). On the other side, self-citations may measure factors other than learning, such as the cumulative nature of the technology and the extent to which innovators are able to benefit by their own research efforts (Hall *et al.*, 2001).

To classify patents according to project outcomes, we exploit the information provided by the dataset, where a patent search was conducted for each compound and one or more relevant patents protecting the compound were identified.[12] Since our data source only provides citation information for US patents, we restrict analysis to those projects that can be matched with US patents (either directly or via the patent family). By doing this, we also avoid institutional factors, as different patent offices may adopt different examination procedures which may lead to different citation behaviors (Breschi and Lissoni, 2004, Michel and Bettles,

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[11]We define pharmaceutical patents as those in classes A61K and A01N according to the International Patent Classification (henceforth, IPC; see Lanjouw and Cockburn (2001)) and US classes 424, 435, 514, and 800.

[12]The relationship between R&D projects and patents is one-to-many. When more than one patent is associated with a project, we considered all associated patents (and replicated the record accordingly). In our sample, each project is associated with an average of 1.1 US patents.

2001).[13] According to this criterion, we are able to identify the patent history of 49% of projects in the dataset.

We also select patents whose projects have successful outcomes (i.e., a new drug was launched on the market) or failed ones (i.e., the project was aborted, due, for instance, to the emergence of toxicological effects or to lack of effectiveness). We refer to these patents as successful or failed patents, depending on the outcome of the associated R&D projects. Overall, there are about 2,000 projects with informative outcomes.

As a last step to construct the data for empirical analysis, we create a "reference group," i.e., those patents for which we have no information about preclinical or clinical development. For each informative (successful or failed) patent, we randomly match it with a patent from the pool of pharmaceutical patents with the same application year, publication year, and IPC class, but with no information about preclinical or clinical development, that is, the protected compound has not yet entered preclinical or clinical trials.[14] These are projects of "no results," or "uninformative results" in our theoretical model.

3.2 Methodology

We estimate and compare the lag distributions of forward citations (self-citations and citations by other organizations) among different groups of patents, that is, the frequency of citations received (citation intensity) across the time differences between the granting years of citing and cited patents (citation lags).

The analysis of lag distributions aims at revealing some interesting dynamic patterns of forward citations according to patent groups. We use the double-exponential function to model the citation lag distributions of successful and failed

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[13]We further excluded old compounds and/or natural products, which do not have any associated patent.

[14]Our dataset contains all preclinical and clinical trial information in the United States and major European countries. Some projects may have been misclassified as inconclusive because their trials were conduced in other countries and not reported in the dataset. However, absent a mutual recognition precedure, the Food and Drug Administration and the European Medicines also consider the outcome of clinical trials conducted in third countries as inconclusive for drug launches in the United States and Europe respectively. Thus, we are confident that this does not significantly bias our result. If at all, it only works against our hypothesis that failed projects provide more information than inconclusive ones.

patents *vis-à-vis* uninformative patents. This model provides a flexible framework to study the process of citation generation: An exponential process to capture knowledge diffusion is coupled with a second exponential process to capture knowledge obsolescence (Jaffe and Trajtenberg, 1996, Caballero and Jaffe, 1993). We use the following specification as in Jaffe and Trajtenberg (1996):

$$p(t, T, \tau) = \delta_0^\tau(t, T) \exp[-\delta_1^\tau(T - t)](1 - \exp[-\delta_2(T - t)]), \qquad (10)$$

where $\tau \in \{s, f, n\}$ is the project outcome of the cited patent (s for success, f for failure, n for uninformative outcome), t the granting year of the cited patent, and T the granting year of the citing patent, with $T > t$. Therefore, $p(t, T, \tau)$ is the likelihood that a patent granted in year T will cite a patent granted in year t with outcome τ. Parameter $\delta_0^.$ is related to the overall likelihood of being cited (average citation intensity). Parameters $\delta_1^.$ and δ_2 capture the rates of knowledge obsolescence (i.e., citations to patent granted in year t decrease and eventually stop, as the patented innovation is replaced by new knowledge)[15] and knowledge diffusion, respectively. We assume that granting years T and t only affect average citation intensity $\delta_0^.$, and that the project outcome of cited patent τ affect both δ_0^τ and the rate of obsolescence δ_1^τ, but not the rate of diffusion δ_2. We keep δ_2 constant over time and project outcomes, to avoid identification issues.[16]

To estimate equation (10), we compute the observed citation frequency as the ratio between $C(t, T, \tau)$, the number of citations received by patents of outcome τ and granted in year t from patents granted in year T, and the potential number of citations, i.e., the number of citations which would have been observed if all patents granted in year T had cited all patents granted in year t with outcome τ:

$$p(t, T, \tau) = \frac{C(t, T, \tau)}{N(t, \tau) \, N(T)},$$

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[15]Higher δ_1 corresponds to faster obsolescence, i.e., the citation function is shifted to the left for higher values of δ_1.

[16]Increases in δ_2, holding δ_1 constant, increases the overall citation intensity, i.e., they are very close to increases in δ_0. As a result, models in which both δ_0 and δ_2 vary as a function of the same set of characteristics are not identified. Convergence problems also forbid the inclusion of all cited-year effects. We follow the literature and solve the problem by introducing cited-year effects defined on the basis of 5-year time periods (Jaffe and Trajtenberg, 1996).

where $N(T)$ is the number of (citing) patents granted in year T, and $N(t, \tau)$ the number of (cited) patents granted in year t and with outcome τ. For estimation, we use nonlinear least squares and weight each observation by $[N(t, \tau)N(T)]^{1/2}$.

3.3 Results

The results from the double-exponential analysis are shown in Figure 1 and Table 1. Note that the regression results are obtained by comparing the citation patterns of informed patents (success or failure) against the benchmark (those patents with no information about preclinical or clinical development).[17] In Figure 1, we plot the estimated citation lag distributions of different groups of patents, including those without known results. We distinguish self-citations from citations by other organizations. The horizontal axis is the citation lag, i.e., the difference in granting years between citing and cited patents $(T - t)$, and the vertical axis is citation intensity. We use results from Model 2 in Table 1 to draw the fitted lines in Figure 1. The vertical line at the lag of eight years (after the cited patent is granted) indicates the average project duration (from patent application to achievement of project outcome) in our data.[18]

Our hypothesis predicts that successful patents receive more citations than failed ones, which in turn have a higher number of forward citations than patents with no results. In Table 1, the estimates of overall likelihoods of forward citations for failed patents (δ_0^f) and successful patents (δ_0^s) are both greater than one when citations by other organizations are taken into account, whereas in the case of self-citations we cannot reject the null hypothesis that the failed and successful patents have an average citation intensity that is equal to the one of the uninformative patents. This means that failed and successful patents are more likely to be cited

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[17]We stress here that our analysis was undertaken by comparing the three groups of patents in terms of numbers of citations. A known source of noise in citation studies comes from the fact that citations in the final patent document are not only those declared by the inventors, but also added by the examiner. Recent literature shows that analysis based on pooled sets of citations may suffer from bias (Alcácer and Gittelman, 2006). As long as the number of citations added by the examiner is unrelated to the outcome of the associated R&D project (which is unknown when the patent is granted), our *relative* comparison is unaffected by the examiner-citation issue.

[18]The average length is 7.8 years for failed projects and 8.3 years for successful ones. These figures are consistent with previous studies on the duration of the drug development process (Abrantes-Metz *et al.*, 2004).

Citations by other firms
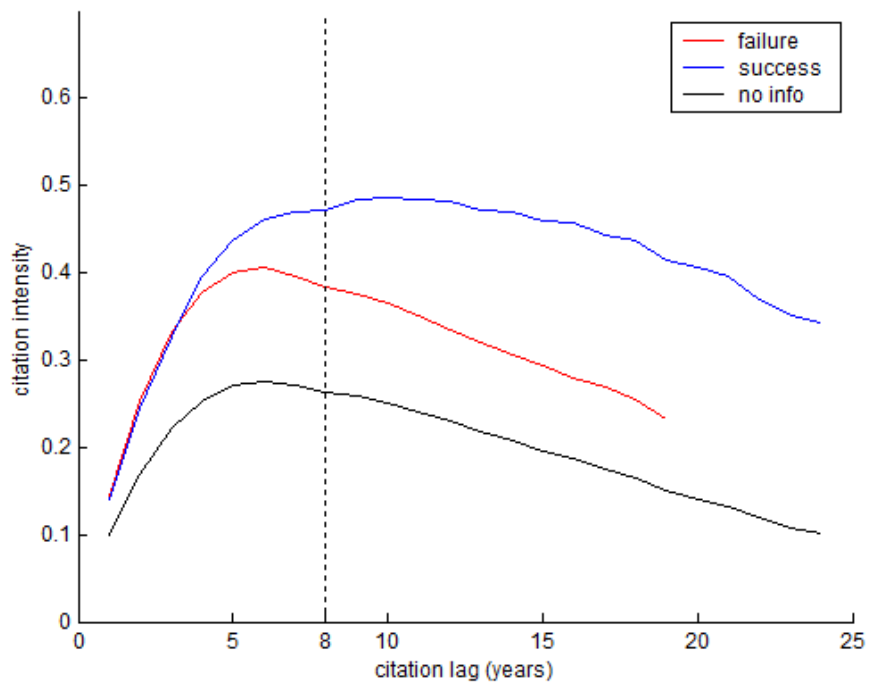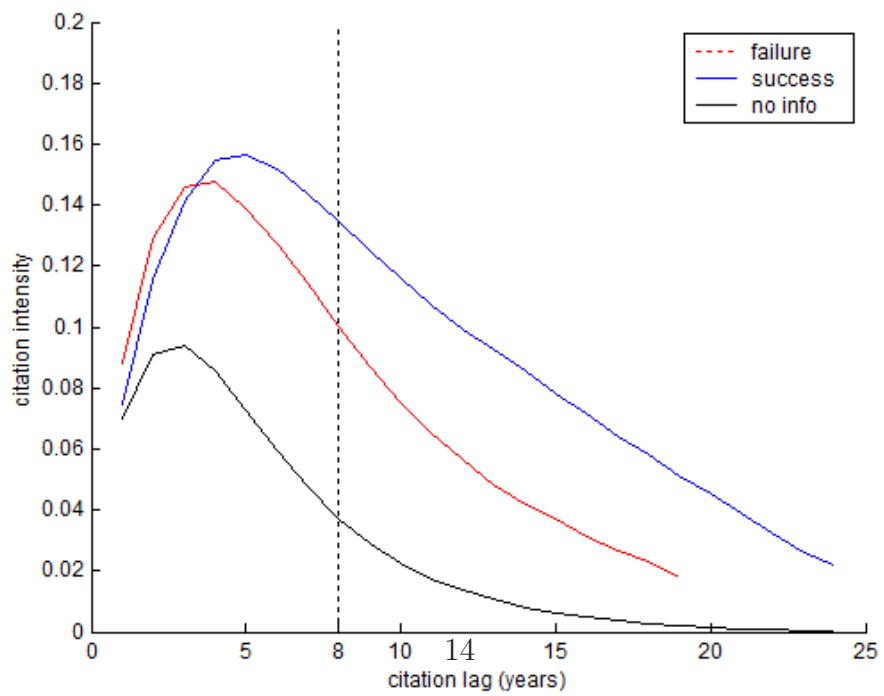
Self-citations

Figure 1: Estimated citation lag distribution function, citations by others and self-citations

by other organizations than the reference group, i.e., those without any project information. In Model 2, we can also reject the null hypothesis that δ_0^s equals δ_0^f at the 5% level, meaning that in the case of citations by other organizations, our hypothesis is supported by our data. On the contrary, this is no longer true when self-citations are taken into account. This result is also illustrated in Figure 1, where the fitted line for failed patents lies between the fitted lines for two other groups of patents. Previous literature emphasizes a positive correlation between the value of a patent and the number of forward citations it receives (Trajtenberg, 1994, Lanjouw and Schankerman, 1999, Harhoff *et al.*, 1999, Jaffe *et al.*, 2000, Trajtenberg *et al.*, 1997, Jaffe and Trajtenberg, 2002, Gambardella *et al.*, 2008). From this point of view, our result thus suggests that there is a value attached to a failed patent that spills over firm boundaries. Although the compound associated with the patent will never reach the market (e.g., due to the emergence of toxicological problems or lack of effectiveness), the open research approach and related information is subsequently exploited by other inventors.

The double-exponential model allows us to examine the dynamics of the knowledge diffusion process further. When citations by other organizations are considered, failed patents have an earlier "peak" of forward citations (i.e., modal lag) than successful ones.[19] Another interesting feature is that the citation patterns for successful and failed patents differ significantly only five years after patent grant. For the first five years, there is no significant difference between the two trends. Comparison of the estimates of δ_1 (rate of obsolescence) reveals a difference between successful and failed patents in terms of citations by other organizations, whereas the difference fades away when self-citations are considered. In this aspect, when citations by other organizations are considered, failed patents share very similar dynamics as with patents with no results. The value of δ_1^f is very

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[19]Our results are consistent with the estimates of the Drugs and Medical sector in Hall *et al.* (2001), except that we obtain a lower value of δ_2, the rate of knowledge diffusion. However, comparison is made difficult by the fact that we separately analyze citations by other organizations and self-citations. This limitation notwithstanding, note that Hall *et al.* (2001) report a citation lag distribution in the Drugs and Medical sector that is flatter than in other sectors such as Computers and Communications, Electrical and Electronics, Chemical, and Mechanical sectors, where higher peak tends to come earlier in time. In other words, knowledge in the Drugs and Medical sector diffuses less rapidly and takes longer to become obsolete. Important information about protected compounds, such as toxicological effects and effectiveness, is revealed over time, and leads to a lengthier process to generate citations.

Coefficients	Citations by others		Self-citations	
	Model 1	Model 2	Model 3	Model 4
δ_0^f	1.264*	1.329*	1.194*	1.121*
	(0.182)	(0.111)	(0.197)	(0.173)
	[1.451]	[2.964]	[0.985]	[0.699]
δ_0^s	1.309*	1.511*	0.926*	0.903*
	(0.158)	(0.108)	(0.141)	(0.127)
	[1.956]	[4.731]	[-0.525]	[-0.764]
δ_1	0.107*	0.084*	0.323*	0.300*
	(0.008)	(0.013)	(0.027)	(0.037)
δ_1^f	0.827*	1.049*	0.710*	0.653*
	(0.135)	(0.108)	(0.086)	(0.087)
	[-1.281]	[0.454]	[-3.372]	[-3.989]
δ_1^s	0.554*	0.604*	0.491*	0.413*
	(0.087)	(0.077)	(0.060)	(0.066)
	[-5.126]	[-5.143]	[-8.483]	[-8.894]
δ_2	0.114*	0.248*	0.094*	0.197*
	(0.014)	(0.042)	(0.013)	(0.061)
Cited year effects	no	yes	no	yes
Citing year effects	no	yes	no	yes
R-squared	0.686	0.858	0.609	0.641

Dependent variable: citation intensity

Standard errors in parenthesis.

In square brackets: t-stat. for H0: parameter = 1 (if relevant)

* statistically significant at 5% level.

Table 1: Results of estimation of double-exponential function

close to one, which implies no significant difference between the rates of obsolescence in the two groups. On the contrary, the value of δ_1^s is significantly lower than one, i.e., the knowledge embedded in patents protecting marketed compounds becomes obsolete less quickly than knowledge in other groups. Indeed, the citation intensity of marketed compounds is quite stable after marketing, whereas the citation intensity of failed patents decreases substantially. When self-citations are considered, both δ_1^s and δ_1^f are lower than 1, pointing to smaller obsolescence rates of failed and successful patents with respect to the uninformative ones.

We now dig further into the citation patterns of successful and failed com-

pounds after the outcome is known. Figure 2 and Figure 3 compare the average number of citations received by failed and successful patents with the control group of inconclusive patents before and after the outcome of the project is disclosed (i.e. either the compound is marketed or termination of the trial is announced). First, we compute the ratio of the citations received by s- and f-patents to the average number of citation in the control group (n) each year after the publication.[20] Then, the ratio are arranged around the time when the outcome of the project becomes known: time 0 is the time of market launch for successful drugs or the time of announcement of discontinuation for failed projects. We distinguish citations by others (Figure 2) from self-citations (Figure 3).

Figure 2 shows that 5 years before the outcome is known the number of citations to failed and successful patents is about twice the number of citations to patents without information about clinical trials. Few years before the outcome, the two series start to diverge. On the one side, successful compounds pass phase III of clinical trials and enter the registration status, so people get to know that the product will be launched soon. Conversely, early evidence of problems in clinical trials (e.g., side effects, lack of effectiveness, toxicity) is likely to emerge for those compounds that are deemed to fail. For failed patents, once the outcome is announced, the number of citations slowly converges to the number of citations of non-informative compounds. However, citations to failed patents are significantly higher than citations to the uninformative ones even several years after the clinical trial outcome is known. The gap between citations received by failed and uninformative patents quantifies the informative contribution of failed drug to the innovation process in pharmaceuticals.

Figure 3 depicts a similar pattern for self-citations. However, the converge of the failed patents curve to the uninformative benchmark is faster. Since the likely outcome of the clinical trial is known to the sponsoring organization well before the public announcement, self-citations can anticipate citations by others.

All in all, we show that failures play an important role in pharmaceutical research, especially for unmet medical needs in which no effective treatment has been developed yet. Patents covering drug candidates that failed to pass clinical trials obtain a larger number of citations by other innovators than patents without

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[20]Ratios are computed grouping patents based on publication year.
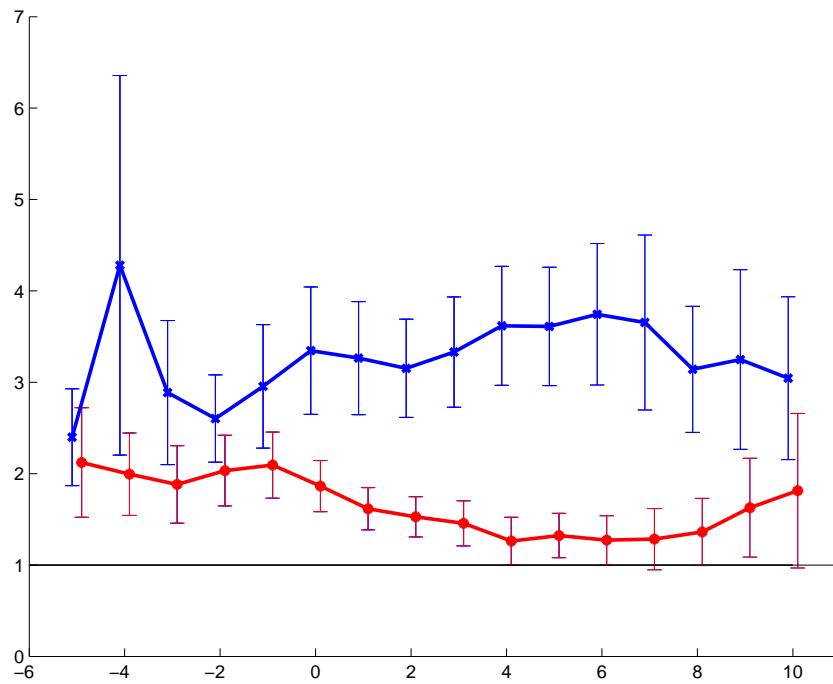
17

Figure 2: Relative number of citations by others for failed (red line) and successful patents (blue line) as compared to the uninformative ones (reference line equal to 1) before and after the project outcome is disclosed (time 0), in years. 95% confidence interval are also reported.
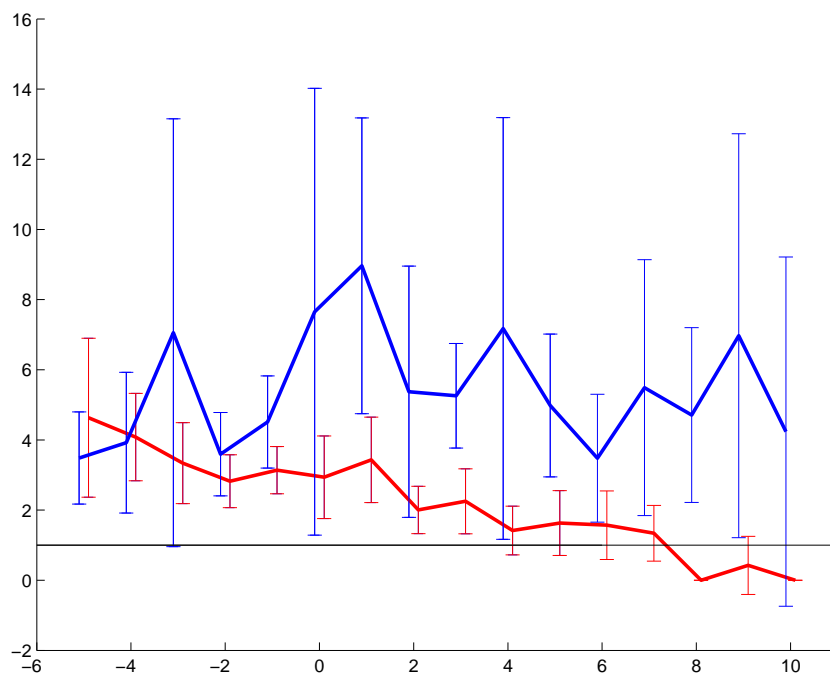
Figure 3: Relative number of self-citations by others for failed (red line) and successful patents (blue line) as compared to the uninformative ones (reference line equal to 1) before and after the project outcome is disclosed (time 0), in years. 95% confidence interval are also reported.

clinical evidence. In pharmaceutical R&D, researchers tend to cumulate on failed drug development attempts over a long time span.

4 Concluding Remarks

In this paper we present empirical evidence of the contribution of failure *vis-á-vis* success to the pharmaceutical innovation process. We also suggested a theoretical framework to capture the learning mechanism. Overall, the prediction generated by the theory are consistent with the empirical results. In other words, failures as well as successes contain valuable lessons for future endeavor.

In light of this finding, an important policy question is whether an inventor should be rewarded for failures, or negative results; and if so, how to construct a proper incentive mechanism, which may be highly sensitive to the technological and organizational features of the prevailing context. In the world of innovation, for instance, for firms in our dataset, patent policy, such as infringement issues, determines whether they can reap some reward from their failure. And in other fields, inventors may not be able to secure a patent based on their failures in the first place. To the extent that this knowledge should also be rewarded, this problem may be somewhat mitigated (for academic players at least) by the introduction of (peer-reviewed) journals of *negative results*, such as *Journal Negative Results - Ecology and Evolutionary Biology*, *Journal of Negative Results in Biomedicine*, *Journal of Pharmaceutical Negative Results*. But whether this is sufficient, and more generally, how to reward failure in other contexts, such as in a profit-maximizing firm, remain an interesting topic to be tackled.

Our work also contributes to the ongoing debate on the disclosure of clinical trials information. Traditionally, data collected by pharmaceutical companies while conducting clinical trials have been considered confidential and legally designated as trade secret. However, the situation with regard to clinical trial disclosure is changing at a fast pace. In the United States, the Food and Drug Administration Amendment Act (FDAA) of 2007 requires that results of completed clinical trials of FDA-approved or cleared drugs to be electronically available in a public reg-

ister.[21] Unsuccessful trials were not covered by the result disclosure policy even if an extension of FDAAA to cover failed clinical trials is currently under discussion (Zarin *et al.*, 2011). Our findings on the information value of failed clinical trials provide support to the extension of the results disclosure policy to include unapproved drugs.

Another line for future study is to extend and enrich the analysis in this paper. To focus on learning, we left out some important concerns in our model. Among others, we disregarded strategic behavior in our theoretical treatment It would be interesting to investigate how strategic concerns (both in market competition and R&D competition) affect a firm's decisions to exploit others' as well as its own successes and failures, and how these factors distort the value of failure in the innovation process for small and big research organizations.

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[21]http://www.clinicaltrials.gov.

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