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Commercializing biomedical research through securitization techniques

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Biomedical innovation has become riskier, more expensive and more difficult to finance with traditional sources such as private and public equity. Here we propose a financial structure in which a large number of biomedical programs at various stages of development are funded by a single entity to substantially reduce the portfolio's risk. The portfolio entity can finance its activities by issuing debt, a critical advantage because a much larger pool of capital is available for investment in debt versus equity. By employing financial engineering techniques such as securitization, it can raise even greater amounts of more-patient capital. In a simulation using historical data for new molecular entities in oncology from 1990 to 2011, we find that megafunds of $5–15 billion may yield average investment returns of 8.9–11.4% for equity holders and 5–8% for 'research-backed obligation' holders, which are lower than typical venture-capital hurdle rates but attractive to pension funds, insurance companies and other large institutional investors.

Consensus is growing that the bench-to-bedside process of translating biomedical research into effective therapeutics is broken. A confluence of factors is responsible for such pessimism but one of the most widespread is the sense that the current business model for life sciences R&D is flawed[1–3]. The productivity of big pharmaceutical companies—as measured by the number of new molecular entity and biologic license applications per dollar of R&D investment—has declined in recent years[4], and their stock-price performance over the past decade—an annualized return of −1.2% for the New York Stock Exchange Arca Pharmaceutical Index during the period from 2 January 2002 to 4 January 2012—has been equally disappointing. 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[5]. Life sciences venture-capital investments have not fared much better, with an average internal rate of return of −1% over the 10-year period from 2001 through 2010 according to VentureXpert data (**Supplementary Empirical Results**).

However, these dismal returns contrast sharply with the many promising breakthroughs that have occurred in biomedicine in recent years, including gene therapies for previously incurable rare diseases, molecularly targeted oncology drugs, new modes of medical imaging and radiosurgery, biomarkers for drug response or for such diseases as prostate cancer and heart disease, and the use of human genome sequencing to find treatments for diseases that have confounded conventional medicine, not to mention advances in bioinformatics and computing power that have enabled many of these applications. Moreover, there are many life-threatening diseases for which the number of afflicted individuals continues to increase—if for no other reason than population growth—implying a growing demand for therapeutics from a grateful and price-insensitive clientele. Why, then, does the industry appear to be so challenged?

Here we propose one explanation for this apparent inconsistency and a possible solution. Our proposed explanation is the trend of increasing risk and complexity in the biopharma industry. This trend can be attributed to at least two distinct sources: scientific advances and economic circumstances. That biomedicine is far more advanced today than even a decade ago is indisputable, but breakthroughs such as molecular biomarkers for certain diseases generate many new potential therapies to be investigated, each of which requires years of translational research at a cost of hundreds of millions of dollars and has a substantial likelihood of failure. Although such complexity offers new hope to the afflicted, it also presents an enormous number of uncertain prospects that must be triaged by researchers, biopharma business executives, investors, policymakers and regulators.

A host of economic and public-policy conditions has also contributed to this uncertainty, including declining real prescription-drug spending; rising drug-development costs and shrinking R&D budgets; the 'patent cliff' of 2012 during which several blockbuster patents will expire; increased public-policy and regulatory uncertainty after the Vioxx (rofecoxib) debacle; the potential economic consequences of healthcare reform; less funding, risk tolerance and patience among venture capitalists; narrow and unpredictable windows of opportunity for conducting successful initial public-equity offerings; unprecedented stock market volatility; and the heightened level of financial uncertainty from ongoing repercussions of the recent financial crisis. Consequently, the lengthy process of biomedical innovation is becoming increasingly complex, expensive, uncertain and fraught with conflicting profit-driven and nonpecuniary motivations and public-policy implications. Although other industries may share some of these characteristics, it is difficult to find another so heavily burdened by all of them.

This trend of increasing complexity and risk implies that the traditional financing vehicles of private and public equity are becoming less effective for funding biopharma because the needs and expectations of limited partners and shareholders are becoming less aligned with

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the new realities of biomedical innovation. The traditional 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 science and translational research. Private equity may afford more latitude for risk taking and deferred exits, but the scale of capital commitment is considerably smaller and funding decisions are often driven less by scientific breakthroughs than by business cycles and windows for conducting initial public-equity offerings[3,6,7]. Recent financial research suggests 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[8,9]. Industry professionals cite the existence of a 'valley of death'—a funding gap between basic biomedical research and clinical development. For example, in 2010, only $6–7 billion was spent on translational efforts, whereas $48 billion was spent on basic research and $127 billion was spent on clinical development that same year[5,10].

We propose an alternative for funding biomedical innovation that addresses these issues through the use of 'financial engineering'[11,12], mathematical and statistical models for structuring and pricing various financial securities to achieve specific objectives. Our approach involves two components: (i) creating large diversified portfolios—'megafunds' on the order of $5–30 billion—of biomedical projects at all stages of development; and (ii) structuring the financing for these portfolios as combinations of equity and securitized debt so as to access much larger sources of investment capital. These two components are inextricably intertwined: diversification within a single entity reduces risk to such an extent that the entity can raise assets by issuing both debt and equity, and the much larger capacity of debt markets makes this diversification possible for multi-billion-dollar portfolios of many expensive and highly risky projects. One indication of this larger capacity is the $1 trillion of straight corporate debt issued in 2011 versus the $41 billion of all initial public-equity offerings (excluding closed-end funds) that same year[13].

The need for such large amounts of funding follows directly from the combination of the large out-of-pocket costs required to determine the therapeutic potential of a single compound from its preclinical stages to either approval or withdrawal, and the number of such projects required to achieve a reasonably attractive risk-reward profile for typical investors. The key feature of portfolio diversification is the reduction in uncertainty achieved by undertaking many programs simultaneously. Even though it may be impossible to predict which of these programs will succeed or fail, the likelihood of success increases with the number of programs undertaken.

This obvious statistical fact has some less-obvious financial implications. With enough programs in a portfolio, the potential revenues become more certain, more easily valued by potential investors and more attractive from a risk-reward perspective. As a result, these programs are more readily packaged for a much larger population of investors through financial-engineering techniques such as securitization[14], a financing method in which a pool of investment capital is raised by issuing equity as well as several classes of bonds that differ from each other in their risk-reward profile to a diverse population of investors, and in which the funds are used to invest in various assets that serve as the collateral for the bonds. Moreover, these assets may be diverse, spanning the full range of preclinical research to new drug applications and including royalty interests and licensing agreements as well as private and public equity.

Also, debt financing can be structured to be more 'patient' than private or public equity by specifying longer maturities; 10- to 20-year maturities are not atypical for corporate bonds. Indeed, in May 2011, the Massachusetts Institute of Technology issued $750 million in 100-year bonds at the historically low rate of 5.623%. Such long horizons contrast sharply with the considerably shorter horizons of venture capitalists and with the even shorter quarterly earnings cycle and intra-daily price fluctuations faced by public companies. Through financial engineering, bonds with different maturities can be issued by the same megafund to accommodate the different investment horizons of various types of investors. Therefore, a megafund can tailor the investment horizon of its funding to suit the programs in its portfolio, enabling research to follow the most scientifically productive paths instead of being constrained by financially driven business deadlines.

These benefits are especially relevant for biopharma R&D, for which untimely interruptions due to financial constraints almost always destroy considerable economic value, even for genuinely effective therapeutics. Even the possibility of such interruptions may be enough to alter important strategic decisions regarding research direction in the early stages of drug discovery. The megafund structure mitigates these scientifically perverse (but economically rational) effects, and debt financing still provides useful financial discipline and motivation for the borrower because of the need to make periodic interest payments. However, the ability to defer much larger principal payments is ideally suited to projects with longer-term payoffs such as those in biomedicine.

The megafund in context

Our proposal differs from existing business structures and practices in several important ways, and is not equivalent to creating a large venture-capital fund, a new pharmaceutical company or a biopharma mutual fund.

First, neither the biopharma industry nor their venture-capital investors currently use securitization to finance preclinical or early-stage drug development. Of course, the industry has long recognized the benefits of diversification, as demonstrated by the increasing number of biopharma mergers, acquisitions, consolidations and licensing deals over the past decade. Moreover, debt financing has also been embraced. For example, the $46.8-billion acquisition of Genentech (S. San Francisco, CA, USA) by Roche Holdings (Basel) in March 2009 was partly financed by Roche's $16.5-billion bond issue a month before; this was the second-largest corporate-bond offering of all time. However, both Roche and Genentech are well-established companies with clear and easily valued revenue streams. In the current climate of uncertainty, biopharma companies seem more focused on reducing risk and increasing operating efficiency—by engaging in mergers, acquisitions, licensing deals and joint ventures to produce more reliable revenue streams—than on investing in early-stage projects that are even riskier than their existing business lines.

Second, our proposal is to create a single financial entity that invests in multiple biomedical projects at various stages of their development cycle financed by securitized debt and equity, not to create another large publicly traded pharmaceutical company. Although big pharma companies are central to the later stages of drug development and the marketing and distribution of approved drugs, they do not currently play as active a role at the riskier preclinical and early stages of development for the reasons described above. Megafunds can fill this gap by funding more speculative early-stage R&D in exchange for a percentage of future royalties or proceeds from any subsequent sale of the intellectual property. Such speculative investments require a

much broader set of assets to achieve sufficient risk reduction, which is precisely what a megafund is designed to do.

Also, at earlier stages of development, the required resources per project are smaller and the ability to change direction by discontinuing less promising projects and redeploying capital to more productive assets is considerably easier. Compared with the plethora of small pharmaceutical companies currently pursuing just one or two projects, these savings are especially important for a megafund. It is considerably harder to cull compounds efficiently in a small company because the livelihoods of the employees and management depend on the continued development of the company's few compounds—in these cases, development tends to continue until the money runs out. With a megafund, this conflict is greatly reduced—capital can be more efficiently allocated to projects that are likely to succeed, and failing projects and compounds can be abandoned rapidly. In fact, for megafunds that have invested in a sufficient number of early-stage projects, it may be worthwhile to build and operate shared facilities for conducting preclinical studies motivated by the megafund's projects. Such a 'preclinical incubator' could provide the megafund with valuable economies of scale as well as reduce duplicative costs in the industry.

Third, our proposed megafund is not a biopharma mutual fund, which is simply a pooled vehicle for equity investors and therefore restricted to investing in companies that are already publicly traded. A megafund may invest in such companies, but it can also invest in startups, existing private companies, royalty streams, intellectual property and other assets. Moreover, a megafund will issue both debt and equity, making its capital structure materially different from that of a mutual fund; the business pressures, priorities and horizons it faces are correspondingly different. A megafund's portfolio manager is likely to be much more actively engaged in the scientific and engineering aspects of the portfolio assets, not unlike a traditional venture capitalist; in contrast, a biopharma mutual fund manager is essentially a stock picker whose only involvement in the management of the portfolio companies is through proxy voting decisions.

Despite these differences, a megafund does bear some resemblance to an existing class of business entities in the biopharma industry—drug-royalty investment companies—and this similarity supports the basic premise of our portfolio approach to financing biomedical innovation. Companies like Royalty Pharma (New York), Cowen Healthcare (Stamford, CT, USA) and DRI Capital (Toronto) are investment vehicles that acquire ownership interests in the royalty streams of approved drugs, rather than the equity of biopharma companies. By combining these ownership interests into a single portfolio, these vehicles are able to provide more attractive risk-reward profiles for their investors and can issue debt to finance their acquisitions. For example, the largest of the drug-royalty investment companies is Royalty Pharma, which owns interests in over 30 approved and marketed products—including such blockbusters as Humira (adalimumab), Remicade (infliximab), Atripla/Truvada (emtricitabine, tenofovir), Januvia (sitagliptin) and Rituxan (rituximab)—and interests in five products in late-stage clinical trials and/or under review at the US Food and Drug Administration (FDA). It has assets of over $8 billion as of May 2012, of which $4.1 billion is securitized debt with the acquired royalty streams of approved drugs serving as collateral. Its most recent debt issue occurred on 24 May 2012, a successful offering of $600 million maturing on 9 November 2018, and priced at 98.5 with a borrowing spread of the London Interbank Offered Rate (LIBOR) plus 3.00%—excellent terms considering current market conditions. All three rating agencies have rated this new issue "investment grade," an important designation that makes this debt eligible for purchase under the investment policies of many institutional investors such as pension funds, endowments and foundations. From 2004 to 2011, Royalty Pharma made $5.8 billion in life sciences investments, a notable amount in comparison to the entire life-sciences venture capital industry's investment of $26.3 billion during the same period.

The key difference between Royalty Pharma and our proposed megafund is the investment mandate. Royalty Pharma invests only in revenue-producing intellectual property (that is, royalty interests in FDA-approved products and in product candidates in late-stage clinical development (phase 3), not in preclinical or early-stage projects). As the investment focus shifts to earlier parts of the drug-approval process, the uncertainty becomes greater, calling for larger portfolios and more sophisticated financing and risk-management techniques to generate the same level of diversification and risk reduction. This inverted financing pyramid in which the biggest portfolios correspond to the earliest stages of translational medicine underscores the value of the megafund vehicle.

The feasibility of a megafund

Our proposal is clearly motivated by financial innovations that played a role in the recent financial crisis; hence, it is natural to question the wisdom of this approach. A full accounting of the causes of the financial crisis has yet to be written, and many mutually contradictory narratives have emerged and are still being developed[15]. Nevertheless, several unambiguous lessons can be learned from the crisis that are relevant to our current context. Although there is no consensus yet as to the ultimate causes of the crisis, there is little doubt that securitization was, and continues to be, an effective means of raising capital. Indeed, it may have been too effective[15,16], allowing potential homeowners to tap directly into a much larger pool of capital instead of obtaining mortgages from traditional banking institutions. But several other factors also contributed to the unprecedented amount of mortgage-related debt issued and the subsequent housing boom and bust[17]: a low-yield environment that motivated investors to take on additional risk to capture higher returns; the positive trend in US residential real-estate values over the four decades before the peak of the housing market in 2006 and the widely held belief that it would persist; competition among commercial banks, investment banks and other financial institutions to diversify their revenue streams by entering new businesses such as mortgage lending and structured financing; financial incentives for all parties involved in the securitization process; regulatory forbearance and accounting practices that obscured financial losses and did not adequately prepare for financial-market dislocation; and politicians who advanced the 'ownership society' initiative through legislation and government agencies, such as the Federal National Mortgage Association (Fannie Mae) and the Federal Home Loan Mortgage Corporation (Freddie Mac).

These factors offer important practical insights into the feasibility of creating biomedical megafunds. For example, one insight is the important role that government guarantees played in supporting the housing market: it is much less costly to provide a guarantee that protects bondholders than to purchase the bonds outright[16]. Therefore, the impact of public funds, such as those allocated to the National Center for Advancing Translational Sciences, can be greatly multiplied by using them to provide guarantees of debt-financed private entities engaged in translational medicine rather than investing in those entities directly (**Supplementary Methods: Credit Enhancement**).

Even so, the analogy between megafunds and the mortgage companies of the financial crisis also points to some potential pitfalls to be avoided. Statistical models of the biomedical portfolio returns should

be based on a detailed understanding of the science and engineering underlying the individual projects in addition to an analysis of historical returns. Portfolio valuations should reflect current market realities at all times rather than hypothetical expectations; otherwise, sharp declines and panic selling may be easily triggered when the market's valuation differs greatly from the portfolio manager's. And regulations surrounding the sale of megafund securities—including proper risk disclosure by issuers, suitability requirements for investors and realistic credit analysis—should be strictly enforced. Securitization is a powerful tool for raising capital, but like most powerful technologies, it can be abused when proper controls are not imposed.

From a broader perspective, the recent financial crisis is by no means unique[18], and bubbles and crashes may be an unavoidable consequence of human behavior coupled with free enterprise. Innovation may inevitably lead to irrational exuberance and unsustainable overinvestment, as with Dutch tulip bulbs in the 1630s, biotech stocks in the 1980s, internet stocks in the 1990s and US residential real estate in the early 2000s. Perhaps the most effective remedy may be to recognize the potential for speculation to emerge in any industry and to ensure that those investors who are ill-suited to such boom-or-bust cycles do not become victims of their destructive forces. More positively, if speculative behavior is a fact of economic life, it may be worthwhile to redirect some of this energy toward social priorities, such as reducing the burden of disease.

Nevertheless, throwing money blindly into an underperforming industry is hardly a recipe for success, as several industry experts have acknowledged[3,19,20]. Apart from the concerns related to the financial crisis, there are substantial organizational challenges to deploying large amounts of capital in the biopharma industry, even if megafund financing is feasible. For example, operational complexities of managing a portfolio of highly heterogeneous biomedical projects also increase with scale, which can reduce some of the benefits of diversification. Many venture capitalists have learned the hard way that small is beautiful, and that beyond a certain level of assets under management, their investment opportunity set begins to suffer from adverse selection, attracting more mediocre opportunities and fewer genuine breakthrough companies. A recent study found that the internal rates of return of venture capital funds peaked somewhere between $100 and $250 million and declined when assets exceeded $500 million[21]. This finding may seem to cast doubt on the wisdom of megafunds. However, as discussed below, megafunds are designed to appeal to a different set of investors. Therefore, the return objectives for megafunds do not have to reach the lofty level of historical venture-capital returns because the risk of these investments is commensurately lower. Nevertheless, potential dis-economies of scale must be carefully weighed in determining the optimal size of a megafund, which is likely to differ from one application to the next and should be determined by balancing organizational complexity against scientific, operational and financial synergies.

New business models as well as novel approaches to management, corporate governance and scientific collaboration may also be necessary before larger amounts of capital can be profitably deployed in this industry. Although these important issues lie beyond the scope of this paper, in the Discussion below we provide a brief review of several of the major business challenges to megafund financing as well as some possible solutions. As outsiders to the biopharma industry, we note that many of these implementation issues are beyond our expertise, but based on discussions with a broad cross-section of industry experts, we believe that megafund financing merits further consideration. The analysis in the sections to follow suggests that if these implementation issues can be addressed, the financing techniques proposed here can greatly expand the current scale of biomedical innovation.

For those who are unfamiliar with financial portfolio theory, we present a highly simplified mathematical model in the next section that provides intuition for our approach in an unrealistic but accessible context. We then describe the mechanics of financial securitization—the creation of new securities that are claims on a portfolio of real assets such as biomedical research—after which we present the main results of our paper: a more realistic multiperiod simulation of the financial performance of a cancer megafund based on historical oncology drug-development databases with over 700 compounds in various stages of preclinical and clinical development from 1990 to 2011. We conclude with a discussion of the potential impact of megafunds on various biopharma stakeholders, some practical challenges of implementation and possible solutions.

Portfolio theory

Consider a hypothetical drug-development program requiring $200 million in out-of-pocket costs over a 10-year period during which no revenues are generated, and with only a 5% probability of success (thus, the total cost of developing a single successful drug is considerably higher). Few investors outside the biopharma sector would be tempted by such an opportunity, even though the expected rate of return on this investment may be quite attractive. In fact, if such a drug were a blockbuster (which is consistent with the assumed 5% success rate), it is plausible to assume that it could generate a net income of $2 billion per year over a 10-year period of exclusivity from years 11–20. The present value of this income stream in year 10 is $12.3 billion (using a 10% cost of capital[22]), implying an expected compound annual rate of return of 11.9% = $(0.05 \times \$12.3/\$0.2)^{1/10} - 1$ over the 10-year investment period (**Fig. 1**). However, investors do not earn 11.9% with certainty, but face two possible outcomes instead: a 95% probability of earning −100% and a 5% probability of earning 51.0% = $(\$12.3/\$0.2)^{1/10} - 1$. These projects may simply be too risky for most investors given the near certainty of getting wiped out and the long wait before any revenues are generated.

Now consider investing in 150 such programs simultaneously through a single investment vehicle with 150 × $200 million = $30 billion of investable capital, which we shall refer to as a 'megafund'. For simplicity, assume that the success or failure of each program is a statistically independent draw. Then the probability of at least one success among 150 independent programs is 99.95% = $1 - 0.95^{150}$, which is quite a different proposition. Although the expected profit of each of the 150 programs remains the same at $12.3 billion, the likelihood of at least one hit is dramatically increased, reducing the risk of the entire portfolio. One simple measure of this risk reduction is the s.d. of the annualized return, which is 423% for an individual draw, but only 34.6% = 423%/$\sqrt{150}$ for the annualized portfolio return. The more risky and less correlated the underlying assets are, the greater the benefits to pooling them, not unlike an insurance pool that provides

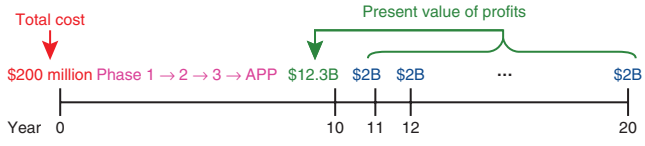

Figure 1 Timeline of cash flow for simplified example of a typical drug-development program in which out-of-pocket costs with present value of $200 million at year 0 generate annual net income of $2 billion in years 11–20, implying a present value of $12.3 billion at year 10 (based on a 10% cost of capital). APP, approval; B, billion.

protection for each of its participants by spreading any given individual's losses over the entire membership. Such pools become more effective as the number of participants increases, and the same is true for megafunds of drug-development projects.

This risk reduction is not costless, but comes at the expense of a much greater capital commitment. Also, unless the individual assets in a portfolio are mutually uncorrelated (which is exceedingly improbable), modern portfolio theory[23] shows that there is a limit to the amount of risk that can be eliminated through diversification. This limit and the optimal size of the megafund depend on several factors, including the pairwise correlations between the assets' returns, the natural scale of the investment in each asset and the risk appetite, expected-return requirements and investable wealth of the population of potential investors. Although some investors may prefer the high-risk/high-return profile of a one-shot drug-development program, there seems to be a much larger pool of investors who prefer the lower-risk/lower-return profile of a portfolio of programs, as suggested by the relative sizes of the venture capital industry ($176 billion) and the mutual fund industry ($11.8 trillion)[24].

Although this example is a caricature of the drug-development process and employs a blockbuster drug metaphor for expositional simplicity (see **Supplementary Analytics** for a nonblockbuster version), it does illustrate one of the key benefits of the megafund structure: the risk reduction from diversification would allow the megafund to issue large amounts of debt as well as equity, greatly broadening the pool of potential investors willing to fund such projects.

To see why, suppose each of the 150 projects was undertaken by a separate company, yielding 150 companies with development costs of $200 million apiece. The all-or-nothing nature of each company's payoff implies that even if a company issued only a small amount of debt, the default probability of such bonds would be 95%. With default nearly guaranteed, debt financing is virtually impossible for these single-project entities, and the riskiness of a single project implies that an initial public-equity offering is also unlikely.

However, a single entity with 150 such programs could issue $24.6 billion of zero-coupon bonds—bonds that pay only one lump-sum payment at maturity—maturing in year 10 with a default probability of only 0.4% (the probability of less than two successes because two hits yield a present value of 2 × $12.3 = $24.6 billion in year 10, just enough to pay off the bondholders). This default probability is comparable to the historical realized 10-year default rates of the highest-rated category of debt (Aaa) from 1920 to 2010, according to the bond-rating agency Moody's[25]. As of February 2012, Moody's reported the average yield of seasoned Aaa corporate bonds with ~30 years to maturity to be 3.85%[26], which is a reasonable proxy for the yield of a 10-year bond with identical credit quality. At a yield of 3.85%, 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 s.d. would be 21.5% and 78.9%, respectively. These values are higher than those of an all-equity-financed case (11.9% and 34.6%) because of leverage, but are still within the range of risk-reward profiles of publicly traded equities. A megafund's ability to issue both debt and equity with attractive terms to a larger pool of potential investors provides greater scale and diversification benefits, yielding greater risk reduction and bigger overall impact on biomedical innovation. Of course, the degree of risk reduction depends entirely on the number of assets in the portfolio and the pairwise correlations of the individual projects' financial returns, which we have assumed to be zero for expositional convenience. Greater correlation reduces the benefits of diversification, and the extreme case of perfect correlation implies no benefits at all. In our simulation study of an oncology megafund described below, we assume pairwise correlations of 20%.

The lower-risk/lower-return profile of a megafund may have little appeal to venture capitalists—especially when compared to an investment in a single compound—but is likely to be of much greater interest to pension funds, insurance companies, money market funds, banks and other large financial institutions, who control a vastly larger pool of investment capital. For example, at the end of 2010 the California Public Employees Retirement System held $226 billion of investable assets, the Norwegian government pension fund held $537 billion and nongovernment US institutional money market funds held $1.1 trillion. Moreover, as of the end of 2010, the total size of the US bond market was $35.2 trillion. In relation to these magnitudes, a megafund of $30 billion no longer seems as unattainable if debt-financing is feasible.

Of course, the required size of a megafund is determined by many factors as we show in our simulation study below, and although our simple portfolio example adopts the standard blockbuster revenue model, neither that analysis nor the simulation results hinge on discovering blockbusters (**Supplementary Analytics**). This is especially important in light of recent challenges to the blockbuster revenue model from changes in patent laws, payer reimbursement policies and the discovery of biomarkers that reduce the population of patients for certain drugs[20,27]. Portfolio theory applies to any level of drug development, and its effectiveness is determined by the combination of expected revenues, probability of success and correlations among drug-development programs, not by the scale of the portfolio's assets.

We have grossly oversimplified the economics of the biopharma industry in the above example to provide intuition for the mechanism by which investment performance can be enhanced through diversification. The main results of this paper consist of a detailed multiperiod simulation of an oncology megafund that reflects more realistic features of the drug-development process, including correlation among assets, stochastic transitions from one phase to the next over time and realistic valuations of compounds that are sold during intermediate stages of the clinical trials process. Before turning to these results, we first address the challenge of raising large amounts of capital, which may seem impractical given recent corporate consolidations, budget cutbacks and capital scarcity[28]. This challenge can be met by the second component of our framework: securitization.

Securitization

Given the scale of financing needed for creating a truly diversified portfolio of drug-development investments and the time lag between capital commitment and return, private-partnership structures, such as venture capital, may not be the best source of funding for this industry. Instead, we propose tapping public capital markets directly through securitization[14], a common financing method in which investment capital is obtained from a diverse investor population by issuing debt and equity securities that are claims on a portfolio of assets—in our case, biomedical research. A common form of securitization involves 'cash-flow' transactions in which a portfolio of assets—typically mortgages, auto loans, student loans or credit-card receivables—is acquired using money raised by issuing equity and bonds of different seniorities. These assets and the cash flow they generate are pledged as collateral for the debt.

In our proposed application, the assets include the initial capital raised from investors, all the subsequent biomedical R&D and licenses acquired, and all the profits generated by these activities or through sales of these assets in later periods. The application of securitization

to early-stage clinical and preclinical biomedical assets has not been described previously, and we shall refer to debt that is collateralized by such assets as 'research-backed obligations'.

To ensure that the portfolio of assets is used only to satisfy the payments of the newly issued research-backed obligations, the megafund forms a stand-alone legal entity called a 'special-purpose vehicle' for the express purpose of purchasing the collateral and issuing and servicing the securities. Equity holders own equity in the special-purpose vehicle and thus have a claim on the residual assets and cash flow that remain after all debt obligations have been satisfied. The special-purpose vehicle is managed by a separate management company, but for simplicity we shall refer to both the special-purpose vehicle and the management company that structures the biomedical R&D acquisitions and licensing deals as the megafund.

To provide different levels of risk and expected return for the broadest possible set of potential investors, the megafund divides research-backed obligations into distinct classes or 'tranches' with different repayment priorities. The senior tranche has highest priority, meaning that in each payment period its obligations must be satisfied first before those of any other tranche, and each of the more junior tranches are repaid in order of their priority. In the event that the assets do not generate sufficient cash flow to make all promised payments to bondholders in any given period, the senior-most tranche will be paid first, followed by the next most senior tranche and so forth, until the available cash is exhausted. Therefore, the senior tranche is the least likely to experience losses; thus, it will have the lowest risk and offer the lowest yield, which appeals to the most risk-sensitive investors such as money market funds, banks and smaller pension funds.

More junior tranches have higher loss probabilities and must offer correspondingly higher yields to compensate investors for this increased risk, which attracts more risk-tolerant investors such as large pension funds, endowments and high-net-worth private investors. The most junior tranche is often structured as equity—and sometimes called the 'equity tranche'—with no promised payments whatsoever but with unlimited upside potential once bondholders are repaid in full.

Equity holders stand to reap the biggest gains if the megafund's underlying assets do well, but they are the first to suffer losses if those assets are not profitable. As a result, this is the riskiest tranche and is likely to be purchased by the most risk-tolerant portion of the investor population (that is, hedge funds, funds of funds and deep-pocketed institutional investors including large endowments and pharmaceutical companies). The size and order of the tranches is known as the special-purpose vehicle's 'capital structure' and the motivation for multiple tranches should now be clear: regardless of how risk averse or risk seeking an investor is, there is likely to be a particular tranche of this special-purpose vehicle's debt issue that will satisfy the investor's risk preferences.

In addition to the different levels of priority, research-backed obligations can be customized in several important ways. For example, they can be structured to have varying maturities ranging from short term (to appeal to more impatient investors like commercial banks and money market funds) to long term (to appeal to pension funds, endowments and sovereign wealth funds). By providing the desired maturity for each type of lender, research-backed obligations may appeal to a broader cross-section of investors while reducing the shorter-term pressures of generating earnings and preparing for an initial public-equity offering, which can often lead to the distressed sale of promising but early-stage assets. Typical securitizations employ debt maturities of 15 years or less; for example, in August 2007, DRI Capital (Toronto) issued $356 million of 8- and 15-year bonds backed by major royalty rights to the FDA-approved biopharmaceutical products Enbrel (etanercept), Remicade, PREOS (preotact) and FluMist (trivalent live attenuated influenza vaccine).

Additional features known as 'credit enhancements' and 'triggers' are often used to provide further protection for the research-backed obligations' most senior tranches. These features include default insurance through credit-default swaps, over-collateralization, the use of interest- and debt-coverage ratio thresholds that trigger accelerated payments when breached, and government guarantees and tax incentives (**Supplementary Methods: Credit Enhancement**).

The special-purpose vehicle's capital structure, priority of payments and various coverage tests and credit enhancements are collectively known as the 'cash flow waterfall'—a reference to the manner in which cash flow from the special-purpose vehicle's assets spills over from senior to junior tranches—which fully determines the financial structure of each of its corresponding securities and how investors will be compensated in all circumstances (**Fig. 2**).

Once the special-purpose vehicle's cash flow waterfall is specified, the economic value of the securities it issues can be directly related to the performance of its assets. If the statistical properties of the cash flow of each of those assets can be quantified, the risk-reward profile of the special-purpose vehicle can be estimated, its securities can potentially be rated by bond-rating agencies and these securities can be evaluated and purchased by a broad universe of investors. Therefore, one of the key factors in determining whether a pool of assets can be securitized is whether the stochastic properties of the underlying assets' returns over time can be measured and managed. In the multi-trillion-dollar mortgage-backed securities market, the answer was (and still is) yes, as is the case for corporate debt and several other asset classes[29]. We believe the same may be true for biomedical research. By creating a large portfolio of well-diversified biopharma investments and by spreading the risks and rewards of such a portfolio across a much larger and more diverse group of investors through securitization, it may be possible to facilitate large-scale and long-term biomedical innovation in a sustainable and, ultimately, profitable manner.

A cancer megafund as an illustrative example

To illustrate the practicality of megafund financing, we present a detailed simulation of a hypothetical funding vehicle for cancer drug

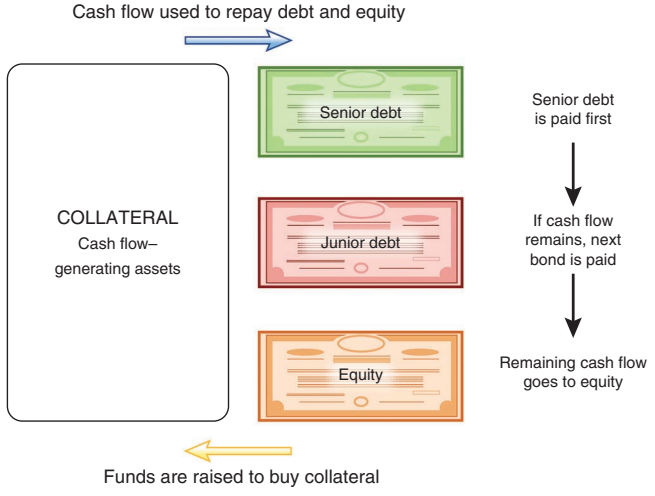

Figure 2 Schematic of the waterfall of cash flow for a typical research-backed obligation securitization.

development programs. Our focus on cancer is motivated by three considerations. First, cancer is a leading cause of death. The lifetime probability of developing cancer in the United States is 1 in 2 for men and 1 in 3 for women[30], and the number of deaths caused by cancer worldwide will grow to over 12 million per year by 2030 (ref. 31), creating an urgency and visibility that will greatly facilitate fundraising for a cancer megafund. Second, because cancer is a complex group of over 200 diseases, the multiple approaches to anticancer therapies yield greater opportunities for portfolio diversification, offsetting to some degree the megafund's singular focus on cancer. And finally, several comprehensive databases of cancer drug-development programs exist, allowing us to construct more realistic simulations of the possible risks and returns from a cancer megafund. These simulations are critical for capturing the complexities of the oncology drug development process and for communicating the megafund's risks and rewards to potential investors, a prerequisite of any successful fundraising effort.

These motivations must be tempered by the caveat that a megafund devoted solely to cancer is likely to understate the benefits of diversification and megafund financing for at least two reasons: the unavoidable correlation among cancer drug discovery programs due to common biochemical pathways and pathologies, and the fact that since 2004 cancer-drug approval rates have been the lowest among all therapeutic areas (6.7% in oncology versus 12.1% in all other areas combined as of 2011; ref. 32). A more effective approach would be to target many diseases in addition to cancer so as to increase diversification. Moreover, our simulation focuses exclusively on the development of anticancer compounds, which ignores several other important facets of cancer care, such as diagnostic tools, radiosurgery and gene therapy for which we have much less historical data to draw on.

As with any simulation, each of our parameters can be challenged as being too conservative or too optimistic, and our hypothetical business structure may be viewed as too simplistic. We acknowledge these concerns at the outset and encourage readers to experiment with our simulation software using their own calibrations (our complete source code is available in both R and Matlab under an open-source license that enables all researchers to use, modify and distribute it).

For concreteness, the financing mechanism we consider in this illustration relies on the securitization of experimental drug compounds only, and the objective of the special-purpose vehicle would be to finance the development of each of its compounds while satisfying the megafund's obligations to its bondholders and providing attractive returns to its equity investors. The business structure of the special-purpose vehicle is illustrated in **Figure 3**, and the types of payments made by the special-purpose vehicle during its life include the following.

Startup expenses and purchases. The special-purpose vehicle will deploy its initial capital by acquiring economic rights to anticancer compounds in exchange for upfront and milestone payments as well as funding R&D and clinical trials (see **Supplementary Methods: The Drug Approval Process** for a summary of the clinical trials process).

Initial post-launch expenses and principal and interest. Because it may take several years before its investments begin generating revenues, the special-purpose vehicle will set aside an initial cash reserve to fund clinical trials for its portfolio of compounds during the life of the transaction. These reserves will also ensure that timely payments of interest can be made on the research-backed obligations.

Ongoing R&D and financing expenses. The special-purpose vehicle will pay for ongoing R&D expenses of its portfolio assets during the life of the megafund. As part of this process, the special-purpose vehicle may decide to sell some of its assets and engage in other corporate transactions to realize gains, meet funding needs or for strategic reasons.

Management costs. During each year, the special-purpose vehicle will pay salaries to its staff, fees to external service providers and other operating costs that are part of the management fee, which is typically assessed as a fixed percentage of the special-purpose vehicle's total assets under management.

Sale of portfolio. Upon the maturity of the longest-dated research-backed obligation, the special-purpose vehicle portfolio will be liquidated and the proceeds paid out to the equity holders.

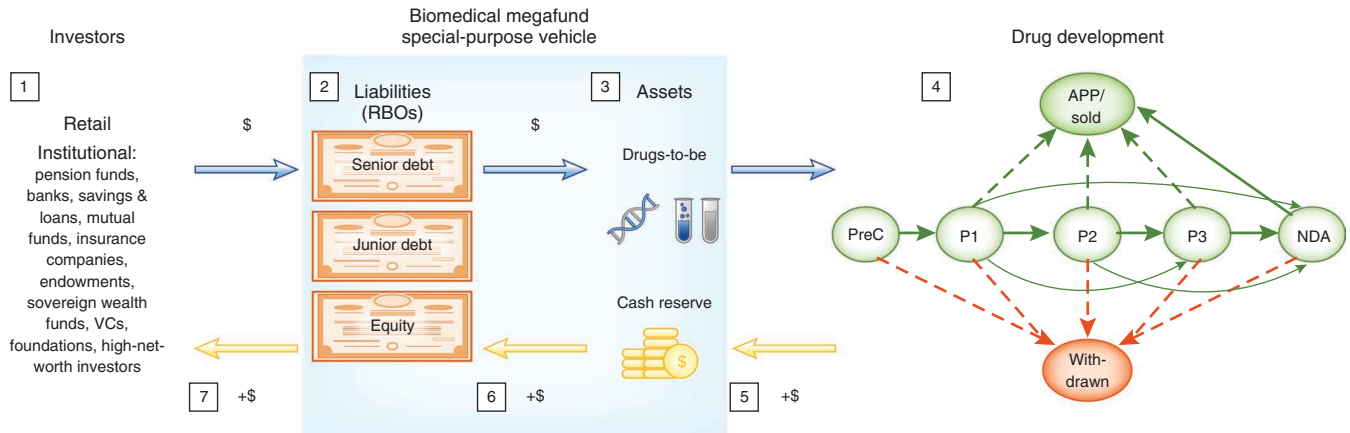

Figure 3 Business structure of a biomedical megafund special-purpose vehicle. Funds are raised from retail or institutional investors (1) through the capital markets issuance (2) of various types of debt and equity. These funds are invested in molecules being developed to cure cancer (3). Some funds are reserved to pay for later clinical development costs and, if required, to cover the first few periods of coupon payments. The portfolio of drugs is developed over time (4). At any time a compound can be discontinued or move to the next or subsequent phases, based on the results of the trials. It is also possible that compounds can be sold before their FDA approval for marketing if it is necessary to monetize them to cover some of the fund interest or principal payments. Any compound that is approved for marketing as a new drug is sold to a biopharma company. At the end of the life of the fund, all remaining compounds in the portfolio are sold (5). After bondholders are paid back (6), the residual cash is used to pay back the equity holders (7). VC, venture capitalist; RBO, research-backed obligation; PreC, preclinical; P, phase; NDA, new drug application; APP, approval.

Table 1 Summary of valuation and cost assumptions for the biomedical megafund simulation[a]

Parameter	Preclinical	Phase 1	Phase 2	Phase 3	NDA	Approved
Compound valuation assumptions ($ millions)						
Mean	16	30	82	425	1,515	1,870
Max.	100	250	500	1,000	2,500	5,000
Lognormal mean	2.4	3.0	4.0	5.8	7.4	7.2
Lognormal s.d.	0.9	0.9	0.9	0.9	0.9	0.9
Pairwise correlation	0.2	0.2	0.2	0.2	0.2	0.2
Investment assumptions ($ millions)						
Upfront	2.5	7.5	20.1	75.2		
Milestone	1.3	3.8	10.0	37.6		
Development cost assumptions ($ millions)						
Mean expected cost	6	19	50	188		
s.d. cost/phase	6	16	47	132		
Max cost/phase	20	50	120	500		
Lognormal mean	1.5	2.7	3.7	5.1		
Lognormal s.d.	0.8	0.7	0.8	0.6		

[a]The means and s.d. of the lognormal distribution of costs and valuations were calibrated based on published studies and public databases; details are provided in **Supplementary Methods: Simulations**.

Our analysis involves simulating the revenues and costs in each period during the life of the special-purpose vehicle as compounds advance through the R&D and approval process. We use historical industry values that are summarized in **Table 1** and derived from various research studies and data from financial information and news provider Bloomberg (New York)[4,33–35]. To calibrate the simulation of the clinical-trials process, we merged two data sets: the DEVELOPMENT optimizer database provided by Deloitte Recap (San Francisco) and a data set provided by the Center for the Study of Drug Development at Tufts University School of Medicine (Medford, MA, USA). The merged data contained over 2,000 compounds that, after removing duplicates and compounds for which there was not enough information, yielded a final set of 733 new molecular entities developed primarily for anticancer indications that entered clinical trials between January 1990 and January 2011. These compounds were developed by biotech or pharmaceutical companies and were either therapeutic compounds or vaccines (summary statistics for the data are provided in **Supplementary Methods: Simulations**). Using these data and the results of Paul *et al.*[4], we define seven distinct phases of drug development—the initial preclinical phase, the three stages of the clinical-trials process (phases 1, 2 and 3), new drug application, approval and withdrawal—and estimate the transition probability matrix P given in **Table 2** using standard statistical methods (**Supplementary Methods: Simulations**).

Using this transition matrix and assumptions regarding the revenues, costs and correlations of the drug-development process—summarized in **Tables 1** and **3**—we performed two simulations labeled 'Simulation A' and 'Simulation B' (**Fig. 4**). Both simulate a series of six-month periods during which compounds are either withdrawn, sold or advance to the next clinical stage depending on whether or not they achieve various milestones. Simulation A corresponds to early-stage investments in compounds that begin in the preclinical phase, which—if they are not sold for other reasons earlier—are sold when they transition to phase 2. Simulation B corresponds to later-stage investments in which compounds are acquired in phase 2 and sold when they are FDA approved. This division acknowledges the major scientific and business differences between early-stage investments, which are typically the domain of venture capitalists, and later-stage development typically undertaken by large biotech or pharma companies that license compounds predeveloped by smaller biotech companies and finance their development until discontinuation or approval by the FDA. By conducting two separate simulations, we are implicitly allowing different sets of investors to participate during different phases of the drug-development process. This structure permits the maturities of the bonds to be much shorter than would be the case if compounds were funded by the same investors throughout the full cycle from preclinical development to FDA approval, which can often exceed a decade. Full-cycle simulations can also be performed within our framework. Taken together, the two simulation experiments performed in this paper provide a compelling case for megafund financing throughout the entire drug-development cycle.

The simulation experiments are done in pairs, each pair consisting of a traditional all-equity fund—similar to a venture capitalist or mutual fund—versus a matching research-backed-obligation structure with a senior tranche, a junior tranche and an equity tranche, where the size of the equity investment is the same in both (we use three tranches only for expositional simplicity; in practice, more tranches could be offered). Unlike the simplified example above, in which we assumed that the cash flow from each drug-development program in the portfolio was uncorrelated, our simulations impose a more realistic 20% positive correlation between the valuations of all pairs of compounds to capture the potential for the clustering of negative outcomes in any given period (**Supplementary Methods: Simulations**).

Table 4 contains the results of a megafund with $5 billion of initial capital invested over 7.5 years in a target portfolio of 100 preclinical and 100 phase-1 compounds, with a $1.25-billion senior tranche, a $1.25-billion junior tranche and a $2.5-billion equity tranche, implying a modest leverage ratio of 2-to-1 for the special-purpose vehicle. In a simulation consisting of 500,000 independent sample paths, an average of 102 compounds reached the goal of entering phase 2. As, historically, there is a very small but nonzero probability of transitioning from phase 2 to phase 3 in less than one semester (e.g., due to concurrent trials), the transition matrix P allowed for this possibility and the simulations generated a small number of compounds that

Table 2 Transition probability matrix for simulating the clinical trial process (in percent)

	$PreC_{t+1}$	Phase 1_{t+1}	Phase 2_{t+1}	Phase 3_{t+1}	NDA_{t+1}	APP_{t+1}	WD_{t+1}
$PreC_t$	50.0	34.5	0.0	0.0	0.0	0.0	15.5
Phase 1_t	0.0	80.8	13.3	0.5	0.0	0.0	5.3
Phase 2_t	0.0	0.0	84.5	6.7	0.3	0.1	8.5
Phase 3_t	0.0	0.0	0.0	84.8	6.8	2.1	6.3
NDA_t	0.0	0.0	0.0	0.0	56.7	41.2	2.2
APP_t	0.0	0.0	0.0	0.0	0.0	100.0	0.0
WD_t	0.0	0.0	0.0	0.0	0.0	0.0	100.0

Details are provided in **Supplementary Methods: Simulations**.
PreC, preclinical; phases 1–3; NDA, new drug application; APP, approval; WD, withdrawal; time subscript t indicates current six-month simulation period and t+1 indicates the following six-month simulation period. Entries in each row may not sum to 100% due to rounding.

Table 3 Additional parameters of the biomedical megafund simulation

Parameter	Assumed value in simulation
Time	
Tenor of the research-backed obligation	7.5 years (15 semesters)
Time to deploy capital	1 semester
Time to sell each compound	2 semesters
Capital structure	
Total amount of capital	$2.5–15 billion
Tranches	Senior bond, junior bond, equity
Leverage	2 or 2.5 times
Bond annual yield	Senior bond 5%, junior bond 8%
Redemption senior bond	Equal semiannual installments from semester 5 to 8
Redemption junior bond	Equal semiannual installments from semester 9 to 12
Cash-out equity	Period 17
Investor protection rules	
Interest coverage test	Senior debt (2), junior debt (3 or 3.5)
Cash reserved at start	To cover 2 periods of interest and expected drug development costs
Other	
Number of compounds per fund	Between 40 and 200
Equity ownership of each asset	85%
Research-backed obligation service fee	0.5% per year of total assets under management
Return on excess cash	1% per year

See **Supplementary Methods: Simulations**, for details.

reached phase 3, new drug application and approval before the end of the life of the fund.

The results in **Table 4** show that the megafund is almost always profitable. The senior-tranche research-backed obligation investors received an annual coupon payment of 5% and were repaid in full 99.9% of the time, which is comparable to historical default rates of the highest-rated bonds according to Moody's and Standard & Poor's[25,36], the two largest bond-rating agencies in the financial industry. Junior-tranche research-backed obligation investors were paid an annual coupon payment of 8% and repaid in full 99.1% of the time. Finally, equity-tranche investors received an average annual return of 8.9%, and in over a third of the simulated sample paths their average annual return exceeded 15%. Although such returns may not be sufficiently attractive to traditional venture capitalist investors, large institutional investors such as pension funds, insurance companies and endowments are likely to show more interest. Recall that unlike venture-capital funds and all-equity structures where the possibility of substantial or total loss can be nontrivial, the megafund structure offers both debt and equity—risk-seeking investors can purchase the latter and more conservative investors can participate through the former. Because there are substantially larger pools of conservative investment capital, research-backed obligations allow the biopharma industry to greatly expand its drug-development efforts by tapping into this tremendous asset base. In fact, certain types of financial institutions may find research-backed obligations especially attractive either because they serve as natural hedges to existing business risks, such as annuity providers (whose costs increase when people live longer), or because their corporate mandate is to support socially relevant activities but precludes them from investing in equity (in which case, they can now invest a portion of their endowment's assets in research-backed obligations rather than just awarding grants from the annual interest on those assets).

The higher risk of the equity tranche is accompanied by the benefits of leverage provided by the bond issue, which allows the special-purpose vehicle to invest in a larger and more diversified portfolio of assets. This effect can be quantified by comparing the results of the equity-and-debt case with the all-equity simulation, in which the special-purpose vehicle contains the same amount of equity capital ($2.5 billion) but no debt (**Table 4**). In the all-equity simulation, the megafund invests in 50 preclinical and 50 phase-1 drugs, successfully carrying 52 to phase 2 and generating an expected annualized return of 7.2%. The fact that this is lower than the 8.9% return in the research-backed obligations case is explained by the correspondingly lower risk of the less-leveraged portfolio (note that the probability of a negative return is 17% in the all-equity case and 20% in the research-backed obligations case).

In simulation B, compounds are acquired in phase 2 and each can transition to its next development phase, be discontinued or be sold. Any compounds that are approved for the market are automatically sold. **Table 4** presents the results of 500,000 independent simulated sample paths of a megafund with $15 billion of initial capital invested over 7.5 years in a target portfolio of 100 phase-2 compounds. The capital structure consists of a $6-billion senior tranche (with 5% yield as in simulation A), a $3-billion junior tranche (with 8% yield), and a $6-billion equity tranche, implying a 2.5-to-1 leverage ratio. On average, the simulation yielded just under 8 compounds approved for sale and over 21 compounds advanced to phase 3 or new drug application (because they did not have time during the life of the fund to reach market approval or were sold to finance principal and interest payments to bondholders). The investment performance of this special-purpose vehicle is even more attractive than the early-stage simulation. Senior-tranche research-backed obligation investors were repaid in full 99.9% of the time, junior-tranche investors were repaid in full 99.4% of the time and equity-tranche investors received an average annual return of 11.4%, which compares favorably with the results offered by the equity-only fund. In fact, an equity-only fund with the same equity capital ($6 billion) would finance the development of 40 phase-2 drugs, with only 6 advancing to phase 3 or new drug application, 5 to market and offering investors an expected annualized return of only 7.2%.

Will rates of return of 8.9–11.4% for equity and 5–8% for debt attract capital of $5–15 billion as we have assumed in these simulations? The answer depends on the type of investor. Such returns may be of little interest to the private-equity and venture capital community, but for more conservative and larger institutional investors, such as pension funds, insurance companies, money market and mutual funds, endowments, foundations and trusts, these returns may be more compelling.

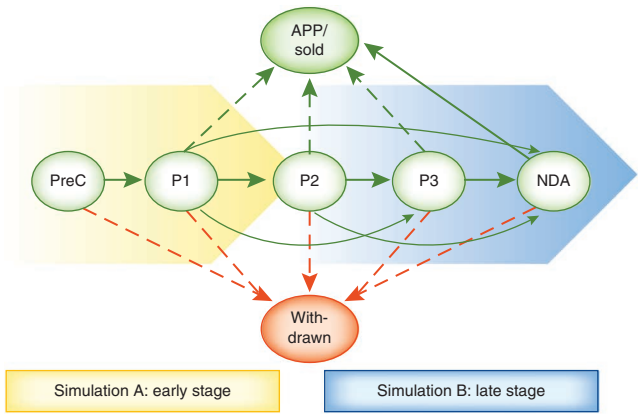

Figure 4 Simulating two distinct business stages of a biomedical megafund. PreC, preclinical; P, phase; NDA, new drug application; APP, approval.

Table 4 Performance summary statistics of the biomedical megafund simulations

	Simulation A		Simulation B	
Variable or summary statistic	All equity	Research-backed obligations	All equity	Research-backed obligations
Number of compounds				
Preclinical	50	100	—	—
Phase 1	50	100	—	—
Phase 2	—	—	40	100
Phase 3	—	—	—	—
Research impact				
Number of compounds to reach phase 2	52.8	101.7	—	—
Number of compounds sold in phase 3 and NDA	0.9	2.3	6.0	21.3
Number of compounds sold once APP	0.6	1.0	5.1	7.6
Liabilities				
Capital ($ millions)	2,500	5,000	6,000	15,000
Senior tranche ($ millions)	—	1,250	—	6,000
Junior tranche ($ millions)	—	1,250	—	3,000
Equity tranche ($ millions)	2,500	2,500	6,000	6,000
Equity tranche performance				
Average annualized return on equity	7.2%	8.9%	7.2%	11.4%
Prob. (return on equity < 0)	17%	20%	17%	10%
Prob. (return on equity > 5%)	61%	68%	63%	79%
Prob. (return on equity > 15%)	15%	35%	14%	40%
Debt tranches performance				
Senior tranche: default prob., expected loss (bp)	—	1, <1	—	6, <1
Junior tranche: default prob., expected loss (bp)	—	87, 27	—	60, 30

bp, units of basis points or 0.01%; prob., probability.

To see why, consider the fact that the median rates of investment return of public pension fund assets over the 5-, 10-, 20- and 25-year periods ending 31 December 2011 were 2.0%, 5.7%, 7.7% and 8.3%, respectively[37]. Moreover, in a July 2012 survey of 126 state and local government pension funds, the median target investment return was 8.0%[37]. This number represents more than just a survey response—it is incorporated as an actuarial assumption that affects a pension fund's investment and pension-benefit decisions; hence a target return of 8.0% is a relevant hurdle rate for such institutions, which account for $3 trillion in investable assets as of the first quarter of 2012 (ref. 37). Of course, institutional investment decisions also depend on other characteristics besides return potential, such as risk and correlation to broadly diversified stock and bond portfolios (which are the vast majority of these institutions' holdings). These considerations are precisely the motivation for offering multiple tranches, each with a different risk-reward profile. One of the primary advantages of securitization over more traditional methods is the ability to customize financing arrangements to suit the particular characteristics of the assets and investors (e.g., more tranches, staggered debt maturities, permanent equity and payments that are contingent upon reaching certain research milestones). Greater customization implies a broader population of investors for which these customized securities may be appropriate investments.

Of course, our simulation results depend on our choice of simulation parameters, which represents just one of many possible sets of assumptions. To allow readers to evaluate the feasibility of megafund finance under their own preferred scenarios, we have placed our simulation software in the public domain with an open-source license to run, modify and distribute the code (**Supplementary Software**).

DISCUSSION

Despite the promising simulation results for oncology compounds, any implementation of megafund financing must overcome several practical challenges. In this section, we provide a brief summary of these challenges and some possible solutions (for a more detailed discussion, see **Supplementary Discussion**).

The challenges of implementing megafund financing can be loosely grouped into two broad categories: raising capital and deploying capital. The feasibility of raising billions of dollars for biomedical applications is predicated on the ability of investors to assess the risk-reward trade-offs of the investments. Historical biopharma data may not be an accurate guide to the future because of the rapidly shifting landscape of translational medical research and its economic implications for the industry. However, the inability to accurately predict translational research outcomes does not imply an inability of investors to assess the financial risks of and commit capital to a diversified portfolio of such outcomes. The changing nature of biomedical innovation can be complemented by changing the nature of the corresponding funding vehicles—greater risk, even unknown risk, can often be managed effectively through more sophisticated financial engineering.

A less obvious but equally important concern is that megafund financing works too well. In addition to their potentially attractive risk-reward profiles, biomedical megafunds are naturally positioned to benefit from the 'socially responsible investing' trend in the financial industry. This growing trend is a powerful force that could quickly turn a niche product into a cottage industry. The rapid growth and subsequent crash of the US mortgage-backed securities markets has provided us with several important lessons for managing this potential boom-or-bust pattern. Rules regarding sales practices, disclosure requirements, permissible corporate governance structures and suitability criteria for investors must be imposed and strictly enforced to ensure that megafunds serve their purpose without jeopardizing the stability of the financial system.

Deploying megafund capital is likely to pose a greater challenge than raising capital, especially if capital is raised quickly. There are at least four elements to this challenge that require further investigation. The first is whether academia and the biopharma industry have

sufficient physical and intellectual capacity to make use of megafund capital. The second is whether the market for compounds, licenses and royalties will become sufficiently deep and liquid to generate enough cash flow to service megafund debt. The third is whether any single organization can successfully manage the complexity of a megafund portfolio. And the fourth is whether the political and regulatory environment—including healthcare reform and the FDA approval process—will support the kind of innovation implied by megafund financing.

We believe that all four of these challenges can be met.

With respect to capacity, based on published research as well as informal discussions with academic and industry insiders, it is clear that there are more innovative ideas, graduate students and professionals in biomedical research than there is funding to support them.

With respect to the secondary market for biopharma projects, the recent experience of the mortgage-backed securities industry suggests that market depth and liquidity are highly correlated with asset growth; if tens of billions of dollars flow into biomedical megafunds, that alone is likely to enhance secondary market activity substantially.

With respect to the organizational complexities of megafund management, as financial economists and biopharma-industry outsiders, we are not qualified to judge the feasibility of this endeavor. Even so, the fact that the leading drug-royalty investment company, Royalty Pharma, manages $8 billion in assets with a full-time staff of only 19 professionals (albeit with the support of a much larger network of biomedical experts as consultants) suggests that managing a $30-billion megafund is not impossible. Moreover, size confers benefits as well as costs, including economies of scale and scope, research synergies, greater stability, staying power and marketing clout.

Finally, with respect to the political and regulatory environment, given the current climate of political deadlock, a concerted effort by the private sector to reduce the burden of disease may be one of the few initiatives capable of generating truly bipartisan support. In the same way that other markets have benefited from various forms of government support, a biomedical megafund should be an attractive cause for ambitious politicians to adopt.

One final challenge facing the megafund that involves neither raising nor deploying assets has to do with the inherent conflict between the business culture and the world of science and medicine[2]. This conflict is not new to megafunds but has existed since the very beginning of the biotech industry. However, the sheer size of a megafund may magnify these conflicts to an unsustainable level.

The combination of social relevance and the profit motive may seem confusing and inappropriate to some, but this trend is becoming more prevalent as we face societal challenges that require an unprecedented scale of collaboration among millions of individuals. Although charitable giving is an important part of translational medical research, the magnitude of such giving is dwarfed by the pool of investment capital seeking a reasonable rate of return. By creating financial incentives for solving social problems like cancer, society is able to tap into this much larger pool of assets.

The megafund can be viewed as another example of the broader trend toward 'venture philanthropy' as practiced by existing organizations, such as the Gates Foundation (http://www.gatesfoundation.org/), the Robin Hood Foundation (http://www.robinhood.org/) and the Children's Investment Fund Foundation (http://ciff.org/). Another form of this trend is public-private investment programs, in which private-sector institutions provide financing under certain types of government sponsorship. Such programs played an important role in dealing with the recent financial crisis by raising over $29 billion of investment capital to purchase distressed securities[38]. Several important government initiatives are already under way for speeding up translational medical research, such as the US government's National Center for Advancing Translational Sciences (which is part of the Cures Acceleration Network) and the Israeli Life Sciences Fund. But with budgets of only $575 and $200 million, respectively, these efforts will eventually also require substantial private-sector funding—megafunds may be one solution.

In 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, much greater resources can be marshaled 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 can greatly magnify a megafund's likelihood of success.

Our proposed application of securitization may be untested, but the techniques are used extensively in the financial industry. Some of these uses involve mortgage-related securities that played a central role in the recent financial crisis, which has created a backlash of skepticism and distrust among certain investors and issuers. However, rather than shying away from such techniques because of the crisis, a more measured response may be to acknowledge their strengths, address their weaknesses and use them wisely to meet the most pressing social challenges. Despite the lack of consensus regarding the ultimate causes of the financial crisis, its magnitude provides compelling evidence that with the proper incentives and financial structure, securitization is a highly effective means of gathering large amounts of capital in a relatively short period of time. If used responsibly, these tools could play a transformative role in many other socially important initiatives.

Proposing to raise billions of dollars for biomedical research in the current economic climate may seem ill-timed and naive. 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[30]—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.

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Note: Supplementary information is available in the online version of the paper.

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AUTHOR CONTRIBUTIONS

All authors contributed equally to this research. A.W.L. first developed the idea for securitizing biomedical research after conversations with J. Broderick in March 2007 about a portfolio approach to biomedical innovation. A.W.L. assembled key members of the project team, provided funding through the MIT Laboratory for Financial Engineering and was responsible for overall project management. J.-M.F. was responsible for coordinating all aspects of the project, including directing research assistants, obtaining and processing all input data, calibrating the simulation parameters, running the simulations, and preparing the initial draft of the manuscript, with input and oversight from A.W.L. and R.M.S. R.M.S. developed the analytic framework for modeling the portfolio of drug compounds. R.M.S. and L. Han developed the R code with assistance from J. Noraky and J.-M.F., and input from A.W.L. and A. Singhal. A. Bernard converted the R code to Matlab. A.W.L. and J.-M.F. validated the final version of the Matlab code. R.M.S. also prepared the description of the simulation results, which was reviewed and revised by J.-M.F. and A.W.L. A.W.L. constructed the illustrative portfolio example and prepared the final draft of the manuscript, with input and revisions from J.-M.F. and R.M.S.

COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details are available in the online version of the paper.

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Commercializing biomedical research through securitization techniques

SUPPLEMENTARY INFORMATION

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Supplementary Analytics

Consider a single Bernoulli trial I_i with probability p of success ($I_i = 1$) and probability $1-p$ of failure ($I_i = 0$). Then the probability of at least one success in n independently and identically distributed (IID) trials is:

$$\Pr\left(\sum_{i=1}^{n} I_i \geq 1\right) \;=\; 1 - \Pr\left(\sum_{i=1}^{n} I_i = 0\right) \;=\; 1 - (1-p)^n \,. \tag{1}$$

For $p = 0.05$ and $n = 150$, this probability is $1 - 0.95^{150} = 0.9995$.

Assume that the drug-development process takes 10 years, and a success implies annual net income of X per year from years 11 to 20 (see Figure 1). We assume a 10-year income flow to acknowledge the fact that patents are filed long before drugs are approved, leaving much shorter periods of exclusivity than the stated 20-year life of U.S. patent. The date-10 present value Y_{10} of this stream of cashflows is given by:

$$Y_{10} \;=\; \frac{X}{r}\left(1 - \frac{1}{(1+r)^{10}}\right) \tag{2}$$

where r is the cost of capital associated with cashflows $\{X\}$. For $X = \$2$ billion and $r = 0.10$, $Y_{10} = \$12.3$ billion.

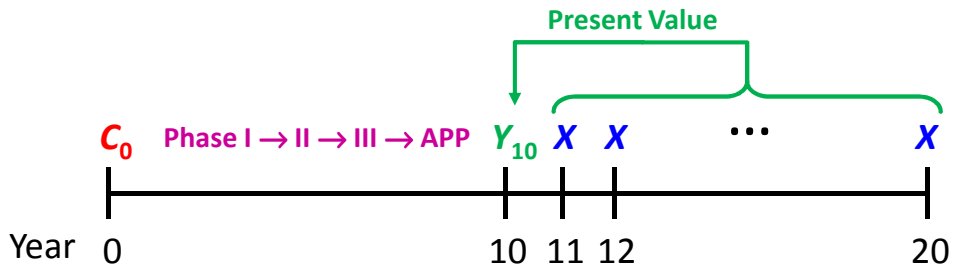

Figure 1: Timeline of cashflows for illustrative example of a typical drug development program in which out-of-pocket costs with present value C_0 at date 0 generates annual net income of X in years 11 through 20, which has a present value of Y_{10} at date 10.

If the date-0 present value of all out-of-pocket costs required to generate X is C_0, the total investment return R_s between date 0 and date 10 for a successful outcome is:

$$R_s \;=\; \frac{Y_{10}}{C_0} \;-\; 1 \;=\; \frac{X}{rC_0}\left(1-\frac{1}{(1+r)^{10}}\right) \;-\; 1\,. \tag{3}$$

The annualized rate of return over this period is:

$$\text{Annualized Rate of Return} \;=\; (1+R_s)^{1/10} \;-\; 1\,. \tag{4}$$

If $C_0 = \$200$ million, the annualized rate of return of a success is 51%.

The rate of return R for this project can then be expressed as the following Bernoulli random variable:

$$R \;=\; \begin{cases} R_s & \text{with probability } p \\ -1 & \text{with probability } 1-p \end{cases} \tag{5}$$

where R_s is defined in (3). The mean and standard deviation of R then follow directly:

$$\mathrm{E}[R] \;=\; p(1+R_s) \;-\; 1 \tag{6}$$

$$\mathrm{SD}[R] \;=\; \sqrt{\mathrm{Var}[R]} \;=\; (1+R_s)\sqrt{p(1-p)}\,. \tag{7}$$

The annualized expected return and standard deviation of return during dates 0 to 10 are then:

$$\text{Annualized Expected Return} \;=\; (1+\mathrm{E}[R])^{1/10} \;-\; 1 \tag{8}$$

$$\text{Annualized Standard Deviation of Return} \;=\; \mathrm{SD}[R]/\sqrt{10}\,. \tag{9}$$

Given the parameters assumed so far, the annual expected return and standard deviation are 11.9% and 423.5%, respectively.

For a portfolio of n identical projects that are statistically independent, the return R_p and its first two moments are:

$$R_p \;=\; \frac{Y_{10}\sum_{i=1}^{n} I_i}{nC_0} \;-\; 1 \;=\; \frac{(1+R_s)}{n}\sum_{i=1}^{n} I_i \;-\; 1 \tag{10}$$

$$\mathrm{E}[R_p] \;=\; p(1+R_s) \;-\; 1 \tag{11}$$

$$\mathrm{SD}[R_p] \;=\; \sqrt{\frac{(1+R_s)^2}{n}p(1-p)} \;=\; (1+R_s)\sqrt{\frac{p(1-p)}{n}}\,. \tag{12}$$

As (11)–(12) demonstrate, the expected return of the portfolio is invariant to the number of programs, but the risk of the portfolio (as measured by standard deviation) declines as the number of projects increases at a rate of $1/\sqrt{n}$. The annualized values of the expected return and standard deviation are given by (8)–(9) as before. For $n=150$, the return standard deviation is 34.6%.

To compute the default probability of a debt-financed portfolio of projects with total asset return R_p, we require the probability distribution of $\sum_{i=1}^{n} I_i$, which is a binomial random variable with distribution function:

$$\Pr\left(\sum_{i=1}^{n} I_i \le k\right) \;=\; \sum_{j=0}^{k}\binom{n}{j}p^j(1-p)^{n-j}\,. \tag{13}$$

The default probability of a 10-year bond at date 0 which pays no coupons and promises to pay F upon maturity at the end of year 10 is then:

$$\Pr\left(Y_{10}\sum_{i=1}^{n} I_i < F\right) \;=\; \Pr\left(\sum_{i=1}^{n} I_i < F/Y_{10}\right) \;=\; \sum_{j=0}^{\lceil F/Y_{10}-1\rceil}\binom{n}{j}p^j(1-p)^{n-j} \tag{14}$$

where $\lceil F/Y_{10}-1\rceil$ denotes the smallest integer greater than or equal to $F/Y_{10}-1$ (note that $\lceil F/Y_{10}-1\rceil+1$ is the minimum number of successful projects needed to repay the debt F), and we assume that F satisfies the inequality $0 < F/Y_{10} \le n$. For $n=150$ and $p=0.05$, the probability of default for $F=\$24.6$ billion is simply the probability of less than 2 successes out of 150 trials, which is 0.00405 according to (14). Note that the large magnitude of Y_{10} creates discreteness in debt capacity and default probabilities that may not exist in practice. For example, if $F = \$36.9 = 3\times\$12.3$ billion, the default probability jumps to 0.0182 (the probability of less than 3 successes). More generally, the debt capacity F^* associated with a desired maximum

probability δ is given implicitly by the solution to the following:

$$\max_{F} \Pr\left(\sum_{i=1}^{n} I_i < F/Y_{10}\right) \;\leq\; \delta\,. \tag{15}$$

For expositional clarity, we have assumed that the n projects are statistically independent. In practice, even the most diverse set of translational medical programs will exhibit some pairwise dependence, reducing the diversification benefits of the portfolio and, consequently, the debt capacity F^*. We incorporate such correlation explicitly in the simulations described below.

For a non-blockbuster numerical example, i.e., one in which the revenues are below $1 billion but the success rate is higher and the out-of-pocket costs of development are lower, consider the case in which the out-of-pocket cost of developing a single drug is $100 million, its expected revenue is $500 million per year for 10 years, and the probability of success is 10%. In this case, a portfolio of 100 such programs that are statistically independent would require $10 billion, yield an expected rate of return of 11.9% and a standard deviation of 29.1%, and each successful program would generate $3.1 billion in net present value in year 10. The probability of at least 4 hits out of 100 is 99.2%, implying that up to $12.3 billion of high-credit-quality 10-year debt could be issued to finance this portfolio. Such a debt issue would imply year-0 proceeds of $8.4 billion at the February 2012 Aaa yield of 3.85%. In other words, over 80% of the required $10 billion can be financed by high-quality long-term debt in this case.

Supplementary Methods: Credit Enhancement

The risk borne by investors participating in securitization transactions can be reduced using a number of protective features called *credit enhancement* mechanisms. Here we describe two types of credit enhancement that may be used individually or in combination.

The first involves the implementation of various types of structural features such as overcollateralization (through the tranching of the capital structure into different classes of securities) to increase the collateral support available for more senior bondholders, or cashflow redirection rules and triggers that accelerate payments to the more senior bondholders when certain test ratios are breached. We discuss an example of these ratios and rules in Supplementary Methods: Simulations.

The second type of credit enhancement makes use of some form of external credit support in which a third party assumes some of the risks to bondholders (e.g., through a letter of credit or bond insurance). A particularly interesting form of external credit enhancement in our context involves various forms of governmental guarantees. There are precedents for such programs. For example, in the U.S. the government sponsored enterprises (GSEs) Fannie Mae and Freddie Mac were created to promote home ownership. The GSEs provide guarantees for the mortgages underlying the securitization transactions that participate in their programs. For a mortgage to be accepted as collateral in a pool of securitized assets, it has to conform to certain quality standards

defined by the GSE. A recent example from the biomedical domain is the Israeli Life Sciences Funds, a venture capital fund of over $200 million jointly launched in 2011 by several branches of the Israeli government and the private sector. To mitigate the risks associated with biotech R&D, the government will assume some of the downside risk.

In light of these precedents, the National Cancer Institute or the National Institute for Health could consider providing some form of guarantee to biomedical megafunds whose collateral conformed to some pre-defined scientific or medical criteria. Alternatively, a private foundation might assume this role.

Credit support from such a benefactor could serve to boost investors' interest in these securities and potentially allow the megafund to assume bigger risks in its investments (e.g., by investing in newer technologies or those with less certain outcomes or that target rarer diseases) while providing a mechanism for leveraging the capital available from the guarantor or benefactor.

Supplementary Methods: The Drug Approval Process[1]

The introduction of a new drug in the market is a highly regulated process. Countries typically have national agencies responsible for authorizing new compounds for sale. For the purposes of this study, we follow the process defined by the U.S. Federal Drug Administration (FDA). Every new pharmaceutical product must undergo a number of tests to ensure that it is safe and effective. The lifecycle of a new drug generally follows the path described below.

In the "Preclinical Phase" the company developing the drug tests the product in animal trials to produce evidence that there is reasonable cause and manageable risk to permit the compound to proceed to human studies, in accordance with FDA guidelines. Following this phase, the sponsoring company files an "Investigational New Drug" (IND) application. If the FDA approves the IND, the drug moves into "Phase I", in which the drug is tested in a small number of healthy volunteers to monitor its absorption, metabolism, and toxicity in the body to get information about its safety and dosage. If the drug is determined to be too toxic or otherwise unfit, it is withdrawn at this point.

Compounds that successfully pass Phase I move into "Phase II", where testing is done with a patient population that already has the disease targeted by the new compound. The sponsor of the trial defines a set of endpoints that exemplify the compound's desired effectiveness and compares these endpoints with the results from the trials in diseased patients.

Upon successful completion of Phase II, the drug moves into "Phase III" in which the drug is tested in a large sample of patients to try to confirm safety and efficacy in a wider number of circumstances and subjects.

Following successful completion of these trials, the sponsor may submit a "New Drug Application" (NDA) or "New Biologics Application" (BLA) to the FDA. If the NDA or BLA is approved, the drug can be legally marketed in the U.S.

Supplementary Methods: Simulations

In this section, we describe the specific assumptions and experimental design used to generate the simulated performance analysis for an oncology megafund. The goal of our simulations is not to define an optimal transaction structure or to defend a specific set of modeling assumptions. Instead, our intent is to demonstrate the feasibility of modeling a simple financial structure—using realistic economic and scientific assumptions—in which large-scale biomedical innovation yields potentially attractive investment and drug development properties. To encourage readers to experiment with the simulation, we provide the complete sourcecode in R and Matlab under an open-source license that enables researchers to use, modify, and distribute it.

Time Units and Tenor

The time unit used in our simulations is a semester (six months). Alternative time steps are possible but we chose one semester to match the semiannual coupon payments of the bonds in the fund's capital structure.

We assume that the life of the fund is 15 semesters (seven and a half years). The scheduled amortization for the bonds occurs in periods 5–8 for the senior bond and 9–12 for the junior bond (we use the term "period" to refer to particular semesters). Thus, the longest-dated bond issued has a tenor (time between issuance and maturity date) of six years. In the 15th period, any remaining assets that have not been either already sold or discontinued are sold and the revenues generated accrue to the equityholders. We have assumed that it takes one year to sell a compound. Consequently, equityholders would get paid at the end of period 17 of the simulation, provided there were no previous defaults that might have shortened the life of the megafund.

Funds and simulations can be easily structured for significantly longer durations. The tenor of the fund should be related to the expected time required for the largest number of compounds to reach their full economic value. Given that Simulations A and B replicate the development of compounds from Preclinical and Phase I to Phase II, and from Phase II to market approval, respectively, we obtained reasonable results for funds of about seven and a half years' duration.

Assets

The assets in the portfolio are assumed to be new drugs being developed by biotech or pharma companies and targeted at curing some form of cancer. Under the current model design, those same companies would be responsible for developing the compounds. The megafund could act as a financing partner and a platform from which funding could be structured, subject to a set of rules that foster collaboration across projects, encourage individual and group success, and avoid moral hazard. Those rules, as well as the processes required to select and manage the assets targeted for the fund (including determining which assets to sell and in which phase of the process to sell them), will need to be defined for each new megafund, depending on its objectives and structure. Finding the right balance between the protection of investors and the development of new scientific

solutions is one of the difficult tasks regarding the implementation of this model. The creation of a blue ribbon Scientific Committee supported by financial experts is a necessary condition for the success of this new type of vehicle. The megafund structure provides an opportunity to revisit the way drug development financing decisions are currently made and to explore new corporate governance structures and organizational designs.

In our experiments, the initial portfolio of assets is composed of compounds in either the Preclinical and Phase I stages (Simulation A) or in Phase II (Simulation B). Simulation A replicates the typical venture capital investment horizon that carries compounds from Preclinical or Phase I to Phase II, when a large pharmaceutical company may acquire or license the compound for later development. Simulation B replicates the subsequent biopharmaceutical investment and development of a compound from Phase II to market approval. Practitioners note that different skill sets and funding budgets are required for each of those horizons, which motivated our decision to split the simulation in this manner. Taken together, the two simulations provide a compelling case for applying megafund financing throughout the full lifecycle of compound development.

We assume that all compounds are acquired during the first semester of the life of the fund and that no new compounds are acquired thereafter. The number of compounds in each of the simulations results from a two-step process: (1) we fix an amount of equity such that the all-equity fund and the RBO fund both have the same dollar amount of equity ($2.5 billion in Simulation A and $6 billion in Simulation B); (2) we determine the maximum number of compounds that we can expect to invest in using all the equity and debt raised in each of the funds. We acknowledge that this is a strong assumption. Deploying several billions of dollars in such a short period of time would require considerable prior due diligence work, some new form of collaboration with the current market players who have developed the expertise in making these types of investments (venture capitalists, biopharma companies, etc.), or a totally new approach to allocate capital across development drugs. While it may be more effective to deploy capital in a less abrupt fashion, i.e., acquiring new compounds throughout the life of the fund, modeling a dynamic and actively traded portfolio would create greater complexity in this simulation experiment. Therefore, for the purposes of our examples we adopt the simpler approach of acquiring the fund's collateral upfront, as is common among current securitization transactions. The composition of the portfolios in our simulation experiments are given in Table 1.

	Simulation A		Simulation B	
	Equity	RBO	Equity	RBO
Assets				
Preclinical	50	100	—	—
Phase I	50	100	—	—
Phase II	—	—	40	100
Phase III	—	—	—	—

Table 1: Composition of initial portfolios of drug compounds in the simulations.

Even though all assets are acquired at date 0, not all of the cash available at date 0 is invested immediately. A cash reserve is required to finance future clinical trials whenever a compound

transitions into a new clinical phase. The fund reserves as much cash as will be required (in expectation) to develop the compounds and to cover the interest payments on the notes for a certain number of semesters. In our simulation experiments, we reserve cash for two semesters' worth of interest payments, i.e., the bonds do not amortize in the first year.

Simulating Portfolio Dynamics

The development of a new drug is a complex process that depends on various scientific and economic factors. Our simulation is based on the assumption that every compound can transition along a series of different predefined states of the approval process: Preclinical, Phase I, Phase II, Phase III, NDA or BLA, Market Approval, and Discontinuation. In our model Discontinuation and Approval are absorbing states, i.e., a drug that is discontinued or approved can no longer transition into any other state. The assumption that drugs cannot be discontinued after being approved is explained by the fact that our megafund would sell all approved drugs to biopharmaceutical companies to be marketed immediately after being approved for their first indication. Also, in our data we observe a small probability that in some rare cases a compound may skip a phase—for example, conducting trials in Phase I and II simultaneously and transitioning directly to Phase III—so our simulation captures this behavior as well.

We simulate the evolution of compounds through the approval process as following a Markov process, which is a common modeling tool applied to systems that transition from state to state over time. This approach has been widely used in finance to represent various forms of credit risk,[2] and we apply it in our context to model the drug-transition dynamics from one phase to the next.

For each state in the approval process, we estimate a vector of transition probabilities based on the analysis of data from the last 20 years of oncology drug development programs. The vector is made up of elements, p_{ij}, each of which represents the probability that a compound transitions from state i to state j in the next time step (one semester in our simulations).

At every time step and for each compound that is still in the portfolio, i.e., the compound has not been discontinued or sold, we generate a random number u from a uniform distribution. The value of u is then compared to the vector of probabilities p_{ij} to determine whether a transition occurs in the next period and if so, to which state. Conceptually, this works similarly to spinning a roulette wheel where the slots represent the different states in the approval process and the size of each slot is proportional to the probability of being in that state one period later.

In the event that a transitioned compound ends up in either an Approval or Discontinuation slot, the compound is sold or dropped from the portfolio, respectively. Otherwise, it continues in the process, but now uses a new probability vector for the new state to which the compound has transitioned.

We implement simple rules to determine which compounds to sell during the life of the fund. In particular, we assume that all drugs that are approved are sold to biopharmaceutical companies who will ultimately be marketing and distributing them. In addition, compounds can be sold prior to approval to meet the interest, principal, or management fee payments. The values and other features of the sale process are described below.

Transition Probabilities

The transition probabilities were calculated in two ways. For compounds in Phase I or later, we used a research database that we constructed for this study. For Preclinical compounds, we refer to existing literature for the relevant probabilities and adjust them for the periodicity of our simulation.[3]

For the compounds in the clinical development phases of our simulation, the transition probabilities were calibrated using two sources of historical data: the DEVELOPMENT optimizer™ database provided by Deloitte Recap LLC and a dataset provided by the Center for the Study of Drug Development (CSDD), Tufts University School of Medicine. Recap's DEVELOPMENT optimizer™ database is built on curated clinical and regulatory histories for approximately 1,450 compounds entered into human clinical development in 2,467 distinct indications by a select group of more than 240 benchmarked biotechnology companies, i.e., the constituents of the Recap Bio-Portfolio Index™, since 1988. The histories are documented and updated daily using multiple primary, public sources of information, including but not limited to: U.S. Securities and Exchange Commission filings, U.S. and E.U. pharmaceutical regulatory documents captured and analyzed from the Food and Drug Administration (FDA) and the European Medicines Agency websites, peer-reviewed journal articles and scientific abstracts, government databases such as http://clinicaltrials.gov, and corporate press releases and investor presentations. The CSDD data were compiled from publicly available information reported by companies involved in the development of cancer drugs. The compounds targeted consisted of new molecular entities developed primarily for an anti-cancer indication for which an IND application was filed with the FDA and that entered clinical trials between January 1990 and the start of 2011. The compounds in the database were developed by biotechnology or pharmaceutical companies and were either therapeutic compounds or vaccines.

We merged the Recap and CSDD databases to yield a combined database of over 2,000 compounds. After removing duplicates and compounds for which there was not enough information about their start or transition dates, or that did not conform to the criteria defined in the paragraph above (e.g., compounds only approved for marketing outside of the U.S. or that were reformulations of existing drugs), we arrived at a final set of 733 compounds. The summary statistics for this final database are contained in Table 2.

Using these data, we calculated the transition probabilities by first estimating a continuous-time generator matrix and then converting this to transition matrices in a discrete-time setting where the time unit is the semester.[4]

For compounds in the Preclinical phase, data is more difficult to collect, in part because drug development companies have little incentive to provide information about their research and sometimes unsuccessful programs. To estimate transition probabilities for Preclinical compounds, we used statistics reported in Paul et al. (2010) and also adopted the definition of the Preclinical period used in that paper.[3] We then scaled these long-run probabilities to arrive at the probabilities for a single semester. In doing so, we assume that compounds in this phase could only transition from Preclinical to either Discontinuation or Phase I, and that the mean time in the Preclinical phase was one year, as reported in Paul et al. (2010).

Stage	Total	in %
Approved:	38	5%
Discontinued (NDA)	2	0%
Discontinued (Phase I)	174	24%
Discontinued (Phase II)	171	23%
Discontinued (Phase III)	30	4%
Still in process as of end compilation period:		
In NDA	4	1%
In Phase I	17	2%
In Phase II	221	30%
In Phase III	76	10%
Total	733	100%

Table 2: Composition of the final database of 733 oncology compounds in various clinical phases (percentages do not sum to 100% due to rounding).

The resulting transition matrix estimate $\mathcal{P}$ is given in Table 3 and the mean long term transition probabilities (the limiting probabilities) and mean times to transition resulting from this probability matrix over the period of time covered by the study are presented in Table 4. These phase transition probabilities are comparable to those reported elsewhere in the literature for similar compounds, as shown in Table 5.[5–8]

$$\mathcal{P} = \begin{array}{c} \\ \text{Preclinical}_t \\ \text{Phase I}_t \\ \text{Phase II}_t \\ \text{Phase III}_t \\ \text{NDA}_t \\ \text{Approved}_t \\ \text{Withdrawn}_t \end{array} \begin{array}{c} \begin{array}{ccccccc} \text{Preclinical}_{t+1} & \text{Phase I}_{t+1} & \text{Phase II}_{t+1} & \text{Phase III}_{t+1} & \text{NDA}_{t+1} & \text{Approved}_{t+1} & \text{Withdrawn}_{t+1} \end{array} \\ \begin{pmatrix} 50.0 & 34.5 & 0.0 & 0.0 & 0.0 & 0.0 & 15.5 \\ 0.0 & 80.8 & 13.3 & 0.5 & 0.0 & 0.0 & 5.3 \\ 0.0 & 0.0 & 84.5 & 6.7 & 0.3 & 0.1 & 8.5 \\ 0.0 & 0.0 & 0.0 & 84.8 & 6.8 & 2.1 & 6.3 \\ 0.0 & 0.0 & 0.0 & 0.0 & 56.7 & 41.2 & 2.2 \\ 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 100.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 0.0 & 100.0 \end{pmatrix} \end{array}$$

Table 3: Estimated transition matrix used in all simulations (in percent). Time subscript t indicates current six-month simulation period and $t+1$ indicates the following six-month simulation period. Note: entries in each row do not necessarily sum to 1.00 because of rounding.

Asset Valuations

In this section, we discuss the distributional model we use for simulating the values of drug compounds at the time of sale. An important feature of our model is the presence of correlation among

	Preclinical to Phase I	Phase I to Phase II	Phase II to Phase III	Phase III to NDA	NDA to Approval
P (Transition)	69.0%	72.4%	45.2%	58.6%	95.2%
Avg (months in phase)	12.0	31.2	38.6	39.6	13.8

Table 4: Average transition probabilities and time per development phase.

Source	Time Period	Number of Compounds	Preclinical to Phase I	Phase I to Phase II	Phase II to Phase III	Phase III to NDA	NDA to Approved
Megafund*	1990–2010	733	69.0%	72.4%	45.2%	58.6%	95.2%
Natanson*	1988–May 2010	164	—	72.6%	40.3%	66.7%	90.6%
Reichert et al.*	1990–2006	920	—	78.0%	43.0%	52.0%	89.0%
Walker et al.*	1995–2007	974	—	77.0%	44.0%	52.0%	—
Dimasi et al.	1993–2002	838	—	76.8%	59.4%	57.1%	—
Paul et al.	15 years	—	69.0%	54.0%	34.0%	70.0%	91.0%

*These probabilities are calculated only for cancer related compounds.

Table 5: Comparison of cancer compound transition probability by development phase.

the valuations of different compounds, which can be observed empirically to some degree and is often noted by venture capitalists and other experts in this domain. We begin by assuming that the market values of drug compounds are approximately lognormally distributed, which implies a larger number of moderately low valuations interspersed with a smaller number of large "blockbuster" valuations. In addition, we induce correlation among the valuations of compounds in the collateral portfolio. Although correlation does not affect the mean return on the overall portfolio, because of the overlay of tranching and the impact of the waterfall rules, the mean return and variability of returns on *specific tranches* will be affected by contemporaneous clusters of particularly high or particularly low valuations.

To induce correlation among the sale values in our model, we begin by generating correlated standard normal random variables which we then rescale and exponentiate such that the resulting (correlated) lognormal random variables have means and standard deviations that are consistent with the valuation assumptions described in Supplementary Methods: Simulations (Calibration of Valuation Parameters). This mechanism may be thought of as specifying a stochastic process for the value of a compound in which there is a common unobservable factor.

Next, we specify that the value Z_{ij} of the standard normal draw for the ith entity in the jth economic state of the world is the sum of two components: (1) a common (systematic) component that affects all valuations in the portfolio in economic state of the world j; and (2) a compound-specific (idiosyncratic) component that only affects compound i in economic state of the world j. More formally:

$$Z_{ij} \;=\; \beta_i^S S_j \;+\; \epsilon_{ij} \qquad , \qquad S_j \;\sim\; \mathcal{N}(0,1) \;,\; \epsilon_{ij} \;\sim\; \mathcal{N}(0, 1-(\beta_i^S)^2) \tag{16}$$

and β_i^S describes the magnitude of the impact of the systematic factor S_j on Z_{ij}. We assume that all error terms and cross terms are mutually statistically independent.

Under these assumptions, for compounds with a common value $\beta_i^S = \beta_S$, and recalling that $Z_{ij} \sim \mathcal{N}(0,1)$, it can be shown that

$$\beta_s \;=\; \sqrt{\rho} \qquad , \qquad \epsilon_{ij} \;=\; \sqrt{1-\rho}\,\eta_{ij} \tag{17}$$

where $\eta_{ij} \sim \mathcal{N}(0,1)$ is IID over i and j, and ρ is the correlation between the Z_{ij} (note: ρ must be greater than or equal to 0 and less than or equal to 1). This specification is similar to common one-factor credit models with correlated defaults (however, in our case the transition probability is not driven directly by the asset value—as might be the case in models of correlated default—since the transition probability is determined primarily by the drug approval process).[9] In cases in which there is a common correlation among all compounds in the portfolio ($\beta_i^S = \beta_S$ for all i), the value of the ith compound in the jth simulation path is given as

$$X_{ij} \;=\; \exp\left(\mu + \left(\sqrt{\rho}S_j + \sqrt{1-\rho}\epsilon_{ij}\right)\sigma\right) \;=\; \exp\left(\mu + Z_{ij}\sigma\right) \tag{18}$$

where

$$\begin{aligned} \mu &= \ln(m_v) - \tfrac{1}{2}\ln\left(1+\tfrac{s_v^2}{m_v^2}\right) &&\equiv \text{ the estimated mean of log-returns} \\ \sigma &= \left[\ln\left(1+\left(\tfrac{s_v^2}{m_v^2}\right)\right)\right]^{1/2} &&\equiv \text{ the estimated SD of log-returns} \end{aligned} \tag{19}$$

and m_v and s_v^2 are the estimated mean and variance, respectively, of the observed valuation data (or are derived from other qualitative approaches).

To avoid very large (and potentially unrealistic) simulated values for compounds at the time of sale, we also impose a maximum (M_i) on the value of the compound such that the final value is given as

$$V_{ij} \;=\; \min(X_{ij}, M_i)\;. \tag{20}$$

The introduction of an upper bound affects the mean of the distribution. We adjusted the values of μ to accommodate the capping that occurs as a result of the imposition of the upper bound. This adjustment ensures that the mean of the distribution is consistent with our data. The values for μ, σ, and M_i are presented in Table 6 for each compound phase.

In our simulations, drug compounds are sold infrequently and tend not to cluster in time except at the end of the transaction. Thus, simulations in which the (unobservable) systematic component is updated each period result in relatively little correlation among prices, even though our simulation horizons are short (i.e., on the order of 5–7 years). Furthermore, because the current structure of the portfolio is static, i.e., the portfolio of compounds is purchased at the beginning

of the fund transaction and then winds down, it is natural to think of a common factor affecting the whole portfolio. Such a factor could be general economic conditions, regulatory shifts, or sweeping technological advances.

Accordingly, we assume that the valuations of compounds are lognormally distributed and governed by the dynamics in (16), and that the systematic shock occurs once at the beginning of each simulation path, such that a particular string of sales within that path will *all* be influenced by the shock. This induces correlation among all valuations in the portfolio, rather than just between those in which sales occur in a single period.

To implement this approach, in each path we simulate a single value for S_j (in the jth path) and then, for each compound being sold, simulate ϵ_{ij} and calculate a valuation for compound i (V_{ij}) as in (20). Importantly, although S_j is drawn only once per trajectory, the compounds in the portfolio themselves evolve (e.g., transition, get funded, etc.) in each time step of the simulation.

Calibration of Valuation Parameters

A critical set of assumptions in our simulations involves the valuations of individual drug assets at a given stage of development. Such valuations are difficult to estimate due to significant heterogeneity across the assets with respect to a compound's scientific merits, its commercial potential, the expertise of the managers in charge of its development, etc. Furthermore, many oncology assets have traditionally been privately held, or developed as part of a larger suite of products, and thus accurate data on individual valuations are not readily available.

To estimate the mean and variance of compound valuations for our model, we used data from Bloomberg to build a dataset of initial public offerings (IPOs) since 2000, and market valuations (as of the end of the first quarter of 2011) of publicly listed companies in the U.S. focused on developing and marketing cancer compounds and which had a market capitalization of at least \$5M. For each company for which we could gather enough information, the value per approved compound was calculated by dividing the market capitalization of the company by the number of approved compounds it owned. We realize that this method may overestimate the value of compounds given that this calculation assigns a value of zero to earlier stage compounds and that the company may hold other assets not considered. Alternate methods to estimate the value of compounds such as discounted future cashflows could be applied to future developments of this model. For our simulations we decided to approximate the value of a compound using observed market valuations. The resulting mean value for a marketed compound is \$1.87 billion and its standard deviation is \$2.24 billion.

The valuations corresponding to the compounds in earlier development phases were calculated using a binomial-tree valuation model in which the value of each compound is estimated by taking into account the probabilities of success and failure per phase, the expected values in each case, and the time required to move from one phase to the next.[10] The inputs for the transition probabilities and times in each phase were derived from our transition matrix. The discount rates used to calculate the discounted values per phase were 15% for the Market to NDA phase, 25% for NDA to Phase III, and 30% for the earlier phases to reflect the higher risk of early-stage projects. In addition, upper bounds for valuations were imposed to prevent the model from generating un-

reasonably large values. These upper bounds were chosen qualitatively based on the empirical distribution of values (see Supplementary Methods: Simulations (Asset Valuations)).

To compute the standard deviation of each of the values per phase and per compound, we used data from Bloomberg. First we calculated the standard deviation of the value of marketed compounds (the $2.24 billion cited above). Next we calculated the ratio (1.19) of the standard deviation to the mean value of marketed drugs (the $1.87 billion cited above) in our Bloomberg database. Finally, we applied this ratio to the mean values per compound and per phase to estimate each of the standard deviations corresponding to each of the phases.

The mean, standard deviation, and upper bounds were used to fit the lognormal distributions from which the value of each compound is drawn in our simulations. Table 6 shows the values of the estimated original mean and upper bounds as well as the cap-adjusted μ and σ used to estimate the value of the drugs.

			Cap Adjusted	
	Original	Cap	μ	σ
Preclinical	16	100	2.36	0.939
Phase I	30	250	2.96	0.939
Phase II	82	500	4.00	0.939
Phase III	425	1000	5.80	0.939
NDA	1515	2500	7.35	0.939
Approved	1870	5000	7.24	0.939

Table 6: Parameters for valuation functions, where μ and σ correspond to the mean and standard deviation of the lognormal distribution from which valuations are randomly drawn.

Finally, as a proxy for the (normal) correlations, we use the mean pairwise correlation of the equity returns on small biopharmaceutical firms, also calculated using Bloomberg data. These are related somewhat to the valuations of individual compounds since it is often the case that small firms have only a single drug that they are either researching or producing. Thus the price of the firm may be related to the value of these compounds.

In our sample, the equity correlations we estimated were on the order of 20%, which is the value we use in the simulations. This value is within the range of observed correlations among public firms in typical credit-portfolio models, and is consistent with empirical estimates of publicly traded oncology biotech firms. We expect correlations associated with very small private firms to be lower than for those of public firms, and correlations among the valuations of single compounds in our simulation to be lower still.

Note also that the correlation in returns does not translate directly into an equivalent level of correlation for realized valuations, due to the calculation of the former on returns (in normal space) and the latter on levels (in lognormal space). In general we observe that valuation levels are correlated to a lower degree than are the equity returns (i.e., the correlation among valuations is lower than 0.2), which is consistent with our expectations.

Investment Structure and Development Costs

The investment structure we assume is based on the licensing framework commonly used in the biopharmaceutical industry. In our model, during the course of the drug's development, both upfront and periodic payments are made by the megafund to finance additional research and to compensate the developers for successful completion of key milestones (such as the completion of a phase). In addition, the megafund finances all clinical trial costs. In exchange for this funding, the megafund is granted 85% of the economic value of the compound when it is sold. The remaining 15% is assumed to be retained by the founder and management team developing the compound. The structure of the payments made by the megafund is detailed below.

Phase	Upfront Payment	Milestone	Development Cost
Preclinical	2.5	1.3	Random*
Phase I	7.5	3.8	Random*
Phase II	20.0	10.0	Random*
Phase III	75.0	37.6	Random*

*See Supplementary Methods: Simulations (Drug Development Costs).

Table 7: Investment costs (in $millions).

In practice, upfront and milestone payments for a specific compound are derived through negotiations based on the novel features and properties of the compound, its expected value, the amount of investment required to carry the compound to the next phase(s), and the negotiating power of the parties. It is therefore difficult to define what the standard terms of any particular deal might be. For our model, in addition to the commitment to fund the development of the drugs, we estimated the upfront payments to be 40% of the expected development costs per phase and the milestones to be 50% of the upfront payments.

We confirmed the plausibility of these investment parameters through conversations with experts, and by using data from public presentations made by practitioners[11] and the Recap DEAL builder™ tool. However, recent trends seem to favor smaller upfront payments and larger milestone payments. Future research may confirm this point, which would necessitate changes in the simulation parameters.

Drug Development Costs

We assume that development costs per phase and per compound follow a lognormal distribution with parameters based on previous results reported in the literature.[3,12] Some authors have since argued that the costs reported in these studies may be overstated,[13] but we adopt these figures to be conservative.

For compounds in preclinical and clinical phases, Paul et al. (2010) provides estimates of the cost of development at each clinical stage based on industry benchmarking data provided by the

Pharmaceutical Benchmarking Forum along with fifteen years of project level data from Lilly's R&D portfolio. Dimasi et al. (2003) bases results on survey data collected from the commercial sponsors of 68 randomly selected approved compounds in the CSDD database, representing multiple therapeutic areas including, but not limited to, oncology.

To estimate the mean cost per phase we have chosen to use the results of Paul et al. (2010) because they are more timely and they result in more conservative expected costs. However, we omitted the submission and launch costs proposed ($40 million) which appear to include launch preparation costs that we expect to be borne by the biopharma companies acquiring these compounds post-approval (recall that under our current assumptions, once drugs are approved for their first indication, they are sold to an industry incumbent for marketing and distribution).

We further increase our cost estimates in two ways. First, since the statistics in Paul et al. (2010) are calculated in 2008 dollars, we used the U.S. GDP deflator index to inflate the numbers to 2011 dollars. Separately, we adjust for the additional cost of developing cancer compounds relative to other types of therapies. Adams and Brantner (2006)[14] analyze the capitalized cost of new drug development by indication and show that the cost of developing an oncology product is 20% higher than the sample mean (across all compounds in their dataset). Accordingly, for our analysis, we adjusted the costs upward by a factor of 1.2 to reflect the higher than average cost of oncology development. Both of these adjustments yield higher costs and, therefore, more conservative profits in our simulations.

Using our mean estimates, the resulting mean out-of-pocket costs invested per compound from Preclinical to the end of Phase III is $263 million.

Paul et al. (2010) do not provide an estimate of the standard deviation of the costs per phase. For our experiments, we assumed that the variability of development costs for oncology compounds is related to that presented in Dimasi et al. (2003). We then calculated the ratio of the standard deviation to the mean cost reported in this paper (ranging from 0.70 to 0.94) and applied that ratio to the adjusted costs per phase obtained as previously explained.

In addition, we imposed a maximum cost in each phase to cap the expenses incurred per compound and per phase. The sum of the cap costs assumed per phase yields a total maximum out-of-pocket cost per compound of $690 million, which is quite conservative compared to figures contained in the literature. The resulting adjusted mean costs per phase and corresponding standard deviations are shown in Table 8.

These figures can be used to estimate the parameters μ and σ of the lognormal distribution that we use to simulate development costs, which are drawn randomly for each compound in each phase. We adjusted the values of μ to accommodate the capping (the maximum cost per phase) to ensure that the mean of the distribution would remain consistent with the observed data. The resulting parameters used are given in Table 9.

The out-of-pocket costs per approved compound may be estimated according to Paul et al. (2010) by calculating the number of drugs needed to obtain a single approval. Under our assumptions, eight Preclinical projects are needed to bring one new drug to market on average. Starting with eight compounds in the Preclinical phase, if we multiply the expected number of compounds that transition to each phase by the expected cost per phase we get an estimate of the out-of-pocket

	Mean cost Paul et al. (2010)	Mean adjusted for oncology factor (in USD2011)	Dimasi et al. (2003) SD/Mean ratio	SD per phase	Max cost per phase
Preclinical	5	6	0.92	6	20
Phase I	15	19	0.84	16	50
Phase II	40	50	0.94	47	120
Phase III	150	188	0.70	132	500
Total		263			690

Table 8: Asset development out-of-pocket costs.

	Adjusted Mean Cost	Cap Adjusted μ	σ
Preclinical	6	1.53	0.79
Phase I	19	2.72	0.73
Phase II	50	3.65	0.79
Phase III	188	5.06	0.63
Total	263		

Table 9: Parameters μ and σ of the lognormal distribution used to simulate development costs.

cost to develop a new compound of $693 million. Following Paul et al. (2010) and Dimasi et al. (2003), we capitalize these costs over time to account for the cost borne by investors to finance the development of drugs. The resulting mean total capitalized cost per approved drug using a discount rate of 10% is $1.2 billion.

Cost	Megafund Simulation	Paul et al. (2010)	Dimasi et al. (2003)	Dimasi (2007)	Adams (2006)
Out-of-pocket cost	693	654	403	672 / 559	—
Capitalized	1,220	1,104	802	1,318 / 1,241	868

Table 10: Comparison of development costs of a single approved drug (from Preclinical to Approval).

Capital Structure and Cashflow Waterfall

In our experiments, we assume a very simple capital structure and cashflow waterfall. Our capital structure has three tranches: a senior bond, a junior bond, and an equity tranche. A more sophisticated implementation would almost certainly take advantage of a more efficient capital structure and more involved waterfall rules.

The bonds receive semiannual coupons and are amortized in equal installments over various periods of time as presented in Table 11. The senior bonds have a maturity of 4 years and their owners receive coupon and redemption payments ahead of the junior and equity-tranche holders. The junior bonds have a maturity of 6 years and they are paid back before any cashflows accrue to the equityholders.

The securities are assumed to be quite basic (fixed-rate amortizing bonds and common equity), but a more sophisticated model might make use of less standard securities to better match investors' preferences.

	Coupon (annual)	Amortization Schedule (start and end semester)
Senior Bond	0.05	Periods 5 to 8
Junior Bond	0.08	Periods 9 to 12
Equity	—	Period 15

Table 11: Capital structure parameters used in simulations.

In addition to overcollateralization (which involves holding more collateral than the par value of the tranche), the structure includes an interest coverage ratio test (IC test) designed to protect bondholders. The ratio is calculated as follows:

- The numerator of the IC ratio is equal to the cash reserve available plus the future expected cash inflows from the sale of compounds already in process minus the management fee (50 basis points per year) minus the interest and principal redemptions due in the current period.
- The denominator of the IC ratio is the required payments for the next k periods of management fees plus interest and principal (k is assumed to be 2 for Simulations A and B).

If the ratio falls below the target IC level, compounds are sold to bring the IC ratio back into compliance. The sale of assets helps ensure that the Special Purpose Vehicle (SPV) will have enough funds to pay the servicing, interest, and principal payments.

Throughout the life of the biomedical megafund, waterfall rules guide the allocation of funds. The waterfall is implemented as follows:

- At the start of each period (semester) all proceeds from any consummated compound sales are added to the current cash balance.
- Also at the start of each period, each compound is tested to see if it has transitioned to a new state. Any compounds that have transitioned into the Approved state (or to the targeted phase in the megafund, i.e., Phase II in Simulation A) are sold and the cashflow from the sale is deferred until the end of the sales cycle (we assume it takes 2 semesters to organize and execute a compound sale).
- If there sufficient cash in the cash account, payments are made in the following order:
  - The megafund management fee is paid.
  - Interest on senior bonds is paid.
  - Scheduled principal payments on senior bonds are paid.
  - Interest on junior bonds is paid.
  - Scheduled principal payments on junior bonds are paid.
- If there is not enough money to meet these obligations, some or all of the bonds are in default and the assets are liquidated. In the event of liquidation, the cash generated by the monetization of available assets flows first to the most senior bondholders followed by the junior bondholders, and any residual amount goes to the equityholders.
- If the megafund is not in default, the IC test is performed. If the IC test is failed, the cash shortfall is calculated and compounds are sold to meet the shortfall and ensure compliance with the IC test.
- From the remaining cash, a portion is reserved to make the servicing, interest, and principal payments over the subsequent k periods of time (k is assumed to be 2 in the simulations).
- If any surplus cash remains, it is used to finance the clinical trials of any compounds that have transitioned but have not yet received funding for their new phase, starting with those compounds that are farthest along in the approval process.

- After all of the above payments are made, cash at the end of the period is calculated.
- If there are no bonds left outstanding, the portfolio is liquidated and all remaining proceeds, net of administrative fees, accrue to the equityholders.

Supplementary Discussion

In this section we review some of the practical challenges of megafund financing and potential solutions. One set of issues involves our choice of simulation parameters: in some cases, they are conservative, in other cases, they are aggressive. On the conservative side, our assumed 8% and 5% coupon rates for junior- and senior-tranche research-backed obligations are higher than those required by today's investors; we assumed a probability-adjusted cost of developing a compound of over $1.2 billion; and we ignored potentially significant synergies and cost savings likely to accrue to a large entity involved with multiple anti-cancer-therapy teams. On the ambitious side, we assumed that compounds that are not discontinued can be sold within one year at some random price drawn from a lognormal distribution, and that a very large number of compounds can be developed simultaneously and efficiently by multiple teams working in parallel. To allow others to evaluate the importance of these concerns by conducting new simulations with their own choice of parameters, we have placed our simulation software in the public domain with an open-source license to run, modify, and distribute the code.

We have also made assumptions regarding the capacity of translational medical research that are harder to test via new simulations. In particular, we have implicitly assumed that there is a sufficient supply of anti-cancer compounds to meet the demands of our megafund; that several billion dollars of capital can be deployed in high-quality research programs over a short startup period; and that there is no shortage of talented researchers, engineers, and entrepreneurs who will staff the various teams needed to develop these compounds. These assumptions are partly motivated by informal discussions with numerous biomedical researchers who seem to have more innovative ideas than they have funding, and who observe that the availability of funding sometimes seems inversely related to the innovativeness of their proposed research. These assumptions are also motivated by reports of 20-year inventories of oncology compounds waiting to be investigated,[15] an increasing number of academic biotech spin-outs,[16], and the increasing number of science and engineering doctorates awarded over the past decade (with the biggest increases coming from the medical and life sciences[17]). Finally, our optimism regarding capacity is motivated by recent theoretical and empirical research in financial economics documenting the positive impact that increased investment activity has on innovation by stimulating an increase in the supply of innovators and truly novel ideas.[18–20] In one such study,[19] the authors conclude that "...the flood of capital in hot markets also plays a *causal* role in shifting investments to more novel startups—by lowering the cost of experimentation for early stage investors and allowing them to make riskier, more novel, investments."

Of course, one of the most speculative assumptions underlying our simulations is that historical drug-development data can be used to calibrate the parameters of our simulation. New trends and nonstationarities in the stochastic process of biomedical R&D may reduce the accu-

racy of such extrapolations. For example, the fantasy of personalized medicine is fast becoming a reality through advances in pharmacogenomics and the identification of genetic and molecular biomarkers for various types of cancer.[21] This recent innovation has had a dramatic impact on the biopharma industry, creating smaller and less correlated biotech niches but also inducing greater correlation among big pharma companies that are targeting the same molecular pathways.[15] More accurate targeting of drugs also affects pricing and reimbursement policies[22] which, in turn, have important consequences for biopharma revenues, business priorities, and, ultimately, research-and-development decisions. The parameters of our simulation are clearly affected by such considerations, hence these and other context-specific issues must be addressed in any live application of our approach.

We acknowledge the inherent imprecision of any extrapolation of current research agendas and business trends. However, the inability to accurately predict translational research outcomes does not imply an inability of investors to assess the financial risks of and commit capital to a diversified portfolio of such outcomes. With sufficient scale, time, and expertise, biomedical megafunds may well yield attractive investment opportunities to a much broader universe of investors than those who currently invest in the biopharma industry. Securitization addresses scale and time, but obtaining the necessary expertise requires an unprecedented level of collaboration between academia and industry, and among doctors, scientists, and engineers,[23] including financial engineers. By incorporating more specific knowledge about industry trends, transformative scientific discoveries, and potential interactions between various drug-development programs into a megafund's portfolio construction process, investment performance can be improved substantially. More importantly, domain-specific expertise can provide more accurate risk assessments of a megafund's holdings, reducing the element of surprise for investors, portfolio managers, and researchers.

The fact that such collaboration does not yet exist may be a symptom of a deeper divide between academia and the biopharma industry: a cultural gap between scientific research and commercial enterprise. In a comprehensive study of the business of science—with particular emphasis on biopharma—Pisano (2010) provides an eloquent summary of this gap:[24]

> Science is a world focused on "first principles" and methods; in contrast, business worries about commercially feasible products and processes. Science is inhabited by academics; the manager, the industrial scientists, and the engineer dominate business. Both science and business are intensely competitive worlds but their markets and currency are distinct. In science, score is kept by peer review and grant givers, and measured ultimately by reputation; in business, score is kept by capital markets and measured by profitability. Publication is synonymous with science, secrecy synonymous with business.

While the research-backed obligation structure with long-term debt relieves some of the exigencies of shorter-term funding, it does not address the fundamental conflict between science and business.

However, the new structure of a megafund presents an opportunity to re-engineer the business of biomedical science. With sufficient financial clout to invest for the long run and withstand economic downturns, but enough flexibility to change the composition of its portfolio in response

to new scientific breakthroughs or shifts in economic or political climate, the megafund may be the ideal balance between stability and agility. To achieve this balance, the corporate governance structure and investment process of the megafund must be carefully crafted to promote collective intelligence while maintaining focus on the overall purpose of easing the burden of disease. In particular, the objectives of a megafund would not be the same as those of grant-making agencies such as the National Institutes of Health whose primary focus is supporting basic scientific research (therefore, megafunds would be complementary, not competitive, to current government funding). Accordingly, its investment team must be staffed by a combination of industry professionals with scientific, engineering, and business expertise, and with access to a wide network of scientific advisors to serve both as consultants and talent scouts. Too much centralization and control can sometimes stifle creativity and independence, so these staffing decisions must be made carefully to yield sufficient diversity while operating as a coherent group. New business arrangements may also need to be crafted to support truly innovative research. For example, investing in early-stage research may take the form of royalty-sharing agreements with university technology-licensing offices in which younger academics working in key areas of research—even if they have no immediate interest in preclinical applications—are offered unrestricted research funding in exchange for a small percentage of any future royalties that may be derived from their work.

It is well known that the complexity of managing organizations grows more than proportionally with size,[25,26] which may explain the recent empirical evidence that smaller more-focused biopharma companies seem more efficient than big pharma, producing a comparable number of new molecular entities at the same rate but at lower cost.[27] An even more relevant "proof-of-concept" of the efficiency of a megafund vehicle is offered by Royalty Pharma, which currently manages $8 billion with a full-time staff of 19 individuals (though they employ a much larger network of biomedical experts as consultants). A megafund can be managed effectively with a much smaller staff than a large pharmaceutical company because of the nature of its business—investing in biomedical projects, not operating drug-development, marketing, and distribution facilities. At the same time, megafunds can benefit from the staying power associated with deep pockets. This dual nature of megafunds is one of its most significant features—its impact on the industry is greatly multiplied by financial leverage, not by number of employees or the size of its plant and equipment.

Financial size offers several distinct benefits. By raising a large pool of capital dedicated to eradicating disease, the biomedical megafund can significantly increase public awareness for both the burden of disease and the potential for its cures, allowing the fund to gather proportionally greater resources to achieve its mandate. These resources involve more than just capital, long horizons, and financial diversification. They also include: research synergies, efficiency gains, and greater collective intelligence among multiple R&D teams (who would otherwise be prevented from exchanging ideas if they worked for unrelated competing companies); centralized management of clinical trials and shared information about their outcomes (especially negative results, which are currently not reported anywhere[28]); complementary educational synergies (e.g., facilitating a larger pipeline of M.D./Ph.D.s); stronger political support due to higher visibility among voters (e.g., government guarantees, tax incentives); and greater drawing power for hiring leading experts.

This last feature of a biomedical megafund may be the most effective way to bridge the cul-

tural gap between scientists and business executives. The most talented biomedical researchers may not be motivated by financial gain. However, an opportunity to join an elite team of like-minded researchers, engineers, and clinicians devoted to a worthy humanitarian challenge—with a vast pool of capital at its disposal that is more patient than the longest-horizon venture-capital fund, and an organization focused on reducing the burden of a disease they care deeply about—may be considerably more compelling.[29] And with current challenges such as cancer, heart disease, dementia, Alzheimer's disease, diabetes, obesity, malaria, and influenza, there is no shortage of projects with great social significance to support several biomedical megafunds. Large-scale diversified drug-development efforts facilitated by megafunds not only increase the likelihood of success, but also increase the economic value of these enterprises to all stakeholders. With sufficient scale, it becomes possible to do well by doing good.

The combination of social relevance and the profit motive may seem confusing and inappropriate to some, but this trend is becoming more prevalent as we face societal challenges that require an unprecedented scale of collaboration among millions of individuals. Although charitable giving is an important part of translational medical research, the magnitude of such giving is dwarfed by the pool of investment capital seeking a reasonable rate of return. By creating financial incentives for solving social problems like cancer, society is able to tap into this much larger pool of assets. The megafund can be viewed as another example of the broader trend toward "venture philanthropy" as practiced by existing organizations such as the Gates Foundation (gatesfoundation.org), the Robin Hood Foundation (robinhood.org), and the Children's Investment Fund Foundation (ciff.org). Another form of this trend is public-private investment programs, in which private-sector institutions provide financing under certain types of government sponsorship. Such programs played an important role in dealing with the recent financial crisis by raising over $29 billion of investment capital to purchase distressed securities.[30] Several important government initiatives are already underway for speeding up translational medical research such as the U.S. government's National Center for Advancing Translational Sciences (which is part of the Cures Acceleration Network) and the Israeli Life Sciences Fund. But with budgets of only $575 and $200 million, respectively, these efforts will eventually also require substantial private-sector funding—megafunds may be one solution.

Government can play other important roles in addition to providing seed funding. The regulatory approval process for therapeutics is one of the most critical drivers of risk and return in the biopharma industry, and innovations in "regulatory science" can increase productivity and reduce risk. Such innovations include more effective use of clinical data and providing more detailed feedback to the industry regarding the approval process, and the U.S. Food and Drug Administration has undertaken several initiatives along these lines (see, for example, the academic Partnership in Applied Comparative Effectiveness Science).[31] The government can offer broader incentives for translational medical research by extending the patent life of therapeutics in certain high-priority and areas such as cancer and heart disease.[32] More targeted support can be provided in the form of tax incentives (e.g., allowing corporations to repatriate offshore assets at reduced tax rates if invested in designated public-private partnerships designed to support biomedical innovation), guarantees for investors' assets in biomedical megafunds, and the establishment of a blue-ribbon advisory panel of leading academics and business leaders to accelerate public-private investment partnerships in this industry.

Government involvement is also likely to be necessary because of ethical and humanitarian considerations, which affect the biopharma industry more directly than others. Financial innovations that explicitly address such concerns in advance may also be worth exploring.[33] For example, if a cure for a lethal type of cancer is developed, should its price be whatever the market will bear? What about rare/orphan and developing-country diseases? Government intervention would almost surely impose price limits in the former and subsidies in the latter because of the ethical considerations surrounding life-or-death choices linked to economic profit. The inevitable consequences of the political economy of public health suggest that pure profit-maximizing behavior in the life sciences industry may not be sustainable. One approach to addressing this issue is to incorporate broader social objectives directly into the capital structure of the megafund. For example, beyond a certain threshold of profitability, a portion of the megafund's excess profits might be used to subsidize drugs for those least able to afford them. The immediate effect of such corporate policies would likely be reduced upside potential for equity-tranche investors; no doubt, the market price of the research-backed obligations' equity tranche would adjust swiftly to reflect these new policies. However, if such policies lead to a larger and more sustainable enterprise and broaden the appeal of the securities issued under such terms to a wider investor population, the ultimate impact on the amount of capital raised and the megafund's likelihood of success may, in fact, be positive. This possibility bears further investigation.

Finally, in much the same way that securitization may have been too successful in raising large pools of capital for U.S. residential real estate, megafunds may also enjoy rapid success that brings a new set of challenges which should be anticipated and addressed in advance. Rules regarding sales practices, disclosure requirements, permissible corporate governance structures, and suitability criteria for investors must be imposed and strictly enforced to ensure that megafunds serve their purpose without jeopardizing the stability of the financial system. Although it is impossible to guarantee that megafunds will generate attractive returns, much can be done to ensure that all stakeholders are fully aware of its risks.

Supplementary Empirical Results

Data from the ThomsonOne database, VentureXpert (VX), indicates that over the last decade the biotech and healthcare venture capital (VC) investments have exhibited significantly lower returns than in the past. This pattern suggests that venture capital investment in this sector may be suffering from a secular downturn in returns. In VX, the biotech sector includes human therapeutic biotechnology, industrial biotechnology, and biosensors, and the medical/healthcare sector covers pharmaceutical research, therapeutics, diagnostics, and other healthcare related services. The VX database provides returns from all stages of venture investment, and reports 1-year rolling-horizon internal rates of return based on cash inflows and outflows in each year. Those returns include results from both active and liquidated funds (avoiding survivorship bias in the data), and are net of management fees and carried interests.

Figure 2 contains the 1-year IRR (the blue and green lines) and trailing 10-year IRRs (the orange lines) for the biotechnology and medical/healthcare sectors, where the 10-year IRRs are computed by compounding the 1-year IRRs over the preceding decade.

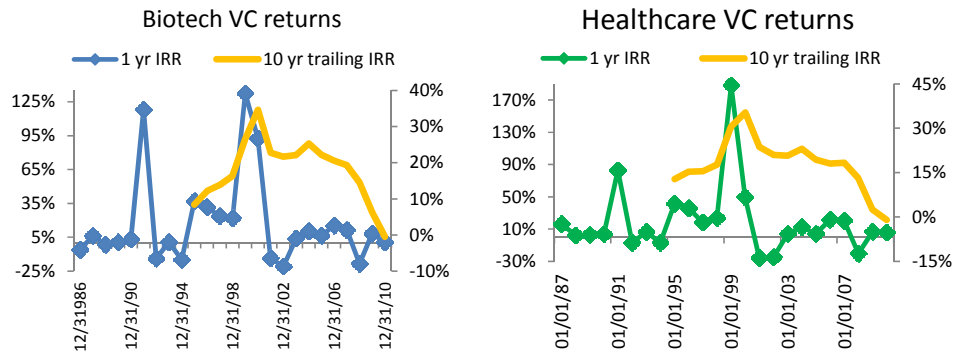

Figure 2: 1-year and trailing 10-year internal rates of return for the U.S. biotechnology and medical/healthcare sectors.

A recent paper by Booth et al. (2011)[34] also discusses the return of life sciences venture investing over the 2000–2010 period using information from a benchmarking database from Cambridge Associates (an investment advisory firm). Focusing on returns from deals (not funds), they examine the gross (including fees) pooled mean IRR for healthcare VC investing and its subsectors, and report a return of 15% for realized deals in the healthcare sector and 7.4% if unrealized deals are included.

Table 12 compares the 2000–2010 results from VX and Booth et al. (2011) (realized and unrealized deals) with the simulations results from our model. Using parameters derived from historical data on valuations from 2000 to the first quarter of 2011, the megafund yielded an annual return of 7.2% for both Simulations A and B with an all-equity capital structure. Simulations in which the capital structure consists only of equity are closest in structure to a large venture capital fund, hence a comparison of these results to those from VX and Booth et al. (2011) seems appropriate. The VX database shows an IRR of 2.7% for healthcare and 5.7% for biotech during 2000–2010. Since these returns are net of fees, we must add back the fees before comparing them to our simulation returns. The standard VC fees are approximately 2% per annum of assets under management plus carried interest (which we estimate to be an additional 1% per annum). This implies annual gross returns of 5.7% and 8.7%, respectively. The Booth et al. (2011) estimates of 12.8% and 7.6% already include fees. The megafund simulation yields net-of-fee returns of 7.2%, or 7.7% if we add the 0.5% service fees included in our simulation. Even though the assets involved in each of these cases do not match exactly, they are similar and, based on these comparisons, our simulation results seem consistent with recent historical experience in the biopharma industry.

Finally, it is important to note the downward trend in investment returns in the biotechnology and pharmaceutical venture capital sector over the past decade. In fact, if the year 2000—the last year the biopharma industry experienced large positive performance—is dropped from the sample, the IRRs for biotech and healthcare become negative according to VX (-0.5% for biotech and -0.7% for the medical/healthcare). This sensitivity to outliers suggests the importance of monitoring the investment performance of both sectors so as to recalibrate the simulations as needed.

Source	Raw	Gross of Fees
Simulated Megafund	7.2%	7.7%
VX (Healthcare)	2.70%	5.70%
VX (Biotech)	5.70%	8.70%
Booth et al. (2011) (All healthcare)	—	7.40%
Booth et al. (2011) (Pharmaceuticals)	—	12.80%
Booth et al. (2011) (Biotech)	—	7.60%

Table 12: Comparison of historical returns of VC equity investment from 2000–2010 and simulated megafund returns.

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