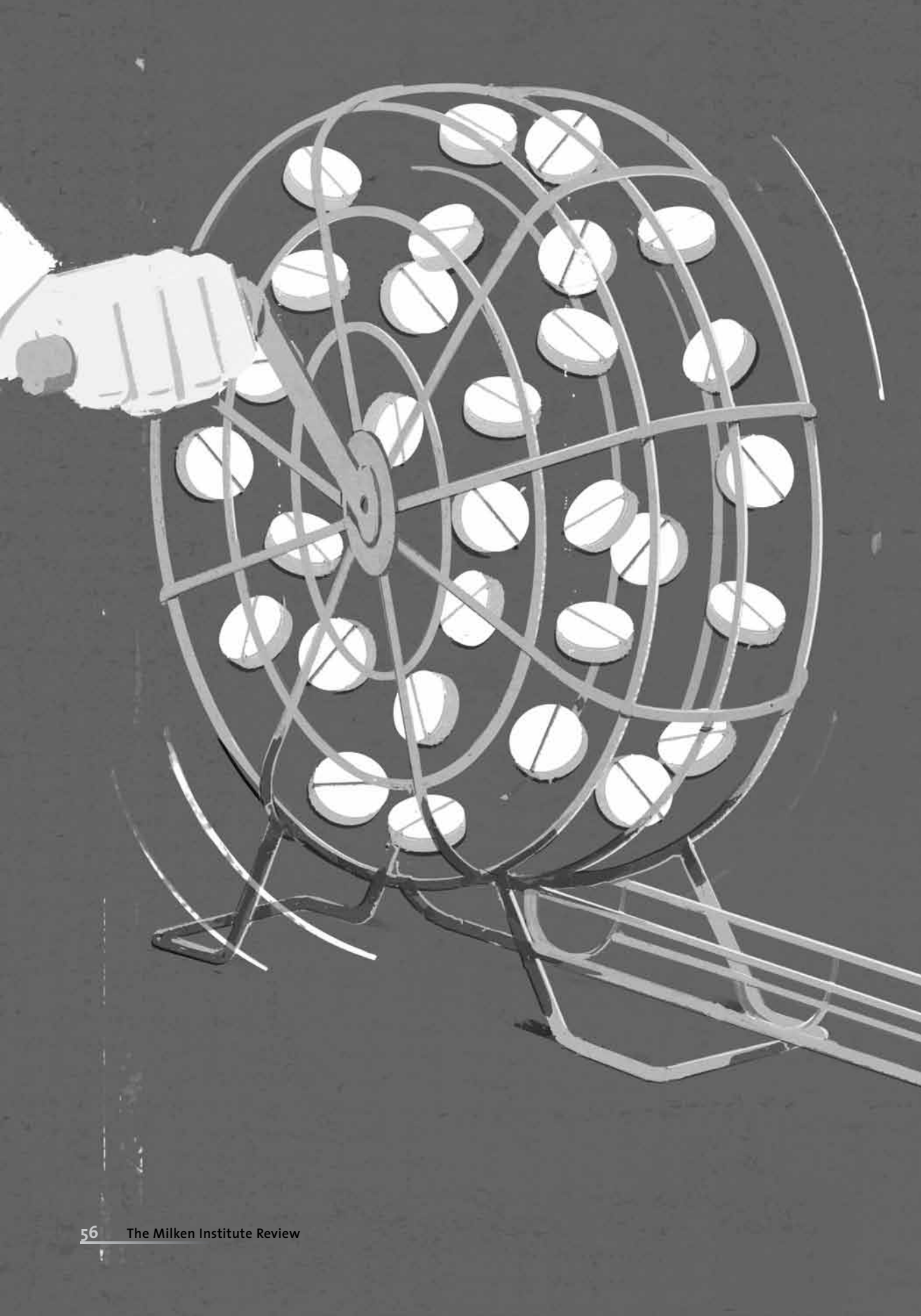
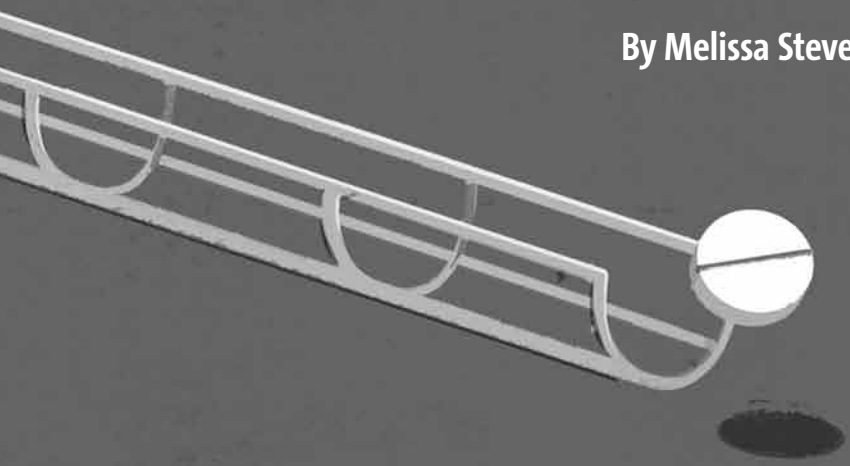


Financing High-Risk Medical Research

A Proposal from FasterCures

By Melissa Stevens



In the past few years, the media has showered us with headlines about record-setting biotech financing – outsized venture-capital rounds, unprecedented public market appetite for IPOs, and robust sector returns. But a closer look suggests there is more froth than substance at this frontier of medicine and science.

Even with substantial investment inflows, capital constraints continue to hamstring our ability to advance all of the truly novel and potentially life-changing treatments that technology is making possible.

There are 10,000 known diseases, yet there are viable treatments and cures for only about 500 of them. Certainly money alone won't bridge the innovation chasm. But more capital, and more of it directed to early-stage research, would do much to increase medical R&D productivity.

THOSE DEVILISH DETAILS

Life-science venture funds are clearly raising money – and lots of it. In 2015, the mainstays of the sector, among them Flagship Ventures, Atlas Ventures and MPM Capital, took in more than a quarter-billion dollars each. But an analysis of venture data by the journal *Health Affairs* shows that the sector is becoming more conservative, moving away from funding companies with technologies in earlier stages of development toward those with technologies in later stages. In 2009, the early-late distribution was 62 percent and 38 percent, respectively. Five years later, only 45 percent of funding was being allocated to early-stage companies.

Why the shift? It all comes down to risk – scientific risk, regulatory risk, reimbursement risk. Only 1 in every 10,000 discoveries made at an academic research bench ever ends up in the hands of patients.

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Preclinical research is a critical phase in the early-stage R&D process. It is where general scientific knowledge starts to be applied to drug development in preparation for testing in humans. However, only 5 out of 250 compounds will make it through the preclinical stage to clinical trials. And the growing realization of how long the early-stage odds really are has led investors to opt for ventures with assets that are already progressing into later clinical development.

An analysis of the trend by Bruce Booth of Atlas Ventures drives home the point. Despite the growth of venture investment, for years the funds have collectively financed only 100-150 companies (and only 20-30 true startups) each quarter. What's more, almost half of the financing in the second quarter of 2015 was allocated to the top-10 deals. So the lion's share of that increased cash is flowing to a chosen few already approaching the finish line. Life-science venture capital is thus failing us, in the sense that the sector is not diversifying into the wild-card ideas from which true breakthroughs are likely to emerge.

CRISIS BREEDS CREATIVITY

That said, there's a glimmer at the end of the tunnel. New players and practices are emerging to manage biotech risk more efficiently, making earlier investment more palatable. First, pharmaceutical companies, which have traditionally focused on clinical trials rather than on preclinical research, are starting to partner earlier in the R&D process to find assets to fill their clinical pipelines. Also, accelerator organizations, like BioMotiv, which is a

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DRUG DISCOVERY
10,000 COMPOUNDS
6.5 YEARS
PRE-CLINICAL
250 COMPOUNDS
6.0 YEARS
CLINICAL TRIALS
5 COMPOUNDS
1.5 YEARS
FDA REVIEW
1 APPROVED DRUG
CLINIC
THE TORTUOUS PATH FROM DISCOVERY TO APPROVAL

key component of the public-private Harrington Drug Discovery Project, are building specialized expertise to help move compounds through early-stage research in a capital-efficient way. Their work prepares technological innovations for clinical testing with the ultimate goal of passing the baton to large pharmas for later stage development.

But perhaps the most profound change under way is the entrance of venture philanthropy into life-science finance. Philanthropy accounts for only about 3 percent of total health R&D investment in the United States, but can have an outsized impact because it can be nimbly deployed to offset risk in early-stage research. Mainstream disease research foundations are flexing their financing muscle. In fact, many organizations in FasterCures's TRAIN (The Research Acceleration and Innovation Network) group of mission-driven foundations are utilizing their capital to move promising research across key funding gaps.

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For example, the Juvenile Diabetes Research Foundation committed $5 million to T1D Innovations, a for-profit venture-creation entity focused on developing Type 1 diabetes therapies. The Leukemia & Lymphoma Society has funnelled millions of dollars directly into companies through its Therapy Acceleration Program, and the National MS Society has done the same through its Fast Forward venture-like vehicle. And let us not forget the landmark work of the Cystic Fibrosis Foundation, which strategically deployed $150 million in Vertex Pharmaceuticals over several years that culminated in FDA approval of Kalydeco, the first cystic fibrosis medication that treats the disease itself rather than the symptoms. This foundation funding is creating business incentives to overcome private risk aversion and smooth the journey from R&D to commercialization.

REVAMPED VENTURE FOR A FASTER CURE

The Milken Institute and its FasterCures center, which is focused on accelerating medical solutions, set out to design a new venture vehicle that would harness these trends – appetite for new assets, capital-efficient preclinical development and venture philanthropy used to limit private risk – in order to focus investment on early-stage companies, where it is needed most.

The FasterCures Ventures (FCV) model is a blueprint for a financial instrument that brings together investor classes with different interests and aligns disparate risk-reward ratios for each to achieve both competitive private returns and high social returns. The idea is to mix and match three types of investors – market investors, pharmaceutical companies and venture philanthropy – all of which are stakeholders in developing new treatments.

Market Investors (Class A). Resources from these investors, which include traditional venture limited partners such as institutional

investors, endowments and large family offices, would put up half the funds. Limited partners are looking exclusively for financial returns – they want the greatest return on their capital for the lowest risk.

Pharmaceutical Companies (Class B). These investors would provide 20 percent of the total funding. They seek new compounds that are ready for human trials, the links in the R&D value chain where pharmas have the greatest expertise. This is most valuable to them because, if successfully brought to market, these drugs would bring billions of dollars to their top lines.

Philanthropic Investors (Class C). These investors – disease-specific public charities, private foundations and individual philanthropists or families – would contribute 30 percent of the total fund. They are primarily interested in the social returns on their investments, moving potentially life-saving drugs from the preclinical stage. Their focus is on preventing experimental therapies from being shelved for lack of investors with an appetite for risk. They also want their money to go further and thus are interested in mechanisms that afford greater recyclability than grants alone.

WINDFALLS AND WATERFALLS

The power of FCV is in the alignment of the interests of the three investor classes. To this end, the "waterfall" of claims against revenues is structured using preferential payouts and capped returns. First, the market investors and pharmaceutical companies would recoup their investments and earn up to a 3 percent internal rate of return (IRR) before the philanthropists got back any of their capital. But the pharmaceutical companies would forfeit any additional returns in exchange for having a first right of negotiation for assets financed by FCV.

Next in line on the revenue waterfall, philanthropic investors would get their capital back. But they would accept a below-market return thereafter – perhaps 1 percent – so that market investors could look forward to more upside. Finally, the residual returns would flow to market investors.

One asterisk here: it would make sense to give the philanthropic investors a share of any exceptionally high payout – a "home-run" clause, if you will. The FCV model suggests that, once market investors achieved a 20 percent internal rate of return, additional revenues would be shared by the philanthropists and market investors in proportion to their initial investments.

Consider the way the FCV aligns incentives across these three investor classes. Because of the downside protection offered by the venture philanthropists, market investors would be partially insulated from loss. All of their capital would be returned even if the fund lost 30 percent of the capital of the fund and never earned a penny. Moreover, they would have an enhanced upside since the capped returns for the other two investor classes would shift almost all of the additional earnings to them.

Meanwhile, the FCV offers pharmaceutical companies a good chance of getting all their capital back plus a modest return; more important, it gives them an inside track on compounds that have made it past preclinical hurdles. Philanthropic investors, for their part, would have a chance to make a nominal financial return. But as important, they would leverage their philanthropic investment by contributing only 30 percent of the fund's total capital.

TESTING THE FCV

We modeled the capital structure in order to understand the economics and thus the

feasibility of using FCV to finance preclinical drug development. Multiple steps must be completed before a compound can move into clinical testing. For instance, one must identify which compounds hit their biological target, then optimize their chemical structures to enhance their specificity and minimize toxicity and finally test these compounds in animals to get some sense of how they might perform against human disease. Past experience suggests that up to 40 percent of compounds are likely to fail to make the transition from one preclinical step to the next. Thus, molecules that complete all of these preclinical steps have been stripped of much of the risk of failure and are, of course, more attractive to commercial partners down the line.

INVESTMENT FUND SCENARIOS

	BEST CASE	AVERAGE CASE	WORST CASE
Assets Developed	35	21	14
Total IRR	30.87%	13.14%	1.05%
Investor Class A IRR	20.48%	11.36%	4.01%
Investor Class B IRR	3.00%	3.00%	3.00%
Investor Class C IRR	13.66%	1.00%	–100.00%

We modeled the impact of a $100 million fund that would deploy capital over five years. Again, we assume an asset would be licensed-in at the time that lead candidates are identified and would be licensed-out to a pharmaceutical company once the compound was selected for clinical trials or was approved by the FDA for testing in humans. FCV would finance the relevant drug-development work between the entry and exit points.

Once a molecule is licensed to a pharmaceutical partner, the company would bear the costs of development through the three phases of clinical trials. Payments back to FCV would be triggered upon completion of major development and commercialization milestones, including the completion of Phase I, II and III trials, securing an NDA (that is, FDA approval of a new drug application) and completion of first commercial sale. Additionally, a small royalty based on sales of the drug would be paid back to FCV.

The financial model was created using industry averages for development costs at each stage, historical success rates to estimate transition probabilities for moving between steps along the preclinical drug development chain and industry averages for meeting milestones in the clinical testing phase.

We developed three scenarios (best, average and worst case) to understand the robustness of the model. Under the best-case scenario, we assumed the shortest development times, highest transition probabilities, lowest development costs and highest milestone payments. Under the worst-case scenario, we assumed the polar opposite. The average-case scenario uses the midpoints for each of these variables.

As noted above, in our average-case scenario, the $100 million FCV could finance the preclinical development of 21 assets and generate market investor returns of 11.36 percent. Life-science venture capital IRRs have averaged 15 percent over the past decade, so market investors would sacrifice some upside in return for having downside protection provided by the investments of the pharmaceutical and the philanthropic investor classes.

The worst-case model highlights the differentiating element of the FCV. Because philanthropic investors would absorb the most risk and take a loss of up to 100 percent of invested capital, market investors' worst-case yield is still an estimated 4.01 percent IRR.

Under best-case assumptions, market investors would garner just over a 20 percent IRR. Yet, because of the home-run clause, philanthropic investors would be able to

In all three scenarios, the pharmaceutical companies would earn what they really need: preferential access to compounds ready for clinical trials.

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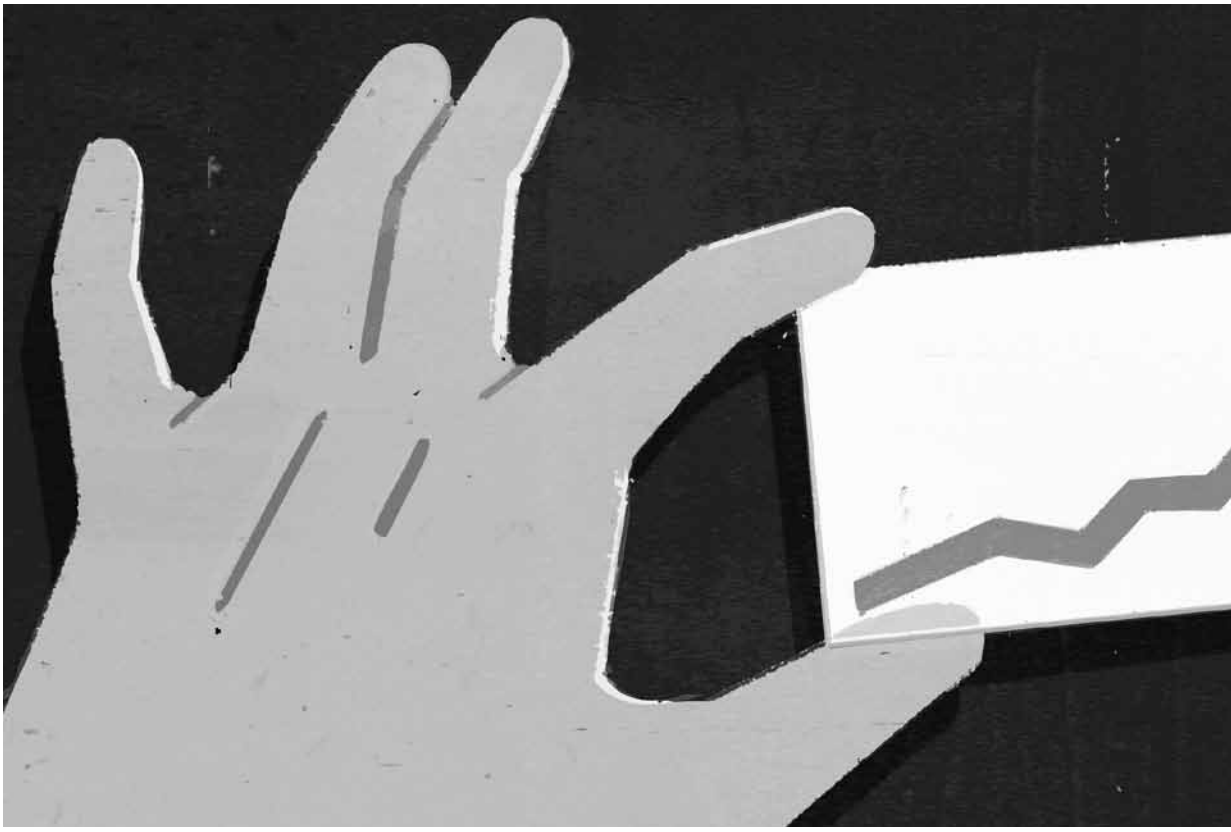
partake in some of the upside of these extraordinary returns. Thus, in this scenario, philanthropic investors could expect to earn an IRR of 13.66 percent.

Note that in all three scenarios, the pharmaceutical companies would earn the capped 3 percent IRR along with what they really need: preferential access to compounds ready for clinical trials.

RISKS & CONSIDERATIONS

There's no free lunch here, of course. First, the fund tie-up – the period in which there would be no capital recovery and no income –



would necessarily be considerably longer than what biotech investors have come to expect. This is because drug development and testing is a long and arduous process. Currently it takes 10-15 years for an academic discovery to make the journey to prescription pad.

Thus, the time to exit is long, as is the time to recoup revenues through the subsequent milestone payments and royalties from commercial sale. We see the FCV as a 20-year fund, compared with 7-10 years for the typical life-science venture capital fund today. To compensate for the total duration, we assume that returns would be passed through to investors as soon as they are available. So in the average case, market investors would receive returns in years 7 to 20, and pharmas would receive returns in years 7 to 11, while the philanthropist would receive returns in years 12 and 13. Returns would start a year earlier in the best-case scenario and a year later assuming worst-case conditions.

Aligning the interests of the three classes of investors would not always be possible. There is an inherent tension between the interests of market investors that would want to manage risk as much as possible through financing a diverse portfolio of compounds and the laser-like attention of the philanthropists most likely to participate. A fund focused on a specific disease, like lung cancer or Alzheimer's, would appeal to single-purpose foundations or wealthy families touched by a specific medical condition. But the success or failure of assets within individual disease classes is more correlated, which raises the risk of the portfolio as a whole.

So, additional consideration would need to be given to diversification strategies that minimize the tension. One approach would be to launch multiple FCV structures across diseases and formulate the capital structure such that philanthropic investors take the first-loss tranche with respect to a specific

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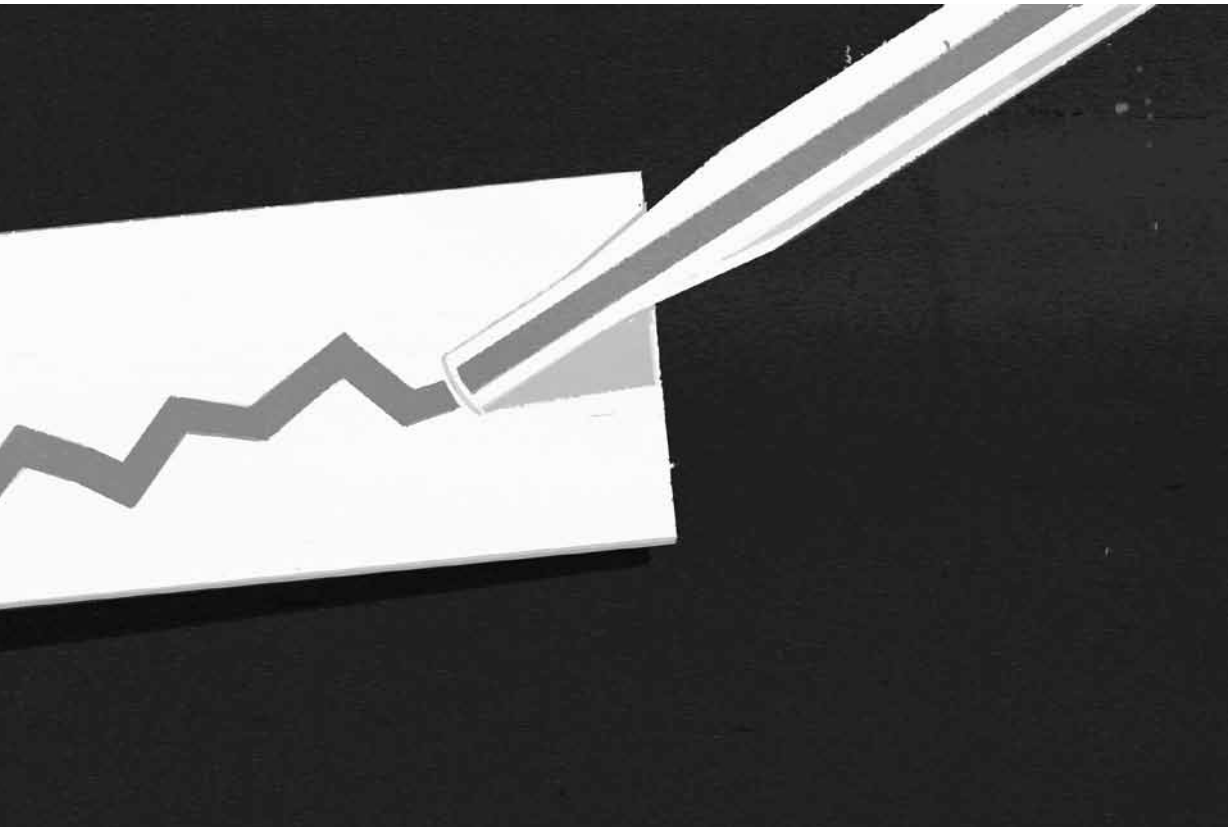

disease, while market investors participate in the upside across funds in all diseases.

THE WAY FORWARD

This type of stacked capital financing has been shown to be effective in attracting new capital to close key funding gaps in other countries. For example, the Israeli Life Sciences Fund (ILSF), whose financial architecture was designed with the help of a Milken Institute Financial Innovations Lab, uses a similar model of preferential returns and first-loss positioning. The ILSF was a response to the flight of life-science intellectual property to other countries for development. It was established in 2012 to finance the development of both drugs and medical devices within Israel's borders.

The government provided some $50 million as a limited partner. Its funding serves as the first-loss capital through a preferred return scale, which allows for positive returns to other limited partners even if the fund suffers as much as a 10 percent loss. This structure has proved an attractive proposition for the fund managers (OrbiMed Israel Partners LP), who were able to raise the $172 million on top of the government's $50 million.

We think market conditions are right to pilot the FCV model in the United States. For one thing, there is a deep appetite for alternative assets, and market investors want exposure – albeit predictable exposure – to the life sciences. For another, venture philanthropists, buoyed by some well-publicized successes, seem eager to get into the driver's seat on drug development.

We have an opportunity – really an obligation – to challenge the status quo of the medical research system, including its traditional financing. Through FCV, we can overcome investor silos, align interests and incentives, and direct capital to early-stage research, where the potential gains to society are greatest.