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## Financing drug discovery via dynamic leverage

Vahid Montazerhodjat<sup>1,2</sup>, John J. Frishkopf<sup>3</sup> and Andrew W. Lo<sup>1,2,4,5</sup>, alo-admin@mit.edu

We extend the megafund concept for funding drug discovery to enable dynamic leverage in which the portfolio of candidate therapeutic assets is predominantly financed initially by equity, and debt is introduced gradually as assets mature and begin generating cash flows. Leverage is adjusted so as to maintain an approximately constant level of default risk throughout the life of the fund. Numerical simulations show that applying dynamic leverage to a small portfolio of orphan drug candidates can boost the return on equity almost twofold compared with securitization with a static capital structure. Dynamic leverage can also add significant value to comparable all-equity-financed portfolios, enhancing the return on equity without jeopardizing debt performance or increasing risk to equity investors.

### Introduction

New advances in biology and breakthroughs in genetic research have presented the biotechnology and pharmaceutical industry with a host of promising new targets and compounds to treat a range of diseases. However, the drug development process remains underfunded, with investors shifting capital to other sectors because of mediocre returns on perceived high-investment risk. A comparison of five-year periods before and after the recent financial crisis (2004–2008 versus 2009–2013) shows that total funding of drug R&D dropped 21%, from US\$21.5 billion to US\$16.7 billion [1]. Between 2004 and 2012, funding for the National Institutes of Health (NIH) declined by 1.8% per year in real terms [2]. Although funding seems to be improving over the past year in response to a number of prominent biotech initial public offerings, the capital inflows are highly

concentrated among a few large deals, and the number of new startups is not increasing [3]. In fact, the lack of funding is particularly severe in early-stage development, before Phase II clinical trials. For example, between 2004 and 2011, funding for prehuman preclinical R&D in the pharma industry declined by 2.3% per year [2]; 2013 saw only 63 first-time Series A financings in biotechnology, almost 30% lower than the peak of 89 in 2006 and the lowest level in a decade [1]; and the number of active US biotech venture capital firms declined from 201 in 2008 to 138 in 2014 [4].

Fernandez *et al.* [5] proposed a ‘megafund’ financing approach, applying portfolio theory and securitization techniques to reduce the risk and enhance the expected returns of a group of investments in drug development projects. Unlike a traditional venture capital fund, the megafund issues equity and debt

(‘research-backed obligations’ or RBOs), and the portfolio of projects – candidate drugs, licensing agreements and other intellectual property – serve as collateral for the RBOs. This approach diversifies the typically binary drug investment results across a portfolio of therapeutics, smoothing the portfolio’s payout and reducing the volatility of its returns. Securitization also changes the way that cash flows are distributed from a pool of biomedical projects, allowing a broader array of investors to participate in the risk and expected return of drug development according to their risk appetite.

However, issuing securitized debt generally requires collateral that generates a reliable and well-understood stream of cash flows such as an approved drug. Investments in early-stage biomedical projects usually yield no cash flow until they reach Phase IIb and, even then, they provide

cash only sporadically (e.g. when they are out-licensed or sold). The unpredictability of the amount and timing of these cash flows suggests that the megafund is impractical for portfolios exclusively focused on early-stage drug discovery and development.

In this article, we extend the concept of the megafund to allow for time-varying amounts of debt or 'dynamic leverage', which can accommodate the startup phase of a fund focused purely on preclinical R&D and early-stage translational medicine. Dynamic leverage adjusts the amount of debt that a securitization vehicle can sustain, based on parameters related to its default probability (the likelihood of the entity being unable to meet its payment obligations on a timely basis). It is directly tied to a second concept, 'dynamic risk measurement', in which the default risk of a bond is periodically measured via certain credit metrics and performance indicators. Together, dynamic risk measurement and dynamic leverage enable us to construct a time-varying securitization structure that reflects the evolving nature of the portfolio's assets and optimizes the fund's capital structure accordingly.

### Dynamic leverage

Dynamic leverage is motivated by a simple observation: as a portfolio of biomedical projects progresses its risk should decrease. Therefore, the amount of debt of a given default probability that can be supported by this portfolio, as a percentage of the total invested capital required, should increase, effectively decreasing the amount of equity required. Because cost of debt (assumed to be 5–8% here) is lower than cost of equity (usually in the 15–30% range), the substitution of equity by debt yields an increase in return on equity. This default probability corresponds to a rating by a Nationally Recognized Statistical Organization (NRSO) such as Moody's Investors Service or Standard & Poor's. The default probability is also referred to as a solvency standard, whereas the debt as a percent of capital is referred to as an attachment point.

At any point during the life of the fund there is solvency risk, the risk that the vehicle has insufficient cash to make scheduled interest and/or principal payments. For each rating category there is an associated solvency standard that specifies the maximum acceptable risk of insolvency for that rating class until the notes are repaid – see Table S1, provided by Moody's Investors Service [6] (Supplementary Material online). The risk is calculated by examining all of the potential outcomes, and determining what percentage of these outcomes results in an

insolvency event. Therefore, the risk is related to a measure of the volatility of future cash flows.

For any given rating tranche the volatility of the corresponding cash flows can change over time, and therefore the insolvency risk can change. Two factors determine the potential for change in insolvency risk. The primary factor is whether the drug development process is proceeding in accordance to an expected plan (or to the mean of all possible outcomes) at each time instant. If the performance is ahead of the plan, then the probability of insolvency should be lower than the assumed value. In fact, if the performance is on plan, the probability should be lower as well because the dispersion of future paths has narrowed, lowering the effective volatility. The second factor is the possibility that volatility has increased because of changes in external factors, e.g., the environment or improved data and forecasts. However, this class of exogenous events is outside the scope of this paper. For more details and an illustrative example on dynamic leverage see Supplementary Material online.

Dynamic measurement can be made more precise by employing adaptive trials, during which the posterior probability of success is continuously updated; hence, the amount of debt can be adjusted accordingly. However, for simplicity we do not use adaptive clinical trials in our model. Dynamic risk measurement is not only useful in determining dynamic leverage but in any application in which changes in risk have a material impact. For example, in a financing structure that employs guarantees, the guarantee fee can be adjusted dynamically based on the risk profile of the portfolio over time.

### Dynamic leverage for an orphan drug fund

For concreteness, we use the statistical model described in [7] to illustrate dynamic risk measurement and dynamic leverage. The focus of Fagnan *et al.* [7] on orphan drugs targeting rare diseases is particularly well-suited for dynamic leverage because these therapies are relatively new and not likely to be able to generate much cash flow at fund inception. To highlight the role of dynamic leverage we employ the identical orphan drug parameters as in Fagnan *et al.* [7]. Following [5,7], a discrete-time finite-state Markov chain is employed to model the evolution of each compound through the development cycle. The assumptions regarding the average cost, success rate, duration and valuation of each phase are listed in Table 1. Under these assumptions, consider an RBO structure to finance a portfolio of investigational therapeutics through their development cycle. In exchange

for a pledge of the future royalty cash flows, equity and debt investors purchase notes and receive a portion of these cash flow streams.

Our simulated RBO portfolio comprises nine compounds in the preclinical stage and ten compounds in the clinical Phase I stage. The employed capital structure is composed of one equity tranche and two debt tranches, namely mezzanine and senior tranches. The initial amounts of capital for the equity, mezzanine and senior tranches are US\$373.75 million, US\$30 million and US\$25 million, respectively, and the annual coupon rates for the mezzanine and senior debt tranches are 8% and 5%, respectively. The maturity dates for the senior and the mezzanine tranches are four and six years, respectively, and the outstanding balance of each tranche is paid in four equal installments over the two years (four semesters) preceding the maturity dates. After 13 semesters (6.5 years), the portfolio of the remaining compounds is liquidated. Assuming that the drug sale takes a year to settle, the cash proceeds from the sale go to the equity investors in the fifteenth semester. Furthermore, any compound, upon reaching a pre-specified target phase (Phase III in the simulations), gets sold regardless of how far into the life of the fund it is.

As the portfolio of compounds progresses and its risk decreases over time, the size of the debt tranches – and therefore the leverage – can be adjusted to maintain a desired probability of default for each tranche. For simplicity, the tranche size adjustment in the simulations is performed only for the mezzanine tranche, and up until the junior bonds start principal repayment (i.e. until the fourth year). Figure 1 illustrates the expected size of each tranche as well as the total capital deployed in the portfolio, from the equity and bond investors, over time.

Several trends in Fig. 1 are worth noting. As seen in Table 1, the compounds need progressively larger amounts of funding as they proceed in their development cycle. If the total required capital is raised in its entirety at the beginning of the fund's life, in anticipation that the compounds will follow their expected path of development, it will impose a drag on the fund's returns. Should this capital be raised by calling more equity, the return on the equity tranche would be diluted. Alternatively, if the financing structure keeps the level of the invested equity constant, issuing more debt at the beginning to meet the expected needs of future drug development, the probability of default for the debt tranches would inevitably increase. In this approach, used in [7], the probability of default increases because the deterioration in portfolio

**TABLE 1**  
**Simulation parameters for orphan drug discovery and development**

Phase	Cost (US\$ millions)	Success rate (%)	Duration (years)	Valuation (US\$ millions)
Preclinical	5	69	1.00	7.1
Phase I	5	84	1.66	27.6
Phase II	8	53	2.09	75.6
Phase III	43	74	2.15	321.5
NDA	–	96	0.80	701.9
APP	–	–	–	817.6

value leads to more debt, whereas the equity is the same as before. Therefore, the probability of default and the magnitude of loss will increase if more debt is issued at fund inception.

Dynamic leverage can mitigate this issue. Specifically, the mezzanine tranche should increase in size over time to provide the capital required to fund the development of the compounds moving forward in their development cycle. This is done only if raising more debt does not hurt the probability of default for the junior notes (i.e. if it does not increase the solvency risk). Hence, the increase in the mezzanine tranche is slow in earlier periods, when the risk of the portfolio is relatively high, and the debt utilization accelerates as the portfolio moves forward in time and risk is reduced.

A second trend seen in Fig. 1 relates to the size of the equity tranche, which decreases over time. This is due to distributions made to the equity investors when the portfolio is on or above the expected path. These distributions come from the sale of those compounds that have reached their target phase of development, and from a portion of the debt raised. MATLAB code with

an open-source license is provided in Supplementary Material online to allow readers to examine the specifics of how the tranche sizes are determined at each time, and/or to use different values for parameters used in the model.

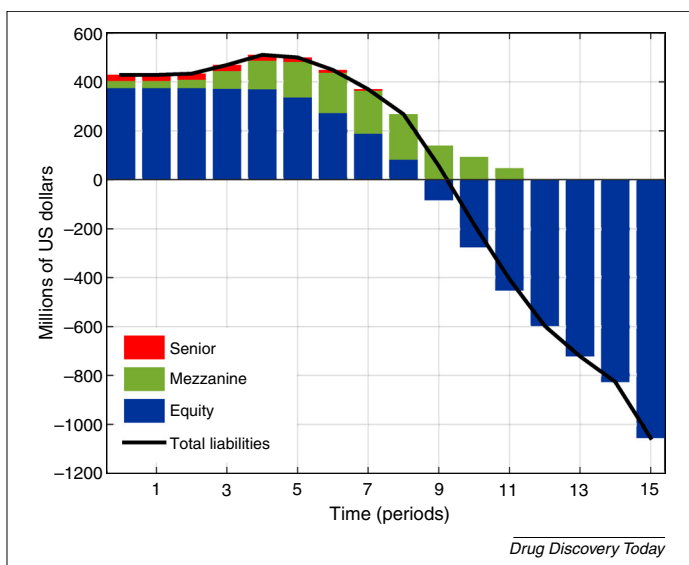
As the risk of the portfolio decreases, we can replace an ever-increasing amount of equity with debt to yield a higher rate of return to the equity investors. This can be achieved without jeopardizing the solvency of the portfolio, as can be observed in Table 2, where the simulated expected annualized internal rate of return (IRR) is more than 25%, and the probabilities of default for the senior and mezzanine tranches are less than 0.1 bps and 36.2 bps, respectively. These probabilities of default and the expected losses, reported in Table 2, over the life horizon of the senior and junior notes are comparable to that of AAA/Aaa and A+/A1 rated notes, respectively (Table S1 in Supplementary Material online).

#### Comparison to all-equity financing

The third column of Table 2, 'All-EQ 1', compares the RBO structure with an equity structure in

which a portfolio of seven compounds in the preclinical stage and six compounds in Phase I is funded using the same level of equity as used in the RBO structure (i.e. US\$373.75 million). As observed in Table 2, fewer compounds can be financed during the life of the fund under the equity structure compared with the RBO portfolio because there is no additional injection of capital into the equity portfolio after the initial equity draw. The scientific impact of the equity structure is, consequently, smaller than that of the RBO portfolio as measured by the number of the compounds that are sold in Phases II and III. Not only is the scientific impact smaller in the equity structure, but also the return characteristics of the equity tranche are not as promising as those of the RBO structure. Owing to the debt issuance over time, in the RBO case, more equity is returned to the investors earlier. In contrast, in the equity structure the return of capital to the equity investors is constrained by the speed with which the compounds reach the target phase and are sold.

The fourth column in Table 2, 'All-EQ 2', compares the performance of the RBO fund and the performance of the same portfolio of compounds financed by equity alone. The amount of equity used to finance this portfolio is matched to the peak value of the total capital deployed in the RBO structure (i.e. US\$510.70 million) as observed in Fig. 1. This level is almost 37% more than the RBO's initial equity level of US\$373.75 million. As is seen in Table 2, the scientific impact of this new equity structure is the same as that of the RBO structure. However, the financial performance of the equity structure is still less promising than the performance of the RBO because more equity is deployed in the equity structure than in the RBO structure. The only area in which the equity portfolio outperforms the RBO portfolio is the probability of negative returns on the equity. In the equity structure, there is a 10.3% chance of delivering a negative return to the equity investors, whereas this chance is 10.6% for the RBO portfolio because the equity tranche in the RBO structure is the first



**FIGURE 1**  
Capital structure and total deployed capital in the fund for each six-month period.

TABLE 2

**Performance results for the RBO portfolio, two equity-financed portfolios and the static RBO portfolio**

	RBO <sup>a</sup>	All-EQ 1 <sup>a,b</sup>	All-EQ 2 <sup>a,b</sup>	Static RBO <sup>c</sup>
<b>Number of compounds acquired</b>				
Preclinical	10	7	10	8
Phase I	9	6	9	8
<b>Research impact</b>				
Compounds sold in Phase II	2.6	1.8	2.6	2.2
Compounds sold in Phase III	5.5	3.8	5.5	4.7
<b>Liabilities (US\$ millions)</b>				
Capital	428.75	373.75	510.70	575.00
Senior tranche	25.00	–	–	86.25
Initial mezzanine tranche	30.00	–	–	115.00
Equity tranche	373.75	373.75	510.70	373.75
<b>Equity tranche performance</b>				
Expected annualized IRR	25.1%	20.7%	22.0%	13.4%
Pr(IRR = –100%)	38.4 bps	<0.1 bps	<0.1 bps	60 bps
Pr(IRR < 0%)	10.6%	14.5%	10.3%	13.1%
Pr(IRR > 10%)	77.3%	69.8%	74.6%	66.7%
Pr(IRR > 25%)	49.8%	39.9%	42.0%	18.4%
<b>Debt tranches performance</b>				
<b>Senior tranche</b>				
Probability of default	<0.1 bps	–	–	0.8 bps
Expected loss	<0.1 bps	–	–	<0.1 bps
<b>Mezzanine tranche</b>				
Probability of default	36.2 bps	–	–	56.0 bps
Expected loss	9.1 bps	–	–	15.0 bps

Abbreviations: RBO, research-backed obligations; Pr, probability; IRR, internal rate of return; bps, basis points (1 bp = 0.01%).

<sup>a</sup> All reported numbers are obtained using 20,000,000 Monte Carlo simulation paths for each portfolio.

<sup>b</sup> All-EQ 1 is an equity-financed portfolio where the initial investment is set equal to the initial amount of equity in the RBO portfolio, whereas All-EQ 2 is another equity-financed portfolio where the initial investment is set to the maximum amount of capital in the RBO portfolio (Fig. 1).

<sup>c</sup> For static RBO, see Fagnan *et al.* [7].

to absorb any capital losses. For the same reason, the probability that the equity is wiped out [i.e. Pr(IRR = –100%)] is larger for the RBO portfolio compared with the equity-financed portfolios. However, the upside of the RBO portfolio is much higher than that of the equity portfolios, as measured by the right-tail probabilities of their returns reported in Table 2 [i.e. Pr(IRR > 10%) and Pr(IRR > 25%)].

It is clear that adding dynamically leveraged debt to the picture, when feasible and as needed to fund drug development, can enhance the scientific and the financial impact of the portfolio with little downside risk. Furthermore, if the effect of dynamic leverage were replicated using an equity-financed portfolio, the amount of required equity upfront would be significantly larger (almost 37% more initial equity than the RBO's initial equity as observed in Table 2).

**Comparison with static capital structure**

For comparison, the performance statistics of the RBO structure with a static capital structure, which was used in [7], are reported in the last column of Table 2, labeled 'Static RBO'. The dynamic RBO clearly outperforms the RBO with a static capital structure from scientific and financial perspectives. This performance superiority is achieved without jeopardizing the debt performance. Not only does dynamic leverage increase the return on equity but it also helps reduce the probability of default for the bondholders in comparison to a static

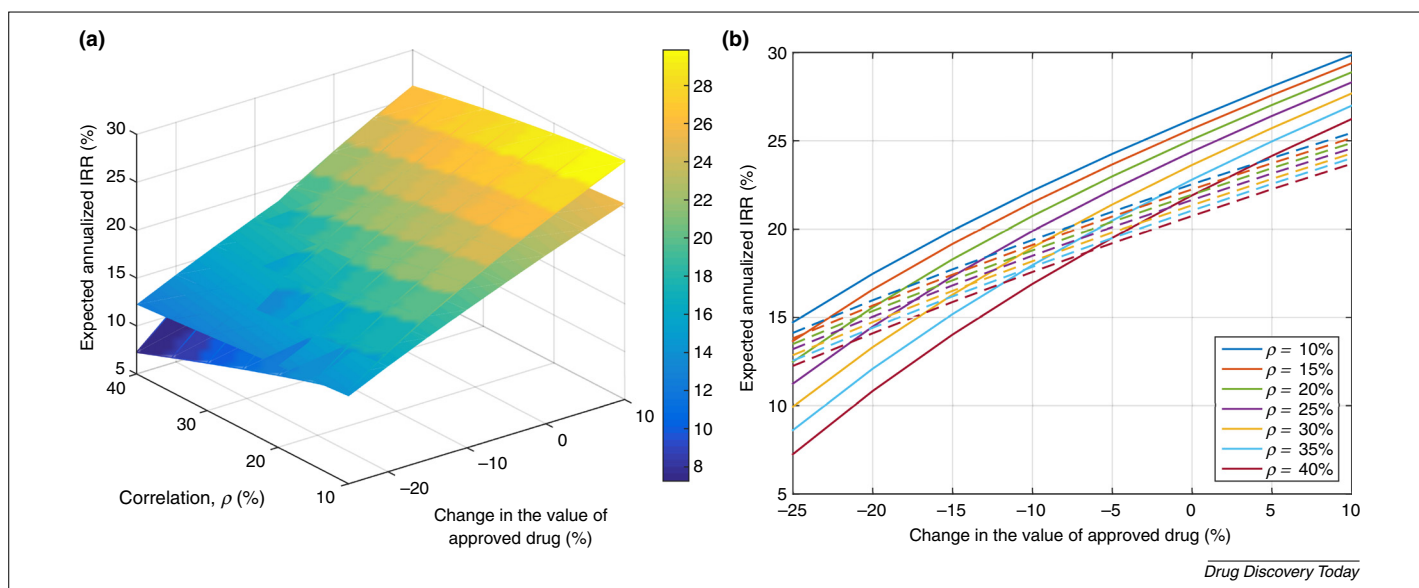


FIGURE 2

Expected annualized internal rate of return (IRR) for the research-backed obligation (RBO) and equity structures. The textured shading in (a) and the solid lines in (b) correspond to the RBO structure.

capital structure. This is achieved because less debt is borrowed initially and more debt issuance happens over time only if the risk of the portfolio permits taking such action. Furthermore, because the probability of default is smaller for this dynamic capital structure than the static RBO used in [7], the volatility of the return on equity is consequently smaller too.

### Robustness analysis

We check the robustness of our results by varying two key parameters: the value of the approved drug (the bottom right entry in Table 1) and the correlation ( $\rho$ ) of the asset values. Whenever applicable, we also conduct the same tests on one of the all-equity-financed portfolios introduced earlier, All-EQ 2, to distinguish the role of under- and over-borrowing from the role that asset mispricing plays. The details are reported in the Supplementary Material online, and they yield two key observations. First, the dynamic RBO portfolio maintains an acceptable performance over a wide range of correlations and expected approval values. Second, the dynamic RBO portfolio outperforms the all-equity-financed portfolio over a wide range of correlations and asset values unless the presumed values for the parameters of the model are far more optimistic than their realized values. In this case, the incorrectly determined high leverage in the dynamic RBO fund would exacerbate the fund's poor performance compared with the all-equity-financed portfolio.

These findings are summarized in Fig. 2, which shows that the equity performance of the RBO fund – measured by its IRR – is superior to that of the all-equity-financed portfolio over a wide range of correlation ( $\rho$ ) and expected-approval values. The equity-financed portfolio, however, outperforms the RBO portfolio for large correlations (e.g.  $\rho = 40\%$ ) and small approval values (e.g. if the realized approval value is 25% less than the assumed value). For further details and a comparison of other performance measures see Supplementary Material online.

### Concluding remarks

The application of portfolio theory and securitization techniques to financing drug development has the potential to be a disruptive technology. In this paper we propose a more efficient structure and higher returns to equity for investors by adding dynamic leverage, a novel securitization technique, to the megafund structure proposed in [5,7]. There are, of course,

a number of practical challenges to launching and managing a megafund. A comprehensive discussion of these challenges is beyond the scope of this article, but we address some of the most pressing issues in the Supplementary Material online such as how the fund would be managed, whether the parameters we have assumed are realistic and how existing bondholders might react to increases in leverage. Several other recent studies offer more-detailed analysis of these challenges and how they can be addressed [8–13].

The main finding of our study is that a fund incorporating dynamic leverage requires less upfront equity to finance the development of the compounds in the portfolio than previous implementations, and generates higher returns with similar risks of default and loss. Furthermore, the volatility of equity returns is lower compared with a megafund structure with a static capital structure. Borrowing more debt over time does not adversely affect the scientific outcome because, in the dynamically leveraged approach, the additional debt is only needed if the portfolio is on its expected path.

Dynamic leverage magnifies positive and negative performance. If the actual performance of the portfolio of projects is better than indicated by prior assumptions, then the fund with dynamic leverage will outperform an equity-financed portfolio. If the portfolio underperforms, however, then the equity-funded portfolio will perform better. This result is expected, given the nature of leverage. The higher volatility (risk) of equity returns in a megafund with dynamic leverage, as compared with an all-equity-financed portfolio, is accompanied by a higher expected equity return. Nevertheless, if further securitization technologies are introduced into the pharmaceutical portfolio structure we expect commensurate improvements to equity returns.

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### Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.drudis.2015.12.004>.

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Vahid Montazerhodjat<sup>1,2</sup>

John J. Frishkopf<sup>3</sup>

Andrew W. Lo<sup>1,2,4,5,\*</sup>

<sup>1</sup>MIT Laboratory for Financial Engineering, Sloan School of Management, Cambridge, MA, USA

<sup>2</sup>MIT Department of Electrical Engineering and Computer Science, Cambridge, MA, USA

<sup>3</sup>NewStar Financial, Inc., Boston, MA, USA

<sup>4</sup>MIT Computer Science and Artificial Intelligence Laboratory, Cambridge, MA, USA

<sup>5</sup>AlphaSimplex Group LLC, Cambridge, MA, USA

\*Corresponding author.