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Essays on Innovation and Technology Commercialization

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Spring 2016

Abstract

This dissertation studies the types of innovations produced by high-tech startups and technology commercialization strategies of the firms. Chapter 1 examines the strategic conditions that drive entrepreneurial innovators to pursue novel innovation rather than innovation closer to existing technologies. Because breakthrough innovation is more difficult to communicate than its incremental counterpart, entrepreneurial innovators seeking commercialization partners may avoid breakthrough innovation for which the cost of developing credible information is exceedingly high. This study finds that entrepreneurs are more likely to bring novel innovations to market when a policy called the Orphan Drug Act (ODA) helps developers deliver convincing information about the prospect of novel technologies to partners. Chapter 2 investigates how the changes caused by ODA impact the timing and the formation of partnership between startups and established partners seeking technology commercialization. Lastly, focusing on the investment strategies of venture capitalists (VCs), Chapter 3 shows that ODA promotes VCs to finance radically novel innovations at an early development stage.

Category: Strategy; Innovation; Entrepreneurship

Keywords: Innovation, Entrepreneurship, Technology Commercialization Strategy, Partnership Formation, Venture Capital

Executive summary

My dissertation consists of three chapters studying the types of innovations produced by high-tech startups and the technology commercialization strategies (TCS) of the entrepreneurial firms. The major goal of this project is to understand what types of innovations startups bring to market. In addition, I study how the changes in the direction of entrepreneurial innovation affect the formation of partnership between startups and established commercialization partners as well as the investment strategies of venture capitals (VCs), one of the most important sources that finance entrepreneurial businesses.

Specifically, the first chapter examines the strategic conditions that drive entrepreneurial innovators to pursue novel innovation rather than innovation that is closer to existing technologies. Startups at a nascent stage lack assets and knowledge necessary to mass-produce and commercialize their innovation. Therefore, entrepreneurs often license technological intermediaries to large incumbent firms to access partners' well-established commercialization assets. The market where startups and established partners transact innovative technologies is often called the "market for ideas."

The market transaction of an immature technology, however, requires a costly exchange of information between two organizations. In particular, radical breakthrough innovation is often more difficult to communicate than its incremental counterpart because of a lack of available information necessary for valuation. When it is nearly impossible to convey credible information about the prospect of novel innovation, startups may avoid pursuing radically novel projects even when they are capable of undertaking such innovations. My research aims to understand what constraints entrepreneurs face in seeking to commercialize novel innovations and how they overcome these pitfalls using policy incentives.

Why should we care about the novelty of entrepreneurial innovation? First of all, the significant impact of breakthrough innovation on social welfare is well documented. Second, entrepreneurs are claimed to have better capabilities and incentives to develop radical innovations that disrupt the existing market structure governed by established incumbent firms. Lastly and most importantly, as long as incumbent firms are capable of incrementally improving existing technologies originated by them, it is not efficient for entrepreneurial entrants to use limited social resources to redundantly pursue the similar type of innovation.

While prior research studying market inefficiency has primarily focused on the danger of unwanted spillovers, this study suggests that the enormous costs of transferring information to a partner can also be a source of market inefficiency. As many small startups draw upon market mechanisms to bring their innovation to market, limited transferability of novel innovation may distort the incentives of entrepreneurial innovators, which could be a source of inefficiencies existing in the "market for ideas."

The results of this chapter show that exceedingly high communication cost indeed drives entrepreneurs to pursue less uncertain innovation with higher transferability, compared to high-risk-high-return type of innovation. The empirical findings contribute to an existing literature on technology commercialization strategies and innovation of entrepreneurial firms in the following ways. First, this study is one of the first papers that empirically trace the change in the quality of entrepreneurial innovation, rather than the quantity. With few exceptions, the direction of entrepreneurial innovation has been

overlooked as a result of measurement challenges. Investigating the types of commercialized innovations is even more difficult because one cannot use patent data: filing a patent does not necessarily mean that a patent holder commercializes the technology. This empirical study brings a new measure of the novelty of marketed technologies based on the originality of the scientific mechanisms behind a drug.

Second, the results shed a light on the decision-making process of startups regarding the choices of projects and commercialization modes. Prior research has analyzed the commercialization choices of entrepreneurs through the lens of the sequential decision-making process: a startup innovates and then decides how to market its technology. In reality, however, entrepreneurs consider external factors that affect profit generation from the beginning in determining which projects to advance and ultimately bring to market. When cooperation with an established partner is the only available option to commercialize innovation, for example, a startup may primarily take into the transferability of a technology into account on top of the ultimate expected returns from pursuing the innovation. In this sense, the innovation and marketing decisions of entrepreneurs are endogenous to environmental conditions. My findings support the view of entrepreneurial decision making in the context of technology commercialization.

The empirical findings also have practical implications for startups and policy makers regarding how to moderate the problem of translating the prospect of radical breakthrough innovations. Moreover, this research traces the entire stream of revenues generated from novel technologies beyond the initial commercialization success and thus provides novel insight into the long-term effect of pursuing novel innovation on the growth of an individual firm.

I use an empirical approach called a difference-in-difference (DiD) method to measure whether entrepreneurs are more likely to bring novel innovations to market when a policy change unexpectedly helps them to convince partners of the prospect of novel technologies. The idea behind the DiD is that I compare the changes in the novelty of innovation from a group of firms disproportionately affected by the act to those in a less affected group. The empirical context analyzed in this paper is the Orphan Drug Act (ODA) enacted by the European Union (EU). The act originally aimed to facilitate the development of treatments for rare diseases. Interestingly, small drug developers have found that the policy incentives ease the development of “proof-of-concept” products of novel drugs that may attract partners.

To briefly explain, entrepreneurial drug developers have previously faced a chicken-and-egg game. Because it requires a series of massive-scale clinical trials to verify the efficacy and the safety of a drug, a startup has to find established partners that have a set of well-organized assets necessary to run clinical trials and to deal with regulatory requirements. In order to convince a partner, however, a startup should be able to bring partners credible evidence about the prospect of a drug that is not available until the startup actually runs large scale, costly-demanding clinical studies. When it comes to drugs closer to existing drugs, an entrepreneurial developer suffers less from the problem, since it can still refer to the performances and the effectiveness of drugs adopting the similar technologies to persuade a potential partner. By contrast, there hardly exists such prior art necessary to value a drug depending on radically novel technologies, which prevents startups from developing novel breakthrough drugs.

ODA is originally designed to provide a series of incentives to organizations of which drug candidates are designated 'orphan drug status.' The essence of the ODA incentives is to allow a drug developer to test a designated drug candidate in a small clinical trial setting specifically designed for a rare disease drug development, under the support and the close guidance of regulatory agencies such as the Food and Drug Administration (FDA) in the United States and the European Medicine Agency (EMA) in the EU. Unexpectedly, the act avails a new type of drug development strategy as follows. A biotech startup first develops a novel drug as an orphan drug to benefit from the ODA incentives. Then, when the developer generates enough amount of information to persuade large partners through the small-scale clinical trials, it reaches partners to suggest that they collaboratively expand the use of the new drug to treat other general diseases than an initially targeted rare disease. The availability of the new drug development strategy encourages startups to develop radically novel drugs rather than those that are closer to existing drugs.

For example, consider the case of Remicade that was initially approved as an orphan drug but soon became a blockbuster drug. Centocor, Inc, a biotech company founded in 1979, developed Infliximab, one of the first drugs based on monoclonal antibody (mAb) that intervenes in tumor necrosis factor (TNF) to moderate inflammatory responses. The company believed that Infliximab could be used to treat a series of autoimmune diseases. However, the company could neither afford to conduct costly independent clinical studies nor find a financing partner without having prior evidence. Alternatively, the company developed Infliximab as a treatment for the Crohn's disease, a rare inflammatory disorder. By doing so, the firm took advantage of the incentives provided by ODA. Moreover, because the rare disease affected only a small number of patients, the company did not need to recruit many patients for clinical studies, which generated considerable cost savings. When Infliximab was approved as Remicade in 1998, Johnson & Johnson immediately recognized its potential to treat other—more common—inflammatory diseases, such as rheumatoid arthritis and psoriatic arthritis. Two years later, as an independent subsidiary of Johnson & Johnson, Centorcor, Inc, expanded the drug's labels to treat more than eight disorders. Remicade became the first anti-TNF biologic therapy to treat one million patients worldwide, and it is considered one of the most successful orphan drugs. The Remicade example demonstrates how a biotech startup can convince a large partner of the value of a radical drug by showcasing it in a small market using ODA incentives.

I address that the goal of this paper is not to evaluate the direct impact of ODA on orphan drug development. Rather, this research provides new insight into a positive externality of ODA: the act reduces information asymmetry between entrepreneurial innovators and large incumbent firms seeking to collaborate for novel innovation.

Next, I explain how I measure the novelty of innovation in the context of the pharmaceutical industry. I measure the novelty of drugs using the originality of the mechanisms used by drugs. A drug intervenes in the human body through a specific mechanism. For example, angiogenesis-inducing cancer drugs block the oxygen delivery channels to tumor cells to induce the natural death of cancerous cells. Some mAb-based cancer drugs deliver toxins directly to the problematic cells. Most allergy medications block histamine receptors to reduce the level of histamine absorbed in the body. These mechanisms are called Mechanism Of Actions (MOAs). MOA is not only a widely used

term among drug developers and researchers in related fields but also an important measure of the novelty of drugs, as indicated in the following Nature article.

> "As a productivity year I'd give [2014] a 3 out of 3," says Chris Milne, Director of Research at the Tufts Center for the Study of Drug Development in Boston, Massachusetts, USA. In terms of innovation, however, Milne ranked the 2014 approvals only "a 2 out of 3." The reasons being, drug companies seek approvals for agents that act on *the same proven targets and indications.* For example, among four drugs approved for type 2 diabetes, two are second- and third-in-class sodium-glucose cotransporter 2 inhibitors to treat type 2 diabetes and the other two are fourth- and fifth-in-class glucagon-like peptide 1-receptor agonists. "There is some of that herd mentality here," he notes (Mullard 2015).

I identify each MOA used by a therapeutic molecule. I then sort molecules by MOA, disease category and entry date to generate a sequence number. If the number is 1, then the molecule introduces a brand-new mechanism to treat a disease category for the first time. 2 indicates that a drug is the second one adopting a novel mechanism. In that sense, the sequence number is used as a "novelty score."[1] In addition, I construct a binary variable that assigns a value of 1 to the first five drugs that use a novel mechanism and 0 to the others, to take into account that several drug developers often compete on a novel mechanism so one might not say the first one precedes the second one. I conduct robustness checks by adjusting the number of drugs that use a brand-new mechanism—1, 3, 5 and 7—and by using the novelty score itself as a dependent variable. The empirical results are robust to the modifications.

Upon the construction of this measure on the novelty of drugs, I develop a panel dataset that includes the detailed development and commercialization histories of therapeutic molecules. The dataset includes all drug development projects across the globe from 1980 to 2014. I combine multiple sources to develop this dataset.

The study primarily draws upon the Pharmaproject database to collect the list of pharmacological research projects and associated characteristics. I collect the unique drug ID; drug name; originator; licensees; target disease indications; related patent numbers; and dates of main events such as dates of entry, patent application, licensing agreement, approval, and expansion to new disease indications. Additionally, the dataset comprises detailed molecule-specific characteristics including the mechanism of action, route, origin, weight, molecule structure (the number of hydrogen bond (H.Bond) donors, H.Bond acceptors, and rotatable bonds), diffusion speed within a human body (logP), whether a molecule is patented, and whether it is a New Chemical Entity (NCE). The database is widely used by researchers in life science as well as in innovation and management.

I complement the database with clinical trial data and orphan designation data. The clinical trial data are collected from clincialtrial.gov. The US orphan designation data is obtained from the FDA website, and the EU data is from the EMA website. The final

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[1] Note that an MOA is not subject to patenting. Although patents offer strong protection for pharmaceutical inventions, patents do not award exclusionary rights over the scientific principles underlying drugs.

dataset includes a detailed history of each drug candidate, including both successful drugs and discontinued drugs, from entry to approval and label expansion (or discontinuation in the case of discontinued products).

To summarize, using a new measure of the novelty of innovation and a panel dataset of therapeutic molecules, this empirical study shows that biotech startups are more likely to market breakthrough drugs in areas affected by ODA. In addition, I find two related findings. First, this research finds that, in ODA-affected areas, entrepreneurial firms individually hold novel projects longer before contracting with licensee partners. It suggests that, as a response to ODA, biotech firms are more likely to play active roles in advanced R&D compared to established pharmaceutical partners, in the purpose of generating credible information of the quality of novel drugs benefitting from ODA. It leads me to study the changes in the timing and the formation of partnership between startup innovators and established partners in Chapter 2.

Second, I find that startups make more profits from pursuing novel drugs as a result of ODA. Biotech firms in ODA-affected areas expand the use of novel drugs to treat a greater number of diseases – i.e. commercialize new products in more markets – than those pursuing novel drugs in less affected areas. Of course, however, it takes huge resources to bring a drug to a single market, particularly in terms of financial support. How do novel drugs get financed? Does the act similarly affect financial investors to support novel innovations than before? To answer those questions, I look at the changes in the investment strategies of venture capitals (VCs) in a response to ODA in Chapter 3.

In the second chapter, I find evidence that the propensity of licensing increases in a group of drug molecules disproportionately impacted by ODA. The policy shift helps biotech firms deliver meaningful information enough to convince established partners. Interestingly, the results of the second project report the delayed timing of forming a partnership. As a result of ODA, biotech firms are more likely to engage in partnership during clinical trial stage rather than during pre-clinical stage. The delay of partnership implies that startup firms advance their innovations further so that they can convey rich information on the prospect of drugs to potential partners. In fact, the more advanced a molecule of interest is, the superior bargaining position a drug originator achieves against a commercialization partner. Lastly, this study documents that the relationship between licensing and drug approval outcomes becomes less tight. It means that biotech firms increasingly decide to independently commercialize drugs rather than depending on the commercialization capabilities of established partners. In other words, an independent commercialization mode becomes an available option due to the ODA incentives. The close communication with and the guidance of regulatory agencies led by ODA enable entrepreneurial firms to build their own commercialization assets. Still, however, the independent capabilities of biotech firms do not appear to be enough to independently go through a set of complicated and risky clinical trials. The approval of novel drugs requires a way more comprehensive and meticulous clinical studies than the approval of drugs similar to existing ones and, thus, still heavily depends on the partnership with established pharmaceutical partners.

This project makes several implications. The determinants of the propensity and the timing of partnership between venture firms and large established firms have received a sheer volume of attention from researchers. The previous literature mainly focuses on the impact of intellectual property protection on the technology commercialization

strategies of entrepreneurs. While the significance of complementary assets has been acknowledged as an important factor, relatively less research reports causal evidence. Possibly, the lack of evidence is due to the rareness of shocks that exogenously affect the acquisition of complementary assets by startups. As the knowledge and resources required for commercialization tend to accumulate slowly over time within an organization, it is difficult to find an empirical context that changes the status quo. ODA provides an ideal setting to test the impact of complementary assets on the formation of inter-firm collaboration, by unexpectedly decreasing the cost of acquiring a subset of complementary assets.

Also, this paper sheds a new light on the evolution of partnership for technology commercialization. A grand volume of literature has examined the alliances between entrepreneurial innovators and established partners, but still more examinations are required to unveil determinants of detailed characteristics of alliances beyond the incidence of those. While some studies on economics and strategy look at the contract terms of the licensing agreements, the terms and conditions should be closely related to the configuration of division of labor among different-sized firms. This paper traces how an institutional change impacts the structure of partnership, contributing to the pervious studies on the contract for cooperative technology commercialization between a startup and an established partner.

Lastly, this study helps practitioners in search of suitable technology commercialization modes. It documents that biotech firms take advantage of ODA to attain useful resources under the close guidance of regulatory agencies and leverage the capability to play active roles in getting drug sales approval. It increases both the propensity of finding a licensing partner and the success rate of independent commercialization.

In Chapter 3, I study how ODA affects the timing and the feature of investments of venture capitalists (VCs). VCs invest in innovations at a nascent stage, which inherently incorporates huge risks. Because it is difficult to valuate the prospect of novel technologies at an early development stage, however, VCs may be herded into finance advanced-stage – less uncertain - projects for which an archive of scientific knowledge and commercial performances necessary for a correct valuation is available.

The additional information provided by ODA helps VCs to better understand the prospect of radically novel drug candidates at an early stage, thereby affecting the timing and the attributes of investments made by VCs. I compare investments made by VCs that take place in technology areas disproportionately affected by ODA with those in less affected areas, within the boundary of bio-pharmaceutical fields. I find that VCs are more likely to invest in early-stage innovations in areas significantly affected by ODA. Also, VCs investing in innovations at a nascent stage syndicate the investments with other investing firms rather than bet a large amount into a single firm as a sole investor.

In addition, I explore how ODA affects the performance of VC-backed startups in the affected areas. While ODA may provide trustworthy information to help VCs make fully-informed decisions, it is possible that the act may lead VCs to speculate on immature technologies. The two situations posit different implications on how we think about the economics behind the effects of ODA. I document that the exit performances of VC-backed startups do not get worse as a result of VCs investing into early-stage innovations. It suggests that VCs are indeed enabled to make fully-informed decisions thanks to

information provided by ODA, rather than merely speculate on risky and highly uncertain projects.

This project joins the discussion on the determinants of entrepreneurial financing and their implications on the types of technologies that receive the investments. The results of this project suggest that the availability of a small market test caused by a policy shift leads VCs to better test the ideas of exploratory technologies and, thus, to finance the nascent innovations pushing the scientific frontier. In addition, this study documents the investment tactics of VCs in financing technologies at an embryonic stage but still avoiding high uncertainty associated with the highly certain types of innovations.

Finally, the results of this paper relates to a literature on the links between public policy and the direction of private investments. This study traces how an institutional change encourages VCs to invest in early-stage technologies without decreasing the prospects of the investments. Thus, our findings can aid policy makers design an environment that pushes the trajectory of private VC investments toward breakthrough innovations.