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

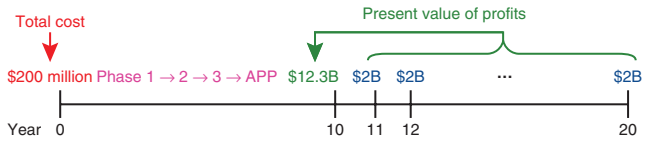

Figure 1 Timeline of cash flow for simplified example of a typical drug-development program in which out-of-pocket costs with present value of $200 million at year 0 generate annual net income of $2 billion in years 11–20, implying a present value of $12.3 billion at year 10 (based on a 10% cost of capital). 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 $2 \times \$12.3 = \$24.6$ 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

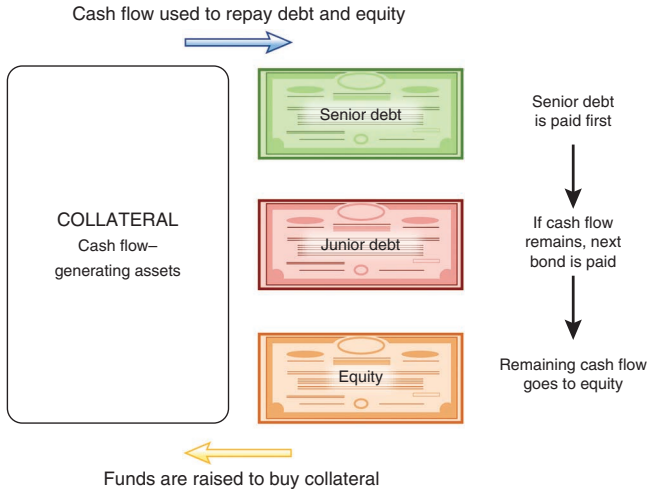

Figure 2 Schematic of the waterfall of cash flow for a typical research-backed obligation securitization.

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.

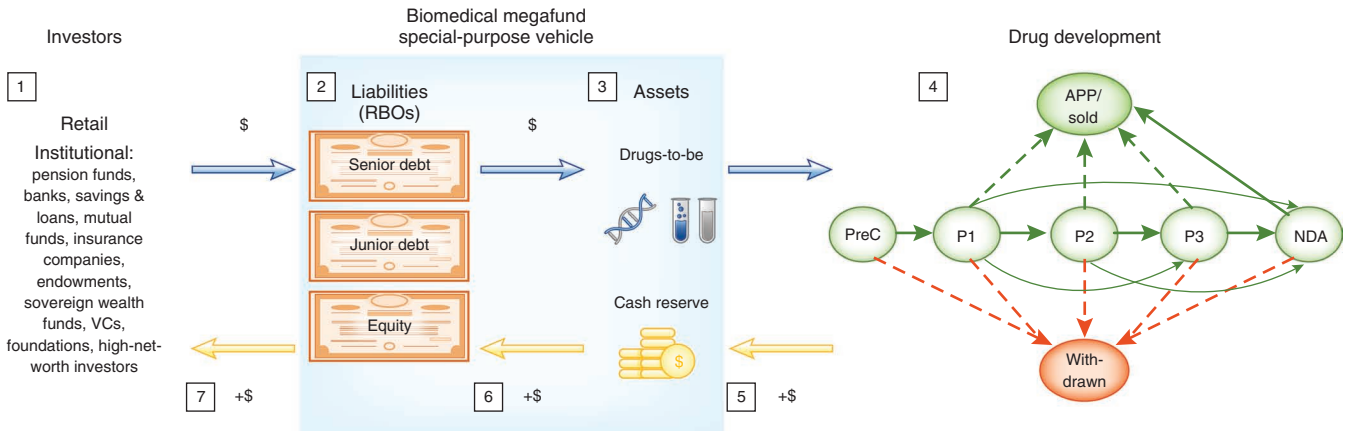

Figure 3 Business structure of a biomedical megafund special-purpose vehicle. Funds are raised from retail or institutional investors (1) through the capital markets issuance (2) of various types of debt and equity. These funds are invested in molecules being developed to cure cancer (3). Some funds 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.

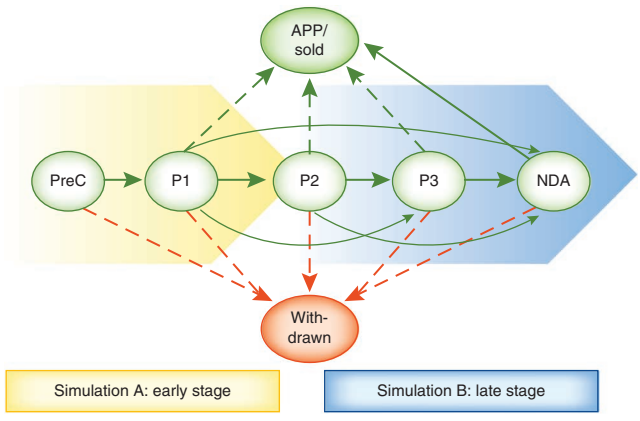

Figure 4 Simulating two distinct business stages of a biomedical megafund. PreC, preclinical; P, phase; NDA, new drug application; APP, approval.

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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COMPETING FINANCIAL INTERESTS

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

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