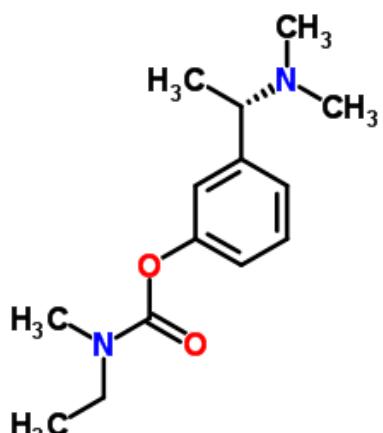


# MODELS FOR BIOMEDICAL INNOVATION AND COMMERCIALIZATION

Financial Innovations Lab®



Another project of the California-Israel Global Innovation Partnership

August 2018

## **Acknowledgments**

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The Lab was carried out under the auspices of the Israel Innovation Authority and as part of the California–Israel Global Innovation Partnership project.

## **About Financial Innovations Labs**

Financial Innovations Labs bring together researchers, policymakers, and business, financial, and professional practitioners to create market-based solutions to business and public policy challenges. Using real and simulated case studies, participants consider and design alternative capital structures, and apply appropriate financial technologies to them.

## **About the Milken Innovation Center**

The Milken Innovation Center at the Jerusalem Institute focuses on developing market-based solutions to Israel's greatest challenges as it transitions from a startup nation to a global nation. Through the Milken Fellows program, we train some of Israel's best and brightest young professionals in creating pragmatic financing and economic policy solutions, and then deploy them as resources to government ministries, nonprofits, and other key organizations. Our applied research and Financial Innovations Labs serve as a launching pad for transformative change, using innovative financing mechanisms, programs, and policies to bridge social, regional, economic, and technological and productivity gaps within Israel and between Israel and the world. Our goal is to accelerate economic growth, build human capital, and cement Israel's role as a pioneer in addressing global challenges in water, food, education, health, and energy with solutions that others can replicate.

Note: Cover image is the molecular formula C<sub>14</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> for Rivastigmine, also known as Exelon, developed by Novartis, a Swiss pharmaceutical company licensing a technology that treats dementia and Parkinson disease. The drug was discovered at the Hebrew University in Israel and licensed to Novartis by Yissum, Hebrew University's technology transfer office.

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*This report harks back a few years, to a Financial Innovations Lab held in Jerusalem in 2015 that led to new work and major collaborative projects between the Milken Innovation Center and universities in the US. The Lab's focus was on years'-long pipeline in biomedical development and the numerous funding gaps within it, those aptly named valleys of death that occur when the financing burden becomes too onerous and promising compounds and therapies are left behind, under-developed, or undervalued.*

*These valleys of death are painful to drug developers and painfully well known; they lurk at entirely predictable points along the pipeline. One, for instance, falls between translational research and preclinical discovery, two very early stages in the pipeline, when laboratory findings are validated, tested, and winnowed according to their potential as marketable medical therapies. The failure rate here is close to 70 percent; yet every potential cure must be tested for replicability outside its originator's lab. Another crisis point falls in later-stage development, when the costs for funding human trials and government review soar. The result? Unable to attract enough finance themselves, entrepreneurs accept premature exits and lower IP realizations, and sell their interests to large multinationals outside Israel. Big Pharma also feels the sting, but for different reasons. Shareholder pressure make it almost impossible to discard outdated business models that gamble everything on the breakout blockbuster but are setups for expensive failure.*

*Following the Lab, Milken Fellows completed work in 2016 and 2017 with the Israel Innovation Authority on program and capital structures identified in the Lab<sup>1</sup>, and the Israel Innovation Authority (formerly the Office of the Chief Scientist) launched a formal Memorandum of Understanding with the University of California to collaborate on joint research and development projects in biomedical development and other fields of mutual interest, and several of the best practices identified in the Lab have been adapted, launched or expanded their innovative business models, including BioBridge and Harrington-BioMotiv. The pace of investment by the world's leading biomedical/pharma companies in Israeli biomedical ventures, incubators, accelerators, and funds have risen. And the conceptual framework of the research-backed obligation structure presented and discussed at the Lab is under consideration as a collaborative investment and development opportunity between the University of California, Israel, and substantial institutional investors from both markets.*

## EXECUTIVE SUMMARY

Biomedical researchers in labs around the world are discovering potential treatments and cures, and publishing and presenting their findings, but increasingly, these breakthroughs don't reach doctors and their patients. The large pharmaceutical firms (Big Pharma) have been failing on this account: due to the time it takes to develop a drug, or to their business models, and/or pressure from shareholders and investors, they aren't allocating the funds to see many of these projects to market. For the past decade, traditional funding mechanisms have yielded few cures for patients or acceptable risk-return investment profiles. This is especially true in Israel, where promising biomedical intellectual property (IP) and startups tend to move abroad because local funding dries up.

To address this challenge, the Milken Innovation Center convened a Financial Innovations Lab at the Jerusalem Institute for Policy Research in 2015 to focus on designing new finance mechanisms for supporting and scaling the impacts in translational research (i.e., basic scientific research, like cellular research, that targets therapies and cures). This report is based on the findings from the Lab, as well as subsequent and ongoing work. The Lab brought together leaders in biomedical research, pharma, health-care, finance, and government to address key questions.

- 1) How can we bridge the gap between the potential of medical breakthroughs and the lack of financing?
- 2) What kinds of platforms (organizational, managerial, financial, and strategic partnerships) can best leverage capital to invest in Israeli-based life sciences?
- 3) How can we transform the Israeli life sciences sector to help it thrive as a self-sustaining ecosystem of breakthrough and financing?

In addition to the 45 Israeli government, investment, and technology leaders present, several US visitors attended. These included:

- Roger M. Stein, PhD, Professor, New York University's Stern School of Business; Research Affiliate, MIT Laboratory for Financial Engineering (New York City, New York)
- Neil Kumar, PhD, Founder and CEO, BridgeBio Pharma (Palo Alto, California)
- Baiju Shah, JD, CEO, BioMotiv; co-leader, the Harrington Project for Discovery & Development (Cleveland, Ohio)
- Bruce Lehmann, PhD, Professor, University of California–San Diego School of Global Policy and Strategy (San Diego, California)
- Nora N. Yang, PhD., Senior Scientist, Therapeutics for Rare and Neglected Diseases and Director, Portfolio Management and Strategic Operations, National Center of Advancing Translational Sciences, National Institutes of Health (Bethesda, Maryland)
- Issi Rozen, MBA, Chief Business Officer, Broad Institute (Cambridge, Massachusetts)

This Lab built on two earlier Financial Innovation Labs; the first, [Accelerating Medical Solutions in Israel](#),<sup>2</sup> led to the launch of a new financing mechanism for Israel's biomedical venture capital industry.

The second, [Fixes in Financing, Financial Innovations for Translational Research](#),<sup>3</sup> was conducted for the Milken Institute's *FasterCures* center<sup>4</sup> and explored blended business and financial models to accelerate medical solutions. The most recent lab, the subject of this report, addressed potential financial and business models, as well as international perspectives on particular requirements and opportunities for Israel.

The group discussed a number of potential financing solutions focused on five areas.

1. RISK: Use guarantees and technical efficacy insurance to de-risk the investment processes for investors and technology adopters.
2. LEVERAGE: Design structured vehicles that offer both equity and bonds and consider using subordinated tranches and pooled investment vehicles to leverage financing through domestic and international capital markets.
3. VALUE CHAIN DEVELOPMENT: Enhance the mechanisms in the development value chain to permit all links, including the translational and preclinical stages (i.e., early-stage development) to benefit financially through research-backed obligations<sup>5</sup> and other structured-finance and portfolio-management approaches.
4. MARKET CHANNELS: Strengthen market channels for development, partnerships, and sales to make the testing and development cycle more attractive to pharma again and reboot its involvement in these stages.
5. CAPITAL STRUCTURE: Improve the capital structures of business and research transactions, including designs for new financial tools, to create and leverage value over the long term.

Lab participants identified key elements that would go into the design of new financial solutions.

1. BUILD INVENTORY: Select sufficient intellectual property to build a pipeline with initial targets.
2. MODEL THE FINANCING: Build financial model scenarios for maximum benefit from all components of value chain.
3. ID ANCHOR SUPPORT: Identify what government and foundation support may be helpful to sell debt and equity (e.g., guarantees, subordinated loans, etc.).
4. ID BUSINESS MODELS: Identify options for ownership, management, organization, partnerships, and business operations.
5. ID INVESTMENT TERMS: Estimate the benefits needed for all stakeholders and identify investment terms and conditions that may meet these needs.

It's important to take note of one of the most important realizations of the Lab, the reminder that great support and potential already exists for a major collaborative partner: California. This opportunity dates from a 2014 memorandum of understanding for a California-Israel Global Innovation Partnership that came into being in the wake of Financial Innovation Labs in California and Israel on water technologies and Agritech solutions, and follow-up research by Milken fellows,<sup>6</sup> staff, and Lab participants. The MOU cites the mutual willingness to support and encourage professional exchanges in health and biotechnology solutions.

It must be said that investment opportunities in Israeli IP are quite substantial. Yet Israeli startups are struggling without enough backing to get them to full-scale deployment. Israeli IP will only achieve the scale, diversity, and value that large investors require if it is bundled into portfolios with IP products from elsewhere, perhaps California or the European Union.<sup>7</sup> A number of joint ventures and binational funding initiatives are already in existence: the US-Israel Binational Research and Development (BIRD) Foundation; the Binational Agricultural and Research and Development (BARD) Fund; and the US-Israel Binational Science Foundation (BSF) between Israeli research institutions, companies, and University of California research centers. These are not only creating opportunities for research and investment collaboration, but they're building up scale and diversification to support new financing structures, such as the research-backed obligation bonds (RBOs) introduced by the team at MIT Laboratory for Financial Engineering and addressed later in this report.

New structured finance vehicles designed solely for biomedical investing would help the sector in a number of ways.

1. They would pool and securitize projects appealing to pension funds, sovereign wealth funds, foundations that target specific diseases, and patient advocacy groups.
2. By structuring for new investment groups, they would overcome the market failure and investor fatigue of current venture capital models (\$199 billion in VC versus \$40 *trillion* in fixed-income markets).
3. They would strengthen other health R&D funds (like BIRD) as retail vehicles in the Tel Aviv Stock Exchange.
4. They would enable the design of new derivative securities that help reduce the investment risks of drug development.
5. They would encourage collaboration and co-innovation with other biomedical innovation hubs (for example, in California) and public-private-philanthropic partnerships.
6. They would accelerate innovation in medicine, electronic health records, machine learning, and other areas where Israel has competitive technologies.

Fortunately, market conditions are favorable. The low interest-rate environment still favors issuing long-term debt. At the time of the Lab, even years after the financial crisis, there was over \$8 trillion in negative yields in the fixed-income markets, mostly in Europe (as of mid-2018, the figure hovers around \$7.3 trillion). This suggests a large untapped pool of investors seeking products less correlated with traditional asset classes. And Israel, by virtue of its active biomedical research community, its startup culture, and the growth of its securities laws and capital market structures, is well positioned to play a leading role in developing a new asset class comprising biomedical IP. If Israel can develop a market for *biomedical financial products*, its efforts to serve as a hub for innovative finance will advance as well, enabling Israel and its partners to maintain a competitive advantage in biomedical exports.

## INTRODUCTION

Biomedical researchers in labs around the world are discovering potential treatments and cures, and publishing and presenting their findings, but increasingly, these breakthroughs don't reach doctors and their patients. Too many ideas and discoveries with the promise of helping millions of patients stall in the drug development pipeline, trapped in the "valleys of death," the funding gaps between the validation of a lab discovery through early testing and the final stages of large clinical trials.<sup>8</sup> This is the point at which pharmaceutical firms abandon potentially revolutionary therapies because the costs for funding human trials are too high, their business models favor blockbuster drugs rather than lower profit margins, shareholder and investor pressure is too great, and profitability is too far off on the horizon. For the past decade, traditional funding mechanisms have yielded few cures for patients or acceptable risk-return investment profiles. This is especially true in Israel, where promising biomedical IP and startups tend to move abroad because local funding dries up.

"Our goal is to ensure that there is not just money, but *enough money*, in the system to build strong companies."

Avi Hasson, Chief Scientist, IIA

One of the Lab's chief goals was to find ways to bridge the gaps in research, finance, and business models in order to accelerate drug development and make it attractive to investors and large pharmaceuticals again. How, for example, can the tools of financial technology facilitate closer collaborations between pharmaceutical companies, capital markets, governments, and, in some cases, medical philanthropies? How can this work in Israel?



There are numerous examples of firms, cities, states, and national governments pursuing biomedical financing options. Back in 2004, voters in California approved a \$3 billion bond initiative to fund the California Institute for Regenerative Medicine's stem cell research. Its successes and failures can provide valuable lessons. In 2014, the European Commission and the European Investment Bank jointly launched InnovFin, a facility offering financing tools that include loans,

loan guarantees, and equity funding through banks or funds. The expectation was to attract some €24 billion of public-private finance over the five-year life of the program; as of 2018, 13 percent of funding targets the life sciences, medical technology, pharma, and health care R&D. In 2015, London's then mayor, proposed a US\$15.7 billion bio-pharma development mega-fund to support UK biotech firm and drug development, and keep it from leaving the country. In 2016, Swiss investment bank UBS AG

announced it had raised US\$470 million to launch a fund for cancer research. In 2017, BridgeBio, a US biopharmaceutical firm, raised \$13.5 million in financing for its portfolio of early-stage drug development programs held by subsidiary companies. With such precedents in mind, Lab participants set out to design workable options for Israel.

## ISSUES AND PERSPECTIVES

In 2017, for the first time ever, Israel broke into the top 10 list of Bloomberg's "Innovation Index" country ranking (among 78 countries reporting).<sup>9</sup> Also that year, the World Economic Forum's "Global Competitive Report" placed Israel as the world's 16th most innovative country out of a much larger pool of 138 economies.<sup>10</sup>

By other measures as well, Israel's life science output is extraordinary. Its concentration of scientists, at 145 per 10,000, is one of the highest in the world; their output in top-tier academic journals, a measure of scientific innovation and leadership, is also high relative to other countries: from 2010 to 2014 and despite a slight dip, Israel still ranked 14th in number of publications per million citizens and 32nd worldwide in absolute number of papers, according to the Samuel Neaman Institute for National Policy Research.<sup>11</sup> Three Israelis, Aaron Ciechanover and Avram Hershko (2004), and Ada Yonath (2009), have won Nobel Prizes for their life science research.<sup>12</sup> Israeli research successes have led to life-changing blockbuster drugs, such as Copaxone, Exelon, Doxil, Rebif, and Gonal-F. Cutting-edge research continues in stem cell innovations.

In 2015 alone, Israeli life science firms applied for 509 patents, chiefly in biotech (25 percent), medicine (15 percent), and physics, electronics and electro-optics (14 percent).<sup>13</sup> Israeli biotechnology and medical device companies are still some of the highest performers in Israeli equities. And despite the volatility of the TASE in 2017, companies like medical device company Mazor Robotics (MZOR) and clinical-stage biopharmaceutical company Aevi Genomic Medicine (GNMX) continue to perform well (Protalix BioTherapeutics, however, has struggled to regain losses over the past three years).

Yet 2015, when the Lab was held, was also the year that Teva's success story began to unravel. Already Teva had been talking publicly for months about separating its huge generic drug business from its specialty drug arm, which had developed the company's sole proprietary drug, Copaxone, a treatment for the multiple sclerosis symptoms. Copaxone had turned into a blockbuster drug but was soon coming off patent. Despite pressure from activist investors and other analysts to keep growing its R&D side, Teva took a massive gamble on the \$40.5 billion acquisition of Activis, Allergan's generics business.

The result was a catastrophe. Over the next two years, Teva lost \$57 billion in value, leaving it with a remaining market value of \$19 billion today. It currently owes about \$35 billion and faces a cliff of debt payments of \$9.1 billion by 2019 and \$17.5 billion by 2021. Meanwhile, its cash flow is projected

to shrink to \$3.2 billion in 2018 due to heightened competition in generic drug manufacture and the loss of Copaxone's patent protection.

In December 2017, Teva announced the closure of its R&D facility and slashed its overall R&D budget—a dismal ringing out to what many called a “lost year” in Israeli equities. Teva, more than any other company, accounted for the poor performance of all Israeli stock market indexes. Prior to its collapse, Teva’s market capitalization constituted 29 percent of the Tel Aviv 125 Index; as of June 2018, it was 13%.<sup>14</sup> The voluntary de-listing of life sciences firm Mylan from the TASE in February 2018 followed the delisting in 2013 of Mellanox, creating another large hole in the local capital market and a loss for Israel’s role in this important industry.

The example of Teva highlights the urgency for policy and program innovation. The company’s debt restructuring means it no longer has the firepower to fund any kind of drug development pipeline. But Israel could step into the hole that Teva left—helping other biomedical IP and research firms with guarantees, public and private investment, and credit-enhanced research-backed obligations.

This report leans on what we have learned and how we might prevent another collapse like Teva’s. Israeli scientists and entrepreneurs have the academic rigor and business drive to build more life science and technology companies, but they will need new finance and investment vehicles to build self-sustaining drug development and delivery. Change is overdue—it’s no longer enough to rely solely upon tax subsidies for large companies, and the public and private equity markets are too limited, even though they’ve shown some recovery in 2018. We look here at a creative strategy that includes new approaches to financing that we believe will harness competitive strength again in the biotech sector.

## Industry segments and trends

The 2017 Israeli Advanced Technologies Industries (IATI) report confirms that despite consistent growth in health-care IT and digital health, other areas of the domestic life sciences industry, including funding for companies and the founding of new companies, are facing headwinds. Yet the outlook continues to be promising, with regulations on track to streamline drug-approval processes and global demand for health care, especially among aging populations, ticking higher.<sup>15</sup>

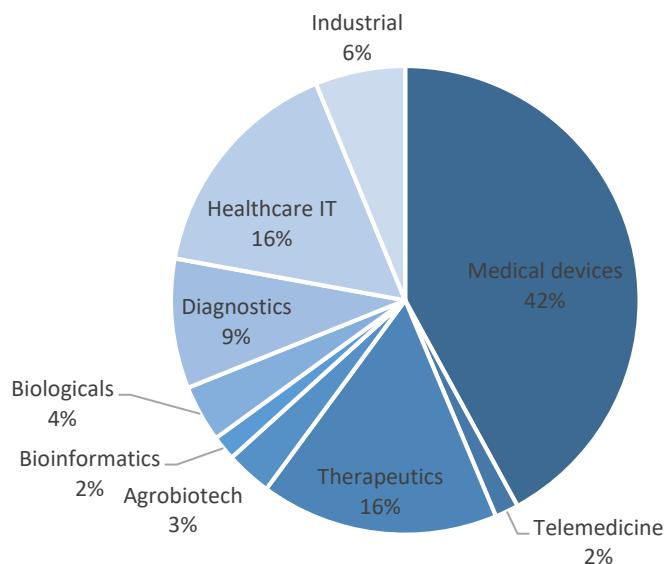
According to IATI, there are more than 1,350 active companies in the life science sector. This is up from 1,000 reported at the time of the 2015 Lab. Of the 1,234 companies established since 2007, 612 are still active today. On average since 2007, 123 life sciences firms came into existence each year; again on average, 62 companies ceased operation each year. Of all active companies today, 513, or 38 percent, are generating revenue; the remainder are still in R&D and early-stage development. Many companies (568, or 42 percent of life sciences market share, as of 2016) are active in medical devices, although market share has dropped from the 53 percent reported in 2014. Figure 1 shows the composition of the life sciences industry.

FIGURE

**1**

## Sector breakdown for Israel's life sciences industry

Life science firms 2016



Source: IATI database 2017

Israeli invention and intellectual property licenses in this sector have been particularly attractive to international industry participants and have contributed the technologies that have produced almost 20.5 percent of the global biopharma sales overall. However, only about .7% of biopharma sales are from Israeli technologies that are produced in Israel.<sup>16</sup>

TABLE

**1**

## Biopharma blockbusters invented in Israel

Product (Company)	Indication	Sales 2012 (M\$)	Academic Institute
Humira (AbbVie/Eisai)	Rheumatoid arthritis	9,380	Weizmann Institute of Science
Enbrel (Amgen)	Rheumatoid arthritis	8,370	Weizmann Institute of Science
Copaxone (Teva)	Multiple Sclerosis	3,996	Weizmann Institute of Science
Rebif (Merck Serono)	Multiple Sclerosis	2,400	Weizmann Institute of Science
Erbitux (BMS & Eli Lilly)	Colorectal cancer	1,800	Weizmann Institute of Science
Avonex (Biogen)	Multiple Sclerosis	1,570	Weizmann Institute of Science
Exelon (Novartis)	Alzheimer's and Parkinson	1,000	Hebrew University
Doxil (J&J)	Cancer	500	Hebrew University
Azilect (Teva)	Parkinson	330	Technion
<b>Total (Developed Globally)</b>		<b>29,346</b>	

Source: Milken Innovation Center

At the Lab, Dr. Ora Dar, head of the Life Sciences Sector at the Office of Chief Scientist (renamed in 2016 to the Israel Innovation Authority) reported that while biopharma<sup>17</sup> constitutes a small percentage of all life science firms, it contributes a very large share of inventions within the sector. Of the 542 active projects reported in 2014 by technology transfer offices (TTOs), 324, or 60 percent, were in biopharma. Only 115 projects, or 21 percent, were in medical devices.<sup>18</sup>

## Strategic partners and markets

Lab participants reviewed the components of the largest global biopharma blockbusters that had their roots in Israeli R&D, and took note of the corporate involvement, disease focus, and sources of IP. These are shown in table 1. The focus to date on rheumatoid arthritis, multiple sclerosis, and various cancers reflects the interests and strengths of researchers in these areas and, of course, their applicability and share (estimated at 11 percent) to targeted biomedical markets. These diseases account for estimated sales of \$266 billion annually,<sup>19</sup> or just less than 1 percent of the \$3.2 trillion in sales on health care in the US alone.<sup>20</sup>

Some of the largest corporate pharma companies in the world, including Johnson & Johnson, Eli Lilly, Merck, and, of course, Teva, have partnered with Israeli technologies. Partnerships such as these have been key to creating sources of sustainable financing; historically, the high costs and long time frame involved with bringing a laboratory compound “from bench to bedside” have proved prohibitive for local companies. Indeed, the innovative financing mechanisms and structures discussed at the Lab (and addressed later in this report) don’t require that exits be for blockbuster drugs.

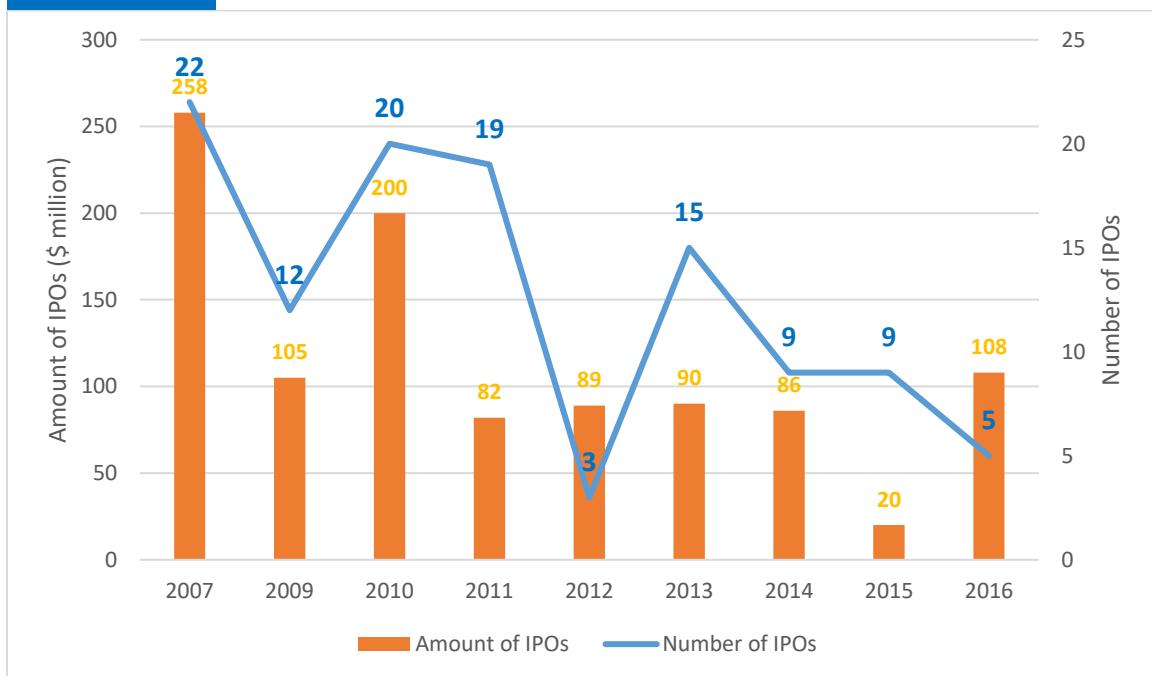
## Capital for survival

There’s a limited domestic capital base, which includes venture capital and the capital markets, for investment in life sciences companies. From 2010 through 2014, Israeli venture capitalists invested \$506 million, or just 13 percent of all their investments, into local life sciences firms, according to PwC MoneyTree Reports.<sup>21</sup> This limited base, largely focused on early-stage investments, underscores the need for more funding in the early stages, when discoveries are being validated—and lasting over the longer term, particularly during very expensive clinical trials. (In 2016, according to IATI, domestic VC in Israeli life sciences placed \$106 million into Israeli life sciences firms, down slightly from 2015. IATI notes that the average annual domestic VC investment from 2011 through 2016 had been about \$105 million.<sup>22</sup>)

**FIGURE**

**2**

## IPOs by Israeli life science companies on the Tel Aviv Stock



Source: IVC-Online Database; IATI

Exit valuations in the capital markets and acquisitions accounted for almost 17 percent of all capital raised by life sciences firms between 2004 and 2014. And time-to-exit declined from almost 17 years in 2010 to under 10 years in 2014. On the surface, that might look like an improvement, but Lab participants suggested that it instead reflects premature exits and lower IP realizations than might otherwise have been achieved had there been longer funding runways for development and commercialization.

**TABLE  
2**

**Biomedical companies listed on the Tel Aviv Stock Exchange**

<i>Company</i>	<i>2017 Market capitalization (000 \$)</i>
Opko <a href="#"><u>OPK</u></a> (TLV)	4,493,251
Compugen <a href="#"><u>CGEN</u></a> (TLV)	228,251
Mazor Robotics <a href="#"><u>MZOR</u></a> (TLV)	501,145
Evogene <a href="#"><u>EVGN</u></a> (TLV)	129,237
Pluristem <a href="#"><u>PSTI</u></a> (TLV)	87,768
Protalix <a href="#"><u>PLX</u></a> (TLV)	146,467
Kamada <a href="#"><u>KMDA</u></a> (TLV)	248,063
Clal Biotechnology Industries <a href="#"><u>CBI</u></a> (TLV)	108,690
Redhill Biopharma Ltd <a href="#"><u>RDHL</u></a> (TLV)	161,728
Elron <a href="#"><u>ELRN</u></a> (TLV)	130,225
Brainsway <a href="#"><u>BRIN</u></a> (TLV)	79,818
Bioline <a href="#"><u>BLRX</u></a> (TLV)	66,113
Itamar <a href="#"><u>ITMR</u></a> (TLV)	101,938
Can Fite Biopharma <a href="#"><u>CANF</u></a> (TLV)	33,125
PhotoMedex, Inc <a href="#"><u>PHMD</u></a> (TLV)	7,719
Intec Pharma <a href="#"><u>NTEC</u></a> (TLV)	51,917
Applisonix Ltd <a href="#"><u>ENDY</u></a> (TLV)	11,723
Kmn Capital <a href="#"><u>KMNK</u></a> (TLV)	8,804
Collplant Holdings Ltd <a href="#"><u>CLPT</u></a> (TLV)	11,781
Elbit Medical <a href="#"><u>EMITE</u></a> (TLV)	60,904
XTL Bio <a href="#"><u>XTLB</u></a> (TLV)	7,539
	6,676,206

Source: Tel Aviv Stock Exchange

The capital markets already play a significant role in financing life sciences companies, but they are poised to play a much larger role. Table 2 shows that in 2017, 19 TASE-listed life sciences companies held about \$7.754 billion in market capitalization—down almost 19 percent in market value since 2015 and the Lab.<sup>23</sup> On the Nasdaq, NYSE, and AMEX for the same period, as shown in table 3, 22 Israeli life science companies (not including Teva), including nine with IPOs in 2014,<sup>24</sup> held a much higher total market capitalization, \$9.8 billion.<sup>25</sup> This difference highlights the significantly lower levels of value realization in Israeli markets relative to US exchanges. On the flip side, with improved liquidity and product diversification in the Israeli stock exchange, it offers potentially greater opportunity and growth and value.

**TABLE  
3**

**Biomedical companies listed on the Nasdaq, NYSE, or AMEX**

Company	2017 Market Capitalization (\$000)
Teva Pharmaceutical Industries Limited <a href="#">TEVA</a> (NYSE)	35,910,000
Taro Pharmaceutical Industries Ltd. <a href="#">TARO</a> (NYSE)	4,780,000
Syneron Medical Ltd. <a href="#">ELOS</a> (NASDAQ)	345,370
Compugen Ltd. <a href="#">CGEN</a> (NASDAQ)	218,910
Mazor Robotics Ltd. <a href="#">MZOR</a> (NASDAQ)	532,270
Pluristem Therapeutics, Inc. <a href="#">PSTI</a> (NASDAQ)	107,590
NeuroDerm Ltd. <a href="#">NDRM</a> (NASDAQ)	617,590
ReWalk Robotics Ltd <a href="#">RWLK</a> (NASDAQ)	37,570
Protalix BioTherapeutics, Inc. <a href="#">PLX</a> (NYSE)	159,700
Kamada Ltd. <a href="#">KMDA</a> (NASDAQ)	260,990
Alcobra Ltd. <a href="#">ADHD</a> (NASDAQ)	34,180
MACROCURE LTD. <a href="#">MCUR</a> (NASDDAQ)	27,080
Redhill Biopharma Ltd. <a href="#">RDHL</a> (NASDAQ)	160,490
Bio Blast Pharma Ltd. <a href="#">ORPN</a> (NASDAQ)	18,690
Galmed Pharmaceuticals Ltd. <a href="#">GLMD</a> (NASDAQ)	267,331
Vascular Biogenics Ltd. <a href="#">VBLT</a> (NASDAQ)	65,540
Oramed Pharmaceuticals Inc. <a href="#">ORMP</a> (NASDAQ)	86,292
Can-Fite Biopharma Ltd <a href="#">CANF</a> (NYSE)	26,286
XTL Biopharmaceuticals Ltd. <a href="#">XTLB</a> (NASDAQ)	5,550
InspireMD, Inc. <a href="#">NSPR</a> (NYSE)	2,910
Total	43,664,339
Market cap without TEVA	7,754,339

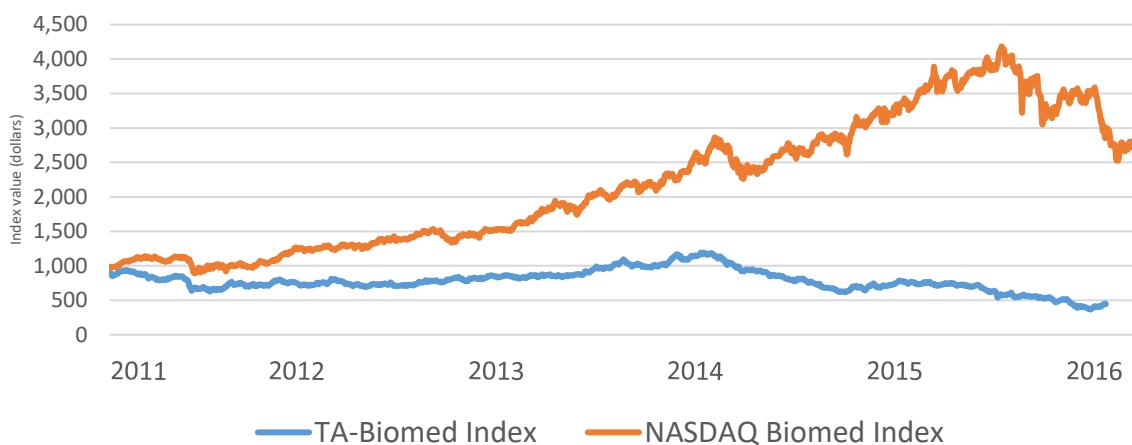
Sources: Nasdaq, AMEX, NYSE

Of note, Israeli biomedical companies trading on US exchanges had an average negative return of 19 percent in 2014, compared with growth of around 23 percent for US health-care sector indexes overall and about 26 percent for the biomedicine and pharmaceutical areas in particular.<sup>26</sup> But biomedical company valuations were also down across most markets, reflecting the need for a new approach to creating and harvesting value.<sup>27</sup> The trends seen in Figure 4 reflect a disturbing trajectory that has been amplified in the case of Israel.

**FIGURE**

**3**

Biomedical index performance on Israel and US markets



Sources: Yahoo Finance, Tel Aviv Stock Exchange, Milken Innovation Center

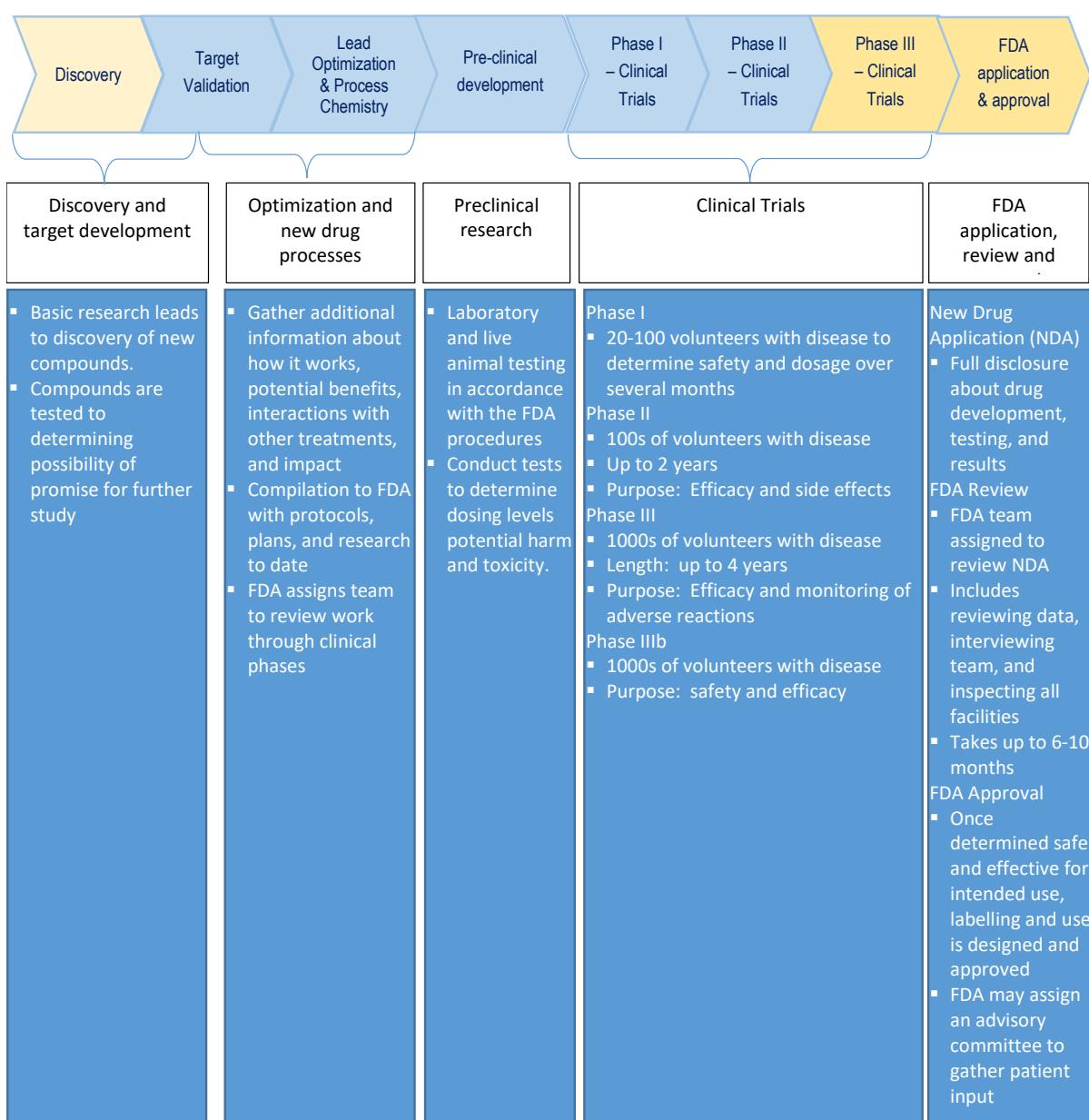
## DEVELOPMENT PROCESS

Israel has the foundation to support biomedical research to feed the discovery process, early stage development to identify targets, confirm and optimize leads, and begin preclinical trials (for example on animals, before clinical trials on humans), and studies to enable investigational new drug filings to streamline the approval process,<sup>28</sup> clinical trials to evaluate how the therapies work, their risks, and appropriate dosages and treatment regimens, and applications to regulators, including filings, reviews, and approvals. The drug development value chain is depicted in the next figure.

FIGURE

4

## Development value chain



Source: National Institutes of Health, FDA

Baiju Shah is the CEO of BioMotiv, which has been called a hybrid US “institutional seed fund.”<sup>29</sup> The for-profit company has partnered with a nonprofit institute and support center that takes products through the early, preclinical testing and “proof-of-concept” stage, while his company aids in commercialization efforts. At the Lab, Shah described the typical development process. It is very lengthy, he said; typically, it takes about 12 years, costs approximately \$212 million for a single

solution in their experience, and offers a scant 1.82 percent probability of success, as shown in table 4.

TABLE  
4

Development stage, timeframe, cost, and probability of success

Stage	Timeframe	Cost	Probability of success	Sources
Discovery	1 year	\$1 million	80%	Government, disease foundations
Target Validation	1.5 years	\$2 million	50%	None
Lead Optimization & Process Chemistry	2 years	\$4 million	50%	None
Preclinical development	1 year	\$5 million	70%	Limited
Clinical trials/FDA Application & approval	6 years	\$200 million	13%	Pharma companies, VCs
<b>Total</b>	<b>12 years</b>	<b>\$212 million</b>	<b>1.82%</b>	

Source: BioMotiv

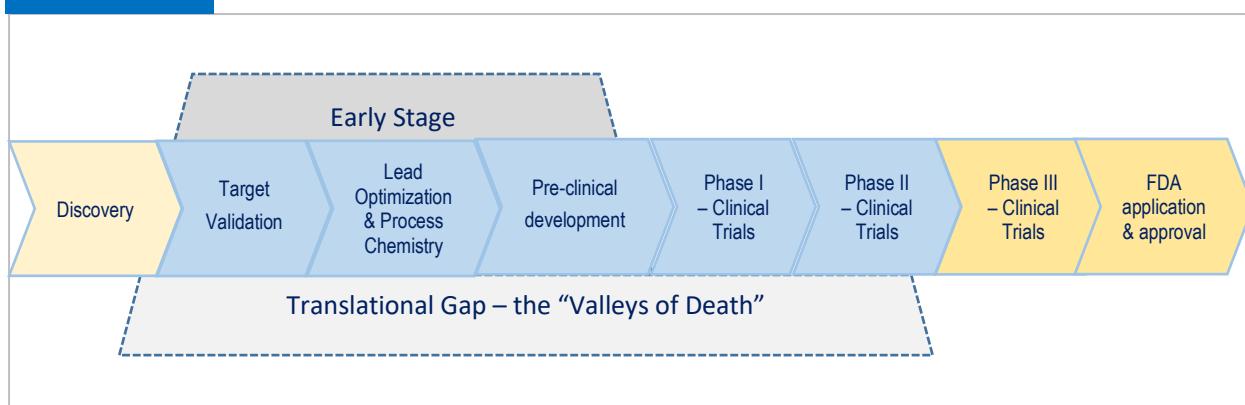
## BARRIERS

Each stage of drug development involves different actors: the dedicated university research labs that fuel discoveries; the university technology transfer offices that identify IP and market it to investors and businesses; incubators and accelerators that provide investment capital, build business capacity, and develop business models; strategic partners that help build marketing channels; and investors (governmental, philanthropic, venture capital, and capital markets) that support various links in the chain. The key objective, said Shah, is to have the right money and manage risk throughout the entire value chain.

**FIGURE**

**5**

**Development process and the Valleys of Death**



Source: Adapted from Faster Cures

The translation of biomedical research into medicine depends, of course, on patents and licensing—the product's commercialization. There are several barriers to this aspect:

1. *Insufficient funding to obtain and maintain patents:* Patents are costly to obtain and maintain, and financial barriers have led to intellectual capital flight from Israel.
2. *IP that is already public property:* Putting IP into the public domain has impeded benefits otherwise derived from protectable rights.
3. *Information asymmetry:* Problems can arise when information isn't shared well between technology transfer offices, the Israel Innovation Authority, and potential development partners or licensors.
4. *High risk:* Investors historically have taken big gambles on single long-shot therapies, hoping for big wins but setting themselves up for expensive failure.

Bruce Lehman, a financial economist at the University of California–San Diego, explained the difficulty of picking winning technologies. Even the largest, most successful pharmaceutical firms struggle, he said, under pressure to set aside otherwise promising drugs in favor of long-shot bets on the next

blockbuster. In their early-stage drug development, three factors weigh heavily in decision making: the nature and probability of risk at different stages in the value chain, and opportunity costs associated with that risk.<sup>30</sup>

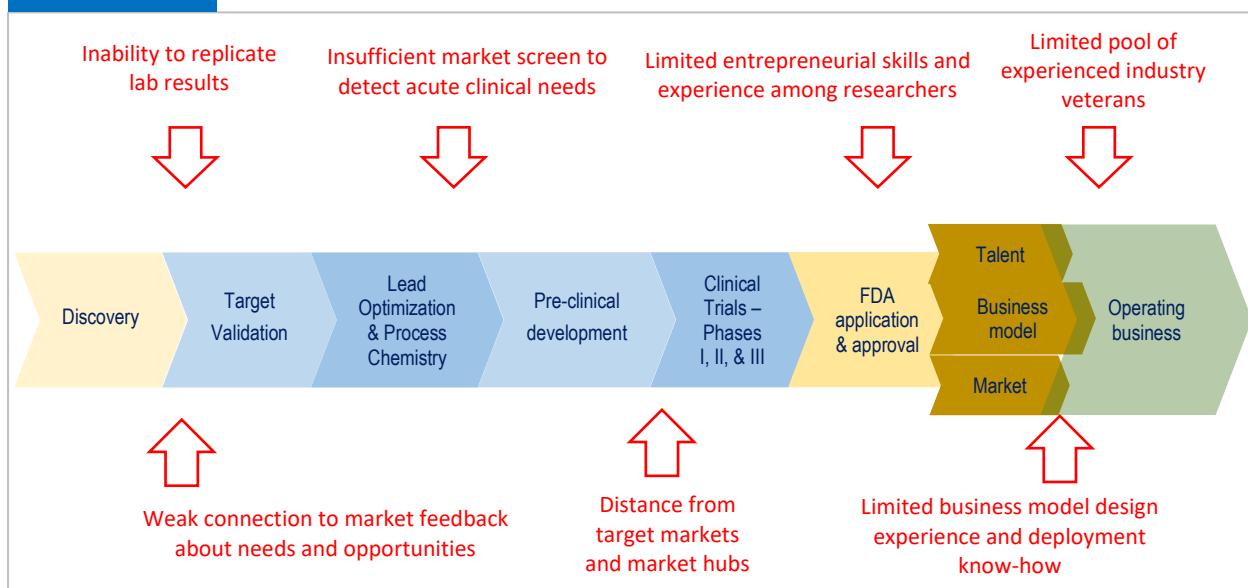
Another barrier, particularly in the development of drug compounds, is the lack of so-called “smart money,” meaning capital from knowledgeable, well-connected investors. Smart-money investors know where development funding is most needed and can help bridge the procedural gaps between the lab and formal FDA filings, for example. They are major links in the value chain, from translation and validation to efficacy and risk analysis—a process that costs enormous sums and consumes years.

Barriers along the value chain fit into two broad categories: business skills and financing. The first barrier, business skills, is shown as it crops up along the drug development value chain, as shown in figure 6. Challenges include a lack of business planning knowledge or know-how to develop a viable investment proposition; the need for market data to determine patient needs or a compound’s medical applications; and limited entrepreneurial business experience. These gaps are particularly crucial to close in the early stages, at the post-translation phase and during preclinical testing.

**FIGURE**

**6**

## Business skills challenges along the development value chain



Source: Milken Innovation Center

Similar skills gaps appear during the later-stage approval and business modeling phases. The company stakeholders may have no industry experience, or they may be located far from their target markets or from marketing hubs. Israel has felt the effects of these insufficiencies in the shift of many business operations abroad, to corporate and market centers in Europe and the US.

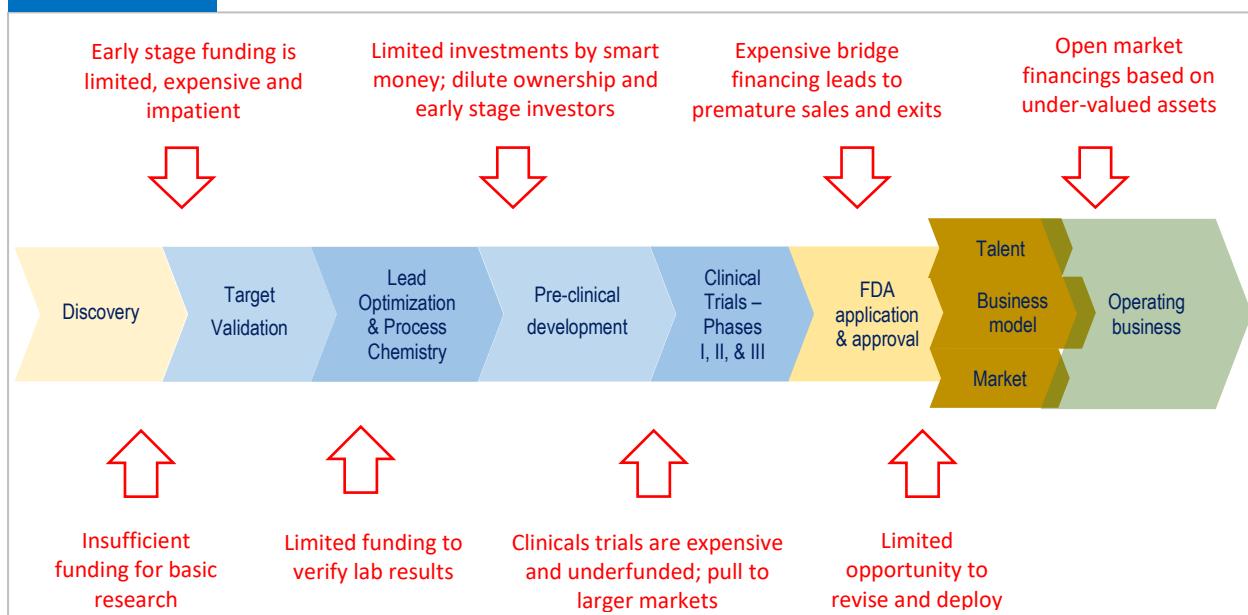
BioMotiv's Baiju Shah pointed out the tension between finding a cure and founding a company, two efforts sharing one goal, but which require different skills, tools, and capital structures. The tension can form a barrier for philanthropic investors who may want to invest in cures for patients, not products.

The second barrier, financing, encompasses the impatience of early-stage investors who've handed over large sums of capital to support the phases heading up to clinical trials. Financing barriers are shown along the value chain in Figure 6. Because they will be asked for much more substantial investments in later-stage clinical trials and market development, investors often ask for a stake in the project, thus diluting ownership. This is one reason why Israel has trouble growing businesses from the early stage, said Anya Eldan, director general of the Israeli Innovation Authority's Startup Division, which funds an incubator program that "graduates" early-stage biomedical projects into businesses. They keep diluting ownership until they've sold so much, they've lost control.

FIGURE

7

## Financial challenges along the development value chain



Source: Milken Innovation Center

Why are owners and investor/owners tempted to sell too early? Because they consider the long timeframe and mountainous expenses of later-stage trials to be insurmountable. Their investors tend to be venture capital firms who want high multiples on their investments; or they may be Big Pharma who come on scene with targeted mixes of market-driven compounds and low patience for failures. If they encounter market changes or setbacks during later-stage clinical phases, they lose interest in funding revisions, new tests, and redeployment of assets. When investors bow out, compounds and projects are left behind, undervalued, under-developed, and abandoned in the valley of death—or “multiple valleys of death,” as participants noted, because financial pitfalls lie all along the long ramp toward commercialization. The risk of running out of funding during the costly testing, verification, and regulatory review stages can be the steepest obstacle to overcome.

Of great concern, there's not enough money in Israel's current ecosystem. And the funding that is available isn't suited for long-term lending through the whole value chain, let alone into scalable companies. Uri Gabai, chief strategy officer of the Israel Innovation Authority, explained that it will take smart money to address this market failure. A key objective, he said, must be to design capital structures and business models that manage risk while enabling long-term financing.

## DRIVERS

### New Money

Looking at current financing sources—VC, debt financing, philanthropy, and structured securitization—is a good starting point for identifying and understanding how to design new finance opportunities. The total VC market, for example, including all stages of equity financing, is estimated at \$128 billion annually, yet only 13 percent of this sum targets biomedical and health-related sectors, according to KPMG.<sup>31</sup> In contrast, long-term, high-yield debt financing is estimated at \$1.6 trillion annually.<sup>32</sup> As for philanthropy, the research foundation Giving USA reports that charitable gifts in the US totaled \$358 billion in 2014, with more than \$30 billion directed toward health categories, including medical research.<sup>33</sup> Finally, the US market of structured asset-backed securities offers not only the cheapest cost of financing, had had over \$2 trillion of new US asset-backed/mortgage-backed securities issuance volume in each of 2016 and 2017, and \$1.4 trillion of US asset-backed securities outstanding. Of this amount outstanding, \$982.9 billion, or 69.7 percent, was rated Baa/BBB or higher, meaning investment grade.

If the biomedical industry could tap this deeper securitization market, it would likely find substantially greater capital resources for accelerating faster cures across a broader range of diseases. This is what excites economists and other experts who design financial instruments.

Roger Stein, the NYU professor working with MIT’s Financial Engineering Lab, discussed two drivers of innovation he and his colleagues have been exploring: an untapped source of finance and a new type of fund that the untapped source may find very attractive.

The untapped source is the vast pool of institutional investors, including pension funds and insurance companies. The Milken Innovation Center estimates that while venture capital represents about \$128 billion of new investment globally each year,<sup>34</sup> traditional investments in fixed-income securities total over \$100 trillion annually,<sup>35</sup> more than 1,000 times as much. These institutional investors are typically limited to investment-grade securities (rated BAA/BBB or higher), but they’re looking for different kinds of investments, even new asset classes, that aren’t pegged to interest rates or commodity prices, said Stein. They’re not targeting the same returns as venture capitalists, a 3 or 4 times multiple on their investments, but longer-term returns of 6–8 percent, provided the investments are sufficiently low risk.

That combination of investment-grade, low-risk, high long-term return is hard to find right now. But Stein and the MIT Lab team have demonstrated that when biomedical assets are packaged into investment-grade securities, they suddenly become attractive, even compelling for these kinds of investors. Stein explained how he, Andrew Lo, and other colleagues had to address potential drawbacks. For example, historically, biomedical investments have been difficult to source and research, and are often not available in sufficient quantities to permit investing at scale and under the

“It’s not just about the amount of capital, it’s about capital structure.”

Glenn Yago

guidelines investors traditionally use to decide their investment policy. Another challenge was how to obtain investment-grade ratings on securities backed by early-stage assets like IP, meaning, before those assets generate any revenue through licenses or other arrangements.

But they demonstrated that it was possible to apply financial engineering techniques used successfully for other asset classes to biomedical assets. In fact, they were able to transform projects that by themselves carried high risk into securities whose risk profiles are similar to those of the assets typically favored by traditional investors of fixed-income securities.

This approach is rooted firmly in modern portfolio theory and relies on diversification to mitigate risk, rather than on picking long shots and hoping for winners. And guarantees from the government, philanthropies, or disease-specific foundations would further reduce risk for these capital structure.

Stein explained the MIT Lab's focus has been in the area of genetic diseases, many of which are designated "orphan" diseases by the US FDA because they affect fewer than 200,000 US patients. Even though these drugs target smaller populations, their successes produce favorable, even attractive returns for investors. But, as is usual, the costs of preclinical and clinical trials can be prohibitive, dramatically reducing the likelihood of new drugs reaching the market.

Nora Yang is director of portfolio management and strategic operations in the Division of Pre-Clinical Innovation at the National Center for Advancing Translation Sciences (NCATS), an agency of the National Institutes of Health within the federal Department of Health and Human Services. She and Roger Stein, an NYU professor and research affiliate with the MIT Laboratory for Financial Engineering, both noted that the historical probability of success for developing a single anti-cancer treatment is only about 5 percent—but that the probability of success (US approval) shoots up to 99.59 percent in a portfolio of 150 potential cancer treatments, even if their markets and prospective financial performance outcomes are statistically uncorrelated. They told the Lab that potential for a higher probability of success goes up for a portfolio of patents on complementary assets when long-term debt financing is used.

## New Structure

Enter the second driver: a financial structure that builds a portfolio of many projects, say 30 or 40 early-stage candidate therapies for orphan diseases. The large number of drug development candidates all undergoing drug trials in this mega-fund reduces the portfolio's volatility and risk to a level consistent with that targeted by institutional investors, and greatly increases the odds of finding cures. And since building such a large portfolio requires significant capital, the MIT researchers also demonstrated that debt can be issued *and* supported by the portfolio in the form of research-backed obligations, or RBOs. These are structured as bonds whose returns are guaranteed by the portfolio's diversity and IP. The bond structure is what makes them attractive to fixed-income investors.

These funds don't yet exist. But the models developed by the MIT researchers can be used to determine the risk levels of such debt instruments, their efficient capital structures, debt terms, and the like.

The RBO model also allows for projects to move out of the portfolio before reaching approval, thus creating early exits and improving liquidity. And since the structure is fully funded at launch for expected costs of clinical trials etc. (with additional funding often available through some of those early exits), the portfolio maximizes its long-term value by allowing those projects requiring more time or more advanced funding to remain in the portfolio.

Since the cash flows into the portfolio aren't regular (it is difficult to predict when payouts will occur), its designers plan for time diversification among the variety of projects, along with the use of "structural enhancements," such as capitalizing interest, funding a cashflow reserve, and pooling transaction, royalty and license fees, that create much smoother cash flows than would be observed with one or a few projects. In addition, governments can provide full or partial guarantees to lower the costs of funding and increase investor confidence.

Building on the description of the RBO model, Prof. Lehman explained that diversification offers greater likelihood of financial success than do Big Pharma development efforts that target individual therapies and where technical and market risks, and cost of capital are increasingly prohibitive. The RBO's prepackaged exits, with an option to remove those portfolio candidates whose projections fall, minimize investment risk and increase capital efficiency because the portfolio remains large and diversified. Larger portfolio size correlates with higher internal rates of return (to a point), reducing the comparable cost of capital, but staying consistent with other lower-risk investments. This combination creates a self-sustaining bridge across the valley of death.

#### Institutional investors' checklist

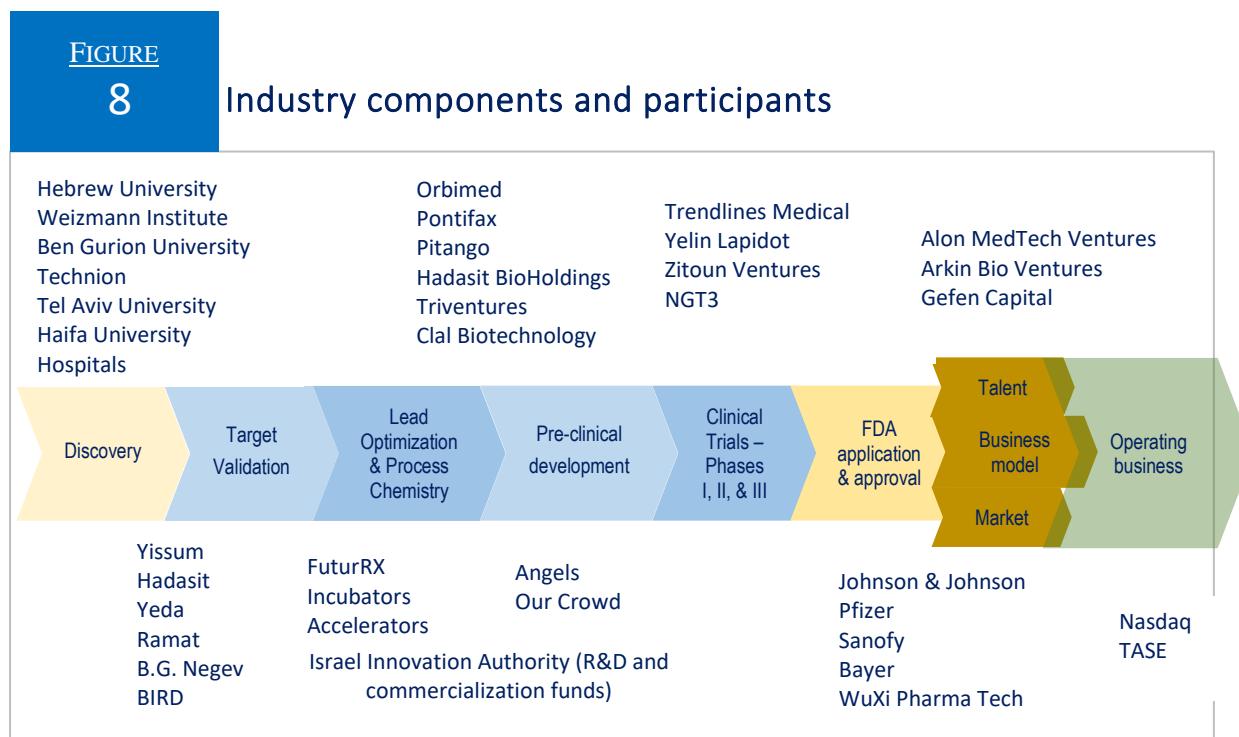
- ✓ Uncorrelated to market
- ✓ Scale
- ✓ Long term
- ✓ Low transaction cost
- ✓ Market return

## CURRENT AND BEST PRACTICES

Two key questions came up again and again in the Lab discussion: How can Israeli researchers derive marketable solutions from their research? And how does one build a sustainable investment model to ensure adequate investment across the length of the drug development value chain?

### Israeli Success Stories

It was a Milken Financial Innovations Lab on biomedical startups in 2008 that focused on the valley of death, that long time lag that crops up in early-stage development and, again, in later-stage clinical and approval phases, when capital is most needed and hardest to come by. In the decade since then, Israel has seen the launch of a number of private and public ventures, many of which are included in Figure 8 according to their missions and the work they do in the development value chain.



Source: IATI, Milken Innovation Center

The Office of the Chief Scientist (now the Israel Innovation Authority), spearheading government leadership in this area, has inaugurated specialty incubators and accelerators, new R&D funding and investment programs, and the venture capital fund managed by OrbiMed, the largest biomedical venture capital company in the world. Follow-on funds by OrbiMed and others, including Pitango Venture Capital, the Pontifax–Hoffman LaRoche partnership, the Israel Biotech Fund, and the Dalian Sino-Israeli Biomedical Venture Capital Fund, have significantly increased the pooled funds available. In this section, we describe several of these, as well as other innovative financing approaches, and discuss the factors that allowed them to succeed.

### ***OrbiMed, the world's largest biomedical VC firm***

One of the key groundbreaking initiatives that followed from the 2008 Lab was the creation, by the then Office of the Chief Scientist in the Ministry of the Economy and the Office of the Accountant General in the Ministry of Finance, of an innovative first-loss capital fund. A formal tender was issued in 2010 to the global VC community, with focus on using the public fund as a limited partner in a VC fund with a subordinate interest in the returns, allowing for private, for-profit limited partners to gain an earlier boost in their returns. This guarantee was meant to overcome the funding gaps of early-stage development; its financial structure was innovative in that the Israeli government, as a limited partner, would receive its return only after the private limited partners had first received their preferred 5 percent return. Thereafter all profits were divided evenly.

OrbiMed won the tender and closed on the financing in April 2011, raising \$222 million, which provided 4.5 times leverage on the government's \$50 million first-loss investment. To date, the OrbiMed Israel Partners Fund has invested in 28 companies in the domestic biopharma sector. The fund is managed by the general partners in Israel, along with OrbiMed's global industry network. Anat Lifshitz, managing partner with the fund and a Lab participant, explained that the government's investment added important moral support and gave confidence to global investors.

Building on the success of the first round of funding, OrbiMed Israel Partners closed on a second fund, OrbiMed Israel Partners II, in 2016, raising another \$307 million. This round eliminated the government's first-loss limited-partnership investment, demonstrating the effectiveness of its role in nurturing the fund's early stages and establishing investor confidence in its novel structure of assets and finance.

### ***FutuRx, Israel's first biomedical accelerator***

With its first-round VC funding in hand and ready to deploy in 2014, OrbiMed led efforts to expand the biomedical industry's domestic business development base. It won a tender from the Office of the Chief Scientist for the creation of a biomedical accelerator. With license and funding from the government, OrbiMed Israel Partners created a joint venture called FutuRx in collaboration with Johnson & Johnson Innovation–Johnson & Johnson Development Corporation and Takeda Pharmaceutical Company, through its own venture group Takeda Ventures. Its mission is to incubate new companies and lead them toward clinical trials and their first significant round of venture capital financing (Round A).



cCam Biotherapeutics: OrbiMed invested \$3.8 million in the immuno-oncology company, which Merck acquired for \$95 million cash and \$510 million in milestones, or about 50 times its investment.



FutuRx provides shared infrastructure, including equipment, team management, labs, and business services. Its financial structure allows for a total of \$2 million per startup, funded by a grant from the Israel Innovation Authority for 85 percent of the project costs. The incubator is granted an eight-year license for all technologies developed there. All three parties to the venture, OrbiMed, Johnson & Johnson, and Takeda, have equal standing and rights, with no party gaining exclusive rights to IP or veto rights over its use.

Sufficient funding and pharma industry depth provide FutuRx with management experience, ability, expertise, and a broad view of applications and marketing channels, creating access to funding, deal flow, and R&D. Its facilities include 40 labs and accommodate up to 10 seed-stage companies at any given time. As of year-end 2015, FutuRx had “graduated” 11 companies.

OrbiMed’s Anat Lifshitz explained that the accelerator’s mission can pose a challenge for the Israel Innovation Authority’s programs because it takes in ventures at very early stage, sometimes with no venture capital in hand at all. Since FutuRx only has access to direct government support for projects *once a company is formed*, it bears all the risk for exploratory investments. This structure is also a change for its partnering Big Pharma companies, which must shift their emphasis to looking at much earlier state intellectual property and considering how to develop medical solutions, rather than companies. FutuRx also recognizes the opportunity of access, through its partners, to IP solutions worldwide, and isn’t limited to IP solely from Israel’s university-based technology transfer offices. This blending of portfolios enables synergies for optimal development, using and translating IP in unexpected ways.

Einat Zisman is the CEO of FutuRx. She explained how beneficial it would be to have pre-project funding to test lab findings for IP marketability even before the IP even enters the accelerator, and BioMotiv’s Baiju Shah agreed, adding that the experimental results from about 70 percent of IP emerging from labs can’t be replicated—a huge challenge for development. Funding to test and validate lab discoveries is a crucial barrier. FutuRx appears to be providing at least a lower-cost solution with early screening out of non-replicable, unmarketable IP.

### ***Pontifax–Roche partnership, an example of international collaboration***

F. Hoffmann-La Roche AG, the Swiss-based global biomedical development company, is one of the largest biotechs in the world through corporate partnerships, including Genentech in the US, Chugai in Japan, and Pontifax in Israel. Pontifax is a life sciences venture capital firm with \$350 million under management. Since its founding in 2004, it has made investments in 40 companies at a variety of development stages, from early seed through clinical testing. Since 2009 the company has partnered with Roche. Pontifax offers knowledge, experience, and local access; Roche brings a depth in science, testing, and global marketing. The joint venture targets early-stage companies coming from the university labs and startups for a period of two to three years with modest investments of approximately \$1.4 million per project. The joint venture establishes rigorous milestones and funding discipline, and to date has established ten companies in Israel.

### ***Hadasit Bio-Holdings Ltd., introducing technology transfer to retail investors***

Hadasit Bio-Holdings Ltd. (HBL) is a publicly traded company that funds biotech startups that have grown out of Hadasit, the technology transfer office of Hadassah Hospital. It focuses on funding through early stages of development, including initial clinical phases, for its portfolio of companies working in oncology, tissue regeneration, and inflammatory diseases. Closely associated with the Hadassah Hospital, it has access to practitioners, researchers, trial candidates and management, and labs. Its initial business model was meant to allow for early licensing and business development at a low valuation using the liquidity for growing companies through its publicly listed vehicle. But IP flows from the university, and the leverage available through its technology transfer office, proved insufficient to grow enough companies to support sustainable market value. The initial capitalization from the IPO yielded a market capitalization of about \$45.7 million, but the market cap in 2018 had fallen to about \$14.29 million



**Hadasit**  
**Bio-Holdings Ltd.**

Examples of commercial transactions in Hadasit's portfolio:

- Synektik - \$4 million investment on milestones over 3 years are yielding a marketing license for Synektik and royalty payments to Hadasit TTO.
- Cellcure - Investments in Cellcure by TEVA and Hadasit give an option to TEVA for an exclusive selling and marketing license; when TEVA exercises its option, it will pay for the development of the company and pay royalties to Hadasit TTO.

## Global models for success

Lab participants included representatives from the US and UK, who discussed their work with innovative and hybrid biomedical business and development models.

### ***BridgeBio LLC, first with a fund of RBOs***

Neil Kumar is the managing director of BridgeBio Pharma LLC, a clinical-stage biotech development company founded in 2015 and based in California. The company uses proprietary mapping along a number of scientific and commercial dimensions of the 7,000-plus genetic disease landscape to identify opportunities for genetic therapeutic interventions. And it is adopting the portfolio approach proposed by the MIT Laboratory for Financial Engineering. The approach will be incremental, allowing for the scaling up of the portfolio as it focuses on “slivers of R&D” whose returns are likely to be higher than the costs of capital. These will likely include therapeutics and mapping of monogenic diseases (those caused by mutations in just one gene), where the science is clearer, the market is known, and regulators are interested in streamlining approval. The portfolio is structured as leveraged project financing (equity and debt financing). Its business model includes assets housed in discrete subsidiaries.



At the time of the Lab, BridgeBio was planning to create a small portfolio of 10 companies in its genetic diseases program for its RBO model. The goal was to create a series of \$10–\$15 million investments in each portfolio company. All the portfolio companies share management, legal, and research support, as well as a diagnostics unit that explores future market paths. It had raised three rounds of funding, with the first round serving as a pooled investment fund. Later-round investors included the global investment firms KKR and Perceptive Advisors, with seven early-stage therapies in development and two in the clinical testing stages. (As of early 2018, BridgeBio had built a portfolio of 15 drug programs in various phases of development.)

### ***BioMotiv–Harrington Project, a blend of for-profit and non-profit***

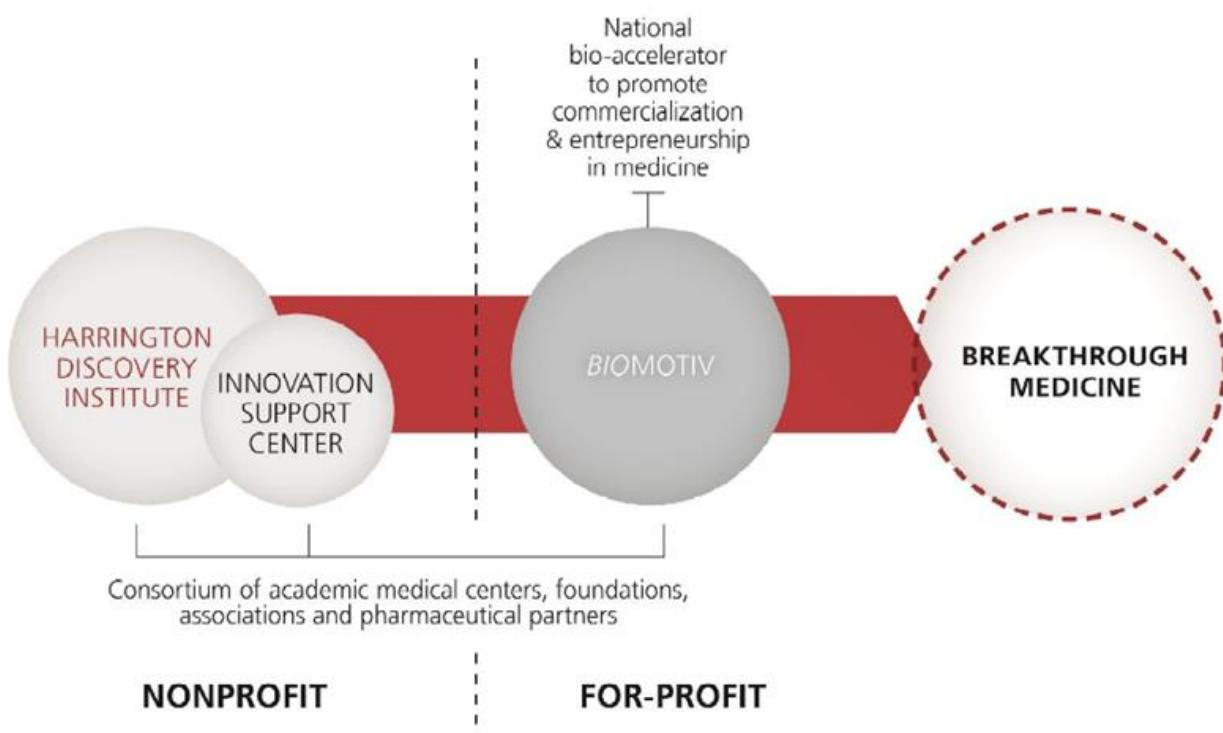
BioMotiv's CEO, Baiju R. Shah, also co-directs the Harrington Project for Discovery & Development at University Hospitals, based in Cleveland, Ohio (University Hospitals serve northeastern Ohio through a network of medical centers). In 2012, the Ron G. Harrington family, owners of a leading US mail-order medical supply company, donated \$250 million to University Hospitals to accelerate drug discovery and bridge the valleys of death during the translational phase of development. The result was the nonprofit Harrington Project: Its two centers, one for discovery and the other for innovation support, fund research and provides expertise through the development phases and technology transfer. The for-profit BioMotiv then advances products toward commercialization. The platform is open to researchers across the US as well, and has partnered with government agencies, disease foundations, institutions, and pharmaceutical companies.

Shah explained that the unique partnership structure bridges the valley of death with more than money. “It is management, experience, capability, and services to support the translation of compounds into solutions for patients, not companies,” he said. With its investments in very early development, the Innovation Support Center increases the investment opportunities. He echoed Einat Zisman of FutuRx, saying that when more testing is performed earlier on lab discoveries, it reduces the risk of proceeding with unverifiable science and shifts the risk of testing and clinical trials, along with higher returns, to investors downstream.

**FIGURE**

**9**

Harrington–BioMotiv value chain



The BioMotiv accelerator works on the reinvestment of royalty returns supported by the early involvement of industry teams, including representatives from Big Pharma. In 2012, the Harrington Project attracted \$150 million from philanthropy and \$100 million from for-profit investors. Today its portfolio has 37 solutions in its non-profit portfolio and 12 on the for-profit side. Shah noted one particular advantage to the portfolio approach: it allows for more effective science and more efficient and practical decision making when a candidate therapy does not work. This is again consistent with the results of work of the MIT Financial Engineering Lab.

## **National Center for Advancing Translational Sciences, modeling for public-private success**



National Center  
for Advancing  
Translational Sciences

Nora Yang, director of portfolio management and strategic operations in the Division of Pre-Clinical Innovation at the National Center for Advancing

Translation Sciences (NCATS). The center was established in 2012 to focus on translational research and has built a portfolio of potential therapies that had been left behind by market-rate investors (i.e. either industry-specific or general investors seeking risk-adjusted returns on their investments) for one reason or another, whether doubts about a compound's efficacy or anticipated profitability. Yang works on initiatives to model public-private research funding partnerships and explained that her team has a free hand to pick solutions left behind by private investors. Their focus on the translational research and testing phase has been particularly challenging, she said, because the portfolios required a diverse mix of operational models for the investment and science teams.

Her team's operating assumption is that an organization's capital structure and investment culture must allow "science to work." The portfolio of orphan cures may be small, she said, but with the right science, milestones, and targeted investment support, returns can be realized. The NIH made a \$24 million annual commitment to implement the program, which focuses on 28 rare diseases in about 15 projects. Since the NIH, as a federal agency, can't bring a drug to the market, her division targets projects near the end of the preclinical stage, and has created a model for best practices. Remarkably, NCATS has had seven exits in five years, with licenses by big pharma and three acquisitions yielding \$1.2 billion<sup>36</sup>

The NCATS model offers some good translational lessons:

1. Focus on medical need, not market. Look where no solutions exist.
2. Add value to projects with the right science, management, and focus.
3. Understand what is needed in the project, and how to find it.
4. Recognize that some projects may not appear to fit the portfolio. But don't screen for "fit."

Instead, see how new possibilities can bring new synergies with existing portfolio projects.

On a systems level, NCATS offers another important lesson: In contrast to company-based, single-goal development efforts, the center takes on more new projects, allows for adjustments and experimentation for existing projects, and encourages a broader view of the market and development system. This approach allows researchers and entrepreneurs to see the value of sharing information, scientific methods, and lessons from successes and failures, said Yang.

**"Our experience shows that we need technology, business, and investment working together at the same time in the same place."**

**Nora Yang**  
**National Institutes of Health**

### ***Oxford Sciences Innovation, a UK technology transfer success story***

In 2015, the University of Oxford and its technology transfer subsidiary, Isis Innovation, launched a new company, Oxford Sciences Innovation (OSI), to develop university research from its math, physical sciences, life sciences, medical, computer science, and engineering departments, and prepare it for commercialization—and “to allow companies to grow to scale without the need to move abroad in pursuit of investment capital needed to fuel their growth.”<sup>37</sup> It typically funds early-stage development and some Series A funding. OSI initially raised a fund of £300 million (US\$474 million) to provide long-term capital for scalable businesses.<sup>38</sup> Three investments totaling £37 million, for OxStem, EvOx, and Vaccitech, were awarded in 2016.<sup>39</sup> As of May 2017, OSI has launched 40 companies, and invested £50 million (US\$67 million). AstraZeneca, GlaxoSmithKline, and Johnson & Johnson, which all sent representatives to the 2015 Financial Innovations Lab, were among large multinationals that have participated as strategic investors in the Oxford Sciences Innovation.



### ***Medical Research Future Fund, a new concept in permanent capital vehicles***

Like OSI, Australia’s Medical Research Future Fund (MRFF) is a substantial, long-term investment fund established in 2015. Starting with an initial capitalization of \$1 billion from the government’s Commonwealth’s Health and Hospital Fund, the fund is projected to reach \$20 billion by 2020–2022; In FY 2016–2017, it had allocated \$65.9 million for health and medical research; for FY 2017-2018, allocations totaled \$121 million, with a fund balance of \$6.9 billion,<sup>40</sup> according to the Australian Association of Medical Research Institutes. The fund’s mission is to create “a perpetual fund capable of generating income over the long term.” It also recognizes that “funding a system for medical research and medical innovation requires a national, coherent, and consistent approach for medical research and medical innovations.”<sup>41</sup> The fund leverages other funds for medical research to spur investment in medical innovations but it isn’t authorized to use its capital to leverage debt.<sup>42</sup>

## Smart Practice Lessons

The following table identifies key lessons reported by Lab participants from these models and their own experiences as investors, researchers, and developers. General comments about smart practices among Lab participants included:

- To encourage the involvement of private investment in the value change, encourage the creation of standardized portfolio license agreement with technology transfer offices, with provisions for milestone payments and benchmarks.
- Attract investment funding that targets resources for business development funding early in the translational phase, especially in the deepest parts of the “valleys of death” when there is a shortage of funding for long-term, business planning.
- Open the door to strategic partnerships with pharma companies to bring technical ability to translational phases earlier (to vet and fast-track compounds).
- Create feedback loops for returns to be reinvested in early-stage projects and even discovery phases.

From the specific examples highlighted in the Lab, table 5 summarizes the features and some of the elements of each smart practice.

**TABLE  
5** Lessons from smart practices

	Program features	• Pros	• Cons
<b>BridgeBio</b>	<ul style="list-style-type: none"><li>• The focus is on orphan disease-specific investment and development vehicles.</li><li>• The mission is to develop companies around IP.</li></ul>	<ul style="list-style-type: none"><li>• BridgeBio works with smaller investment amounts and smaller portfolios</li><li>• The FDA is cooperating and working toward lowering review times, lowering indemnity standards, and lowering commercial risk.</li><li>• Debt fund can leverage more flexible equity.</li></ul>	<ul style="list-style-type: none"><li>• The orphan drug market is highly concentrated and difficult to break into.</li><li>• Debt interest does not include risk premium.</li></ul>
<b>Harrington-Biomotiv</b>	<ul style="list-style-type: none"><li>• The hybrid profit/non-profit deploys philanthropy to bridge valley of death.</li><li>• The project uses a VC model to participate in proven projects.</li></ul>	<ul style="list-style-type: none"><li>• The approach moves VC funds to earlier stages of involvement.</li><li>• There is a more efficient use of capital during early testing and targeting</li></ul>	<ul style="list-style-type: none"><li>• The project focuses on solutions, not business.</li></ul>
<b>NCATS</b>	<ul style="list-style-type: none"><li>• The NIH-based accelerator focuses on unlicensed leftover IP with limited marketability.</li></ul>	<ul style="list-style-type: none"><li>• It has a steady stream of capital.</li><li>• The portfolio approach allows for crossovers and efficiencies.</li></ul>	<ul style="list-style-type: none"><li>• Small scale projects; difficult to grow without large-scale capital</li></ul>

Additional observations among Lab participants about smart practices included:

- To mitigate risk, the project pool must have a relatively large numbers of IP assets into a single portfolio to achieve natural diversification.
- The use of a limited guarantee by government or philanthropic investors at the portfolio level (rather than on the individual projects) is an efficient use of the guarantee and it will offer a considerable benefit in the risk profile and pricing.
- The structure of the debt on the portfolio should conform to standard debt terms and conditions, including a sinking and reserve accounts, and cashflow priority and coverage requirements, to attract market investors.
- Investment structures and terms should be familiar to the investor market, including institutional investors, such as pension funds and insurance companies.
- One of the leverage points in attracting long-term market debt placed with pension and insurance funds is that they can provide a natural hedge in their primary markets (chronic diseases, childhood diseases, longevity, etc.

In summary, the NCATS shows that the right science works. The models and innovative philanthropy partnerships show that we can create structures with enough of the right money to fund development of solutions.

## SOLUTIONS

Based on the range of ideas that Lab members presented and discussed, the group targeted three key solutions: (1) research-backed obligations; (2) philanthropy-public-private partnerships; and (3) co-innovation partnerships.

### Research-Backed Obligations

NYU's Roger Stein presented examples of capital structures for a research-backed obligation bond,<sup>43</sup> a structure that allows for risk segmentation (tranches) in order to appeal to investors with different risk preferences.

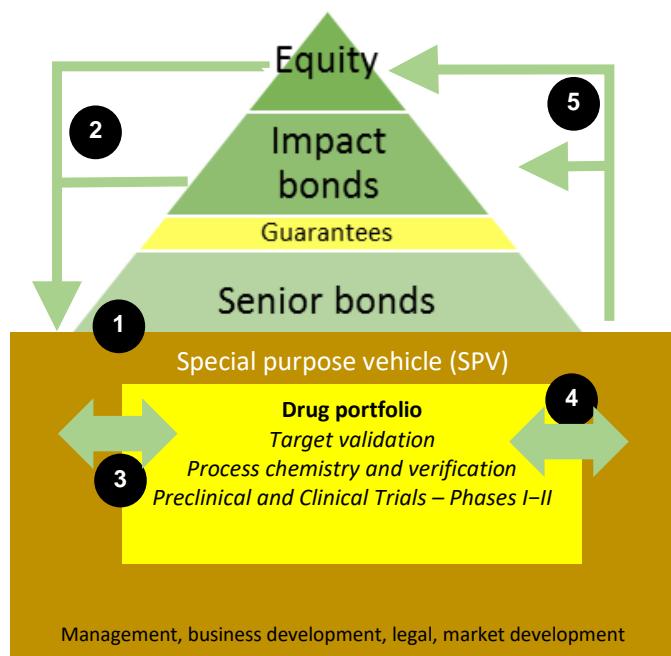
A financing model based on RBOs requires a (1) special purpose vehicle. The SVP would be capitalized by issuing a mix (2) of equity: long-term subordinated bonds that could be sold to hedge-funds, high-yield bond investors, or perhaps at below-market rates to philanthropic investors willing to give up some yield to achieve a mission-related objective; and shorter-term senior bonds, perhaps sold to pension and insurance funds. All investors would have a secured interest limited to the SPV's assets. A limited guarantee could provide a first-loss reserve for the senior bond holders.

The coupon on the bonds would be risk-adjusted, based on its natural credit quality and (optionally) the share of the guarantee pledged. The bonds would amortize after a contractual period (e.g., five years) prior to which regular coupon payments would be made on all outstanding notes. Figure 10 depicts a possible RBO capital structure.

FIGURE

10

Capital structure for a research-backed obligation bond



Sources: Roger Stein, Milken Innovation Center

The SPV would acquire licenses for a portfolio of drug compounds. A *portfolio manager* (typically an individual or organization with extensive experience in both biomedical VC and drug development) would, with the assistance of a *scientific board*, (3) plan and implement testing milestones, outsource trial execution, determine which projects to continue funding, oversee legal documentation and agreements, develop market channels, and negotiate and execute structured exits and investments. Revenues from these activities, including sublicensing, royalty payments, sales, and public offerings, will be returned (4) to the SPV for the repayment of the debt (5) and investment in new projects.

This model relies on several key ingredients,<sup>44</sup> the first of which is a diversified portfolio of biomedical projects. The weighting of the capital structure toward debt allows for a combination of shorter- and longer-term paybacks, with senior debt receiving the earlier cash flows and the junior debt and equity tranches receiving the longer-term cash flows. Pension funds and insurance companies are not unaccustomed to investments with 20- to 30-year maturities. The returns on RBO debt must be competitive with comparable asset classes.

Second, the model must have a large enough pipeline of relevant compounds for that can lead to a scalable portfolio. This requires strong connections with the laboratory sources and world-class strategic partners that can help move the compound through the testing, vetting, and business development processes.

Third, the model must rely on a moderate to large portfolio of compounds and a larger-than-typical pool of investment capital. The financing model is designed around the concept of a diversified and managed portfolio to mitigate risk that can be financed through a lower cost of capital via debt issuance. The advantage of RBOs here is that different portfolios (perhaps based on disease-specific applications or targeted translational development stage) could be structured with different seniority or maturity features and could be issued to accommodate preferences for different types of investors.

The guarantees (either sourced from the government and/or with philanthropic guarantees) aren't actually "part" of the capital structure. They're an alternative source of contingent capital available only when certain legal conditions are achieved. It can't be used for operations and has no share in any upside.

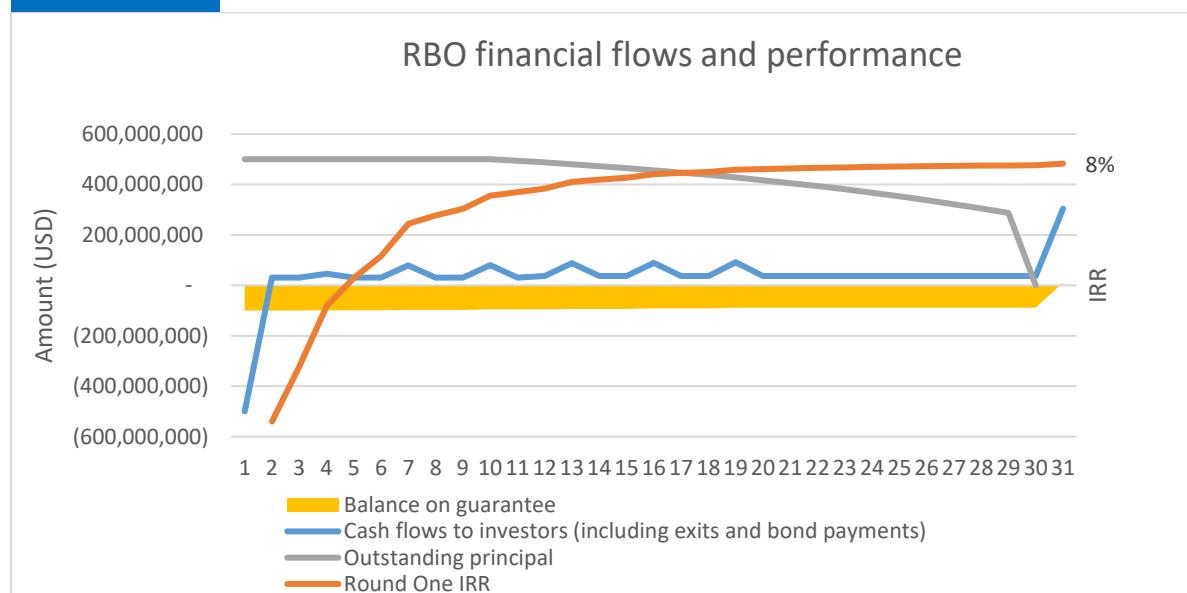
Finally, in most implementations, the RBO approach is used to fund drug development through the early stages associated with the translational period, rather than the final clinical phases and FDA approvals. Thus, compounds are purchased typically preclinical phases and sold in later clinical phases.

Figure 11 offers an investment and cash-flow scenario for a sample RBO portfolio. The assumptions for this scenario are described in Appendix B.

**FIGURE**

**11**

### RBO model financial flows



Source: Milken Innovation Center

The RBO would manage the use of funds for research, testing, and development, and maintain funds for program management and bond payments. Figure 11 illustrates how the funds would flow for debt repayments, and how the net proceeds from exits could be distributed or retained in the fund for new investments. Projects are assumed to begin in the portfolio, although allowances and discounts could be

made to roll existing projects—including other investments (either equity, loans or convertible loans) from the Israel Innovation Authority—into the portfolio.

## Philanthropy-Public-Private Partnership

As Baiju Shah explained, philanthropy can be used in the early, higher-risk translational and preclinical testing stages. Private investments can be leveraged to pick up on more likely prospects among these, lowering the risks and costs of advancing compounds to the market. Still another approach blends philanthropic investment with the limited partnership of a traditional VC, similar to the government's role as a first-loss investor in OrbiMed's first biomedical fund. However, this doesn't accomplish the goal of using philanthropic funds to invest in core research, earlier testing, and involvement of later-stage investors, which is so innovative in the BioMotiv-Harrington model described above among the global best practices.

## Co-Innovation Partnership

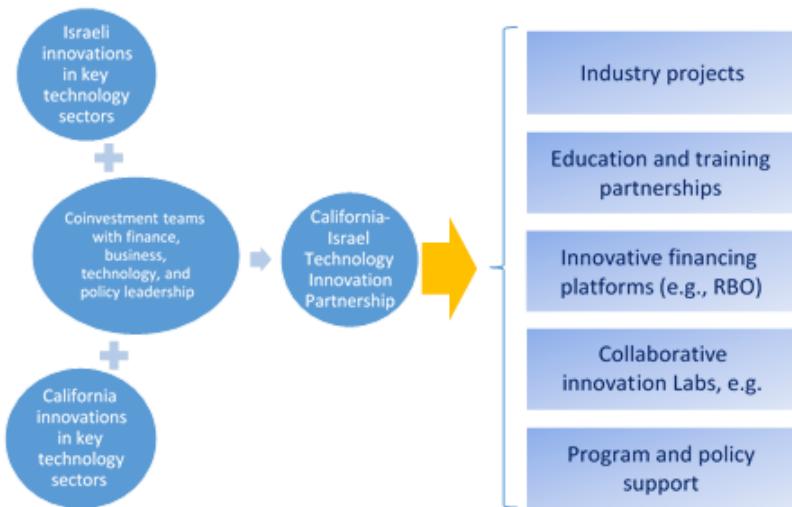
Since the 2014 memorandum of understanding for a California–Israel Global Innovation Partnership, Israel and California have undertaken collaborations in several sectors, including biomedicine and life sciences, water, alternative fuels, energy production, and agritech developments. The combination of their technologies has the capacity to improve the quality of the solutions and grow them to scale faster. This concept is shown in the next figure.

The MOU has led to industry projects, and educational and training partnerships between Hebrew University and the University of California, the development of research initiatives, new approaches to programs regulations, and the potential for a collaboration on innovative financing platform, including the research-backed obligation initiative described above. Indeed, during the Lab, Issy Rozen of the Broad Institute pointed out a number of crossover synergies between pharma and Agritech, and the use of tools and techniques applicable to both.

Israel has compelling strengths in biotech and biomedicine, and would benefit from partnerships with major players, especially California, which has leadership, large presence, and leverage potential in the global biomedical market.<sup>45</sup> One channel for a strategic

FIGURE  
12

Conceptual diagram of co-innovation partnership



partnership would be to continue to develop research collaborations and business partnerships through the California–Israel Global Innovation Partnership, as contemplated in the MOU between the University of California and the Israel Innovation Authority signed in 2017.

New and ongoing partnerships could reinforce and even precipitate efforts in related sectors, such as Agritech. Combining California-and Israeli-generated biomedical compounds in a pool of research-backed bonds could achieve larger-scale diversity and financing.

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## ROADMAP

Using solutions identified from the smart practices and discussions among Lab participants, three solutions—RBOs; philanthropy-public-private partnerships; and co-innovation partnerships—were identified. The financial feasibility for each solution, of course, will be based on the availability of capital for investment, the potential capital structure, and the estimated return on investment to investors. Program feasibility will be determined by the ease of regulatory and policy implementation, the capacity for operations and management, and potential synergies with existing organizations and stakeholders.

The solutions focused on five general areas:

1. Leveraging finance through the domestic and international capital markets with blends of equity and bonds, subordinated tranches, and special pooled investment vehicles;
2. Enhancing the mechanisms in the development value chain to permit all links, including the translational and preclinical stages, to benefit financially through research-backed obligations and other portfolio approaches.
3. Strengthening the market channels for development, partnerships, and sales to bring large pharmaceutical companies into the testing and development cycle earlier;
4. De-risking the investment processes for investors and technology adopters with guarantees and technical efficacy insurance;
5. Improving the capital structure of business and research transactions, including the design of new tools to create and leverage value over the long term.

Again, we note that one of the most important realizations that came from the Lab: the reminder that Israel has four years of goodwill established through the 2014 MOU for California–Israel collaboration and innovation. While the investment opportunity in Israel is substantial, its pipeline of raw IP, solutions, and business formation can achieve scale, diversity, and value only by aligning with partners, and they are in the US and EU. We can build on existing joint ventures, including binational funding initiatives like BIRD, BARD, and the BSF Foundation, and between local companies and universities, such as the University of California research centers. Through partnership, we will find not only opportunities for collaboration, but also scale for new financing structures.

The key features as well as the benefits and obstacles of each of the key solutions are summarized in Table 6 below.

**TABLE  
6**

## Summary of key features of possible solutions

	Program features	Pros	Cons
<b>Research-backed obligation</b> (Generally, this would work as a mega-fund, but it is also appropriate for smaller portfolios whose IP assets show higher probability of success.)	<ul style="list-style-type: none"> <li>The RBO portfolio is characterized by a high level of diversification</li> <li>A combination of equity and debt financing provides access to much larger volumes of patient financing than would equity-only vehicles.</li> <li>The financing model uses a number of securitization techniques.</li> <li>Government and/or philanthropic guarantees are not required in many cases, but often they can make an investment more attractive.</li> </ul>	<ul style="list-style-type: none"> <li>The portfolio greatly reduces risk (standard deviation of return, probability of default) and allows the vehicle to raise debt, even as some of the investment targets very early stages.</li> <li>Equity and debt financing provide long-term capital and access to much larger volumes of financing.</li> <li>The portfolio is designed as a financing model, not a business model, and can be layered on top of a various business structures.</li> </ul>	<ul style="list-style-type: none"> <li>There may be a range of control issues in the management of a broad set of IP operational difficulties; these may require outsourcing</li> <li>There are more restrictions on the portfolio management in order to ensure the credit quality of bonds.</li> <li>The RBO may not be appropriate for conditions (e.g., Alzheimers) for which too few drugs are in development or which show low payoff for success (e.g., repurposing of off-patent drugs).</li> </ul>
<b>Philanthropic, Public, and Private Partnership</b>	<ul style="list-style-type: none"> <li>Create a blended financial facility with philanthropic investors, public investment, and private investment</li> <li>Philanthropic and public investment is structured as subordinated, convertible grants or loans for initial, early stage investments.</li> <li>Private investment is staged on projects as milestones are met</li> </ul>	<ul style="list-style-type: none"> <li>Allows focus on investment efforts and program development on moderate exits without waiting for blockbusters.</li> <li>Increases “shots on goal,” meaning a higher volume of compounds in the pipeline, with increased due diligence by private investors and partners earlier in the process.</li> <li>The use of debt to support eligible tax-exempt uses for partnerships involving Israeli and US-based research programs, including non-profits and universities, may enable the use of tax-exempt financing through a US-based issuer.</li> <li>The structure of these partnerships may open the use of philanthropic investments through philanthropic program-related investments (PRIs), allowing the capital structure to offer a blended investment (junior and senior investments) that will make it more attractive to investors.</li> </ul>	<ul style="list-style-type: none"> <li>Philanthropic focus is on solutions, not projects or businesses</li> <li>Involvement by larger biomedical businesses and investors earlier in the processes may result in earlier sales at lower valuations.</li> </ul>
<b>Co-innovation Partnerships</b>	<ul style="list-style-type: none"> <li>Strategic partnerships with other sources of intellectual properties.</li> <li>Joint research and development projects.</li> <li>Joint investments in translational stages of development.</li> </ul>	<ul style="list-style-type: none"> <li>Larger volume of research sources.</li> <li>Increased participation of broader and deeper research skills.</li> <li>Broader investor base with specific ties to participating partners.</li> <li>Larger capacity than any single partner, making larger projects possible.</li> </ul>	<ul style="list-style-type: none"> <li>Sharing of licenses, royalties, and exit proceeds.</li> <li>Various and possibly conflicting laws and regulations for the host country of each partner.</li> </ul>

Based on these solutions as a framework for best practices, the roadmap forward includes the following steps:

1. Generate enough inventory for IP pipeline and identify initial targets through historical data on university and major labs/incubators in Israel.
  2. Select projects eligible for pooling and build financial models for a value chain based on scope of eligible projects, including their type, size, and diversification potential.
  3. Assess the funding status for these projects (stage, patent status, etc.).
  4. Identify what support and financial facilities are needed to sell debt and equity (e.g., guarantees, tax benefits, placements, etc.) and investment terms and conditions for all stakeholders.
  5. Identify choices for scientific and investment management, ownership, organization, partnerships, and business model of individual portfolio assets.
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## CONCLUSION

Life science technologies save and extend lives, but at a huge financial cost and very high risk for the companies behind them. New and innovative research is continually fueling these technologies, making it possible to meet the needs facing specific populations and ever more specific diseases. But innovation in discovery alone isn't enough to bring these technologies to the market. Financial innovation is also needed.

Based on our work in the Lab and collaboration with Israeli and US experts, we know that Israel has a solid base of science and research on which to build out its life sciences sector, and that it can do more than just provide intellectual property for others to commercialize in the world market. Establishing collaborations and partnerships with other centers of excellence (in California, for example), Israel can build new platforms for drawing investment capital with attractive terms and conditions.

The use of blended financing, involving public private partnerships, philanthropic investors, and innovative securitization will sustain returns to fund future R&D that will itself renew the cycle of financing faster cures.

## APPENDICES

### Appendix A: Participants

<b>Shmuel Abrahamson</b> National Economic Council	<b>Gary Jacobs</b> Jacobs Investment Company LLC	<b>Michal Silverberg</b> Takeda
<b>Shmuel Avraham</b> Arison Group	<b>Neil Kumar</b> BridgeBio Pharma	<b>Benjamin Soffer</b> Technion
<b>Yael Biran</b> Mintz Levin Israel Business	<b>Bruce Lehmann</b> UC San Diego	<b>Roger M. Stein</b> MIT Laboratory for Financial Engineering
<b>Philippe Blumenthal</b> <b>No affiliation?</b>	<b>Netta Linzen</b> Milken Innovation Center Fellow	<b>Nurit Tweezer-Zaks</b> Sanofi Global Research and Development
<b>Yuval Cabilly</b> Israel Biotech Fund	<b>Tamara Mansfeld</b> Pfizer	<b>Glenn Yago</b> Milken Innovation Center
<b>Omri Carmon</b> Milken Innovation Center Fellow	<b>Shai Melcer</b> BioJerusalem	<b>Nora Yang</b> National Institutes of Health
<b>Ran Charag</b> Milken Innovation Center Fellow	<b>Daniel Melzer</b> Milken Innovation Center Fellow	<b>Steven Zecher</b> Milken Innovation Center
<b>Erez Chimonovits</b> OrbiMed Advisors LLC	<b>Yamit Naftali</b> Jerusalem Institute for Israel Studies	<b>Einat Zisman</b> FutuRx
<b>Ora Dar</b> Chief Scientist Office	<b>Anat Naschitz</b> OrbiMed Advisors LLC	
<b>Yulia Eitan</b> National Economic Council	<b>Sraya Orgad</b> Tel Aviv Stock Exchange	
<b>Anya Eldan</b> Ministry of Economy	<b>Micha Perlman</b> Ministry of Finance	
<b>Ifat Falkon-Shnider</b> Israel Securities Authority	<b>Steven Popper</b> Rand Institute	
<b>Roni Frumkes</b> EMC	<b>Eliav Pollack</b> Inbal Insurance Company	
<b>Uri Gabai</b> Chief Scientist Office	<b>Tal Raviv</b> Ministry of Finance	
<b>Viral Gandhi-Stanford</b> Biodesign Program	<b>Tamar Raz</b> Hadasit Bio-Holdings Ltd.	
<b>Itzik Goldwasser</b> Yissum	<b>Issi Rozen</b> Broad Institute	
<b>Gil Granot-Meir</b> Yeda (Weizmann Institute)	<b>Bruno Sfez</b> Economic development consultant	
<b>Avi Hasson</b> Chief Scientist	<b>Baiju Shah</b> BioMotiv, Harrington Project	

## Appendix B: Financial Assumptions for RBO Scenario

Using an RBO model for orphan diseases discussed at the Lab, and in research by Lab participants and others, the Milken Innovation Center developed a scenario for a model portfolio. The model is based on probabilities of survival through each development stage, with an expected valuation and periodic exits at each stage that will yield additional revenues for the fund.

Assumptions	Results
<ol style="list-style-type: none"><li>1. Amount: \$500 million</li><li>2. Pay-in ramp: All debt funding is upfront</li><li>3. Capital structure: 100% debt (for illustrative purposes only)</li><li>4. Terms: 30-year debt at fixed 6% annual interest; 10-year interest-only payments; balloon due at term</li><li>5. Debt coverage limitations: net proceeds each year 120% of required debt payment before new investments</li><li>6. Guarantee: 20% first loss on debt payment; recovered from cash flows as available; 4% preferred share on exit proceeds; guarantee maintained at level of initial closing</li><li>7. Target: Orphan diseases, with a total cost to market of \$100 million per drug through clinical stage 3.</li><li>8. Duration of activity in the fund: 20 years with a 1% per year escalation on investment and costs</li><li>9. Investments in the portfolio will start during preclinical phases and continue through clinical stage 3.</li><li>10. Distributions: 10% of net cash flows upon exits</li><li>11. Royalties and licenses: Yes, but discounted for model</li><li>12. Retained earnings will be reinvested in follow-on and new projects</li><li>13. Management expenses: 0.5% of debt principal</li><li>14. Probability of exit: 2–50%, depending on the stage; 1.8% overall from initial investments.</li><li>15. Valuation multiple on investment at exit: 0.4–2.5%, depending on the phase</li><li>16. Valuation of shares: non-diluted</li></ol>	<ol style="list-style-type: none"><li>1. Preclinical: 60 projects</li><li>2. Clinical 1: 32 projects</li><li>3. Clinical 2: 13 projects</li><li>4. Clinical 3: 11 projects, initial entry into stage only</li><li>5. Cumulative investments: \$1.521 billion (from original debt and retained proceeds from exits)</li><li>6. Estimated nominal valuations of surviving projects at exits: \$3.293 billion</li><li>7. Projected investors IRR: 8 percent</li><li>8. Guarantee net surplus/(loss): \$10.9 million</li></ol>

## ENDNOTES

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- <sup>1</sup> Netta Linzen. "Israel Life Sciences: Funding Gaps and Growth." Milken Fellows Program (2015) [in Hebrew], <https://milkeninnovationcenter.org/publications/israel-life-sciences-funding-gaps-and-growth/> and Tova Wasser, "The Funding Gaps in the Israeli Bio-Pharma Industry and Building a Government Co-investment Fund." Milken Fellows Program (2016) [in Hebrew].
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6. Netta Linzen. "Israel Life Sciences: Funding Gaps and Growth." Milken Fellows Program (2015) [in Hebrew], <https://milkeninnovationcenter.org/publications/israel-life-sciences-funding-gaps-and-growth/>.
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10. World Economic Forum, "Global Competitive Index, 2017–2018," <http://reports.weforum.org/global-competitiveness-index-2017-2018/countryeconomy-profiles/#economy=ISR>.
11. Ruti Levy, "Israeli Scientific Output Falling Behind in World Rankings," *Haaretz* (December 28, 2016), [www.haaretz.com/israel-news/israeli-scientific-output-falling-behind-in-world-rankings-1.5479104](http://www.haaretz.com/israel-news/israeli-scientific-output-falling-behind-in-world-rankings-1.5479104)
12. Aaron Ciechanover and Avram Hershko, both of Technion, Israel Institute of Technology, received the Nobel Prize in Chemistry in 2004 for their discovery of ubiquitin-mediated protein degradation, Ada Yonath of the Weizmann Institute of Science was awarded the Nobel in Chemistry in 2009 for studies of the structure and function of the ribosome.
13. "The Life Sciences Industry in Israel," Invest in Israel, Ministry of Economy and Industry, [www.investinisrael.gov.il/ExploreIsrael/sectors/Documents/LIFE%20SCIENCES.pdf](http://www.investinisrael.gov.il/ExploreIsrael/sectors/Documents/LIFE%20SCIENCES.pdf).
- <sup>14</sup> As of July 30, 2018, the total market capitalization for the Tel Aviv 125 was NIS 649.079 billion. On the same date, TEVA's market capitalization was NIS 86.32 billion.
15. "The State of the Israel Life Sciences Industry: IATI 2017 Summary Report," Israel Advanced Technology Industries (2017) [www.iati.co.il/files/files/2017%20Life%20Sciences%20Industry%20rep1.pdf](http://www.iati.co.il/files/files/2017%20Life%20Sciences%20Industry%20rep1.pdf).
- <sup>16</sup> "Israeli inventions underpin 20% of global biotech revenues," Gali Winreb, Globes, June 6, 2013. See: [https://en.globes.co.il/en/article-1000850515](http://en.globes.co.il/en/article-1000850515).
- <sup>17</sup> Biopharma differs from pharma in that researchers hunt for therapeutics from biological sources—genes, proteins, tissues, blood, cells—rather than synthetic compounds; today, however, almost all pharma also work in biopharma.

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18. Presented at the Financial Innovations Lab, based on 2014 analysis by OrbiMed.
19. According to the Centers for Disease Control, the prevalence of rheumatoid arthritis is 0.4–1.3 percent of the population globally. In the US, estimates are 1.3 million (0.6 percent) adults, with an estimated \$81 billion in direct medical expenditures. See: [www.cdc.gov/arthritis/basics/rheumatoid.htm](http://www.cdc.gov/arthritis/basics/rheumatoid.htm). The estimated prevalence of MS is two cases per 100,000 among men and 3.6 cases per 100,000 among women. The economic cost from MS is estimated \$28 million annually in the US. See V. Y. Ma, L. Chan, L., and K. J. Carruthers, “The Incidence, Prevalence, Costs and Impact on Disability of Common Conditions Requiring Rehabilitation in the US.” National Institutes of Health (2015). Also see [www.ncbi.nlm.nih.gov/pmc/articles/ PMC4180670/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4180670/). In the US, cancer costs are projected to be \$157 billion annually by 2020. See Angela B. Mariotto, K. Robin Yabroff, Yongwu Shao, Eric J. Feuer, and Martin L. Brown, “Projections of the Cost of Cancer Care in the U.S.: 2010–2010,” *Journal of the National Cancer Institute*, vol. 103 no. 2 (January 2011) 117–128, <https://costprojections.cancer.gov/expenditures.html>.
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24. Gali Weinred, “Israeli Biomed Cos. Shun TASE for Nasdaq,” Globes (January 4, 2015), [www.globes.co.il/en/article-israeli-biomed-cos-shun-tase-for-nasdaq-1000997961](http://www.globes.co.il/en/article-israeli-biomed-cos-shun-tase-for-nasdaq-1000997961).
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26. The Marker (January 26, 2015).
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