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Can Financial Engineering Cure Cancer?[†]

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The biotechnology and pharmaceutical industries are currently confronted with a conundrum: despite remarkable scientific breakthroughs over the past decade in our understanding of the molecular biology of disease, the financial returns to biopharma investments have been mediocre at best, and investors are withdrawing capital from this sector.[1] Accordingly, there is a growing concern within and outside the industry that the process of translating biomedical research into effective drugs is broken. Several explanations have been proposed for this state of affairs, but the most common is that the current business model for translational research and development is flawed.[2]

In particular, Fernandez, Stein, and Lo (2012) argue that drug development is becoming increasingly expensive, lengthy, complex, and risky. Each of these characteristics makes investors less interested in investing, *ceteris paribus*, and in combination they can cause significant underfunding for the entire industry. In particular, increasing complexity and risk imply that biopharma's traditional financing vehicles of private and public equity are becoming less effective funding sources because the needs and expectations of limited partners and shareholders are not consistent with the realities of biomedical innovation. The quarterly earnings cycle, real-time pricing, and dispersed ownership of public equities imply constant scrutiny of corporate performance from many different types of shareholders, all pushing senior management toward projects and strategies with clearer and more immediate payoffs, and away from more speculative but potentially transformative research.

Private equity may offer more latitude for risk taking and deferred exits, but the scale of capital commitment is considerably smaller, the time horizon is still shorter than most clinical-trial cycles, and funding decisions are driven less by scientific breakthroughs than by business cycles and windows for conducting initial public-equity offerings.[3] As a result, the riskiest segment of the drug-development process—the translational phase in between basic research and human clinical trials—is now known as the "valley of death" because of the dearth of funding. For example, in 2010 only $6 billion

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[1] For example, the annualized return of the New York Stock Exchange Arca Pharmaceutical Index (stock symbol "DRG") during the period from January 2, 2002 to January 4, 2012 is −1.2 percent, and despite the near doubling of the aggregate R&D budget of the pharmaceutical industry from $68 billion in 2002 to $127 billion in 2010, there has been little appreciable impact on the number of new drugs approved (Evaluate Pharma 2010). Life sciences venture-capital investments have been equally disappointing, with an average internal rate of return of −1 percent over the ten-year period from 2001 through 2010 according to VentureXpert data.

[2] See Pisano (2006).

[3] See Huggett (2012) and Papadopoulos (2011). In fact, Nanda and Rhodes-Kropf (2011) observe that even the mere concern about the availability of future rounds of financing—due solely to the *possibility* of unfavorable economic conditions—is often reason enough for venture capitalists to shun proven and economically viable technologies.

to $7 billion was spent on translational efforts, while $48 billion was spent on basic research, and $125 billion was spent on clinical development that same year.[4]

In this paper, we describe a new approach to financing biomedical innovation that we first proposed in Fernandez, Stein, and Lo (2012) and extend in several ways here: using portfolio theory and securitization to reduce the risk of translational medicine. By combining a large number of drug-development projects within a single portfolio, a "megafund," it becomes possible to reduce the investment risk to such an extent that issuing bonds backed by these projects becomes feasible. Debt financing is a key innovation because the cost of each drug-development project can be several hundred million dollars; hence, a sufficiently diversified portfolio may require tens of billions of dollars of investment capital, and debt markets have much greater capacity than either private or public equity markets.[5] If these bonds are structured to have different priorities, the most senior class or "tranche" may be rated by credit-rating agencies, opening up a much larger pool of institutional investors who can purchase such instruments, e.g., pension funds, sovereign wealth funds, endowments, and foundations.

In Section I we present a highly simplified analytical example of a megafund portfolio to provide intuition, in Section II we describe some simulation results of a hypothetical cancer megafund using historical data on anti-cancer compounds, and we conclude in Section III.

I. A Stylized Example

Consider a hypothetical drug-development program that requires $200 million in out-of-pocket development costs (in present value), a ten-year development period during which no revenues are generated, and has a 5 percent chance of producing an approved drug at the end of the ten years.[6] Very few rational investors would be attracted by such an opportunity, even if a successful drug generates $2 billion in annual revenues over the subsequent ten-year period from years 11 to 20 (the typical amount of patent protection remaining at the time of approval). Using a cost of capital of 10 percent for these cash flows, the expected compound annual rate of return for this project is 11.9 percent, but the return standard deviation is 423 percent due to the extremely skewed distribution of success and failure.

Now consider a portfolio of 150 such projects and assume that they are independently and identically distributed (IID). Then the expected return of the portfolio remains 11.9 percent, but the return standard deviation becomes $423/\sqrt{150} = 35$ percent, yielding a much more attractive investment. Of course, this risk reduction is not easy to come by—it requires $30 billion of capital! However, the reduction in risk allows a significant portion of this capital to be debt rather than equity. In particular, because the probability of at least two successes in 150 IID trials is 99.6 percent, this megafund could issue up to $2 \times \$12.3 = \$24.6$ billion of ten-year zero-coupon bonds at the outset with a default probability of $100 - 99.6 = 0.4$ percent. As of February 2012, Moody's reported the average yield of seasoned Aaa corporate bonds with approximately 30 years to maturity to be 3.85 percent (Federal Reserve Board of Governors 2012), which is a reasonable proxy for the yield of a ten-year bond with high credit quality. At a yield of 3.85 percent, a zero-coupon bond that promises to pay $24.6 billion in year 10 would generate proceeds of $16.8 billion when issued in year 0. If the remaining $13.2 billion were financed by equity, the expected rate of return and standard deviation would be 17.8 percent and 78.9 percent, respectively.[7] Of course, these values depend critically on the assumption that the 150 projects are independent; if they are positively correlated, the amount of risk reduction will be lower. Alternatively, to achieve the same

[4] See Milken Institute (2012).

[5] For example, in 2010, the size of the entire US venture capital industry was $176 billion, whereas the size of the US bond market was $35.2 trillion. In 2011, the total amount of all US initial public-equity offerings (excluding closed-end funds) was only $41 billion, whereas the amount of straight corporate debt issued was $1 trillion. See National Venture Capital Association (2011) and Securities Industry and Financial Markets Association (2012) for details.

[6] This example was first proposed by Fernandez, Stein, and Lo (2012), and we extend it here to allow for correlated transitions.

[7] These values are higher than those of the all-equity-financed case (11.9 percent and 34.6 percent) because of leverage, but are still within the range of risk/reward profiles of publicly traded equities.

level of risk reduction with positively correlated projects, more projects are needed, implying a larger amount of capital. For example, to attain the same probability of at least two successes in the IID case with projects that have pairwise correlation of 10 percent,[8] 600 projects would be required, implying a $120 billion megafund.

Because debt markets are significantly larger and have a much broader spectrum of investors than do private or public equity markets, the issuance of debt dramatically increases the potential funding sources for the megafund. Using securitization techniques, credit derivatives, and third-party guarantees can further increase the megafund's investor base. Guarantees are especially effective, not only because of their impact on credit ratings, but also because of their efficient use of capital. For example, for the case of 150 IID projects with a 5 percent success rate per project, the expected cost of a guarantee to protect the full amount of a $24.6 billion debt issue is $(1 - 0.9995) \times 24.6 + 0.0036 \times 12.3 = \$56.6$ million; hence, the present value of this expected cost at a 2 percent cost of capital is $46.4 million, approximately 19 basis points of the amount guaranteed.

II. Simulating a Cancer Megafund

Cancer research offers a concrete illustration of the potential benefits of megafund financing. As the leading cause of death in the United States as of 2011, cancer is an urgent social priority that has an estimated economic impact of 1.5 percent of gross domestic product. The unconditional baseline probability of successfully developing an anti-cancer therapy is very low (6.7 percent in oncology versus 12.1 percent in all other therapies as of 2011)[9]; the required investment horizon is relatively long (the approval process can take more than a decade); and conditional on approval, the expected return is high (revenues can be on the order of billions of dollars *per year* for the remaining life of a patent). Fernandez, Stein, and Lo (2012) have generalized the stylized analysis of Section I to a more realistic multistate, multiperiod framework which includes path-dependence and correlated asset valuations. In this article we provide an important extension to that framework: an analysis of the impact of guarantees on returns to bond and equity holders.

The need to extend the single-period model of Section I arises from the drug-approval process. At each stage of this process, larger cash inflows are required to fund additional testing.[10] Importantly, new investment at each stage can occur only when there is sufficient capital available that is not required for other uses such as debt service or repayment.

The dominant source of cash flow for the megafund derives from the sale of compounds out of the portfolio. Profits or losses accrue when the megafund purchases a compound in one phase and subsequently sells it at another phase. Analysis of the portfolio primarily involves the specification of four quantities: the transition probabilities, the distribution of trial costs in each phase, the distribution of valuations for each compound that is sold in a specific phase, and some form of dependence among the compound valuations.[11]

As in Fernandez, Stein, and Lo (2012), we consider two "cashflow" securitizations in which portfolios of ownership interests in experimental drug compounds are acquired using capital from the issuance of structured securities (*research backed obligations* or RBOs). The capital pools range in size from $3 billion to $15 billion. Because of the complexities of the waterfall and the drug approval process, numerical simulations are used to evaluate the RBO securities.[12] Fernandez, Stein, and Lo (2012) conduct two sets of simulations, one representing the early stages (preclinical to Phase II) and the other

[8] These calculations make use of the Vasicek (1987) limiting loss distribution; see Fagnan et al. (2013) for details.

[9] Thomas (2012).

[10] See Fernandez, Stein, and Lo (2012) for a more detailed discussion of the various stages of FDA approval.

[11] Fernandez, Stein, and Lo (2012) use historical data on over 2,000 anti-cancer compounds (reduced to 733 after data cleaning)—provided by Deloitte Recap LLC and the Center for the Study of Drug Development at Tufts University School of Medicine—to estimate a transition matrix, $\mathcal{P}$, describing the probability space for each compound in the portfolio. The transition probabilities for the *PRE* state were taken from Paul et al. (2010), and this study was also used to calibrate the parameters of the cost distributions. Estimation of the parameters for the valuation function and valuation correlations was done using data from Bloomberg and other sources. See Fagnan et al. (2013) for details of the models and calibration of the parameters.

[12] Pseudo-code for these simulations is given in Fagnan et al. (2013).

TABLE 1—SUMMARY STATISTICS OF CANCER MEGAFUND SIMULATION FOR ALL-EQUITY (ALLEQ) AND DEBT-AND-EQUITY-FINANCED (RBOS) CASES, WITH (GT) AND WITHOUT (NOGT) GUARANTEES OF PRINCIPAL

Simulation variable or summary statistic	A		A1–RBOs		A2–RBOs	
	AllEQ	RBOs	GT	NoGT	GT	NoGT
Number of compounds to reach Phase II	63.4	103.1	99.0	99.0	103.0	103.0
Liabilities						
Senior tranche ($ million)	—	1,250	2,000	2,000	2,000	2,000
Junior tranche ($ million)	—	750	750	750	—	—
Equity ($ million)	3,000	3,000	2,250	2,250	3,000	3,000
Guarantee ($ million)	—	—	1,000	—	1,000	—
Equity tranche performance (in percent)						
Average annualized return on equity	7.9	9.1	8.9	8.9	9.6	9.6
Prob (return on equity < 0)	15	19	21	21	18	18
Prob (return on equity > 0.05)	65	69	69	69	70	70
Prob (return on equity > 0.15)	18	34	41	41	34	34
Debt tranches performance						
Senior tranche: PD, EL (bp)	—	0.9, <0.1	0.3, <0.1	49, 8	0.1, <0.1	27, 4
Junior tranche: PD, EL (bp)	—	36, 10	39,15	200, 121	—	—
Guarantee cost (2 percent discount rate)						
Prob (cost of guarantee > 0) (in percent)	—	—	2.0	—	0.3	—
Average cost of guarantee ($ million)	—	—	10	—	0.8	—
98th-percentile draw on guarantee ($ million)	—	—	17	—	0	—
99th-percentile draw on guarantee ($ million)	—	—	429	—	0	—

representing the later stages (Phase II to New Drug Approval) of drug development. In this paper, we focus only on the early-stage simulation—Simulation A in Fernandez, Stein, and Lo (2012)—which represents the riskiest portion of the drug-development process and where funding is scarcest. In Simulation A, investments in compounds that begin in the preclinical phase are sold when they transition to Phase II if they are not terminated or sold for other reasons earlier.

Table 1 contains a comparison of the results for 1,000,000 simulated paths for a traditional all-equity fund and a matching RBO structure, each capitalized with $3 billion of equity over seven and a half years, but in the case of the RBO structure, the fund also issues $1.25 billion of senior debt and $0.75 billion of junior debt for a total capitalization of $5 billion.[13] The two columns labeled "Simulation A" show that the megafund is almost always profitable. The senior-tranche RBO investors received an annual coupon of 5 percent, and their principal was repaid in full 99.9 percent of the time, which is comparable to historical default rates of the highest-rated bonds reported by Moody's and Standard and Poor's. The junior-tranche RBO investors were paid an annual coupon of 8 percent and repaid in full 99.6 percent of the time; and equity-tranche investors received an average annualized return of 9.1 percent. In over a third of the simulated sample paths the average annualized return for equity exceeded 15 percent, versus only about a sixth for the case of the equity only fund.

In general, there is a trade-off between skewness and volatility. While the all-equity fund exhibits only a modestly lower probability of negative returns than the RBO equity tranche, it also exhibits a substantially lower probability of very large returns as can be seen in the comparative probabilities of returns exceeding 15 percent.[14] Of course, the most significant impact of the RBO structure is that it brings almost twice as many compounds—103 versus

[13] These values differ slightly from the values reported in Fernandez, Stein, and Lo (2012) because we are using slightly different input parameters and simulation algorithms.

[14] An open question remains the degree to which RBO equity would trade similarly to other structured securities' equity, which has traditionally traded infrequently, or whether investors would require additional liquidity premia for holding RBO equity.

63—to Phase II as the all-equity fund due to financial leverage.

With the addition of a "no strings attached" third-party guarantee,[15] the capital structure can be altered in a number of ways while still preserving the credit risk profile of the bonds. Table 1 reports results for a pair of simulation experiments, A1 and A2, that resemble Simulation A, but in each case, the capital structure is altered to increase the proportion of senior debt by reducing a portion of the more-difficult-to-place securities. In Simulation A1 a capital structure is chosen that reduces the fraction of capital allocated to equity and increases the fraction in the senior tranche, while in Simulation A2 we remove the mezzanine tranche entirely, leaving a capital structure allocated only between equity and senior debt. In both cases, we start with total capital of $5 billion and a guarantee with a maximum face value of $1 billion and report the comparable no-guarantee results to highlight the impact of the guarantee. Not surprisingly, the results in Table 1 show that credit losses are substantially higher without the guarantee. However, the less obvious result is that the expected cost of the guarantee to the provider is small relative to the amount guaranteed, with an expected loss of 0.1 to 1 percent of the face value of the guarantee. In fact, it is likely to be much less than the face value as demonstrated in the extreme quantiles in Table 1. These results suggest that even a small (in expected value) third-party guarantee can materially improve the economics of an RBO transaction.

As with any numerical simulation, the results in Table 1 depend on the various input parameters such as cost, revenue, and transition-probability assumptions, each of which can be debated at much greater length. Rather than attempting to justify them, we have placed our Matlab and R simulation sourcecode in the public domain with an open-source license so that others can run new simulations with their preferred parameters.[16] Also, see Fagnan, Stein, and Lo (2012), Section 4 for a discussion of some of the limitations and extensions of this framework.

[15] A "no strings attached" guarantee is one that does not involve any upfront fees, annual premia, or repayment of draws on the guarantee; in other words, it is a simple guarantee.

[16] http://web.mit.edu/alo/www/RBOtoolbox_final.zip.

III. Conclusion

Cancer is just one of a growing number of large-scale challenges confronting modern society that can be addressed only through the sustained collaboration of thousands of highly skilled, dedicated, and independent individuals over many years. Financial engineering methods such as portfolio theory and securitization facilitate such complex collaborations by providing appropriate financial incentives to all stakeholders. Although altruism and charitable giving are important elements in responding to these challenges, we cannot rely solely on these motivations given the scale of the problems to be solved. By structuring biomedical research funding in a research-backed obligation format, incentives to reduce the burden of disease are distributed to a much broader community of stakeholders. As a result, significantly greater resources can be marshalled to take on such challenges which, in turn, will attract leading experts to join the effort, instilling even more confidence among investors, and so on. Such a "virtuous cycle" presents altruistically motivated organizations with a powerful new tool for achieving social impact.

Proposing to raise billions of dollars for biomedical research in the current economic climate may seem ill timed and naïve. However, today's low-interest-rate environment is, in fact, ideal for issuing long-term debt, and investors around the globe are desperately seeking new investment opportunities that are less correlated with traditional asset classes. More importantly, the cost in terms of burden of disease—as measured by the more than half a million people expected to die of cancer this year in the United States alone or the $263 billion in estimated economic impact according to American Cancer Society (2011)—must be balanced against the risk of failure. Similar trade-offs exist for other grand challenges of this century such as flu pandemics, climate change, and the energy crisis.

Instead of asking whether we can afford to invest billions more at this time, perhaps we should be asking whether we can afford to wait.

REFERENCES

American Cancer Society. 2011. *Cancer Facts & Figures 2011*. Atlanta, GA: American Cancer Society.

Evaluate Pharma. 2010. *World Preview 2016*. London: Evaluate Pharma.

Fagnan, David, Jose Maria Fernandez, Andrew W. Lo, and Roger M. Stein. 2013. "Can Financial Engineering Cure Cancer?: The Unabridged Version." SSRN: http://ssrn.com/abstract=2203203.

Federal Reserve Board of Governors. 2012. "Federal Reserve Statistical Release: Table H.15 (519) Selected Interest Rates." Washington, DC: Federal Reserve Board.

Fernandez, Jose-Maria, Roger M. Stein, and Andrew W. Lo. 2012. "Commercializing Biomedical Research Through Securitization Techniques." *Nature Biotechnology* 30: 964–75.

Huggett, Brady. 2012. "Biotech's Wellspring: A Survey of the Health of the Private Sector." *Nature Biotechnology* 30: 395–400.

Milken Institute. 2012. *Fixes in Financing: Financial Innovation for Translational Research*. Washington, DC: Milken Institute.

Nanda, Ramana, and Matthew Rhodes-Kropf. 2011. "Financing Risk and Innovation." Harvard Business School Working Paper No. 11-013.

National Venture Capital Association. 2011. *National Venture Capital Association Yearbook 2011*. New York: Thomson Reuters.

Papadopoulos, Stelios. 2011. "Profile: Stelios Papadopoulos." *Nature Biotechnology* 29: 184.

Paul, Steven M., Daniel S. Mytelka, Christopher T. Dunwiddie, Charles C. Persinger, Bernard H. Munos, Stacy R. Lindborg, and Aaron L. Schacht. 2010. "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge." *Nature Reviews Drug Discovery* 9: 203–214.

Pisano, Gary P. 2006. *Science Business: The Promise, the Reality, and the Future of Biotech*. Boston: Harvard Business School Press.

Securities Industry and Financial Markets Association (**SIFMA**)**.** 2012. "U.S. Key Stats." Washington, DC: SIFMA.

Thomas, David. 2012. "Oncology Clinical Trials—Secrets of Success." *BIOTech-NOW*, February 24.

Vasicek, Oldrich Alfons. 1987. *Probability of Loss on Loan Portfolio.* San Francisco: KMV Corporation.