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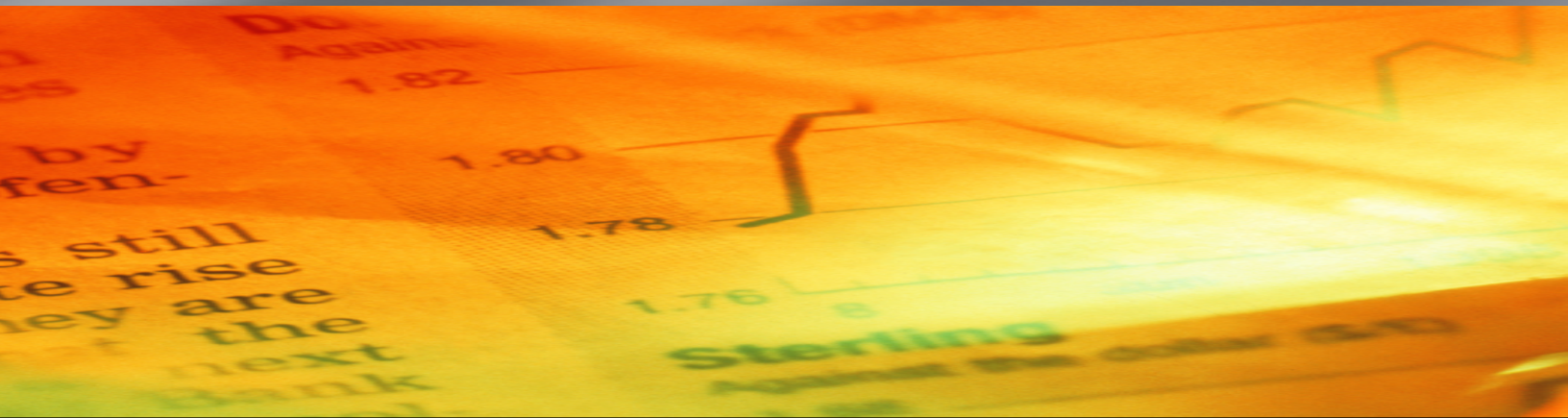
FasterCures
The Center for Accelerating Medical Solutions

Fixes IN Financing

Financial Innovations for Translational Research

April 2012

A FINANCIAL INNOVATIONS LAB™ REPORT




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THE FINANCING GAP FOR TRANSLATIONAL RESEARCH is widening. Traditional investors in translational research—large- and medium-cap biopharmaceutical companies and life science-focused venture capital funds—are becoming increasingly risk adverse in the face of escalating challenges in the early stages of the drug development process. To counteract this trend, the medical research field needs to increase the field of promising research ventures that are also attractive investment opportunities by modifying both the research management process as well as current financing methods. **The industry needs novel approaches to early-stage drug development that better manage risk, lower capital cost and improve research effectiveness, create diverse portfolios, leverage risk-tolerant capital, and access new capital sources.¹**

With these issues in mind, the Milken Institute and *FasterCures*, the Milken Institute's *Center for Accelerating Medical Solutions*, hosted a Financial Innovations Lab™ on July 19, 2011, in New York City. The Lab was convened to address an industry-wide gap in funding for drug development—the so-called Valley of Death.

Financial Innovations Labs are think tanks in action, designed to devise new business models, capital structures, and financial technologies that can achieve concrete goals. These intensive workshops explore the potential of financial tools to solve specific challenges.

¹ For the purposes of this report, “early stage” is considered to be R&D efforts through Phase I, with “later-stage” development referring to Phase II and III.



Our objective was to explore innovative financial strategies that could increase access to capital for translational research.

This Lab brought together a diverse group of more than 40 medical research and financial experts from biotechnology and pharmaceutical companies, medical research foundations, venture capital and private equity firms, academic and entrepreneurial institutions, and credit agencies. Our objective was to explore innovative financial strategies that could increase access to capital for translational research.

The group discussed and debated various approaches for managing and financing translational research, including:

- **Virtual product/portfolio development companies**
- **Venture philanthropy and government-backed investment vehicles**
- **Innovative investor tax incentives**
- **Securitized research-based obligations**

While Lab discussions focused on early-stage biomedical research, all of these innovative business models are easily applicable to other stages of the development process and could potentially be utilized in combination with one another to maximize the benefits of different approaches.

Details of each model can be found in the main section of this report. The last section includes comparisons of each approach and charts that show each model's specifications and location in the drug development pathway.

Framing the Problem: The Translational Valley of Death

WHY IS THIS IMPORTANT?

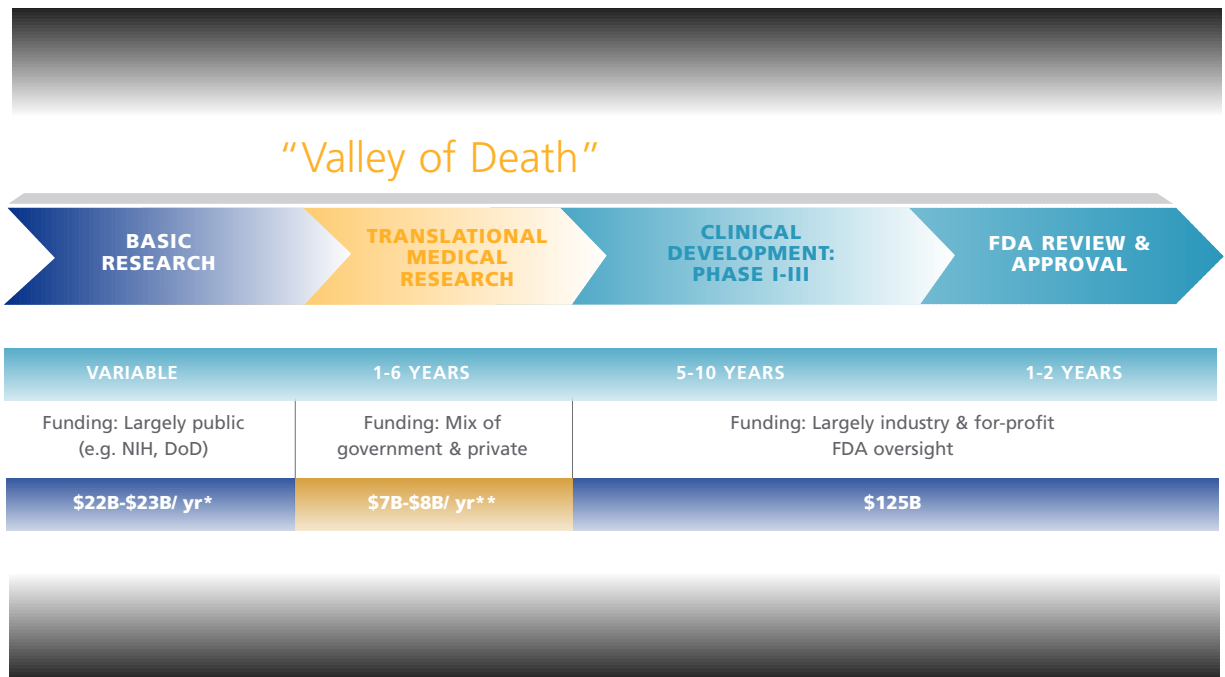
Translational research is a critical phase in the R&D process. It is the first step in the path to developing a new drug—the place where general scientific knowledge starts to be applied to drug development in preparation for testing in humans. The Valley of Death is the funding and resource gap that currently exists between basic research and clinical development, effectively limiting the field of potential novel therapies and drugs for patients.

The Valley of Death is growing wider. As illustrated in Figure 1, translational research is underfunded—with a mixture of public and private entities

providing just \$7 billion to \$8 billion a year in a system where basic research receives \$22-23 billion and industry clinical development boasts \$125 billion annually. Even elevating Valley of Death funding to the same level as basic research would not fully address the problem, as the breadth and expenses of projects can demand more capital than basic research.

Industry stakeholders are not the only groups concerned with the paucity of translational research funding. The National Institutes of Health (NIH) recently established the National Center for Advancing Translational Sciences (NCATS), which seeks to unite and realign programs in NIH institutes that focus on translational research to concentrate on innovative methods and approaches to the development and testing of new drugs and diagnostics.

Figure 1: Translational Valley of Death



*Includes \$21B/yr from NIH academic grants (2011) and \$1.3B/yr from medical research foundations (2009).
 **Includes \$584M/yr from NIH SBIR (2011), \$400M/yr from angel investors (2011), and \$6B from VCs (2011).

SOURCES: RESEARCH!AMERICA, NATIONAL INSTITUTES OF HEALTH, CB INSIGHTS, NATIONAL VENTURE CAPITAL ASSOCIATION, CENTER FOR VENTURE RESEARCH.

HOW HAS DRUG DEVELOPMENT TRADITIONALLY OPERATED?

Drug development is a long process that typically takes more than a decade from discovery to approval. While the process may vary from case to case, the typical drug development pipeline begins in an academic research lab or other federally funded research institution (FFRI). Promising discoveries are then applied to preclinical studies, which include identifying biomarkers, target and pathway validation, and animal model development, all of which increase value by further validating the research. R&D can continue to be handled at the academic lab or the research institute, spun off into a small biotech company funded by venture capital (VC) or government grants, or licensed to a larger biotechnology or pharmaceutical company. If

proof of concept (POC) can be generated, then the research team or company will either raise funds for clinical trials by out-licensing to, partnering with, or being acquired by a pharmaceutical company, or by raising capital on the public markets. Historically, pharmaceutical companies and VCs were much more willing to invest in early-stage assets, and these small companies could secure long-term financing or an exit for their investors before or during Phase I.

HOW DID THE VALLEY OF DEATH FORM?

This gap began forming when large pharmaceutical companies and VCs started to focus more on investing in later-stage clinical research—Phases II and III—due to growing disparities between the costs and risks of investing in early-stage research versus returns on their capital.

Figure 2: Clinical Development Phases

PHASE I	PHASE II	PHASE III
Experimental testing of a new drug on 20-80 people to determine safety, safe dose ranges, and side effects	Experimental testing on 100-300 people to further evaluate safety and determine effectiveness	Experimental testing on 1,000-3,000 people to confirm effectiveness, monitor side effects, compare to current treatment standards, and collect additional safety information

INVESTING IN TRANSLATIONAL RESEARCH

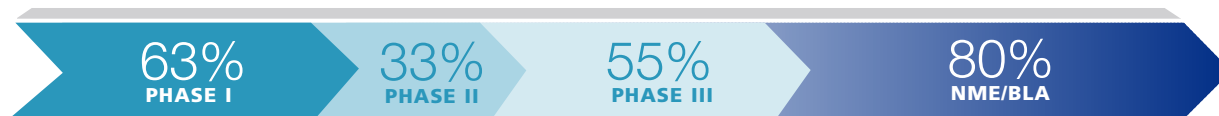
The drug development pipeline is laden with unfavorable probabilities. Even at the start of capital-intensive Phase III trials, the probability of success for lead indicationsⁱⁱ is only 65 percent,² which diminishes the price pharmaceutical companies are willing to pay for both early-and later-stage assets. These gambles are intrinsic to the industry, and experienced practitioners at the Financial Innovations Lab confirmed that, even with an abundance of data, it is incredibly difficult to reliably separate winners from losers at the translational stage. As a result, pharmaceutical companies have become less dependable customers for early-stage assets.

Figure 3: Translational Research Process



ⁱⁱIn drug development, the lead indication is the first disease for which a drug is submitted for treatment approval from the FDA; secondary indications are any additional diseases for which a drug is submitted for treatment approval after initial approval in the first disease category.

Figure 4: Clinical Trials Success Rates for Lead and Secondary Indications



*NME = new molecular entity. BLA = biological licenses application.

SOURCE: BIO/BIOMEDTRAKER CLINICAL TRIAL SUCCESS RATES STUDY, 2011

Further, the paucity of initial public offerings and inactive merger and acquisitions markets makes it harder to raise funds from early-stage investors because, with few buyers, the investors can see no reliable return on—or way to exit—their investment. This seems to be an industry-wide phenomenon, affecting fields of research across most diseases and conditions. **In short, early-stage medical research investors face very risky returns on their investments.**

WHERE ARE WE NOW?

Biotechnology and pharmaceutical companies are facing incredible pressures in drug development, such as the imminent expiration of patents for popular drugs, influx of generic competition, opaque and unpredictable regulatory process, increases in development costs, unattainable market expectations, and the complex biology of disease. In the face of these challenges, industry productivity remains low, and fewer drugs that are truly novel are reaching the market.

All these factors result in an early-stage R&D pipeline that is opaque and risky. For every 5,000-10,000 compounds that enter the drug discovery pipeline, just 250 progress to preclinical development—and only one will become an approved drug.³ While the probabilities of success vary depending on a variety of factors, including disease category and molecule type, the overall chance of a molecule successfully passing through each stage remains low.⁴

Even when a drug is approved, its commercial success is not guaranteed. The industry has seen a 15 percent decline in average long-term sales in recent years.⁵ Further, many companies began

focusing less on innovative therapies, resulting in a slew of therapies that have only incremental benefits or “me too” drugs that enter saturated markets, both of which contribute to depressed sales. With these odds, it is easy to understand why the drug development ecosystem is skeptical of investing in early-stage assets, even in areas of novel and breakthrough science.

WHO ELSE IS COMPETING FOR CAPITAL?

Other industries, such as consumer IT, also face daunting odds of securing early-stage investors. But they face less stringent regulatory standards and generally more predictable returns, thus attracting investors away from early-stage drug development. There is competition for capital from within the health field as well. A recent survey found that 40 percent of VC funds expect to decrease investments in biopharmaceuticals, and 42 percent expect to increase their investments in non-FDA regulated healthcare services.⁶

OTHER THAN FINANCE, WHAT ARE THE CHALLENGES?

Additional obstacles include human resource issues and incentives. Often, academic researchers pioneering these discoveries do not have the proper incentives to move the science forward into translational research, as their career advancement is predicated on NIH funding, publications, and patents. Even those interested in translational research may lack the unique technical expertise and skills needed for pre-clinical development. Thus, simply increasing capital flows will not be enough to bridge the Valley of Death. Instead, a variety of approaches that create valuable assets and align financial incentives across the R&D pipeline needs to be examined.

Managing Risk and Improving Effectiveness

It is clear that the industry needs fresh organizational structures to improve capital efficiency and value creation during the early stages of the drug development process. What is needed are models that break down the R&D value chain to offer an acceptable return on investment (ROI) through each stage of development, effectively spreading the investment risk and reward throughout the entire R&D process. **New proposals focus on restructuring the current funding system: Instead of backing early-stage companies to create the next generation of start-ups, finance a diverse field of promising products.**

DEVELOPING ASSETS INSTEAD OF COMPANIES

The Distributed Partnering Model: Moving the focus from the company to the science
 PRESENTER: DUANE ROTH, CEO, CONNECT

SUMMARY: The distributed partnering model (DPM) focuses on moving products through the development pipeline, not on creating a new company around each

research project. Risk is managed by product portfolio diversification, and investors bet on an experienced management team instead of a single, early-stage asset. Costs are also decreased by utilizing a virtual company structure that outsources experiments and trials to trusted partners. The model is being vetted as a new approach to drug development, with a focus on asset value creation, not company development.

MODEL DESCRIPTION: The DPM forms product development companies (PDCs), which combine expert management and investor capital for the purpose of carrying a new compound or technology through the product definition phase, usually Phase I. The main focus of these companies is to develop assets through proof of concept or proof of relevancy, not to grow sustainable corporations. PDCs would conduct critical experiments to rigorously evaluate compounds to determine early if the assets are worth further development. These experiments would also contribute to continuous efforts to advance research disease models that would improve efficacy in patient care. Vetted compounds or technologies would then be sold to interested parties—(VCs or pharmaceutical companies)—for further development. Instead of focusing on one product, however, management teams would focus on multiple research assets at

Figure 5: Overview of Distributed Partnering Model



once. Thus, investors are managing risk by placing bets on the experience and capabilities of the management team rather than on individual preclinical discoveries.

This model also makes efficient use of funding by outsourcing product R&D to professional service providers (PSPs). Without brick-and-mortar infrastructure to fund, more capital can be allocated directly to highly-quality PSPs that specialize in early development work.

PDCs would likely require an initial investment large enough to address multiple projects—between \$50 million and \$100 million in initial capitalization. The management team may decide to invest \$2 million to \$10 million in a given project, depending on the costs to establish proof of relevancy within three years. Once the management team establishes proof of relevancy and completes the preclinical development process, it will sell the assets and data for a pre-set fee and a small percentage of future royalties (for example, a \$15 million payout with 1 percent in future royalties).⁷ This structure is designed to lower costs and increase the reliability of the flow of early-stage assets to the point of transfer.

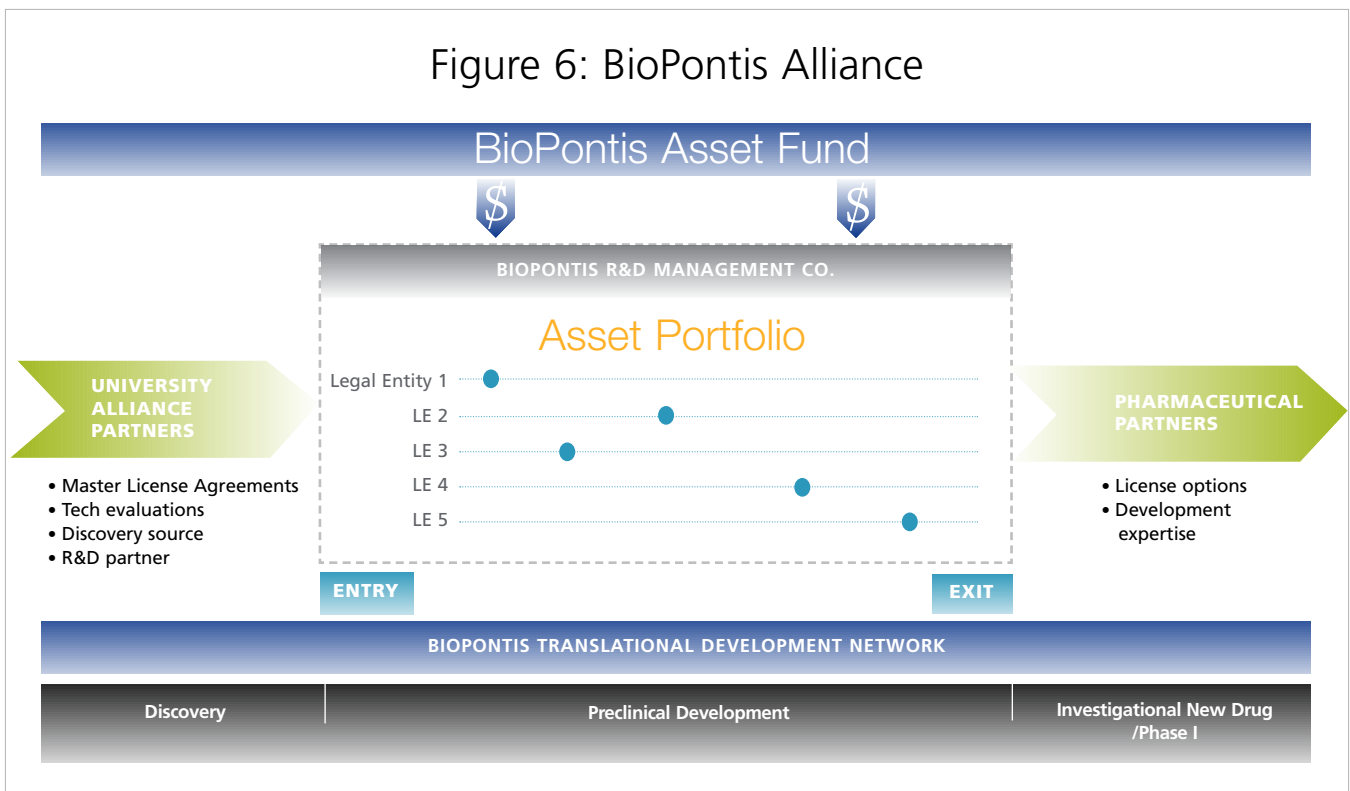
The BioPontis Alliance: An academic product development company

PRESENTER: BARBARA HANDELIN, PRESIDENT, BIOPONTIS ALLIANCE

SUMMARY: This academic PDC focuses on diversifying research risk by developing a portfolio of assets at different stages in the development process. Pre-negotiated licensing of assets and strategic customer roles also ease market transactions and increase efficiency. BioPontis Alliance (BPA) is currently seeking capital commitments.

MODEL DESCRIPTION: A variation on the distributed partnering model can be found within BPA, which essentially consists of a product development company that has partnerships with academic institutions to source drug candidates and relationships with pharmaceutical companies to buy developed products. **Similar to DPM, the purpose of this model is to lower costs through efficient execution of translational research with the additional advantage of giving large pharmaceutical companies an early look at projects in the pipeline.**

Figure 6: BioPontis Alliance



The BPA, illustrated in Figure 6, describes itself as a hybrid investment fund and product development company that takes products from “raw” to “refined.” The model features front-end relationships with university alliance partners (UAPs) to allow expedited licensing of promising discoveries, which will be housed in a legal shell for investment and development. There are currently seven UAPs committed to populating BPA's portfolio.

All R&D will be supervised by one management team, which will utilize BPA's network of technology development partners to complete rigorous experiments on a portfolio of potential drug candidates. The UAPs will be included in the intellectual property (IP) development process, incentivizing the UAP/BPA collaboration to maximize the exit value. The BioPontis Asset Fund is designed to pay for all the IP development up to the point of sale, when the product is either ready for an investigational new drug filing or a Phase I trial. Products will be out-licensed to a pharmaceutical company with licensing revenue shared with the university on a pro rata basis. The shared exit value of the IP replaces up-front licensing fees.

The model also features a “strategic customer” role for large pharmaceutical companies, which provides guidance on product portfolio development and technical assistance. Currently, BPA has partnerships with Johnson & Johnson, Merck, and Pfizer, which benefit from previews of emerging compounds and first right of refusal to license outgoing technologies. These partnerships increase transparency and allow early customer feedback on assets, giving the management team more insight in how to create the most attractive products for licensing.

BPA is in its fundraising period and has not yet closed its fund. Of the several thousand research compounds and technologies that BPA plans to review, it estimates that 20 to 25 assets will be taken through testing and development, with four to five eventually being commercialized.

ADDITIONAL NOVEL APPROACHES TO DRUG DEVELOPMENT

Research effectiveness can also be improved by collaboration on a precompetitive basis and expanded data accessibility to develop a better understanding

Points to Consider:

What are the opportunities to help ensure successful implementation of the product development company models?

- Create better methods to value scientific assets as they move along the development pathway to ensure that those who invested early are adequately compensated and buyers (VCs, pharmaceutical companies, etc.) are paying a fair price.
- Cultivate relationships with potential customers early, as well as critically evaluate what data or services could enhance asset value in order to ease traditional difficulties in selling biotechnology and pharmaceutical assets.
- Increase transparency so PDCs and buyers can easily find one another in the market. BPA manages this dynamic by organizing both their suppliers and buyers from the beginning.
- Explore safeguards against overly complex business processes and customer diversification strategies. PDC models that position big pharma as their customers could be overtaken by the bureaucracy of that industry, and consequently lose the benefits of efficiency.

of the mechanisms of certain diseases, pathways, and targets. Vast R&D undertakings in many areas of vital basic research in biology and disease systems would be prohibitively costly for individual organizations, thereby necessitating pooled resources that would incentivize investment that is too costly for one company to bear alone. Other Lab participants raised the possibility of moving patenting later in the R&D process to upend the current practice of protecting targets regardless of their commercial potential—a practice that has been recently challenged in the courts. Additional novel arrangements that seek to address some of the issues highlighted in this section include:

- **Accelerating Experimentation:** PureTech Ventures, a Boston-based VC firm, and Chorus, an autonomous division of Eli Lilly and Company, are utilizing a model focused on performing critical experiments and streamlining the research process to develop candidate pharmaceutical compounds from discovery through POC, with the final goal of providing developers or investors with enough data about safety and efficacy to make investment decisions.⁷
- **Hybrid Firms:** Imperial Innovations, based in the UK, was originally formed as the technology transfer office for the Imperial College London but has developed into a multi-purpose technology development, business incubation, and VC firm. Imperial Innovations takes equity stakes in some companies and serves as an investment vehicle itself, which allows outside investors to hold a stake in multiple portfolio companies in certain deals. To date, the firm has invested in 18 medical or life sciences companies—five of which are focused on developing clinical therapeutics. Another successful hybrid incubator is qb3, also known as the California Institute for Quantitative Biosciences, which is a government-created organization that supports biotechnology start-ups emerging from UC Berkeley, UC San Francisco, and UC Santa Cruz. Since inception, qb3 has helped launch 65 companies that have raised \$230 million in capital.
- **Paying for Access:** Third Rock Ventures and Pfizer Venture Investments collaboratively funded a Series A round of financing for Ablexis, a biotechnology company developing a transgenic mouse platform for antibody drug development. A consortium comprised of big pharmaceutical companies paid a seven-figure entry fee to access the platform, with an additional eight-figure payment upon Ablexis granting specified non-exclusive rights to utilize the technology in antibody discovery programs. Third Rock Ventures also announced a partnership with Sanofi in early 2012 to finance with an option to acquire Warp Drive Bio, a Third Rock-incubated firm focusing on identifying and developing drugs found in microbial genomes.
- **Precompetitive Collaboration:** The ARCH2POCM (ARCHipelago to Proof of Concept Mechanism) public-private partnership is a novel attempt to pool funding from pharmaceutical companies, government, and academic sources to test molecules against novel protein targets in oncology, immunology, and neuroscience, with a goal of determining which targets are important for disease treatment at the Phase II trial stage. It is an open-access, patent-free partnership that will work on ARCH2POCM targets. Those targets can then be developed by the industry partners by either purchasing exclusive rights from the data of an unpatented drug or by using the research as a starting point to develop their own proprietary molecules.
- **Incubation:** The Foundry, a Menlo Park-based medical device incubator founded in 1998, has found success in a model that focuses on the creation of portfolio companies. Projects are based on ideas from a variety of sources including the company's own internal research, outside inventors, and university collaborations, with about half of the Foundry's companies based on ideas from outside inventors. While the Foundry operates its own labs with an internal research team, it also provides selected outside inventors and start-ups with office and lab space. Once management selects a project to move forward, the Foundry's team literally becomes the new company, resulting in a "partnership" if the inventor is from outside the company. Since the inception of the Foundry, this model has culminated in the founding and financing of 10 medical device companies, which are collectively valued at more than \$1 billion.

Leveraging Capital

Venture philanthropy and government investments or grants can provide important capital that can increase the attractiveness of investment in early-stage assets. These groups have a special ability to leverage capital and direct additional investors to promising opportunities by:

- Co-investing or providing non-dilutive capital (i.e., non-equity stake) in a company
- Taking the riskiest position in structured finance investment vehicles such as biotech-focused VC funds
- Using their own assets as collateral to enhance the credit of a company or investment vehicle, downgrading the investment's credit default risk

All of these strategies can help attract more risk-averse capital, such as later-stage biotech investors from large pharmaceutical companies or VC funds, to earlier-stage investments in the life sciences.

VENTURE PHILANTHROPY

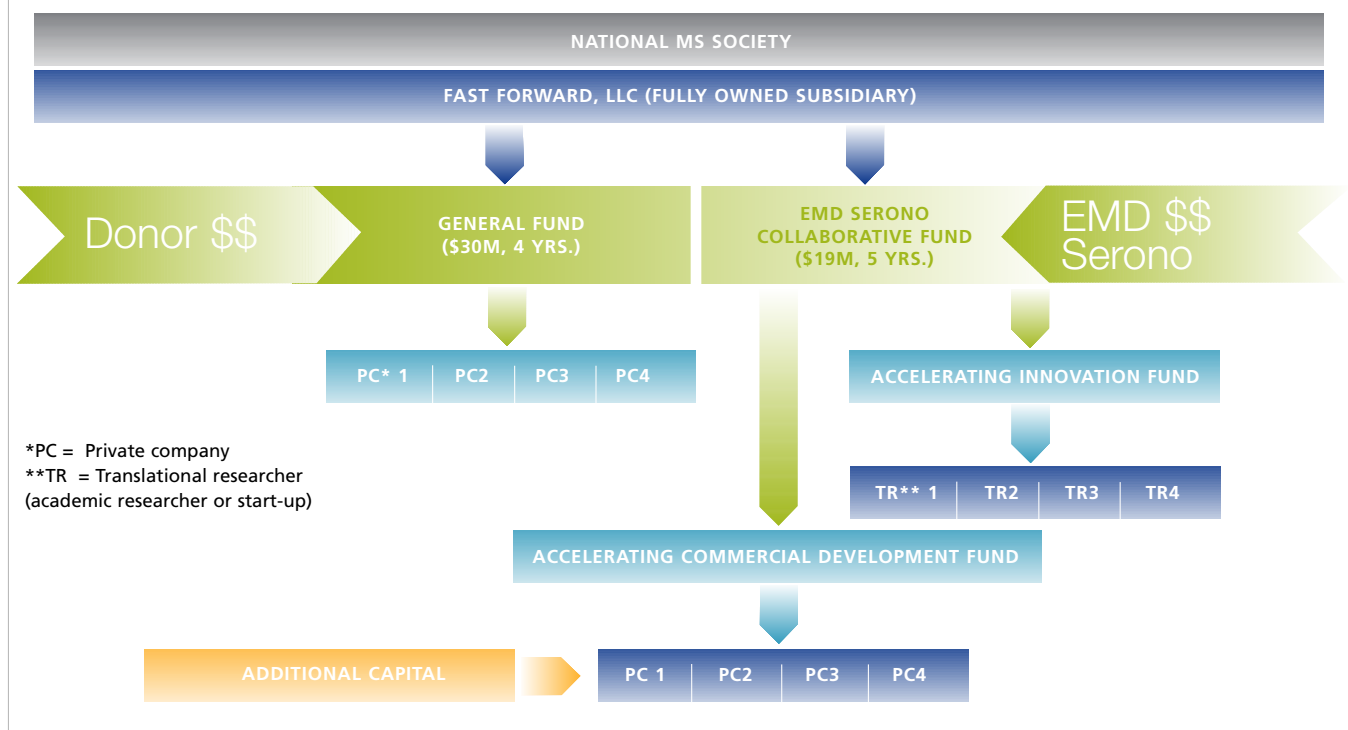
Venture philanthropy is an emerging field that

includes philanthropic investment (usually from medical research foundations) in biotechnology companies to fund high-risk research that might otherwise not receive financing. Medical research foundations choose to support research that is critical to their mission, regardless of potential investment risk. Philanthropic capital provides companies with an alternative source of financing and makes the investment less risky for others such as traditional VC funds that typically focus on later-stage assets.

Fast Forward: A bridge to the capital markets
PRESENTER: SHYAM GIDUMAL, VOLUNTEER CHAIRMAN, FAST FORWARD

SUMMARY: To incentivize investment in multiple sclerosis (MS), the National MS Society created Fast Forward, a venture philanthropy and wholly owned subsidiary that funds promising, early-stage work in MS to expand the field of candidates for later-stage investment. In exchange for capital, Fast Forward accepts either warrants for equity purchase or enters into repayment agreements (with a multiple for the investment).

Figure 7: Overview of Fast Forward, LLC.



MODEL DESCRIPTION: Fast Forward currently operates three different investment funds:

- **General Fund**—This is a four-year, \$30 million fund from philanthropic contributions that makes up to \$1 million in investments focused on research programs in early-stage biotechnology companies
- **EMD Serono Collaborative Funds**—This is a five-year, \$19 million collaboration between Fast Forward and EMD Serono. Investments range from \$250,000 to \$550,000. It includes two funds:
 - **Accelerating Innovation Fund**—for funding start-ups or academics with little or no capital
 - **Accelerating Commercial Development Fund**—for funding early-stage biotechnology companies with existing capital from other investors

To date, the General Fund has invested more than \$4 million in nine programs ranging from symptom management and diagnostic tests and tools, to stem cell therapy and disease modifying therapy. The Collaborative Fund has also issued two requests for proposals (RFPs), which resulted in an initial round of investment of more than \$1.5 million in four translational researchers and companies in the area of nerve repair and protection. The second RFP awarded more than \$1 million to three groups with a focus on immune modulation and axonal protection/restoration. In total, Fast Forward has awarded slightly more than \$9 million in funding.

Fast Forward has an ability to liaise with the entire MS community, identify and fund the development of enabling discoveries that will catalyze further research investment in the field, and bring together multiple parties—companies, regulators, patients, researchers—to provide much-needed capital to early-stage research that could become public domain.

GOVERNMENT-BACKED VENTURES

Governments have long played an important role by funding basic scientific research and some are now taking an additional step: using their funds to leverage third-party investments through public-private partnerships.

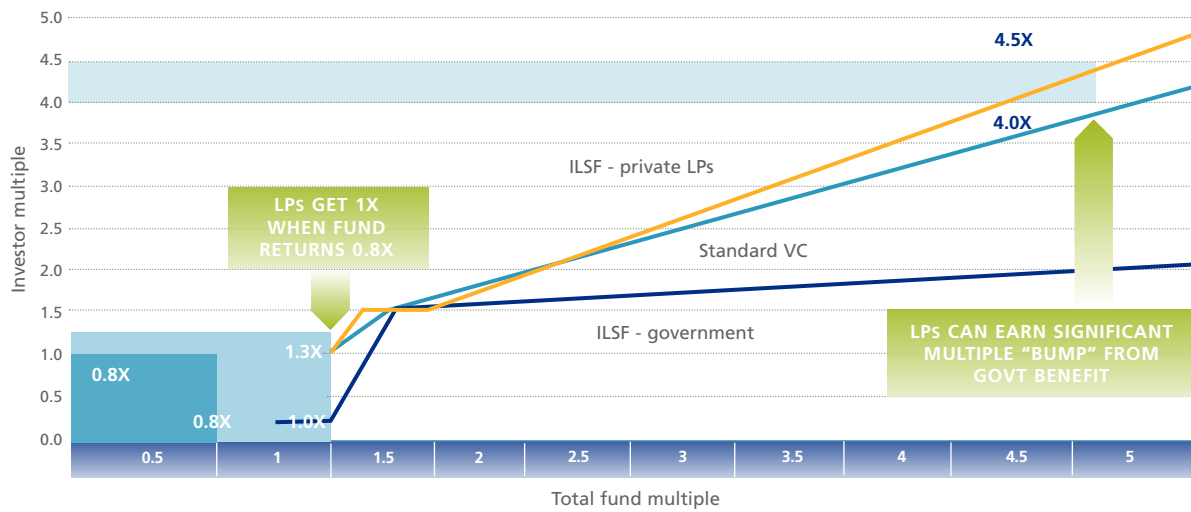
Israeli Life Sciences Fund:
Life sciences as an economic engine
PRESENTER: ORA DAR, HEAD OF THE LIFE SCIENCES
SECTOR, ISRAELI MINISTRY OF INDUSTRY'S CHIEF
SCIENTIST OFFICE

SUMMARY: The government of Israel recently created a VC-like investment fund that leverages government funds to enhance the potential returns for private investors in the biomedical research field. The fund structure is finalized, and initial investments will likely begin in the next couple of years.

MODEL DESCRIPTION: The Israeli Life Sciences Fund (ILSF) emerged from a Milken Institute Financial Innovations Lab held in late 2006 under the auspices of President Peres' Office.⁹ The Israeli government saw a burgeoning opportunity in the biotechnology sector with its skilled workers, large patent base, and growing number of life sciences R&D companies. Policymakers noted, however, that there was serious underinvestment in the local biopharmaceutical industry.

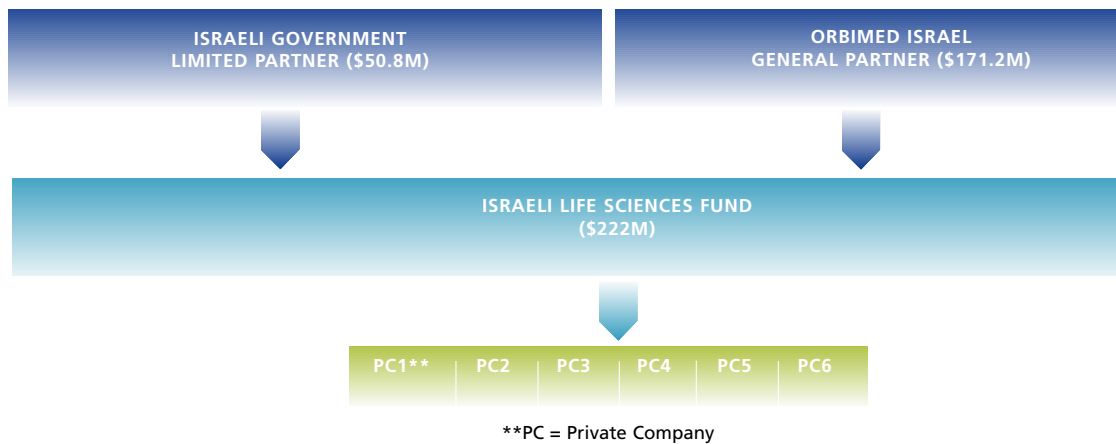
To help address these issues, the government agreed to commit public dollars to absorb much of the investment risk as a way of encouraging private investment from Israeli venture funds. As conceived, the Israeli fund was to operate as a venture fund, with the government as a private limited partner (LP) willing to commit up to \$80 million in multiple private venture funds. The fund was developed to be managed by an experienced team through a bid process. It is structured for the government to take first-loss through a preferred return scale, allowing for positive returns to private partners even if the fund breaks even or suffers a 10 percent loss. Financial Innovation Lab participants questioned the opportunities for a liquidity event or return in the poor IPO environment.

Figure 8: Israeli Life Sciences Fund Multiple



This chart illustrates the anticipated fund multiples relative to overall fund returns for limited partners in the ILSF structure, government returns in the ILSF structure, and limited partners in standard VC agreements.

Figure 9: Israeli Life Sciences Fund



SOURCES: THE MILKEN INSTITUTE FINANCIAL INNOVATIONS LAB 2011, OFFICE OF THE CHIEF SCIENTIST - MINISTRY OF INDUSTRY, TRADE AND LABOR, ISRAEL.

Figure 9 reflects the structure of the fund as announced by the government. OrbiMed Israel, serving as the general partner, raised \$171.2 million in private capital. The government committed \$42.8 million (plus an \$8 million bonus) bringing the size

of the fund to \$222 million. Per the terms of the fund's structure, the money must be invested within five years with 54 percent put toward pharmaceuticals and 46 percent toward medical devices.

OTHER POTENTIAL SOURCES OF LEVERAGED CAPITAL

- **Small Business Innovation Research (SBIR):** The SBIR program and the National Cancer Institute's (NCI) SBIR Phase II Bridge program were mentioned as small-scale but successful federal commercial funding programs. The Bridge program provides \$1 million per year for up to three years of follow-on funding for NIH SBIR Phase II awardees in the areas of cancer therapeutics, imaging technologies, interventional devices, diagnostics, and prognostics.¹⁰ These can fund development efforts including preclinical R&D needed for regulatory filings and/or clinical trials. **Competitive preference and funding priority are given to applicants that demonstrate the ability to secure substantial independent third-party investor funds, thus pairing NCI funds with those raised in the capital markets or from other sources.**
- **Sovereign Wealth Funds (SWFs):** Sovereign wealth funds promote the national goals of their countries and maximize long-term returns. Many accumulate enormous pools of capital for which they are willing to accept low rates of return. Countries like Norway, the United Arab Emirates, Qatar, and China do not need to access the capital in their SWFs, so they could deploy it productively to long-term, high-risk efforts like medical research. For example, the Abu Dhabi Investment Authority has assets estimated at \$400 billion to \$875 billion¹¹ and the Government Pension Fund of Norway reported assets of \$574 billion as of June 2011.¹² As sovereign wealth funds tend not to publicly disclose their investments, possible connections with medical research funding are unclear. **However, as these funds generally have longer time horizons, they may potentially engage in investing in illiquid and alternative assets such as those described in this paper.**¹²
- **Foundation Impact Investing:** Impact investing—also known as mission-related investments (MRIs)—is gaining momentum as a way for foundations to deploy a greater share of their resources to advance missions and increase impact. Market-rate MRIs seek to achieve market or above-market risk-adjusted returns while financing activities aligned with an institution's specific mission.

MRI tools create significant opportunities to collaborate and co-invest with external, often commercial, funders and other investors with mutual interests such as those stakeholders already discussed. Investments can be made across a range of asset classes including debt, private equity, deposits, guarantees, and real assets. A recent survey by the Foundation Center found that about 14 percent of the survey's 1,200 respondents are engaged in MRIs. **Impact investing mechanisms can be used to finance proof of concept, then scale work. They could be deployed in a variety of ways in biomedical research, including financing POC or key safety studies.**ⁱⁱⁱ

ⁱⁱⁱ MRIs differ from program-related investments (PRIs), which are loans, loan guarantees, equity investments, and similar financial instruments that are derived from a foundation's assets and count toward its charitable distribution requirements.

Points to Consider:

How can philanthropic and government investment be leveraged to attract private funding?

- **Expand Fast Forward's venture philanthropy model to include other funding partners.** For example, the fund could invest in structures with venture capital to supplement the co-investment opportunities that currently exist with industry partners. Investments may include products or platforms/precompetitive technologies (as described in the previous section) that could benefit and be made available to the entire field of disease research.
- **Import the Israeli Life Sciences Fund to the United States with a focus on the Valley of Death.** The most recent health reform bill addressed this issue by authorizing the creation of the Cures Acceleration Network (CAN), a grant-based fund financed by the NIH to advance the development of "high need cures" in areas that lack private-sector incentives. Congress appropriated \$10 million for CAN for FY2012.
- **Use venture philanthropy as seed capital to attract additional LPs, similar to the ILSF.** This approach would address challenges—government culture, bureaucracy, complexity of agency statutes, and congressional oversight—that make it more difficult to leverage government funds to attract industry investment. The fund could focus on multiple diseases but would direct money to earlier-stage translational research.
- **Expand SBIR's benefits through additional government funding.** Though small in scale, the SBIR Phase II Bridge program seems to fill a critical funding gap. Partners, such as a venture philanthropy and corporate venture, might also be able to help expand this program by providing matching grants to qualified applicants.
- **Create partnerships between SWFs and those with industry knowledge,** such as venture philanthropies, early-stage venture capitalists, and other research experts, to best direct their investment into mechanisms that fill critical funding gaps including product as well as platform development. SWFs could be leveraged similarly to those government and venture philanthropy-seeded funds discussed in the previous section.
- **Explore how impact investing instruments could be used to deploy the assets of large foundations** above and beyond the required 5 percent distribution to attract investment into the Valley of Death.

Accessing New Capital Sources

As many of the traditional life sciences investors—venture capitalists and the institutional investors that were their LPs—are limiting their participation in the sector all together (including early-stage, translational research), efforts need to be made to access untapped capital sources. Incentives and investment mechanisms should be designed to reach new sources of capital, including high-net-worth individuals, retail investors, sovereign wealth funds, and large foundations. Strategies for accessing new capital sources can include tax-based incentives for retail investors as well as innovative capital structures designed to appeal to different types of investors' (equity, fixed income, or alternative asset class) risk/benefit preferences.

TAX-BASED INCENTIVES

Tax-based incentives are being used in certain industries to encourage high-net-worth individuals to invest in start-up companies performing high-risk R&D. These incentives are an indirect form of government support for different sectors that eschew the need for the public to take a high-risk investment position or pick winners from losers.

Flow-Through Shares: Tax deferral to spur immediate investment

PRESENTER: RICHARD SUTIN,
PARTNER, NORTON ROSE

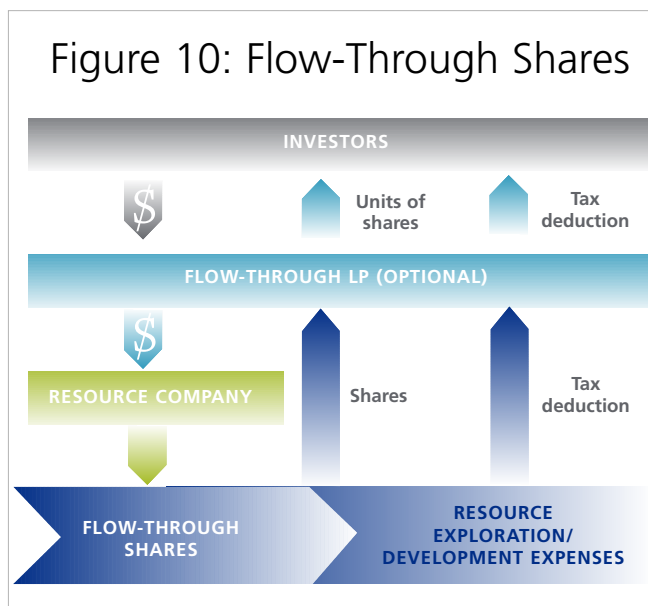
SUMMARY: Flow-through shares (FTS) are designed to increase retail participation in investment in high-risk R&D by passing the company tax savings on to the individual investor. Used previously in the natural resource industry, there is some indication that it could be applicable to funding biomedical research.

MODEL DESCRIPTION: FTS are an innovative tax deduction scheme originally created by the Canadian government to spur private investment in the natural resource sector. The program is set up to allow corporations to issue FTS to investors who receive the benefits of tax deductions for exploration and development (E&D) expenses.

Retail investors can either invest directly in a company or join a limited partnership with other investors to pool funds. FTS investors in private companies usually receive a return when the shares are liquidated into a mutual fund (typically within 18 to 24 months from the close of the LP offering). For public company investment, FTS are converted to common stock after they are issued. Companies must spend the proceeds from the FTS on qualified E&D projects and cannot expense or amortize expenditures that have been renounced to investors. The program has been notably beneficial to junior resource companies that are already in a non-tax position and do not need to deduct their resource expenses.

Applying this mechanism to the biotech industry has been explored to help address the funding gap. FTS would help biotech companies in a similar non-tax position raise funds for capital-intensive R&D projects whose expenditures are not needed to offset revenues. Further, it is argued that providing companies with risk capital through public markets will likely stimulate additional non-FTS capital in the industry.

While the FTS program represents an initial cost to the government in lost tax revenue, a 2008 study by National Resource Canada estimated that every \$1 the Canadian government spent on this program resulted in industry spending \$2.60. A 2010 economic



BIOTECANADA, FLOW-THROUGH SHARES FOR CANADA'S BIOTECHNOLOGY INDUSTRY, 2010.

impact analysis on the extension of the FTS to the Canadian biotechnology sector by Pricewaterhouse-Coopers estimated that expanding the program could increase R&D expenditures among biotechnology companies by \$411 million (representing a 69.5 percent increase in baseline expenditures) and government revenues of \$81 million.¹⁴ Previous studies of the resource industry estimated that mining and petroleum companies saw a 43 percent to 96 percent increase in qualifying expenditures as a result of the program.¹⁵

ADDITIONAL TAX-BASED INCENTIVES OR RETAIL FUNDING PROPOSALS

- **Incentivizing Angel Investment:** The Maryland Biotechnology Investor Tax Credit, an investor-only tax credit focused specifically on the life sciences, is popular among local angel investors. It provides income tax credits equal to 50 percent of an eligible investment (from \$25,000 to \$250,000) for investors in qualified seed and early-stage biotech companies. Participants knowledgeable about the program acknowledged its role in fostering the biotechnology investment community in Maryland through local lawyers, accountants, and others who would not traditionally invest in the industry. The tax credit is now serving as a model for the Innovative Technologies Investors Incentive Act (H.R. 5767), which was introduced in Congress in May 2011 by Rep. Chris Van Hollen (D-Md.).
- **Tax Holidays:** Many U.S.-based multinational companies are holding large amounts of capital overseas to avoid paying punitive taxes on the money. While the

U.S. government authorized a “tax holiday” in 2004 to allow for the return of this money, overseas reserves have crept back up to more than \$1 trillion. Rep. Brian Bilbray (R-Calif.) has introduced the Job Creation and Innovation Investment Act of 2011 (H.R. 1036) that calls for an incremental tax rate starting at zero percent for corporations that use repatriated funds to invest in domestic sponsored research, purchase research, proof of concept centers, venture capital, or manufacturing.

- **Venture Capital Trusts:** The venture capital trust (VCT) model, started in 1995 in the United Kingdom, is designed to encourage individuals to invest directly in a range of small high-risk companies whose shares and securities are not listed on a recognized stock exchange. Investors can buy shares in a VCT, which invests small, high-risk companies to help them develop and grow. Investors enjoy three major tax benefits: the potential for tax-free capital gains, tax-free dividends, and, most crucially, 30 percent income tax relief on the amount invested, which frees up 30 percent of the initial investment as cash that can then be reinvested in order to increase a client's investment base or held for additional liquidity. VCTs are also exempt from corporate tax on any gains from the disposal of their investments.
- **Microfinancing:** Microfinancing and crowdsourcing are also attracting attention as potential sources of alternative funding for translational research, with new Web sites, such as SciFlies.org, Open Source Science Project, and Petridish.org being built to more easily allow scientists to raise funds from small donations.

Points to Consider:

How can opportunities be realized to access new capital sources?

- **Support the work of other organizations**, such as the Biotechnology Industry Organization, focusing on further exploration of mechanisms such as FTS. Attendees praised the benefits of tax-based incentives and mentioned that many early biotechnology companies benefited from R&D limited partnerships in the past.
- **Further investigate VCTs to understand how this mechanism could be used to capitalize PDCs that assemble early-stage products.** Explore the feasibility of exporting this model outside the UK.

Scaling Up: Tapping Capital Markets

The previously discussed models all play important roles in bridging the Valley of Death of financing—improving efficiency and reducing capital requirements, leveraging high-risk capital to absorb risk and redirect private investment, as well as engaging new sources of capital to expand the total funding pie. Creating a portfolio of assets large enough to be statistically likely to result in a dependable flow of Phase III successes, however, would require financing on a grander scale. **Such diversification would not only remove much of the risk of early-stage financing, but could also benefit from investors' desire for steady returns not based on financial markets.** This new approach to funding drug development on a grand scale by both diversifying risk through portfolio construction and leveraging equity through securitization garnered much interest and excitement from attendees.

Research-Based Obligations: An Idea Whose Time Has Come?

PRESENTER: ANDREW LO, ROGER M. STEIN, AND JOSE-MARIA FERNANDEZ, MIT LABORATORY FOR FINANCIAL ENGINEERING

SUMMARY: This model securitizes a portfolio of research assets as collateral to raise funds in the capital markets that appeal to a variety of investors' risk-reward ratios. The presenters plan to circulate a detailed research paper in 2012 to further vet the construct.

MODEL DETAILS: The research-based obligations model is based on an investment vehicle—likely to be funded by institutional or retail investors—that would be structured to offer different risk-reward profiles across various tranches of debt and equity, thereby appealing to a broader spectrum of investor preferences, risk-tolerance levels, and maturity objectives. This vehicle would allow researchers to tap into the capital markets for funding to permit orders of magnitude of capitalization larger than traditional venture capital scales. While the presenters acknowledged that raising billions or tens of billions of dollars might seem like an impossible goal, they offered a back-of-the-

Royalty Monetization

Royalty monetization—most often associated with the BioPharma Royalty Trust—has gained recognition as a source of immediate financing by academic institutions, startups, and other groups in recent years. In February 2011, Ohio University, a faculty member, and a graduate student sold partial royalty income rights to their license for the growth hormone antagonist Somavert®, a drug approved for the treatment of acromegaly in 2003. The buyer, DRI Capital, set up a five-year agreement with the university that includes a minimum lump-sum payment of \$39 million for five years' worth of royalty revenue, with an option to receive an additional \$13 million if the Somavert market grows. Ohio University plans to invest funds in new translational medicine research programs and efforts to commercialize technologies in drug discovery and medical devices. Other academic organizations that have entered into similar agreements include Northwestern University, New York University, University of Michigan, and University of Connecticut.

“Ohio University, inventors to receive up to \$52 million from drug license transactions,” Office of Research Communications, Ohio University, February 15, 2011. Available at: <http://www.ohio.edu/research/communications/royaltymonetization.cfm>

envelope calculation that suggested that a large portfolio of candidate compounds or drug development programs with a high probability of consistent successes could yield reasonably attractive returns to investors. The scale of the funding level, suggested at between \$5 billion and \$20 billion, is the consequence of the high cost of developing a single drug and the relatively large number of programs needed to yield a well-diversified portfolio with an attractive risk-reward profile.

This securitization approach is easily differentiated from other models mentioned during the Financial Innovations Lab by its sheer size and its use of creative financial engineering. As one participant put it, the idea is “audaciously” big. Another transformational element is that this structure alters both the risk profile and timing of payments to investors in that investors receive some return along the way—with the returns reflecting their own risk-reward profile. The presenters reiterated that research-based obligations are for

investors seeking a 5 percent to 10 percent ROI—including institutional investors like pension and sovereign wealth funds—not 20 percent to 50 percent like traditional venture capital investments. However, the risk level of the returns is expected to be commensurately lower, and the structure would offer a higher upside potential than a bond. Audience members also suggested that achieving economies of scale for R&D activities could further decrease portfolio costs. Additional risk mitigation tactics could include government support (in the form of credit enhancement) or investment by disease-related endowments^{iv} that could improve the expected return for other participating investors.

The research-based obligations model was devised in recognition of the need for capital markets-based investment vehicles that address the challenges of lengthy and expensive drug development—such as the development of cancer-targeted therapeutics—which sometimes cannot be met by existing financing vehicles. The presenters plan to circulate a research paper in 2012 that will contain a detailed description of how such a vehicle might be constructed, along

with some sample experimental results. They also plan to make open-source software available in the public domain for those interested in testing or application. The hope is that the proof of concept will motivate financial practitioners to explore implementing the approach.

While the notion of such large-scale funding is captivating, there are numerous problems to overcome from a quantitative perspective. Beyond the technical details, it was noted that there were also more formidable practical challenges relating to both a market structure and transaction implementation that would need to be addressed. The researchers hope this first effort will generate interest in solving these problems among members of the medical research and finance communities.

^{iv} Endowments are sometimes prohibited from buying equity, but might choose to invest in the structured bonds with a lower return requirement than traditional unrelated investors.

Points to Consider:

What are the opportunities to help ensure successful design and implementation of the research-based obligations model?

- **Conduct more work on the assumptions behind the model** (such as aggregate compound success probabilities vs. disease-specific compound success probabilities) **and the design of the capital structure** prior to exploring its implementation.
- **Refine the model design and transition probabilities based on a better characterization of and data about industry-specific issues**, including drug research and development dynamics, emerging regulations, the impact of firm size, and attrition rates for various therapeutic areas.
- **Create better valuation models** to truly vet the construct and address concerns regarding the availability of data and the use of historical data to value research assets.
- **Create the model to reflect a true estimate of demand by customers** who would be ready to acquire assets of this scale.

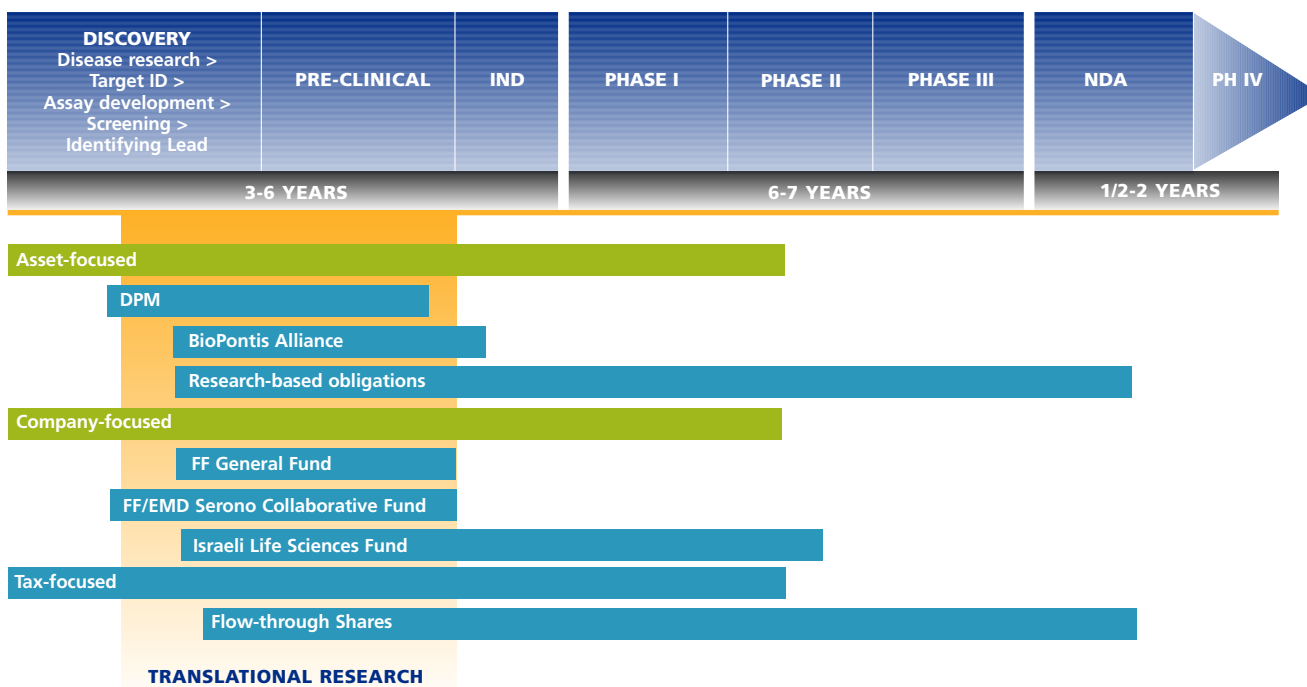
Overview of Models

Figure 11 assesses each model in terms of its ability to incorporate each key approach, which can be used to draw conclusions about the benefits, strengths, and weaknesses of the models. Figure 12 lays out the models in terms of their location within the broader R&D pipeline, giving a clear picture of how different approaches could be applied to each stage of drug development.

Figure 11: Overview of Models by Approach

Virtual product development companies and partnerships	●	●			
Government, philanthropy, or venture philanthropy backed funds	●	●		●	●
Innovative tax structures	●			●	●
Research-based obligations	●		●	●	●
	Better risk management	Improves research effectiveness	Effective diversification	Increases access to capital	Creates leverage

Figure 12: Location of Models in R&D Pipeline



SOURCE: FRANCIS COLLINS, WEBINAR ON NCATS, *FASTERCURES* 2011

Table 1 provides details of model specifications, including proposed portfolio size, overall capitalization, potential investors, and expected returns.

Table 1: Model Specifications

STRUCTURE	OVERALL CAPITALIZATION	INVESTMENT SIZE (PER ASSET)	PORTFOLIO SIZE	PHASE OF DEVELOPMENT	DEVELOPMENT TIMELINE	FUNDERS	ROI
ASSET-FOCUSED							
Product development company (ex: distributed partnering model)	\$50-100M	\$2-10M	10-15	To "proof of relevancy"	3 years per compound	Pharma/VCs/ Hedge funds/ High-net-worth individuals	2-10x initial investment; \$12-15M per asset
Hybrid PDC and investment fund (ex: BioPontis Alliance)	Fund not yet closed		20-25 compounds	To IND/Phase I		Pharma/VCs/ Hedge funds/ High-net-worth individuals	
Fixed-income structured securitization (ex: Research-based obligations)	\$5-20B		40-200+	Pre-clinical through later stages or approval		Retail – institutional fixed-income and equity	Varies
COMPANY-FOCUSED							
Venture philanthropy (ex: Fast Forward EMD Serono Collaborative Fund)	\$19M	\$250-550K	7 companies	Academic, early stage	5 year fund life	Pharma/ Nonprofit funds	EMD has exclusive IP options
Venture philanthropy (ex: Fast Forward General Fund)	\$30M	Up to \$1M	9 academic programs/ companies	Early stage	4 year fund life	Philanthropic contributions	Warrants for equity purchase/ royalties/ repayment
Government-backed venture (ex: Israeli Life Sciences Fund)	\$222M			All stages	5 year fund development	Government/ VC investors	Preferred return (5% hurdle rate)
TAX-FOCUSED							
Flow-through-shares (ex: Canadian natural resource industry)	N/A	N/A	N/A	N/A	N/A	High-net-worth individuals/ Retail investors	Increase in private R&D expenditures

Conclusions and Next Steps

The Financial Innovations Lab explored innovative financial strategies that could increase access to capital for translational research. A central focus of the discussion was how each of the models can help to improve the risk-return ratio for early-stage research to make it a more attractive investment opportunity yielding greater financial and societal rewards.

The group discussed and debated a range of research and funding models—from venture funds to tax incentives and from equity to debt investments—that, when implemented, either independently or in combination, could improve financing for R&D in the Valley of Death. From these conversations, major challenges and proposed solutions have been identified for future discussion and consideration.

Some of the key themes identified in the Financial Innovations Lab include:

- New, unproven operating models may **improve research effectiveness and value creation**, allow better risk management, and reduce overall capital needs.
- Integrating philanthropic and/or government funding into financing structures can **create leverage** and attract greater private investment.
- Opportunities should exist for investment vehicles and incentives to **access new capital sources** based on acceptable risk-return profiles.
- Innovative financial structures can achieve the necessary grand scale of capital needed to support the minimum number of biotech investments for effective diversification and **create stable and attractive investment opportunities along the development pipeline**.

Each model discussed in the Financial Innovations Lab incorporated at least one of these approaches and each could potentially play an important role in reducing the Valley of Death. Although there will be no silver bullet in bridging the Valley of Death, the Milken Institute and *FasterCures* will work with relevant and interested partners to further explore and shape these opportunities.

Appendix 1: Glossary

Biological license application (BLA) – a submission to the FDA that contains specific information on a biological product that, if approved, issues a firm a license to market the product

Credit enhancement – a strategy for companies, organizations, or individuals to increase their credit worthiness through securitization, collateralization, or other methods to decrease their credit default risk

Federally funded research institution (FFRI) – a research institution that is fully or partially funded by the federal government

Initial public offering (IPO) – the first sale of stock by a private company to the public on the open stock market to raise capital and become a publicly traded company

Institutional investors – organizations such as banks, insurance companies, pension funds, retirement funds, and mutual funds that pool large sums of capital for investment

Investigational new drug (IND) – a submission to the FDA prior to testing a new drug in human clinical trials that includes information on toxicology, manufacturing, and clinical protocols; after submission, the agency has 30 days to review the application before the investigator can begin a trial

Merger and acquisition (M&A) – an aspect of corporate strategy that deals with buying, selling, combining, or dividing different companies

Mission related investments (MRIs) – the practice of using financial investments to advance a specific mission and earn financial return; market-rate mission investments seek to achieve market or above market risk-adjusted returns while financing activities aligned with an institution's specific mission

New molecular entity (NME) – novel chemical structures that have previously not been used in clinical practice

Precompetitive collaboration – open collaboration between companies and groups that usually compete for intellectual property

Program related investments (PRIs) – loans, loan guarantees, or equity investments typically made at below market rates that are derived from a foundation's assets but count toward its charitable distribution requirement

Proof of concept (POC) – a point in the drug development process where the key relevant attributes of success are demonstrated and validated

Securitization – the process of pooling a group of illiquid assets that can then be collateralized and marketed as different tiers of asset-backed instruments to be sold to investors

Sovereign wealth funds (SWF) – a state-owned investment fund

Translational research – the translation of medical discoveries into practical applications, including applying discoveries from basic research to the development of drugs for use in trials and human treatment

Valley of Death – a funding gap in the research and development pipeline between basic research and clinical trials

Appendix 2: Participants

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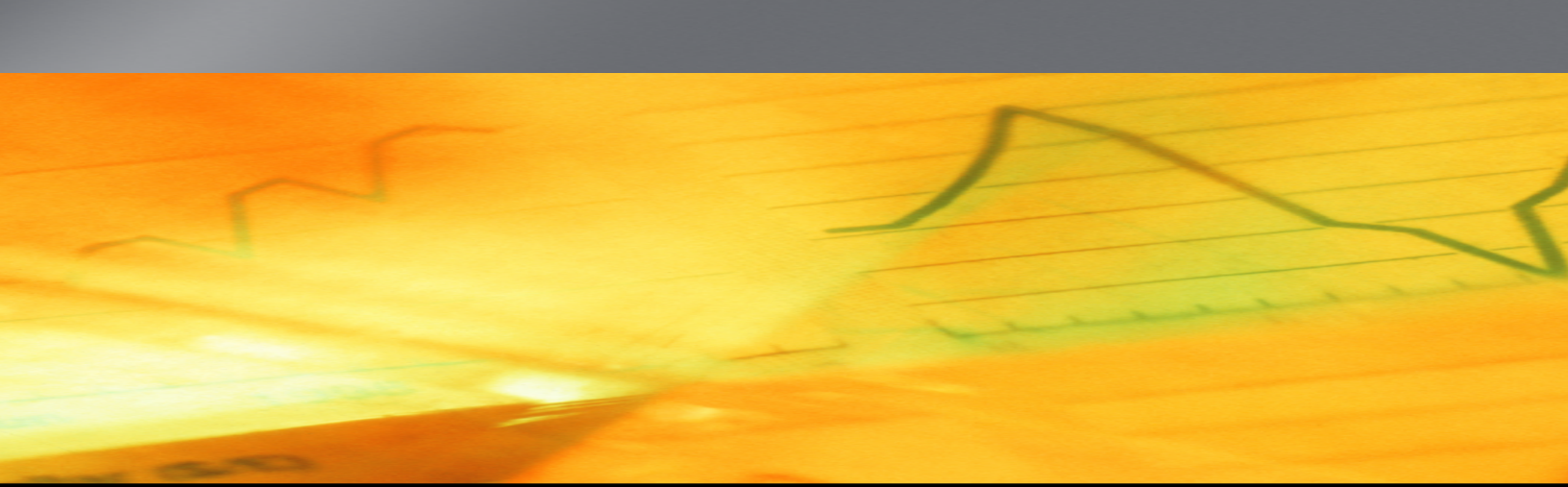
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FasterCures/The Center for Accelerating Medical Solutions is a nonprofit think tank and catalyst for action that works across sectors and diseases to improve the effectiveness and efficiency of the medical research enterprise. *FasterCures*, a center of the Milken Institute, is nonpartisan and independent of interest groups.

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