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The impact of innovation on the profitability of the biotech industry

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Abstract

Since the 1970s, advances in biotechnology have rarely translated into profitable financial opportunities. The recent breakthrough in immunotherapy seems to have turned the tide and improved the productivity growth. We study the impact of this innovation on the profitability of the biotech industry. Constructing a new dataset of cancer biotech initial public offerings (IPOs) and using recent observations on the probability of success in the drug development process, we find that the median return on equity in the cancer biotech industry has increased from 11 percent to 15 percent. This is a noticeable improvement but it is not yet sufficient to significantly increase the inflow of early stage investors. The financial constraints in this sector are still important.

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1. Introduction

The financing of innovation influences firm innovative performance in many areas (Hall et al., 2016) including technological innovation (Hall, 2002, Hyytinen and Toivanen, 2005). This issue is particularly true in biomedical research, where financial constraints are one of the most significant barriers to effective drug development (Brown et al, 2017). In this paper, we study the financing of innovation in the biopharmaceutical industry through megafund. We construct a new dataset of cancer biotech initial public offerings (IPOs) and analyze the implications of the cancer immunotherapy revolution on this industry. We hypothesize that the immunotherapy revolution has increased returns to investors and investigate whether the return compensates for the risk of this industry.

The specific nature of the biopharmaceutical industry makes its funding peculiar and difficult (Hull et al., 2019). First, it is very expensive and the scale of funding requirements needed for creating a truly diversified portfolio outstrips the capital available from venture capital (VC) funding. Private equity (PE) funds which are of larger scale, could be an alternative source of financing, but their focus is to invest in and restructure more mature companies rather than speculating on "long shots". Second, this industry has a very long-time span of 10 to 20 years starting with the drug discovery, followed by the subsequent clinical trials and ending with the Food and Drug Administration (FDA) approval (Lazonick and Tulum, 2011). The duration of the rounds of financing is very long, which reinforces the asymetries of information at the expense of the venture capitalists. Third, it has a substantial probability of failure, with a very low asset tangibility which reduces the salvage value of the firm in case of bankruptcy. Fourth, its business model is not simply based on new technological improvements like in the semiconductors or software industries, but it requires scientific breakthroughs (Malerba and Orsenigo, 2015). Finally, a fifth distinctive trait of the biotech industry is the higher cost of learning for VC investors, which prevents a good coordination among them. These features of the biotech industry worsens the standard problems that VCs must address in the financing of innovation (Hall and Lerner, 2010), and leads to under-provision of capital in this sector (Janeway et al., 2021).

Harrington (2012) found that the cost of equity capital in the pharmaceutical industry varied from 9.8 percent to 16.9 percent between 2001 and 2008. For large pharmaceutical companies, it was estimated at 11.4 percent (Giaccotto et al., 2011). Kerins et al. (2004) found a cost of capital for a well-diversified venture capitalist at 16.7 percent. Cockburn and Lerner (2009) estimated that the cost of capital for biotechnology investments is 20 percent or higher. Thakor et al. (2017) argue that most of the investments in the biotech industry did not meet this 20 percent threshold. This is a substantial challenge to funding biomedical research and development (R&D). To circumvent these challenges, Fernandez et al. (2012) and Fagnan et al. (2013) proposed to use sophisticated financial engineering techniques, to alleviate some of these constraints. Using the historical success rates for cancer projects from 1990 to 2011, Fernandez et al. (2012) found that a megafund would generate an average annual return of 8.9 percent for its equity tranche. Unfortunately, this is well below the cost of capital required by equity investors for biotech companies and much smaller than the average returns of venture capitals reported by Cochrane (2005).

However, since the early 2010s, and for the first time in 60 years, the cost of R&D on new drugs approved by the U.S. FDA has begun to decline. This improvement in R&D productivity can be explained in part by innovation based on immunotherapy, which has led to very encouraging advances in the treatment of cancers. The ability to manipulate parts of the immune system is becoming mainstream oncology. The past few years have been marked by

unprecedented clinical responses, rapid drug development, and approvals from the U.S. FDA. (Kelly, 2018). The cancer drug development process is becoming more efficient and generates a rebound in R&D productivity (Ringel et al., 2020). Consequently, we propose to integrate the recent evolution of the cancer drug development, and work on a new cancer megafund investment opportunity. We use recent data that include the immunotherapy revolution and cover a research period from 2000 to 2015 in the United States. We develop an original dataset of 122 initial public offerings (IPOs) specialized in the development of compounds for oncology.

We pool between 100 and 200 mutually uncorrelated cancer drug programs altogether to form an investable and highly diversified "megafund portfolio" of 5 billion dollars. Because cancer is a complex group of over 200 different diseases, multiple pathways are used to develop cancer drugs. This offers a potentially promising framework for portfolio diversification and risk reduction. Debonneil et al. (2018) or MacMinn and Zhu (2017) have shown that megafunds can support both medical discoveries and pension funding. We finance these portfolios through both equity and debt products. Tapping credit markets through securitized debt allows to address a larger pool of investors and raise the large amounts of capital that are required by this industry. This is in line with Kerr and Nanda (2014), who shows the growing importance of debt for financing innovation. A megafund differs from large venture capital funds, new pharmaceutical companies, or biopharmaceutical mutual funds in the sense that (i) it uses securitization to finance preclinical or early-stage developments, (ii) it invests in many biomedical projects at different stages of their development cycle and (iii) it is financed by both equity and debt. The capital structure of these megafunds is structured into distinct debt and equity tranches to distribute the overall risk of their investments. The debt is issued in the form of bonds collateralized by the portfolio of pipeline compounds and patents. The various risk/return profiles offered by each of these tranches aim at attracting the broadest range of investors and increase the potential sources of funding.

We find that the return generated by this megafund approach has increased up to 14.8 percent. Although improving, it is still short of the usual costs of capital required by the biotech industry, suggesting that this is not yet a viable source of financing. We extend the steam of literature on megafunds that was developed by Marko (2013), Tenenbaum (2013), Yang et al. (2016), Hull et al. (2019) and Lo and Siah (2021). Our analysis complements that of Fernandez et al. (2012) and Fagnan et al. (2013) and incorporates the recent productivity improvement generated by the immunotherapy innovation. The rest of the paper proceeds as follow: Section 2 describes the empirical model and the data. Section 3 presents the results and Section 4 concludes.

2. Methods and data

2.1. Megafund portfolio

We create a highly diversified megafund portfolio of 200 mutually uncorrelated anti-cancer programs with a value of 5 billion dollars. As of 2019, the existence of eight megafunds greater than $1 billion shows that this objective is achievable (Lerner and Randa, 2020). The innovative performance of firms is conditional to their distance from the technological frontier (Coad and Rao, 2006; Rocha et al., 2018). In this paper, we assume that all firms are at the same distance from this frontier. We set up a special-purpose vehicle (SPV) to guarantee that the portfolio's assets are used to service the Research-Backed Obligations (RBO). This

structure is a simple two-tranche collateralized debt obligation (CDO). The senior tranche has priority on the cash flows. The junior tranche ranks second in repayment priority, and pays a higher coupon rate which compensates for the higher risk. Equity holders are residual claimants and receive all the remaining assets and cash flows left after servicing the RBOs. The capital raised is used to finance the development of the compounds in the various phases of the process.

2.2. Cancer Drug Development Markov Chain

The drug development process is split into seven phases: the initial preclinical phase, the phases I, II and III of the clinical trials process, the new drug application (NDA), the approval, and the withdrawal. We model and estimate the revenues and costs at each phase of the drug development process based on a 7-state Markov chain process, with stochastic transitions from one phase to the next over time. Using data of probability of success (POS) for oncology from Wong et al. (2019) from 2000 to 2015, we estimate a new transition probability matrix (Table 1 and Table 2).

Table 1 *Average transition probabilities and time per development phase*

	Preclinical to Phase I	Phase I to II	Phase II to III	Phase III to NDA	NDA to Approval
POS	69.0%	78.7%	53.9%	48.5%	100.0%
Average months in phase	12.0	32.4	44.4	37.2	9.6

Source: Paul et al. (2010) for preclinical to phase I and Wong et al. (2019) for the other phases.

Table 2 *Transition matrix*

	$PreC_{t+1}$	Ph. I_{t+1}	Ph. II_{t+1}	Ph. III_{t+1}	NDA_{t+1}	$Appr._{t+1}$	$Withdr._{t+1}$
$PreClinical_t$	50.0%	34.5%	0.0%	0.0%	0.0%	0.0%	15.5%
Phase I_t	0.0%	80.9%	14.6%	0.53%	0.0%	0.0%	3.9%
Phase II_t	0.0%	0.0%	86.2%	7.3%	0.3%	0.0%	6.2%
Phase III_t	0.0%	0.0%	0.0%	81.4%	7.8%	2.4%	8.3%
NDA_t	0.0%	0.0%	0.0%	0.0%	37.5%	62.5%	0.0%
$Approved_t$	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%
$Withdrawn_t$	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%

Time subscript t indicates current six-month simulation period and t+1 indicates the following six-month simulation period.

We find that the POS from Preclinical phase to approval phase is 14.2 percent. This is higher than the 12.6 percent reported in the literature and is explained by the rebound in the POS since 2012 as documented by Smietana et al. (2016) and Wong et al. (2019). The period witnessed the rise and success of immuno-oncology (IO) drugs. This is particularly visible in Phase II with almost a doubling of the transition rate for IO drugs compared to the traditional oncology averages (Thomas et al., 2021).

2.3. Cancer Drug Development Costs

We model the development costs per phase and per compound as a lognormal distribution process. We use new R&D costs estimates from DiMasi et al. (2016). Adams and Brantner (2006) showed that the cost of developing an oncology product is 20 percent higher than the sample mean development cost. Accordingly, we adjusted the mean costs by a factor of 1.2 to reflect the higher cost of oncology drug development. This gives a mean investment cost per compound from Preclinical to the end of Phase III of $413 million (Table 3). This compares to $263 million in Fernandez et al. (2012) who used estimates from DiMasi et al. (2003). This evolution was mostly driven by an increase in the clinical phase costs and by higher development risks (Lo and Siah, 2021). The cost of developing a new drug has doubled about every nine years from 1950 until 2010 and has made the industry unappetizingly risky from a financial standpoint (Yang et al., 2016).

Table 3 *Development costs and standard deviation per phase*

	Fernandez et al. (2012)	DiMasi et al. (2016)		Lognormal distribution parameters	
	Mean cost oncology	Mean cost oncology m_v	Standard Deviation s_v	μ	s
Preclinical	6.0	6.0	5.5	1.53	0.79
Phase I	19.0	30.4	29.6	3.08	0.82
Phase II	50.0	70.3	50.8	4.04	0.65
Phase III	188.0	306.5	153.3	5.61	0.47
Total cost	263.0	413.2			

Based on these results, we can derive the mean μ and standard deviation σ of the lognormal process generating the development cost process from Equation (1) and Equation (2).

$$\mu = ln(m_v) - \frac{1}{2} ln\left(1 + \frac{s_v^2}{m_v^2}\right) \qquad (1)$$

$$\sigma = \sqrt{ln\left(1 + \frac{s_v^2}{m_v^2}\right)} \qquad (2)$$

Where s_v^2 is the estimated adjusted variance cost per phase and m_v is the estimated adjusted mean cost per phase of the Table 3.

2.4. Investment Structure

We follow the standard investment structure of the biopharmaceutical industry, which is based on licensing agreements (Table 4). The megafund makes regular payments to finance the drug development program and to reward the successful completion of some prespecified objectives, including the completion of a phase. It also funds all clinical trial costs. 40 percent of the expected development costs are paid upfront at the beginning of each phase, and 20 percent are paid at the end when the milestone is completed. The return for the megafund comes from 85

percent of the proceed when the compound is sold. The 15 percent left is for the remuneration of the developers.

Table 4 *Investment structure costs (in $ million)*

	Development costs per phase	Upfront payments	Milestone payments
Preclinical	6	2.4	1.2
Phase I	30.4	12.1	6.1
Phase II	70.3	28.1	14.1
Phase III	306.5	122.6	61.3

2.5. Cancer Compound Valuation

To estimate the mean value and standard deviation of an approved cancer compound, we built an original dataset of 122 IPOs issued between 2000 and 2021 in the United States, from the pharmaceutical and biotech industries, and specialized on cancer therapies. We calculated the value per approved compound by dividing the market value of the company at the end of 2021 by the number of approved compounds. We estimated the mean value of a marketed cancer compound at $2,914 million. This represents an increase of 56 percent compared to the valuation used in Fernandez et al. (2012). It gives an average Tobin's q ratio of 7.1, in line with Morales and Radoniqi (2018). The standard deviation is estimated at $3,996 million, which represents an increase of 78 percent. Then, we used a binomial pricing model to consecutively estimate the value at each phase. The parameters of the model come from the drug development cost assumptions detailed in Table 3, and from the probabilities of transitioning and duration per phase presented in Table 1. We take the standard discount rates per phase used in this industry: 30 percent for preclinical to phase I, phase I to phase II and phase II to phase III, 25 percent for phase III to NDA, 15 percent for NDA to market. These high discount rates are consistent with Ewens et al. (2013), which shows that VCs bear a very high idiosyncratic risk. For the standard deviation, we took an average standard deviation to mean ratio of 1.19. Then, we used these values as parameters of the lognormal distribution to draw the simulation of the compound values at each phase. Results are presented in Table 5 column (1).

The correlation among the valuations of different compounds is a critical determinant of the megafund return. Using our new dataset, we find a mean pairwise correlation of 11 percent over the period 2010 to 2021. However, in our base scenario, we prefer to use a more conservative correlation of 20 percent, like in Fernandez et al. (2012).

Table 5 *Cancer compound valuation lognormal distribution parameters*

	(1) Value (in $ million)	(2) Standard deviation	(3) μ	(4) σ
Preclinical	26.6	36.4	2.75	1.03
Phase I	50.1	68.6	3.39	1.03
Phase II	129.2	177.0	4.33	1.03
Phase III	632.8	866.9	5.92	1.03
NDA	2605.7	3569.9	7.34	1.03
Approved	2914.0	3992.2	7.45	1.03

3. Results

Using the results established in Part 2, we run a 10,000-path simulation, with alternatively two different financing structures: a 100 percent equity financed project and a three-tranches (senior, junior, equity) RBO structure. The time horizon of this project is 15 semesters. The bonds receive semi-annual coupons and are amortized in equal instalments over various periods of time. The senior bonds have a maturity of 4 years. The junior bonds have a maturity of 6 years. These simulations focus on the early stage investments from the Preclinical phase until when the compounds are sold and transition to Phase II. They correspond to the realm of VCs and biotechnological companies as opposed to the late stage investments which are typically the domain of large pharmaceutical companies. Using the method developed in Fernandez et al. (2012), with the probability of success matrix, the costs and the valuation estimates presented in part 2, we simulate the cash flows invested and generated for an investor by the transition of the compounds from the Preclinical Phase to the Phase II.

Table 6 presents the results of the simulation and their summary statistics. Starting with 100 and 200 programs for respectively the all-equity and the RBO structures, we find that 49.7 and 91.8 compounds reach the goal of entering Phase II, compared to 52.8 and 101.7 compounds for Fernandez et al. (2012). This reduction in the number of compounds that reach the Phase II highlights the increasing complexity of passing clinical trials successfully (Marko, 2013). However in our simulation, a higher number of compounds were finally approved by the FDA to be marketed. This reflects the recent rebound in the probability of success following the immunotherapy revolution.

The results of our simulation show that the megafund is profitable on the period from 2000 to 2015. The senior tranche bond investors received an annual yield of 5 percent and were repaid in full 100 percent of the time, which is comparable to historical default rates of the highest-rated AAA bonds. Junior-tranche bond investors were paid an annual yield of 8 percent and repaid in full 96.7 percent of the time. This represents a higher default risk than in Fernandez et al. (2012), and is due to a higher volatility of equity. Equity-tranche investors received an average annual return of 9.7 percent for the all-equity fund, and 9.6 percent for the RBO fund, compared to 7.1 percent and 8.9 percent. These improving performances are even better when we consider the median returns on equity with 10.2 percent for the all-equity fund and 14.8 percent for the RBO fund, versus respectively 7.2 percent and 10.9 percent in Fernandez et al. (2012). This difference between the average and median returns comes the highly skewed nature of the distribution (see Figure 1). The probability of losing money has slightly decreased

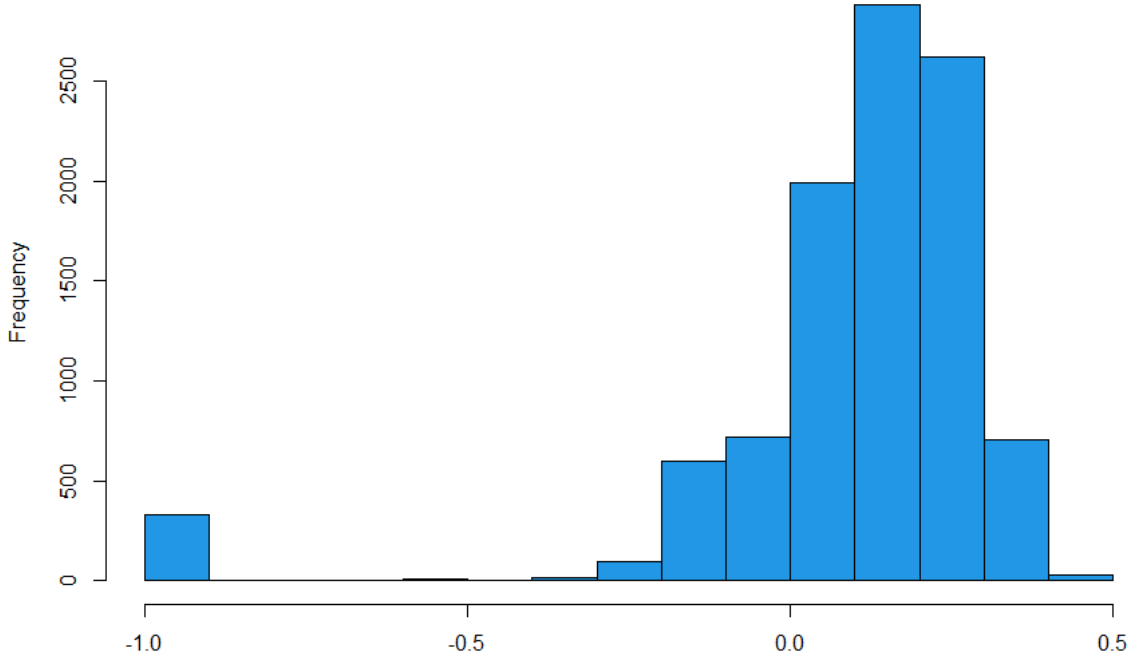
and the probability of earning more than 15 percent has substantially increased. The immunotherapy revolution and the increasing probability of success are reflected into a higher return for the megafund. Nonetheless, albeit progressing, these returns fall short of the rates of return required by VCs and PE investors for this type of early stage investments.

Table 6 *Summary statistics of the simulation results*

	Our results		Fernandez et al. (2012)	
	All-Equity	Research-Backed Obligations	All-Equity	Research-Backed Obligations
Number of Compounds				
Preclinical	50	100	50	100
Phase I	50	100	50	100
Correlation	20%	20%	20%	20%
Number of compounds to reach Phase II	49.7	91.8	52.8	101.7
Number of compounds sold in Phase III	0.7	1.9	0.9	2.3
Number of compounds sold once approved	0.8	1.2	0.6	1.0
Liabilities				
Capital ($ million)	2,500	5,000	2,500	5,000
Senior Tranche ($ million)	—	1,250	—	1,250
Junior Tranche ($ million)	—	1,250	—	1,250
Equity Tranche ($ million)	2,500	2,500	2,500	2,500
Equity Tranche Performance				
Average annualized return on equity (S.E.)	9.7% (9.1%)	9.6% (24.2%)	7.1% (7.7%)	8.9% (15.3%)
Median annualized return on equity	10.2%	14.8%	7.2%	10.9%
Prob. (return on equity < 0)	14%	18%	17%	20%
Prob. (return on equity > 5%)	71%	82%	61%	68%
Prob. (return on equity > 15%)	30%	50%	15%	35%
Debt Tranches Performance				
Senior Tranche: default prob., expected loss (bp)	—	0%, 0	—	0%, 0
Junior Tranche: default prob., expected loss (bp)	—	3.3%, 8.9	—	0.8%, 2.4

bp: basis points.

Figure 1 *Distribution of the returns on equity for the RBO fund*



4. Conclusion

Since 2011, when the FDA approved the first immune checkpoint inhibitors, the cancer immunotherapy revolution has dramatically changed the game in cancer drug development. In this paper, we investigate the implication of this medical breakthrough on the profitability of investment in the cancer biotech industry. We develop a megafund investment proposal that reflects the new realities of this sector by covering a research period from 2000 to 2015 in the United States. We estimate a new Transition Probability Matrix and a new Markov Chain from POS oncology data. We also use a new cancer compound valuation based on an original dataset of cancer biotech IPOs. We calculate new R&D costs assumptions.

Our results establish an improvement in the return of a cancer megafund, but still insufficient to compensate for the risk of this type of investment. The financing of the cancer biotech companies remains a difficult issue, even after discounting the major advances in the immuno-oncology research. It confirms the pessimistic views of Pisano (2006) and Lazonick and Tulum (2011) on the sustainability of the current financial model in the biotech industry. This raises the question of public investments and innovation policies in the face of market failure (Mazzucato, 2016). However, the immunotherapy approach is continuously delivering new treatments like for example the near-infrared photoimmunotherapy (Maruoka et al., 2021). This may dramatically change the current environment. Consequently, it is important to regularly revisit this issue. We leave it for future research.

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