MILKEN INSTITUTE

NEW MODELS FOR FINANCING TRANSLATIONAL MEDICAL RESEARCH IN SINGAPORE:

UPDATE

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ABOUT THE MILKEN INSTITUTE

The Milken Institute is a nonprofit, nonpartisan think tank focused on accelerating measurable progress on the path to a meaningful life. With a focus on financial, physical, mental, and environmental health, we bring together the best ideas and innovative resourcing to develop blueprints for tackling some of our most critical global issues through the lens of what's pressing now and what's coming next.

ABOUT MI INTERNATIONAL

MI International extends the reach and impact of Milken Institute programs, events, and research by focusing on the role that health, finance, and philanthropy play in addressing social and economic issues around the world. We leverage the Institute's global network to tackle regional challenges and integrate regional perspectives into developing solutions to persistent global challenges.

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1. INTRODUCTION

Since 2017, the Milken Institute (the Institute) has engaged with stakeholders worldwide (henceforth "participants") on new models for financing translational biomedical research in Singapore. The Institute convened Financial Innovations Labs® in 2018 and 2019, where participants discussed possible funders and funding models, and directly addressed each other's concerns. Anonymized findings were synthesized in a report, *New Models for Financing Translational Medical Research in Singapore*, published in 2020, proposing three Series A–focused funds to tackle the lack of know-how and funding.

The initial plan for 2020 onwards was for further stakeholder engagement to fine-tune recommendations, derive concrete figures for new financing models, and present a detailed policy paper with broad stakeholder support. However, spurred in part by the COVID-19 pandemic, the Singapore government has since rolled out multiple funding measures and incentives for biomedical research and development (R&D), the effects of which have not fully materialized. In consultation with stakeholders, the Institute ultimately decided that it was best to let newer measures first play out, pivoting its efforts from the specifics of what might be done toward the cultivation of people who may be well-positioned to act.

Since 2020, the Institute has convened six off-the-record private roundtables on biotech financing. Participants included representatives from local biotechs and leading investors and philanthropists from key biotech markets around the world. International participants were curated from the Institute's networks, thoughtfully built over three decades of high-level convenings. More broadly, the Institute hopes to support the development of Singapore's biotech ecosystem on multiple fronts, whether through research on financing mechanisms, socialization of investors with innovative financing, or identification of unique opportunities for international exchanges.

This report is a continuation of the publication in 2020, collating the insights from Institute convenings and research over the years. The previous case studies and suggestions remain relevant and, for brevity, will not be repeated.

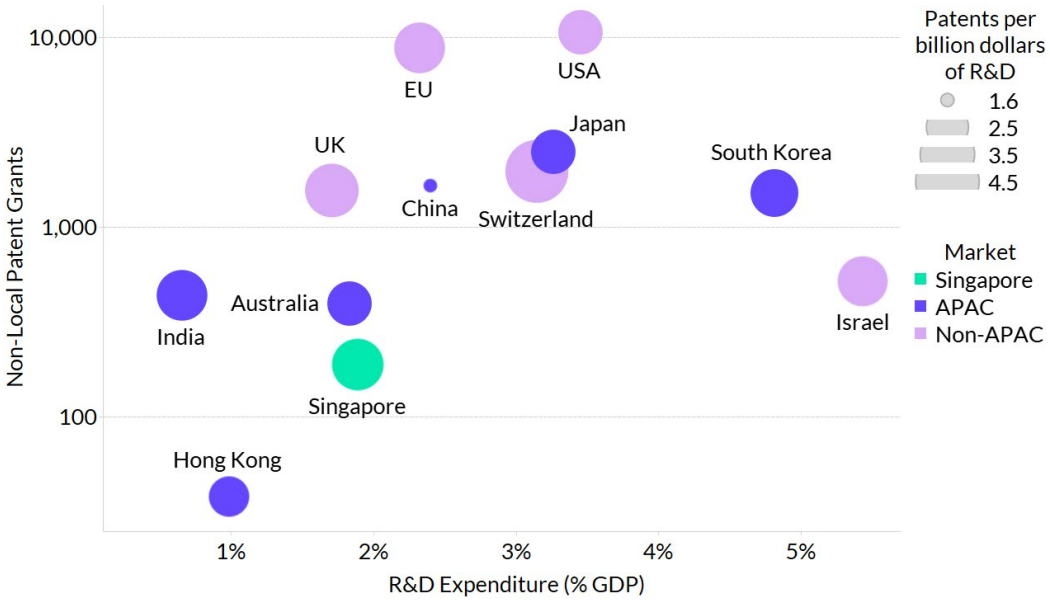
1. Section 2 briefly details initiatives in Singapore since 2020 and examines the performance of other leading biotech markets around the world. Singapore has improved substantially in many biotech areas but is only pulling ahead in a few.
2. Section 3 outlines reasons for continued public and private investments in biotech for financial innovation. It proposes first-loss equity funding and venture philanthropy as reserve financing mechanisms for future consideration.
3. Section 4 details case studies and simulation outcomes of first-loss funding. First-loss funding can de-risk and crowd-in private capital, but commercialization talent must be attracted to improve returns, and investors should collaborate with alternative capital sources.
4. Section 5 details case studies in venture philanthropy. Apart from funding, philanthropy crucially provides leadership to gather and amplify resources across society and should drive mindset changes among funding recipients.

2. BIOTECH LANDSCAPES IN SINGAPORE AND WORLDWIDE

Singapore set out to develop its biotech industry in the 1980s, having seen rising successes in the application of engineering principles to the biological sciences. Biotech was designated as the fourth pillar of manufacturing, and for the past few years, of every 2,000 people in the city-state, one person has a biomedical PhD.[1] However, predictions that the 21st century would be the century of biology were not lost on other larger, more developed markets. Consequently, while Singapore has improved substantially in many biotech areas, it is only pulling ahead in a few.

For example, while expenditures have been rising, the city-state typically spends less on R&D than other leading biotech markets (Figure 1). In fact, Singapore's R&D spending as a share of GDP has hovered around 2.0 percent over the past two decades, in contrast to other leading biotech markets worldwide. China, for instance, raised R&D spending from 1.7 percent in 2010 to 2.4 percent in 2020, and the UK plans to achieve that increase by 2027.[2]

Figure 1: R&D Spending in Singapore and Global Markets



Note: Patents are presented on an exponential scale for visual clarity. The most recent data available are shown for each market, ranging from 2018 to 2020. Patent data are for "Biotechnology" and "Pharmaceuticals" only, while R&D data are economy wide. As a better proxy for patent quality, only nonlocal patent grants are counted.

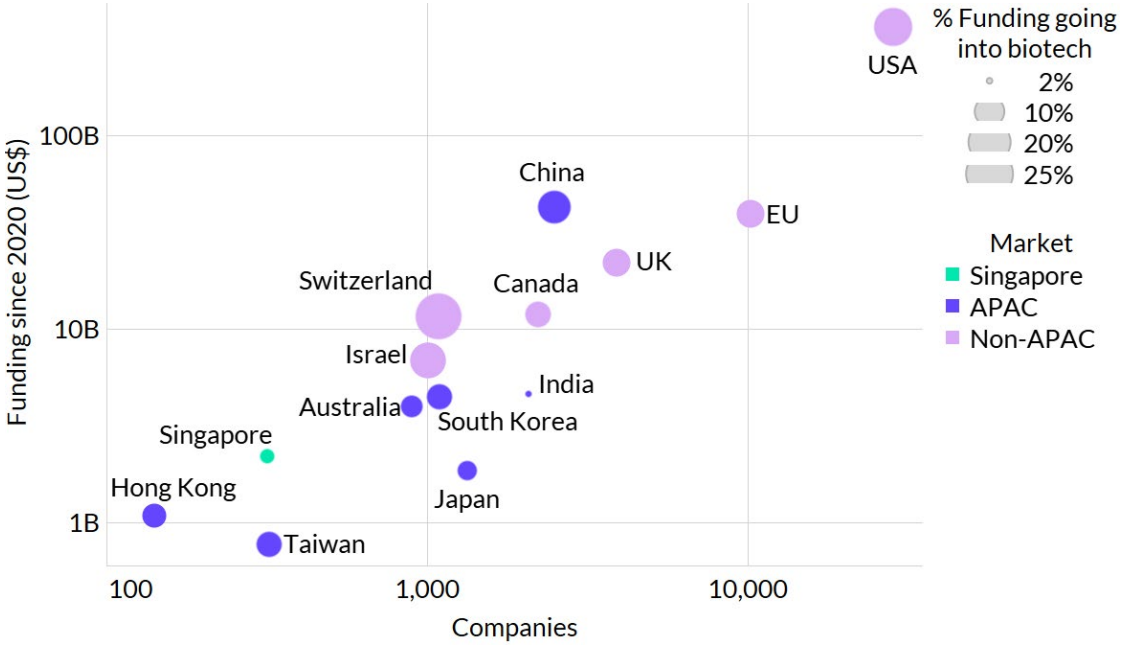
Sources: Milken Institute analysis, World Intellectual Property Organization IP Statistics Data Center (2023) and World Bank database (2023)

In terms of research outputs, Singapore's patent grants in biotechnology and pharmaceuticals have increased over the years, in tandem with efforts to steer biomedical R&D toward commercialization. Although Singapore's stock of patent grants remains small and has plateaued since 2018, it is encouraging that in terms of

patents per dollar of R&D, the city-state edges out nearly every leading biotech market worldwide—one of the many manifestations of Singapore's efficiency and frugality.

Participants have consistently confirmed the high quality of basic research in Singapore, which provides a strong foundation for the commercialization of biomedical R&D. Strong basic research pipelines and robust protections for intellectual property enable Singapore to attract outsized amounts of funding, despite its small stock of biotechs (Figure 2). However, only 3 percent of the city-state's venture funding are invested in biotech, leaving much room for growth. The government understands this situation and, since 2020, has fired on multiple cylinders to develop its biomedical ecosystem further, be it through public grants, the attraction of new investors, or wide-ranging changes to its R&D strategy.

Figure 2: Ventures and Funding



Note: Funding and the number of companies are presented on an exponential scale for visual clarity.

Source: Milken Institute analysis, Crunchbase (2023)

Public Funding

The Singapore government has created or amplified multiple funding schemes in recent years. The Startup SG Equity (SSG-E) scheme, which co-invests with third-party investors, realized a doubling of the co-investment cap to S$8 million per startup, including up to S$3.3 million in the first institutional round.[3] SSG-E also features a fund-of-funds approach, seeding venture builders that have existing relationships with pharmas and a solid understanding of pharma's gaps, to direct local biotechs toward commercial opportunities better.[4] Concurrently, the Singapore Therapeutics Development Review funds early-stage projects up to S$830,000,[5] while the National

Health Innovation Centre offers grants of up to S$1 million for the adoption and scaling of certain health tech projects.[6]

However, these initiatives are new, and their effects will not be fully realized for several years. In addition, because many of these initiatives have specific eligibility criteria, how widely these benefits will be realized is not yet clear. Statistics such as the B-index can measure the results but are unavailable for Singapore.[7]

Nonetheless, where the B-index is measured, it presents a useful picture of R&D strategies (Figure 3). China has strengthened incentives for large companies while weakening incentives for small and medium-sized enterprises (SMEs). Australia, South Korea, and the UK have done the opposite. China, South Korea, and Japan offer stronger incentives for profitable companies, while the UK offers the same incentives regardless of profitability. Most of these changes have occurred in the past decade, indicating a regular focus on and fine-tuning of R&D incentives.

Figure 3: Tax Incentives for R&D, 2022

Note: The B-index estimates the pretax profit a typical company (not specific to biotech) needs to break even on each additional dollar of R&D. (1 – B-Index) is thus the implied subsidy rate, that is, the tax incentive for R&D. Larger incentives have larger circles.

Source: Reference 7, OECD (2023)

Private Investors

In addition to early-stage funding, smart capital to plug operational gaps was identified as a critical need in the Institute's previous report. Since the publication of that report, at least five private investors have entered the Singapore biotech scene. Xora Innovation was established as an early-stage investment platform of Temasek in 2019, investing in at least three biotechs.[8] Novo Holdings entered Singapore in January 2021, funding five domestic and regional biotechs in the same year.[9] ClavystBio was launched

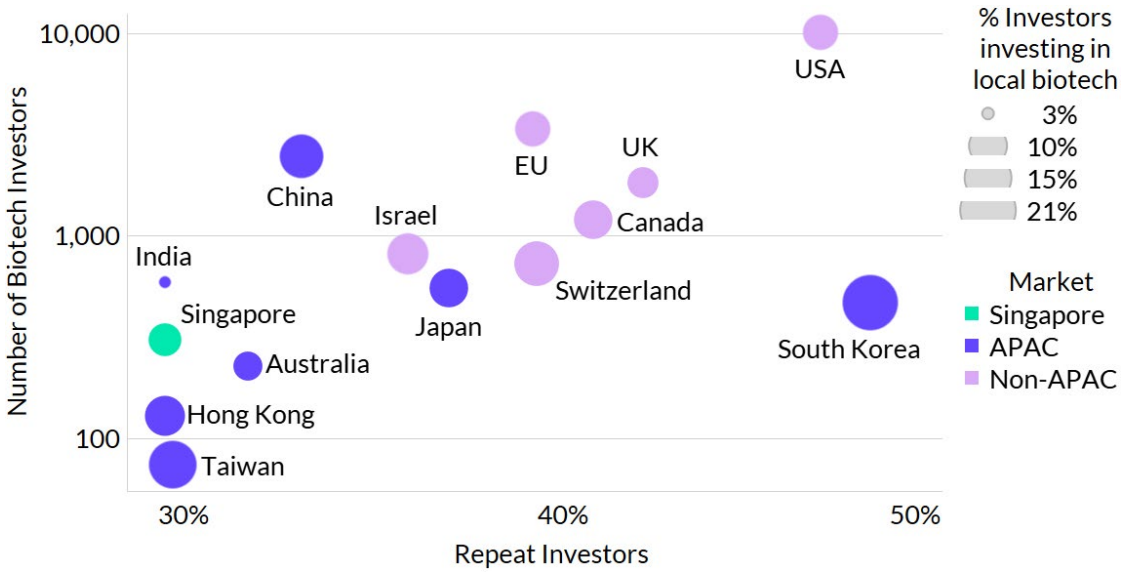
in September 2022 by Temasek subsidiary CLA Real Estate Holdings, investing in eight biotechs—in the same number of months.[10]

The government continues to double down on incentivizing private investments. In February 2023, the government raised the maximum tax deduction for R&D to an impressive 400 percent.[11] In recent years, 700 new family offices have entered Singapore.[12] In July 2023, the government unveiled additional incentives for single-family offices to deploy their capital into charity, blended finance, and non-listed companies.[13] Through these incentives, the government has broadened the scope of eligible investments to qualify for tax exemptions. It now recognizes every S$1 of concessional capital and grants to blended finance structures as S$2 when assessing eligibility for tax exemptions.

However, the rest of the world has also been maintaining their pace of biotech development. According to Institute analysis of Crunchbase data, the number of investors in leading biotech markets has more than tripled from 2010 to 2022, while the number of lead investors has nearly quadrupled.

Yet, in Singapore, only 8 percent of investors have invested in biotech (Figure 4). Among this 8 percent, only three in ten have invested more than once in local biotechs. Two in five are one-off investors, while the rest invest elsewhere. The latter statistic is not surprising because investors typically source for later-stage prospects in larger markets. The former statistic, however, is concerning given the deep expertise required in biotech. As previously found by the Institute, local investor familiarity with biotech has room to grow.

Figure 4: Few Repeat Investors in Local Biotechs



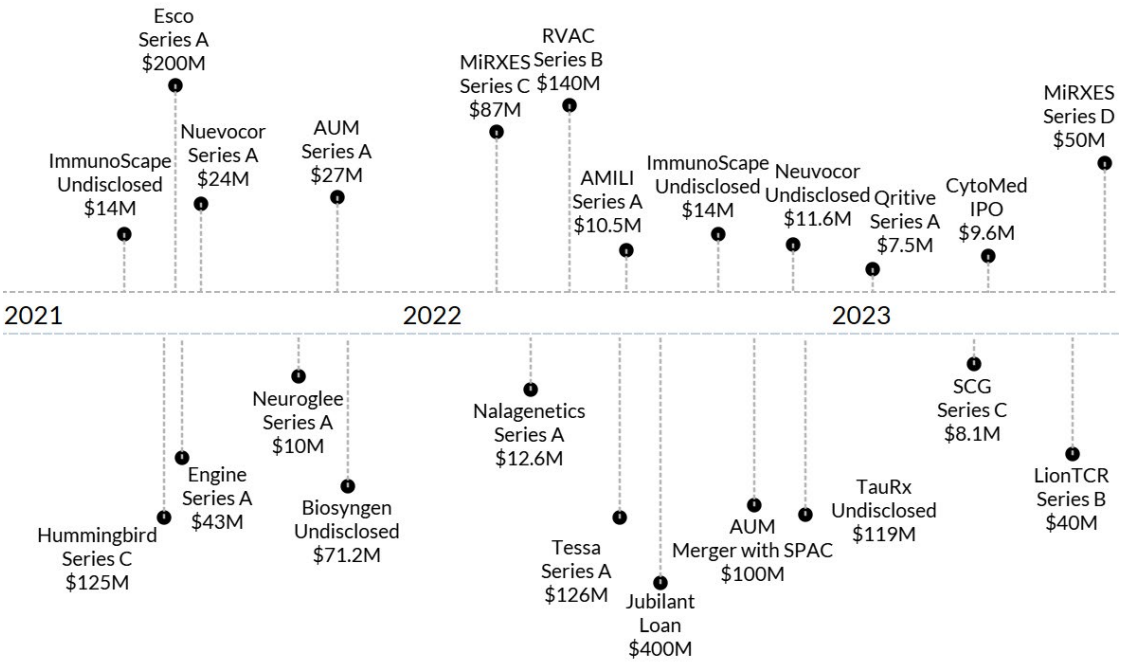
Note: Repeat investors have invested in more than one funding round in the same market. They need not have funded more than one venture. The number of investors is presented on an exponential scale for visual clarity.

Source: Milken Institute analysis of Crunchbase (2023)

Funding Rounds

With the increase in local investors and bullish biotech sentiment during COVID-19, biotech funding rounds in Singapore have surged since 2021 (Figure 5).[14] Importantly, the benefits of these funding rounds extend beyond the individual biotech's development. Each success story demonstrates the viability of biotech as a career and further inspires the next generation of young scientists to embark on their own entrepreneurial journeys. During the past decade, the number of biomedical startups and SMEs in Singapore has grown sixfold,[15] and repeated successes may spur even more entrepreneurial pursuits.

Figure 5: Biotech Funding in Singapore (US$)

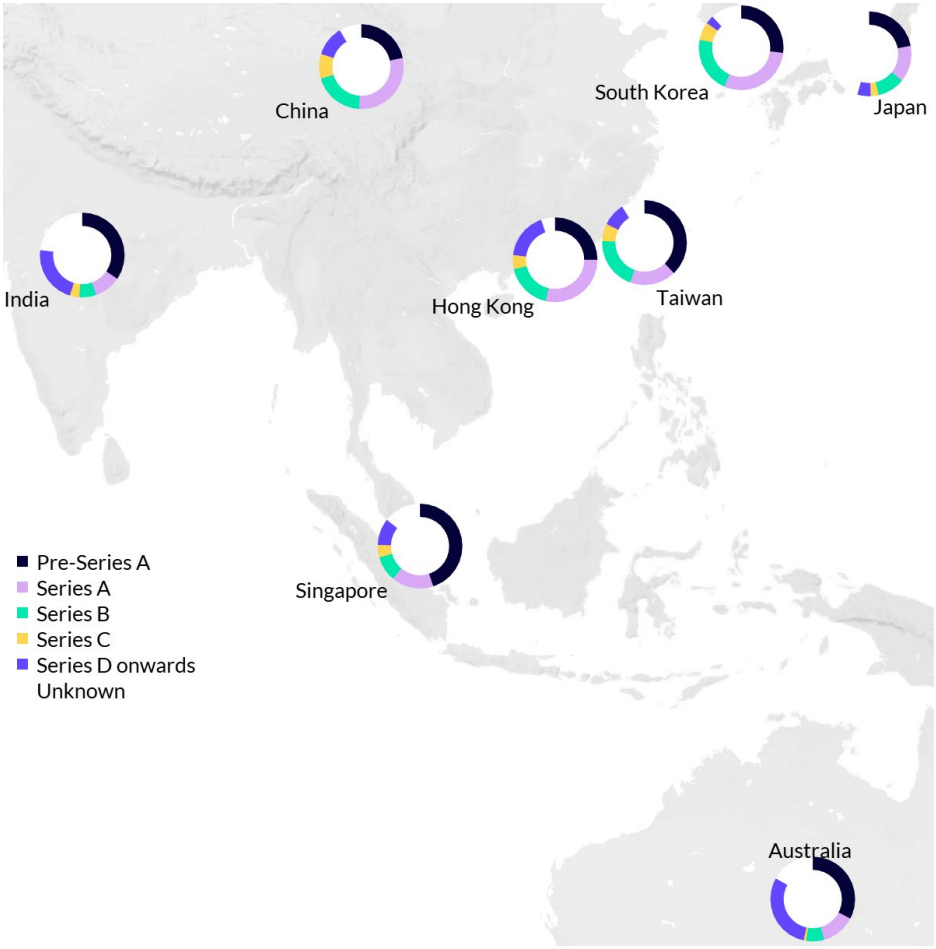


Sources: Reference 14, multiple sources

However, many of Singapore's biotechs are still in their early stages. Nearly half of funded ventures are at the pre-Series A stage, the highest proportion across leading markets in the Asia-Pacific (APAC) (Figure 6). Indeed, even before the COVID pandemic, participants had pinpointed Series A funding as a key bottleneck among local biotechs, in part because of Singapore's geographic distance from larger, established hubs. Therefore, whether the aim is to develop a steady pipeline of molecules getting into clinics, create positive patient outcomes, or justify a significant presence of venture capital, Singapore's biotech market has much room to mature.[16]

But participants also noted that the nascency of Singapore's biotechs can, at times, be advantageous. One participant recalled that first-movers in the US had spent exorbitant amounts to figure out the market for its technology. Conversely, younger biotechs in Singapore observed and optimized the development pathways paved by the trailblazers, thereby generating evidence and proving efficacy much more cost-efficiently.

Figure 6: Venture Maturity Worldwide



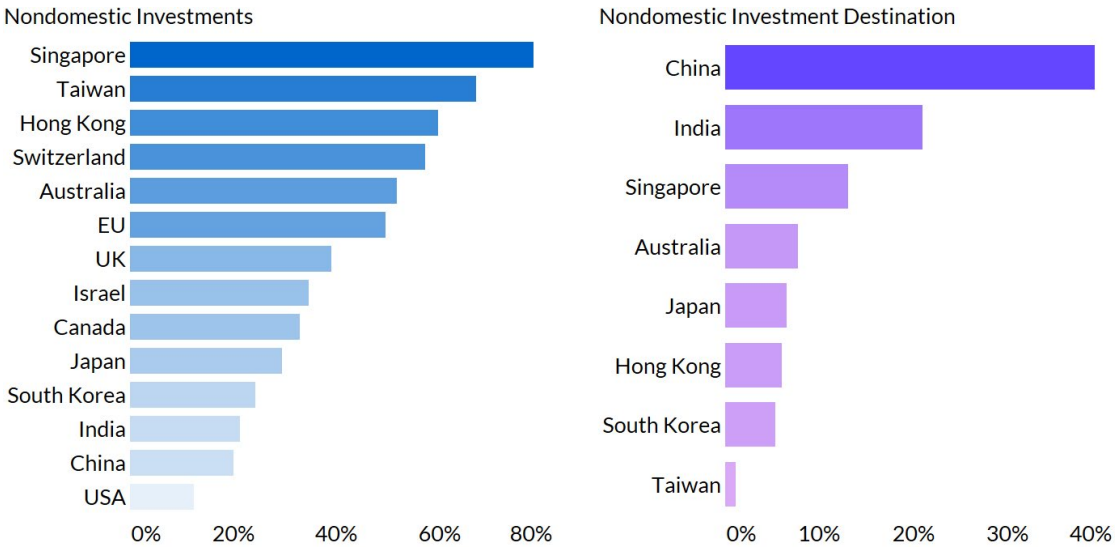
Source: Milken Institute analysis of Crunchbase (2023)

Nondomestic Funding Flows

It is useful to look at nondomestic investments on top of raw investment figures. Biotech markets that receive large amounts of nondomestic funding are winning the confidence of foreign investors, while markets with large funding outflows serve as financing hubs that attract scientific and entrepreneurial talent.

In terms of funding amounts, the US is by far the largest source and recipient of nondomestic biotech funding worldwide. This fact is unsurprising given the size of the US biotech market and investor population. However, proportions-wise, Singapore-based investors are the most outward-looking among leading biotech markets, in line with other industries previously studied by the Institute.[17] Nearly four in five Singapore-based investors seek overseas ventures (Figure 7A), compared to those in large markets such as India, China, and the US, who mostly look inwards for deals. This outward orientation reflects the city-state's efforts to attract international investors who focus on the broader region, particularly given the growing focus on diseases prevalent in Asia.

Figure 7: Singapore-Based Investors Are Mostly Outward-Looking



Note: Fig. 7A shows the proportion of investments in each market that were targeted at a nondomestic biotech worldwide. Fig. 7B shows, among the eight key biotech markets in APAC, the proportion of nondomestic biotech investments received from the rest of the world.

Source: Milken Institute analysis, Crunchbase (2023)

It is also not surprising that Singapore-based biotechs receive a relatively large share of nondomestic venture funding (Figure 7B). Maturing biotechs typically seek resources and markets overseas to continue their growth because later-stage clinical trials are too large and expensive to be viable domestically. Concurrently, the high quality of basic science, strong protections for intellectual property, and Singapore's status as a financial hub help ease foreign investors' entry.

However, there is always room to grow. For instance, among the 40 leading biotech markets analyzed, Singapore ranks 14th in funding from US-based investors. Ideally, this scenario could be better, given that many local biotechs target the US market.

Research and Manufacturing

The outcomes of all this funding were most clearly observed during the COVID-19 pandemic. Singapore was the third country, outside of China, to culture SARS-CoV-2 successfully.[18] Multiple diagnostic tests for COVID-19 were developed locally: Fortitude has been used in more than 45 countries;[19] cPass received emergency authorization from the US Food and Drug Administration (FDA);[20] and PASPORT can test for COVID-19 using only saliva.[21] A vaccine candidate developed by Duke-NUS Medical School is currently undergoing Phase II trials with US-based Arcturus Therapeutics.[22]

Industry has likewise placed its bets on Singapore. In a short span of two years, Thermo Fisher Scientific, Sanofi, BioNTech, Hilleman Laboratories, and MSD have committed to manufacturing vaccines in Singapore.[23] Takeda began a US$14 million manufacturing

expansion in 2021;[24] GSK opened a S$44 million manufacturing and testing facility in 2022 for next-generation cancer treatments;[25] Avantor inaugurated its expanded Singapore Manufacturing and Distribution Hub in 2023;[26] while WuXi AppTec and WuXi Biologics have each planned S$2 billion investments in the city-state over the next 10 years.[27] These moves complement the government's recently established Advanced Cell Therapy and Research Institute,[28] which supports companies from clinical process manufacturing up to mid-scale manufacturing to generate clinical and safety data and understand the applicability of their assets without needing to build out their own labs.

The entry of manufacturing and contract research capabilities enables local biotechs to outsource their knowledge gaps in manufacturing and trials (which are many), keep teams lean and focused, and demonstrate greater fiscal responsibility to prospective investors—a crucial attribute amid the market downturn.[29] In addition, the diversification and strengthening of supply chains de-risks the entry of companies and talent into Singapore.

In fact, supply chain resilience is an area in which Singapore has turned weaknesses into strengths. Because the city-state has such a small domestic market, the need for Singapore to impose export controls to first fulfill domestic needs is unlikely. Singapore's existential reliance on trade further dissuades export controls on its part, given its susceptibility to retaliation. In short, the fundamentals of Singapore's demographics and economy ensure its reliability in the global supply chain, which contrasts starkly with the multitude of export bans witnessed throughout APAC and the world during COVID-19.

Singapore's recent strides do not solely accrue to COVID-19. Local biotech Lucence is the first Asian-headquartered company to secure Medicare coverage for its liquid biopsy test to detect lung cancer.[30] Pacritinib, which received FDA accelerated approval in 2022,[31] had been developed by local biotech S*BIO up to Phase II. In addition, EBC-129, an antibody-drug conjugate therapy for cancer developed by A*STAR and the National Cancer Centre Singapore, was approved to enter clinical trials by the US FDA in January 2023.[32]

Consolidation and Specialization

More recently, Singapore's health system has been undergoing consolidation, exemplified by the move in 2017 to merge six health clusters into three.[33] This consolidation has also given rise to initiatives that aggregate efforts in biomedical R&D at the national level. For example, the Consortium for Clinical Research and Innovation Singapore (CRIS) was established in 2020 to strengthen synergies and develop strategies for national-level clinical research and translation programs.[34]

Participants have welcomed such efforts, stating that past moves to foster competition among health clusters have not always worked in practice.[35] Because of Singapore's small size, any fragmentation quickly hinders the economies of scale that enable

meaningful innovation, such as cross-learning and clinical adoption, availability of funding and patient populations for studies, the scaling of pilots across various organizations and systems,[36] and sharing of data needed to train machine learning models. In contrast, consolidations have seen research efforts accelerate. For example, in the short years since the formation of the Singapore Translational Cancer Consortium, which synergized translational cancer research nationwide, the number of approved clinical trials in oncology nearly doubled.[37]

Even with national consolidation, however, Singapore can never match larger countries dollar for dollar, hence the government's push to focus on specific disease areas. For example, the Research, Innovation, and Enterprise 2020 plan, which laid out the government's R&D plans from 2020 to 2025, specified five areas of focus. In parallel, CRIS's focus areas cover genomic data, cell and gene therapies, translational research in cancer and cardiovascular diseases, health innovation, and the acceleration of clinical trials.[38] In fact, during Institute convenings, private-sector participants from China to Australia expressed interest in collaborating with CRIS. Similarly, to attract pharma, the government is developing centers of excellence that can cultivate entrepreneurship, study health-care needs in Asia, and provide signals back to the industry.[39]

Clinical trials are an area where the aforementioned initiatives would translate into output. Singapore's focus areas for clinical trials are substantially similar to those of global and regional markets. Nearly all leading biotech markets worldwide focus on non-small cell lung cancer, multiple myeloma, type-2 diabetes, rheumatoid arthritis, and breast cancer, as does Singapore. Aligned with its fellow APAC countries, Singapore also focuses on clinical trials for gastric cancer, hepatocellular carcinoma, and chronic hepatitis B. However, in contrast to other markets, cancer-related assets in Singapore lean toward diagnostics rather than cures, according to Institute analysis of BioCentury data.

Partnerships and Collaborations

Singapore is also actively cultivating networks and partnerships worldwide. The city-state is a member of Project Orbis, an initiative of the US FDA that allows for concurrent submission and review of oncology products among member countries.[40] The Singapore Clinical Research Institute supports nine clinical trial and registry networks in the region,[41] such as ADVANCE-ID, a network of more than 30 hospitals across Asia studying the prevention of antimicrobial resistance.[42]

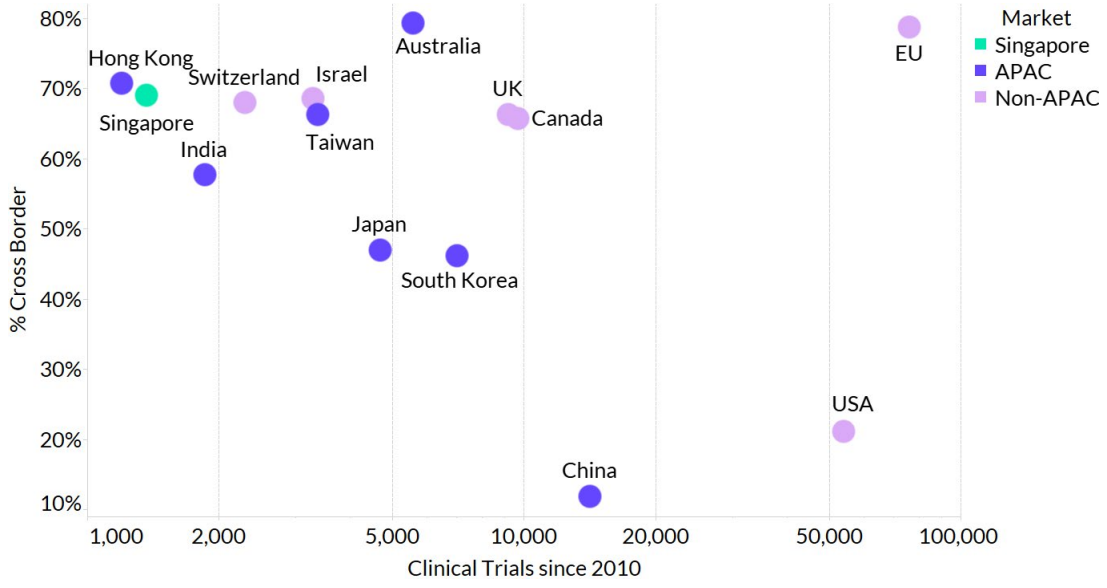
The Centre of Regulatory Excellence (CoRE) at Duke-NUS Medical School was established in 2014 to develop regulatory expertise and policy innovation through APAC. In 2019, CoRE launched the Coalition to Accelerate Patient Engagement, a disease-agnostic platform convening patient groups across APAC to interact with policymakers and regulators.[43] Further, in 2022, the Duke-NUS Centre for Outbreak Preparedness was established to improve regional surveillance and capacity in detecting and sequencing disease threats.[44]

Partnerships with industry are becoming increasingly commonplace. A*STAR has entered into an agreement with WuXi Advanced Therapies to improve the production of cell and gene therapies.[45] Local biotechs Carmine Therapeutics[46] and Hummingbird Bioscience have research partnerships with Takeda and Amgen, respectively, and in 2023, Hummingbird entered into new agreements with Synaffix[47] and Merck.[48] Roche and Sirtex provided S$19.2 million (US$14.5 million) in support for the National Cancer Centre Singapore in 2022 to launch a Phase II trial across 13 sites in APAC for liver cancer.[49]

Initiatives in precision medicine and translational cancer research have also found industry partners in Illumina,[50] Roche,[51] Adagene, and Bristol-Myers Squibb.[52] In addition, local universities are engaged in conversations with government, philanthropists, and industry to seed discovery districts focused on startups and clinical practice to supplement Biopolis, which leans more toward research and pharma.

Nevertheless, in terms of impact and outcomes, it bears repeating that other leading biotech markets have not let up on the accelerator. For example, Singapore may be highly involved in cross-border clinical trials, but so are other leading markets (Figure 8). In fact, Singapore's participation in clinical trials is very low, even compared to markets with similar population sizes, such as Israel and Taiwan. Therefore, continued efforts to push researchers toward translational research, and attract commercialization talent, remain crucial.

Figure 8: Low Participation in Clinical Trials



Note: The number of clinical trials is presented on an exponential scale for visual clarity.

Source: Milken Institute analysis of ClinicalTrails.gov (2023)

Commercialization Talent: CEO-as-a-Service?

The need to push science toward commercialization was well-documented in the Institute's previous paper and other studies. For example, a worldwide survey of drug developers in 2022 found that the lack of specialized knowledge was especially acute in APAC, with over one-quarter of APAC respondents naming it as a top challenge.[53]

In Singapore, participants noted that many early-stage research projects run into a wall when tasked to identify a business case. Other participants mentioned that bureaucracy in universities gears researchers toward citations and licensing rather than company creation, while research careers in government, universities, and public research institutions are much more comfortable than entrepreneurship. Indicatively, universities and research institutions form the vast majority of biomed-related PhD headcount in Singapore,[54] in contrast to the US, where almost half the PhDs in biological sciences are employed by industry.[55]

Consequently, some participants viewed Singapore as a springboard, incubating portfolio biotech companies until they were mature enough to expand to the US, where the talent there can take over. Yet, other participants believed that with more successful fundraising in recent years, recruiting academia to entrepreneurship is increasingly becoming a matter of de-risking, and many researchers would be happy if an experienced CEO could be brought in to lead their teams.

The Singapore government is aware of this dynamic and has initiated a slew of co-funding programs to push researchers toward commercialization, such as through secondments from A*STAR to SMEs[56] or fellowships for researchers to undergo training in business development and commercialization in SMEs.[57] Co-funding proportions are generous and can be as high as 80 percent. The government also implemented a conversion program to attract mid-career researchers to switch to biopharma manufacturing and introduced a work pass for foreign entrepreneurs to start a business in Singapore.[58]

Although these programs may help to fill entry- to mid-level roles over the medium term, participants believed that smart individuals can quickly acquire these skills by themselves. The main challenge is to develop a CEO-level talent pool with deep expertise, not only in the science but also in the regulatory and business environments of the target markets, which are almost always not Singapore. Participants stressed in previous roundtables that the top translational talent needed by Singapore must be sourced overseas. Some participants actively tap into talent pools in the US and even set up offices there. Other participants noted that global pharmas are shrinking their workforces and that Singapore could tap their former directors and vice presidents for talent.

"Business development teams must be based in Boston … US-trained and globally minded. Maybe let A*STAR scholars stay in the US a few more years."

—Biotech Leader, stakeholder interviews

One suggestion was to create an almost "CEO-as-a-service" model—pooling together CEOs, senior vice presidents, or entrepreneurs-in-residence, and allowing each to lead multiple biotechs. For instance, StartCodon in the UK brings in experienced CEOs to serve as chairs for multiple founders in its venture program. Such a platform would enable local biotechs to outsource their gaps in commercial leadership. Concurrently, having CEOs lead multiple companies de-risks their move to Singapore.

In a similar spirit, the Singapore government launched the Overseas Networks & Expertise (ONE) Pass in January 2023, a sector-agnostic pass allowing individuals to work for multiple companies concurrently in Singapore for five years.[59] ONE Pass is renewable and includes provisions for spouses to work in Singapore. What is trickier, however, is the requirement for applicants to earn a gross monthly salary of S$30,000 in a large company in the past year or in their new job(s) in Singapore, which exceeds the salaries of most biotech CEOs worldwide, let alone in Singapore.[60] If ONE Pass is to benefit biotech startups, it is much likelier that applicants would come from big pharmas (where salaries are much higher) or work for an investor.

3. MAINTAINING FUNDING, STOCKPILING OPTIONS

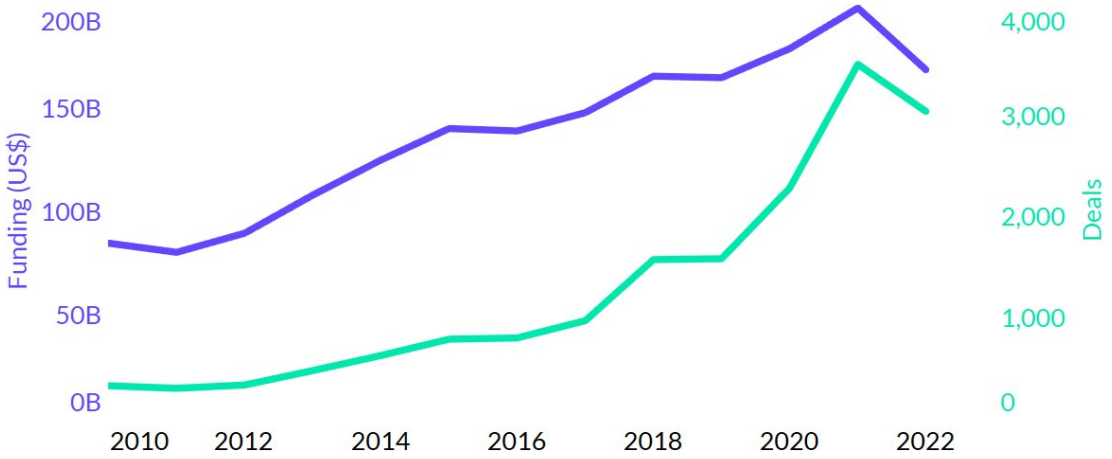
Post-COVID, there is no shortage of reasons for governments to continue their focus on biotech. It has never been clearer that good health is crucial for economies and societies to function properly. If anything, the pandemic is a stark warning of the perils of neglecting the health sector in favor of industries that bring easy returns.

And much work remains. Despite the record pace of vaccine development, most of Asia took more than two years to return to some sense of normalcy. Future pathogens could be much worse,[61] impelling the continued strengthening of biomedical R&D ecosystems in search of new cures.

Unfortunately, private-sector investments in biopharma worldwide have lost momentum (Figure 9). Pharmaceutical stock indexes have already returned to pre-COVID levels, and 2023 venture funding appears to be following suit. Participants noted that amid the economic slowdown, investors are reserving cash for existing portfolio companies rather than investing in new ones. Although big pharma has maintained investment levels, they are providing fewer options for biotechs. Pharmas are also biased toward teams with which they have deep experience, which disadvantages the majority of biotechs lacking deep pharma networks.

In a 2022 survey, 57 percent of small-sized biotechs cited the lack of R&D funding as a key challenge.[62] One tracker counted layoffs in more than 200 biotechs since 2022.[63] Some participants have likewise expressed serious concern for Singapore's biotechs.

Figure 9: Worldwide Biotech Ventures, Funding and Deals



Source: Milken Institute analysis, Crunchbase (2023)

Concurrently, geopolitical tensions in and around Asia can threaten to destabilize the long-term investment outlook throughout APAC.[64] The silver lining is that supply chain diversification could offer some medium-term benefits to countries that are neighboring and neutral. A participant, for instance, noted rising interest in establishing variable interest entities in Singapore to anchor and bridge funding rounds for portfolio biotechs. Some participants even remarked that Singapore's majority-Chinese population could serve as a proxy for patients in China, where data are more difficult to obtain. Another participant stressed the importance of knowing the target market from the start, stating that companies with early-stage US investors may experience difficulties attracting later-stage Chinese investors and vice versa. A biotech finding itself in such a situation could get its intellectual property into Singapore as a solution.

Governmental Support

During such downturns, the biotech ecosystem relies on the government to lean against headwinds and keep upstream pipelines flowing. Notably, in the Institute's previous report on Singapore, almost every financing model proposed by participants (and many others not proposed) required government buy-in and initiation. Therefore, the importance of continued governmental support to local biotechs and investors alike cannot be overstated.

Notably, the US, which is already the leading biotech market in the world, has doubled down on biomedical research. The Advanced Research Projects Agency for Health (ARPA-H) was established in 2022 to advance high-risk, high-reward biomedical and

health research that cannot readily be accomplished through traditional research or commercial activity.[65] ARPA-H differs from the National Institutes of Health in several ways. It is modeled after previous ARPAs in defense and energy to be nimble, hierarchically flat, and autonomous, awarding milestone-based contracts to multidisciplinary teams without heavy reliance on peer reviews for project selection.[66] The agency has already received US$2.5 billion in funding, and US-based participants believed it could be a game changer.

In fact, the "ARPA" model has already inspired multiple governments to create similar agencies. Japan's Moonshot R&D Program was established in 2019, with ¥100 billion (US$705 million) for five years.[67] Germany's Agency for Breakthrough Innovations (SPRIN-D), with an expected total budget of €1 billion (US$1.1 billion) for 10 years,[68] launched its first innovation challenge in 2021 to develop antiviral drugs.[69] The UK formally established the Advanced Research and Invention Agency (ARIA) in January 2023,[70] with £800 million (US$1 billion) for three years and maximum autonomy. ARIA itself, not ministers, will decide project selection and funding allocation.

Broader efforts to boost biotech and biomanufacturing are also underway. Having witnessed export bans and supply shortages during COVID-19 and a subsequent economic slowdown, many large countries are rolling out programs to secure domestic production and investment.

US President Joe Biden issued an executive order on a whole-of-government biotech and biomanufacturing initiative in September 2022 to strengthen domestic supply chains and maintain the US's lead.[71] China's 14th Five-Year Plan for pharmaceuticals in January 2022 aims to grow R&D investment by at least 10 percent annually on average (61 percent in five years) and make supply chains stable and controllable.[72] Emphasis is also placed on leading innovation and commercialization,[73] attracting global pharmaceutical players and internationalizing domestic companies—alongside efforts across recent years to streamline drug approvals.[74]

As such, even as markets transiently wane, governments worldwide continue to extend their lead and position their biomedical ecosystems for success.

Investment Theses

In addition, the current economic downturn, while challenging, does not completely deprive private investors of all opportunities. Falling biotech valuations can and have been seen as overdue corrections from the hype of the past few years. With capital receding, biotech deals are now available at more reasonable prices.

Moreover, many of Singapore's biotechs are at the Series A stage or earlier and less affected by public markets, which are much further downstream.[75] In fact, ongoing contagion from initial public offering (IPO) to Series B markets seen elsewhere[76] is not likely to impact domestic biotechs for now because many obtained their Series A rather recently (Figure 5) and have some years to go before proceeding to the next stage.

Some participants remained quietly confident that experienced investors in biotech are here to stay, although they will deploy capital with more due diligence and discipline. Consequently, the biotech sector should experience additional consolidation and structured deal activity rather than outright contraction.[77] Truly innovative companies will thrive, but projects pushing incremental innovations (which are many) will likely be left behind. Participants believed these events would improve the sector's performance in the coming years.

The economic slowdown has also impacted different areas of biotech differently. Participants believed that biotechs focused on developing cures for major diseases would be less affected because demand for life-saving medicines is inelastic. In addition, demand for services from contract research organizations remains strong and the subject of increasing interest from large pharmas. Conversely, more elective areas, such as gene sequencing and cloud computing, have already experienced declining revenues.

In the medium term, however, there are reasons for optimism. The first reason relates to the "patent cliffs" facing pharmas (Figure 10),[78] that is, when drug patents expire, competition from generics and biosimilars drives down revenues for large pharma, incentivizing a global hunt for biotech deals to refill their pipelines. Multiple participants believed that pharmas can afford to acquire biotechs, as the free cash flows of many of the largest players have increased in recent years. This situation ultimately creates opportunities for biotech exits in the medium term.

The second reason is the improved ability to recruit patients into clinical trials. The COVID-19 pandemic increased the willingness of patients, investigators, and regulators to accept technology. In one global survey of drug developers in 2022, more than two-thirds of APAC respondents were currently conducting decentralized, digital, and remote clinical trials.[79]

In parallel, participants in the US noted that COVID-19 patients easily organized themselves using social media to accelerate research on the pandemic. This change in the research landscape is significant for biotech—patient recruitment for decentralized trials tends to be substantially broader, less expensive, and faster, with lower attrition. One database finds that only 2 percent of decentralized clinical trials have been withdrawn, suspended, or terminated.[80] Unsurprisingly, decentralized trials ranked in the top three opportunity areas in drug development in the aforementioned survey.

Figure 10: Loss of Exclusivity in Drugs

2023	2024	2025	2026	2027	2028
Humira	**Brilinta**	**Descovy**	**Bridion**	**Ibrance**	**Eloctate**
Januvia	**Gilenya**	**Entresto**	**Eliquis**	**Imbruvica**	**Jardiance**
Stelara	**Isentress**	**Inlyta**	**Kadcyla**	**Trulicity**	**Keytruda**
	Simponi	**Soliris**	**Perjeta**	**Xtandi**	**Lynparza**
	Sprycel	**Xeljanz**	Pomalyst	Dovato	**Vyndaqel**
		Benlysta	Revlimid	Tysabri	Opdivo
		Prolia		Xarelto	Otezla
		Yervoy			

Note: Drug names are bolded if the (aggregate) free cash flows of the patent holder(s) increased from the end of 2020 to the end of 2022.

Sources: Reference 82; Milken Institute analysis, Yahoo! Finance (2023)

Third is the innovation in clinical trials to lower costs and shorten timelines in drug development spurred by the COVID-19 pandemic. In the UK, the RECOVERY trial enabled researchers to test multiple treatments concurrently for efficacy rather than one at a time. US-based participants further noted that seamless trials (multiple trial phases conducted simultaneously) were gaining real traction, as were trials conducted with real-world evidence in communities rather than clinical settings. In Europe, the Accelerating Clinical Trials in EU initiative has published working guidelines for complex trials[81] (e.g., multiple candidates investigated in a continuous manner under a shared platform) and decentralized trials and is currently working on facilitating academic-driven multinational trials.[82]

In Singapore, the National University of Singapore's Institute for Digital Medicine has pioneered more than 14 first-in-kind human trials.[83] The Singapore government also continues to fine-tune data privacy, protections, and sharing to strengthen patients' trust and facilitate cross-border trials with other leading biotech markets.

Financial Innovations

But even with enduring reasons for government and private investment, the need for innovative financing methods remains salient due to structural challenges to Singapore, and biotech in general. As raised in the Institute's previous report, funding needed for later-stage trials is simply too high to be met by existing capital pools in Singapore, necessitating alternative sources of capital. Even public-sector participants acknowledged that many local biotechs fail to meet the funding criteria set by the

government. In turn, the more diverse the investor body, the more likely that good ideas will not fall through the cracks.

Concurrently, the life cycle of venture capital (VC) funding is typically less than 10 years, which is usually too short to oversee biotech exits.[84] This misalignment gives rise to the "translational valley of death" even in capital-rich markets such as the US. The biotech sector needs capital investors with longer timelines and higher risk tolerance, such as philanthropy, government, family offices, university endowments, pharmaceuticals, real estate, and biomanufacturing. Participants also noted that investors increasingly rely on syndication and structured deals amid the slowdown. This shift could improve receptiveness to increasingly complex financing models.

In its previous roundtables and report, the Institute highlighted more than 20 case studies, and participants indicated the greatest interest in two: first-loss equity and venture philanthropy. However, the Institute recognizes the importance of letting the slew of government initiatives (Section 2) play out and evaluating their efficacy before embarking on newer funding mechanisms. The reasons are twofold: Singapore's biotech ecosystem is simply at such an early stage that any new funding initiative will likely be helpful, but a sudden and excessive influx of new funding mechanisms may not be efficiently absorbed by the limited pool of biotech assets today. Domestic ventures and innovation need time to mature alongside funding.

Ultimately, however, without a broader and deeper source of patient, risk-tolerant capital over time, the valley of death will continually plague biotechs downstream. It thus behooves funders to stockpile innovative financing models for future consideration. This report highlights first-loss equity and venture philanthropy as reserve options should the need for additional firepower arise in the future. Both approaches supplement the Singapore government's modus operandi of grants and co-investments.

4. FIRST-LOSS EQUITY FUNDING

First-loss (FL) equity funding is a variant of co-investing that seeks to de-risk and crowd-in private investment. This goal is accomplished by having losses below a prespecified threshold borne entirely by the provider, which makes FL distinct from co-investing. (In the fortunate event that no losses are incurred, FL will look the same as co-investing.) FL funding also differs from junior equity in that losses are covered up to a prespecified amount, not unboundedly.

This de-risking element of FL funding is particularly relevant to Singapore. Participants who had newly entered the Singapore market over the years were unanimous in the opinion that Singapore's investors are inordinately risk averse. Only 3 percent of Singapore's venture funding and 8 percent of investors have gone into biotech, and even then, two in five investors are one-off investors in the sector (Section 2). By lowering risk specifically, bystander investors may be more comfortable entering the biotech sector, upon which greater comfort can be gradually cultivated. The short-term goal of

such de-risking measures is for biotech to minimally be a viable sector for diversifying portfolios, if not the primary focus of funds.

On the other side of the coin, providers take up a FL position for several reasons. Some desire to see impact, for instance, to kickstart research and entrepreneurship in a disease area. Others need to tap into the know-how of private investors or crowd-in fence-sitting capital to attain a requisite scale, such as funding a clinical trial.

For example, a foundation focused on a rare disease may have a deeper understanding of risk than investors and thus offer to accept FL funding to give private investors a flavor of biotech investing without assuming too much risk. The hope is that investor exposure will subsequently develop expertise and lower risk perceptions, thereby incentivizing re-investment in the sector with little or no credit enhancement in the future. (If the intention is to phase out FL protections eventually, providers should let investors know upfront.)

Conversely, a government could utilize FL funding to make the biotech sector more commercially viable for private investors to enter. In fact, should FL protections be sufficiently generous, the influx of willing private investors could even create competitive pressures that ultimately improve funding terms for ventures.[85]

The success of OrbiMed in Israel has already been covered in the Institute's previous report and will not be repeated here. The Global Health Investment Corporation is another example, established in 2012 to combine venture capital and FL funding. Its first fund, the Global Health Investment Fund (GHIF), raised US$108 million with 20 percent FL protection by the Bill & Melinda Gates Foundation,[86] crowding in the likes of GSK, Merck, Pfizer, AXA, and JPMorgan Chase.[87] Although GHIF had targeted US$10 million per investment, as of May 2023, it had already invested in 20 biotechs, at least 7 of which had successful exits. However, the speed of exits is partly due to GHIF's focus on late-stage innovations that can be commercialized within three years.

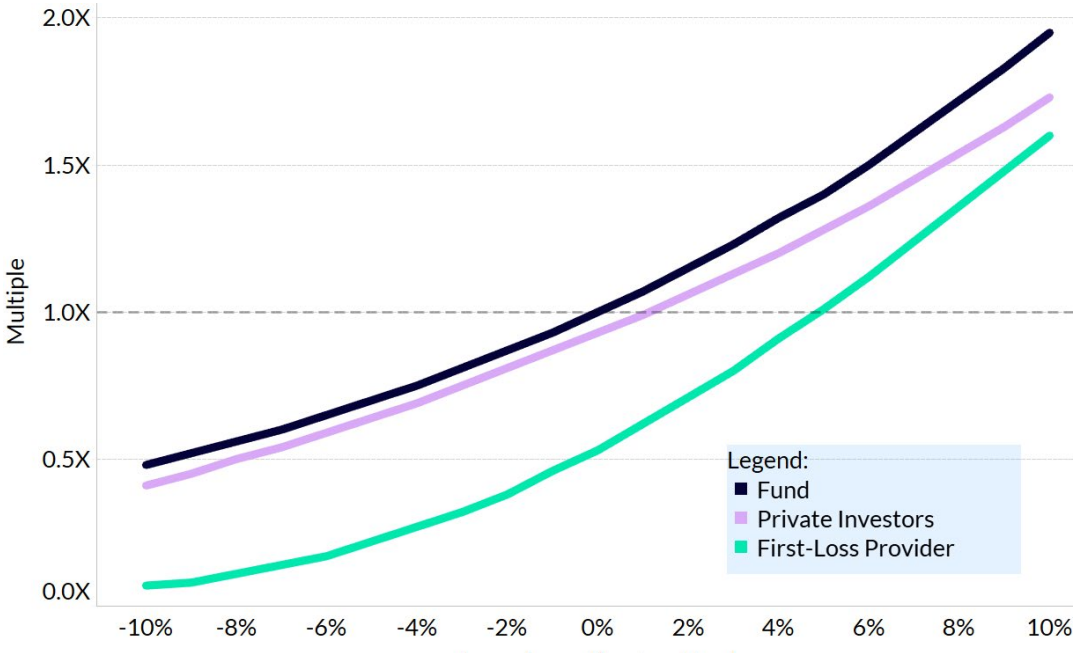
Other examples of FL in biotech funding are necessarily difficult to come by because the terms of negotiations with private investors are not made public. Nonetheless, case studies in development aid[88] and other sectors[89] are increasingly prevalent.

First-Loss Simulations

To better demonstrate FL protections, the Institute has simulated fund outcomes (Figure 11), showing the distribution of financial returns to FL providers and private investors under a variety of scenarios (84,672 scenarios of 100,000 simulations each). For a fund that grows at a mean of 0 percent annually (i.e., realizing losses half the time), the provider receives 0.5x of its principal on average, while private investors receive 0.9x. For a 5 percent mean annual growth rate (i.e., realizing losses 40 percent of the time), investors receive, on average, a 1.3x multiple on their principal, while providers receive 1x. This analysis illustrates the de-risking nature of FL funding in helping to

attract investors who would otherwise have abstained. The full dashboard can be accessed here, where simulation parameters can be modified.

Figure 11: Simulated Distribution of Financial Returns



Simulation settings:

1. 2 percent annual management fee
2. 50 percent hurdle rate for 20 percent carry
3. Provider absorbs all losses, including fees, up to FL (20 percent in Fig. 11; can be changed in the dashboard)
4. After FL, returns, losses, and fees are split according to each party's capital share
5. If the provider loses its entire principal, investors absorb all subsequent losses
6. If investors lose their entire principal, outstanding management fees are not paid

Source: Milken Institute (2023)

Specializations Versus Disease-Agnostic

A lingering tension is the tradeoff between acceleration and equitable funding, even before a biotech reaches the stage of sourcing for Series A funding. The Singapore government typically requires mature startups and established research institutions to find their own funding, preferring to channel public resources into translating the next generation of basic science, and spread resources more evenly across multiple subfields of biomedical R&D. This approach also spares civil servants the tedious need to explain to researchers why some sectors were excluded or address criticisms that the government was picking winners and losers in an uncertain and ever-evolving field. Moreover, participants acknowledged that as the disease focus narrows, so does the target market, which can make it difficult to attract investors and entrepreneurs.

Nonetheless, private-sector participants leaned toward focusing new funds on already-promising disease areas and more-established biotechs, to secure early wins and to further accelerate their scaling. Local and international participants believed that only very mature ecosystems have the luxury of applying a broad focus, and Singapore's limited size dictates specialization so that resources are not spread thin. For instance, one participant who had transitioned from the public to the private sector mentioned that, even in well-established research institutes, projects were typically delayed or blocked because of funding needs for early-stage trials. Many other participants noted that the deep tech ecosystem in Singapore still requires much hand-holding, which again necessitates a selective focus.

How much, then, is considered spreading "too thin"? According to Institute analysis of Crunchbase data, biotechs in APAC that attained Series A raised a median of US$703,000 cumulatively before attaining Series A. Biotechs that missed this threshold took an additional two years on average to attain Series A. Therefore, if government funding and other sources are over-distributed across too many disease areas, multiple biotechs that could have progressed will instead spend additional time fundraising elsewhere while existing funding sources deplete. As a result, the ecosystem may be shepherding large numbers of biotechs toward the valley of death but not across it.

First-Loss and the Valley of Death

As presented in Figure 11, FL protections are not unlimited—such funds generally seek to support projects just below the thresholds of commercial viability by nudging them over that threshold to crowd-in fence-sitting capital. Ultimately, however, innovative finance has no immediate influence over the underlying strength of biotechs in the ecosystem from which portfolios are constructed. The key question then is the growth rate a fund is likely to produce and whether it is close enough to commercial viability.

Of the more than 55,000 biotechs in leading biotech markets worldwide, around one in five have attained Series A, and one in fifteen has attained Series B (Figure 12). The respective proportions for Singapore-headquartered biotechs are slightly lower. The

valley of death features prominently in Figure 12—most biotechs take a long time to attain seed and Series A funding and fail to raise subsequent rounds. Conversely, the minority of biotechs that attain Series B and later are inherently more "successful" from the start and can achieve milestones in less time, hence on average, it takes longer to Series A than Series B. Of the biotechs that attained Series B, they did so on average 2.5 years after attaining Series A.

Figure 12: Biotech Funding Stages across Leading Markets

	Pre-Series A	Series A	Series B	Series C	Series D onwards
Avg Funding Quantum (USD)	3M	14M	32M	41M	51M
Avg Age	5y	6-7y	5-6y	7y	9y
Avg Investors	1-2	2-3	4	5	5
Proportion of Biotechs	19%	20%	7%	3%	1-2%

Source: Milken Institute analysis of Crunchbase (2023)

Some simplistic modeling can be further performed based on Figures 11 and 12. Assume that a fund invests in multiple Series A rounds averaging US$14 million each, and a third of its portfolio successfully exits at an average US$32 million Series B. The expected return would be 43 percent, which equates to 1.7 percent compound annual growth over a seven-year life cycle. With a 20 percent FL as shown in Figure 11, private investors can expect nearly a 1.1x return post-management fees. Higher levels of FL protections will push these returns up further, for example, a 50 percent FL would raise investor returns to 1.2x.

Smart Capital

Of course, biotech investing is not as simple as picking a representative biotech from leading markets. In addition to the commercialization talent discussed in Section 2, investment talent is crucial. One participant noted that many investors in Singapore made their money in public equity and real estate and therefore have developed a reliance on conventional investment metrics, which seed-stage biotechs obviously lack. Another recounted several examples of projects getting buy-in from established foreign investors, in stark contrast to the multiple rejections from local investors.

Multiple participants expressed a similar underlying sentiment: smaller investors want greater collaboration opportunities with established lead investors. Some participants raised the idea of creating nationwide platforms that house all prospective biotech

deals. Others suggested cooperatives or co-investment platforms that facilitate the pooling of resources by investors. Still others wished for more concrete communication channels with leading institutional investors in Singapore so that the recent influx of family offices can better tap into domestic opportunities.

More broadly, for Singapore to make the best use of its entire capital base, biotechs and investors alike need to consider all capital sources objectively and utilize them with greater efficiency. A global survey of family offices in 2023 found that 76 percent of respondents in APAC were likely to invest in medical devices or health tech, while 49 percent worldwide were likely to invest in gene therapies.[90]

Yet, some participants have lamented that family offices and private equity are at times perceived as "dumb" capital, as opposed to the "smart" capital of institutional investors, such that even family offices with a track record in biotech investing find it difficult to lead funding rounds. One participant who had transitioned from venture capital into a family office opined that the ability to secure institutional funding is largely influenced by connections, presentable teams with good storytelling abilities, and the opportunity to name-drop board members. These factors can be particularly disadvantageous to founders who are not articulate in English (including some Singaporeans).

Participants believed that the surest way to correct such stigmas would be successful exits, which would take time. In the meantime, participants hoped for more open communication with institutional investors so that they could partake in the full gamut of domestic investment opportunities.

5. PHILANTHROPY

Although the Singapore government is the largest source of early-stage funding and is typically participants' first choice in seeding new models, it cannot be the sole catalyst. Similar to those of other governments worldwide, Singapore's budget is very tight post-COVID. Further, the Singapore government is highly risk-averse in funding, necessitating more diverse capital sources so that fewer biotechs and disease areas fall through the cracks.

Using rare diseases as an example, although the government may want to provide funding support, it is difficult to justify deploying millions of taxpayer dollars for any disease that affects a small number of individuals. Yet, in total, rare diseases have higher prevalence than cancers,[91] and to ignore them would forgo much progress in health. Well suited in such cases is capital that is highly patient, autonomous, and insulated from shareholders and the general public—namely, philanthropy.

The Institute has articulated the value of philanthropy in biomedical R&D for decades; philanthropy has long timelines and no expectation of financial returns, making it well-placed to fund high-risk, high-reward projects. The Chan Zuckerberg Biohub, for instance, seeks to support projects with a 10- to 15-year timeline[92]—far exceeding the horizons of most private investors. Philanthropic funding can thus play a unique

and outsized role in chaperoning young but promising biotechs through their most challenging phases to the point where their assets can be assumed by industry. More broadly, such funding plugs gaps in the biomedical R&D ecosystem that neither the government nor private sector are willing or able to fund, particularly in early-stage drug development and rare diseases.

Perhaps more importantly, philanthropy has the power to shape the research environment. To accelerate iteration, philanthropists can mandate the open publication of research data and findings. To maintain accountability, funding can be disbursed in stages upon the attainment of predefined milestones. To break down academic silos and cross-pollinate research across different fields, foundations can require researchers to work in multidisciplinary, cross-institutional teams. To enforce commercial discipline, research teams can be led by industry veterans.

"People told me they couldn't divulge their work … because it was going to be published in Nature or Cell. I told them if … their work was so groundbreaking, they would have no trouble raising money (elsewhere) … Within six months, everyone decided they could share."

—Michael Milken, Global Conference 2023[93]

Leadership over Funding

In Asia, philanthropy has dominantly been focused on education, such as building schools, funding programs, and sponsoring scholarships. Anecdotally, even medical philanthropy largely continues to take on a flavor of education because many grant recipients are researchers employed in universities. Another challenge is that philanthropy in Asia tends to be highly discreet, which makes it incredibly difficult to hear of, learn from, and improve upon case studies. Ultimately, this environment hinders opportunities for philanthropists to crowd-in external funding to amplify their resources and impact. Further, their lack of public reputation complicates their ability to attract the deep expertise typically needed in biotech.

This philanthropic environment stands in contrast to that of the US, where funds have leveraged initial donations to crowd-in several multiples of external funding. In the case of the Harrington Project for Discovery and Development in Ohio, a US$50 million donation in 2012 eventually crowded-in US$140 million from other philanthropic sources and US$150 million from private investments. Similarly, the JDRF's T1D Fund raised more than US$100 million from donors in just five years,[94] while the Prostate Cancer Foundation in the US received more than US$80 million from donors from 2019 to 2020.[95] In these cases, the focus of the initial philanthropic gift is not so much the funding quantum as it is leadership—making it easy for others to join the cause and serving as the key conduit to channel diverse sources of funding into a focus area.

"Philanthropy is not just dollars; it is social capital: government, media, networks."

—Philanthropy Leader, private roundtable at Asia Summit 2023

Philanthropy has the potential to extend beyond one-off grants without subsequent follow-up. In the US, many philanthropic foundations—and even the Institute's own Innovation Competitions—heavily emphasize creating networks among alumni to build a lasting community and legacy.[96] For instance, the Michael J. Fox Foundation for Parkinson's Research (MJFF) actively organizes convenings for grant recipients with fellow researchers, patient communities, industry, and policymakers.[97] To further support research efforts, many other foundations share lab tools, data, and biosamples from previous studies with grantees and have even curated disease databases, patient registries, and clinical trial networks over the decades.

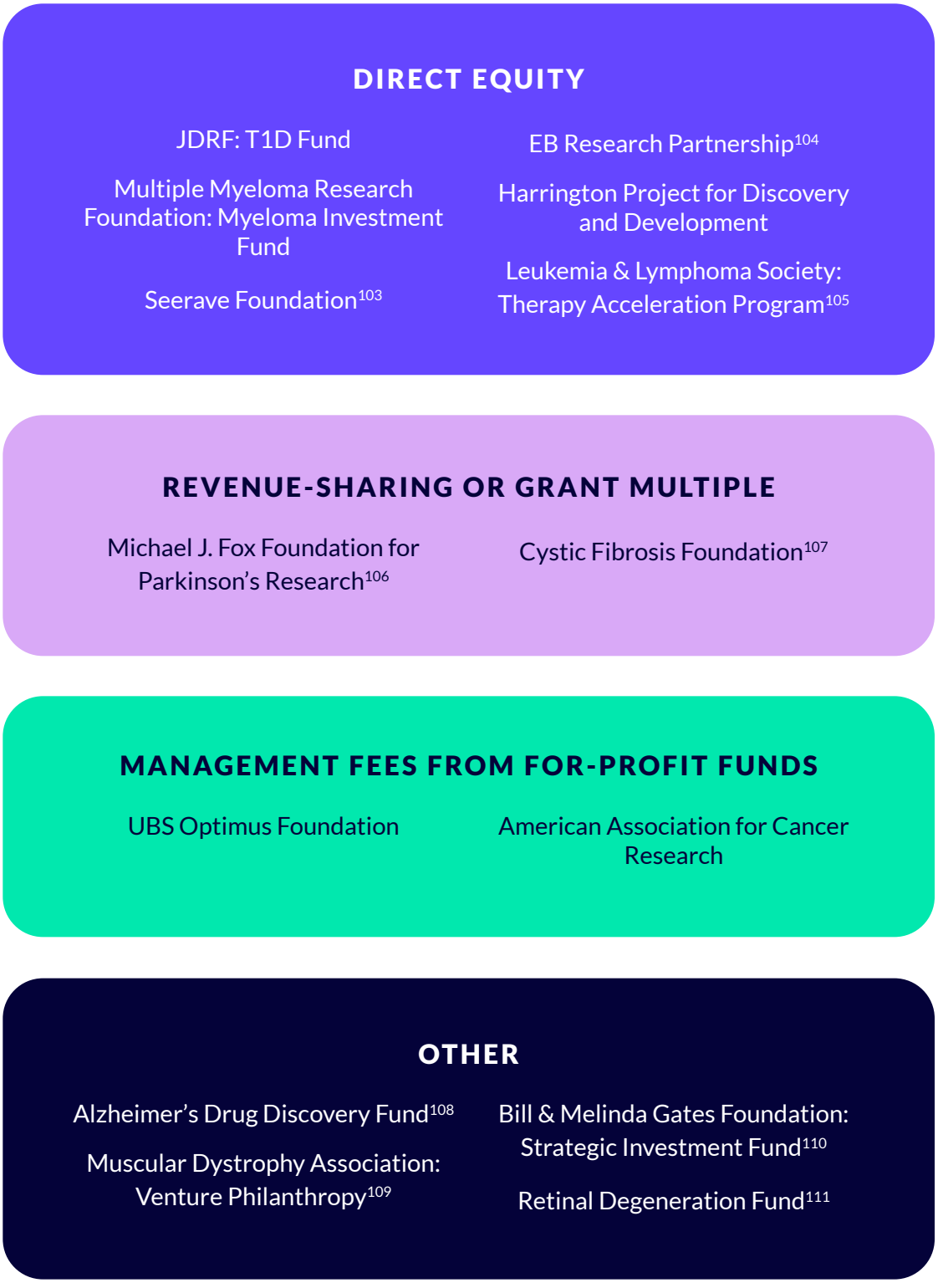
Venture Philanthropy

Philanthropists worldwide are increasingly deploying their capital into blended financing. In one global survey of high-net-worth individuals in 2022, 17 percent of respondents indicated that they were using their funding to catalyze further investments.[98] In the same survey, APAC was ranked as the best region for investment returns, and biotech was ranked the second-best sector. In congruence, the Philanthropy Asia Alliance was launched by Temasek Trust in 2022 with US$200 million committed to Asia-focused blended financing for ventures and impact investing, with health being one of its key themes.[99]

The trend of venture philanthropy (VP) mostly began in the US. After seeing limited patient impact from academic research,[100] philanthropists shifted toward VP—directly funding clinical trials or early-stage, for-profit biotechs. Some foundations also retained a portion of any financial returns from funded assets for recycling into future investments. Among the funds with published data (Figure 13), returns have ranged from 10 to 60 percent over five to 20 years. Of course, successful funds are more likely to publish their returns.

Returns are generated by taking direct equity, requiring royalties in perpetuity or up to some grant multiple, or even drawing from performance fees (Figure 13). For instance, MPM Capital's Oncology Impact Funds 1 and 2, which have raised more than US$1 billion since 2016, take a 1 percent royalty on drugs that go to market but also 20 percent of the management performance fee, to be donated to the UBS Optimus Foundation and American Association for Cancer Research. Although the contribution from royalties is expected to be larger, contributions from management fees naturally kick in earlier. For example, as of 2021, Oncology Impact Fund 1 had donated US$8 million in total,[101] of which US$7 million was derived from the management fee.[102]

Figure 13: Venture Philanthropy Funding Models



Note: Other financing models include (but are not limited to) debt, convertible notes, volume guarantees, credit enhancement, and the specified funding models above.

Sources: Individual websites; Milken Institute research (2023)

Individually, donors may enjoy tax deductions depending on their jurisdiction. Moreover, donors are commonly offered the right of first refusal when a sufficiently developed asset is to be sold to the private sector. VP thus mimics some attributes of biotech investing. However, fundamentally, VP is distinguished by its patience and prioritization of impact over returns.

The Cystic Fibrosis Foundation (CFF) is perhaps concurrently the most famous and infamous example of VP in biotech. In 2015, the foundation sold royalty rights for FDA-approved Kalydeco for US$3.3 billion, subsequently supporting many other drug development efforts for years to come.[112] However, the high price of Kalydeco caused critics to question whether foundations can truly put patients first when they directly benefit from higher drug prices.

Nonetheless, it is important to bear in mind that high drug prices and massive cash flows through nonprofits are not salient in Singapore and are not necessarily a feature of VP per se; that Kalydeco and many other treatments would not exist without VP; that the control of drug prices ultimately rests on governments and not foundations; and that prior to the FDA approval, CFF had invested billions without much success but nonetheless persisted in its endeavors for six decades.[113]

Changing Mindsets

As presented in Figure 13, the most common practice for a VP fund is to take direct equity in a biotech. However, participants warned that investors dislike complicated capitalization tables, and over-diluting a biotech's shares at the early stages could dissuade later-stage investment. This issue is not exclusive to Singapore—for instance, MJFF explicitly states that it does not claim ownership or intellectual property, and it ensures that grants are non-dilutive to ease the entry of private investors at later stages.[114]

Participants thus wondered if a locally developed VP fund would be amenable not to take board seats or be open to other funding models. Anecdotally, participants who have engaged with local foundations have seen revenue-sharing models more than equity, which is encouraging.

Multiple participants also stressed the need for VP funds to exercise commercial discipline themselves, as well as to cultivate it within funded ventures. Aside from prioritizing projects with commercial promise, foundations must be prepared to terminate unpromising projects quickly so that talent can be recycled back into the ecosystem.

> "There is no point having 10 high-net-worth individuals supporting a founder out of friendship; later-stage investors will have concerns."
>
> **—Biotech Investor, stakeholder interviews**

What is more concerning in Singapore are policies and regulations that, sometimes by omission or lack of awareness, inadvertently exclude VP as a potential avenue. For example, some participants stated the government's one-to-one matching of donor funding does not apply to projects that generate financial returns, such as VP. Other participants recounted instances where university funds could not be deployed to the private sector. Consequently, instead of investing in an existing biotech, funding went into a lab with the goal of spinning off a company.

To eliminate duplications and inefficiencies, foundations must be clear and upfront about the mindset changes they expect in funding recipients. Participants also stressed the importance of disbursing funding in stages, based on the attainment of predefined milestones, to keep recipients accountable.

Inclusivity

Unlike in FL funding, participants were more confident that VP would have a narrow focus, that is, specific disease areas of a deeply personal nature. Although this focus better funnels resources, it can also shrink the talent pool and potential target markets. VP funds in the US address this challenge by sourcing projects worldwide, again contrasting with Asia, where philanthropy is often limited within national borders.

The key difference suggested by participants was that larger foundations in the US are staffed by diverse professional teams and veteran scientists with the expertise and capacity to evaluate projects worldwide and conduct due diligence. In contrast, foundations in Asia tend to be smaller and run by family members or professionals with little exposure to biotech. Indicatively, several participants lamented that local high-net-worth individuals and family offices tended to limit their consideration of public researchers to just the top few based on their publications. Participants have stressed across the years that publications and citations are poor indicators for drug development and entrepreneurship. Intellectual property measures, such as patent grants, are more relevant.

> "Good academic science does not mean good investment."
>
> **—Biotech Investor, stakeholder interviews**

> "In our decades of grant-making, the worst 'return on philanthropy' comes from funding scientists at the peak of their careers. Look for young, promising researchers."
>
> **—Philanthropy Leader, private roundtable at Asia Summit 2019**

In rare instances, a foundation partners with government and industry to focus on a broad range of diseases. As one example, the Global Health Innovation Technology Fund was established in 2013 with funders including the Bill & Melinda Gates Foundation,

the government of Japan, and several Japanese pharmaceuticals.[115] The fund focuses on malaria, tuberculosis, and neglected tropical diseases, and actively supports Japanese innovation and internationalization while facilitating cross-border partnerships. As of May 2023, it has deployed more than US$205 million into 177 investments.[116]

This effort, of course, requires a sizable presence of domestic pharmas, which Singapore does not have. Consequently, participants reiterated the need for any fund, whether FL, VP, or otherwise, to focus on the broader region, even if it has slight preference for deals in Singapore. In this regard, it is encouraging that the latest enhancements to tax incentives for family offices will allow qualifying donors based in Singapore to claim tax deductions for overseas donations.[117]

6. CONCLUSION

Singapore has made substantial progress toward developing its biomedical ecosystem in recent years, and some key gaps, such as investor knowledge, are gradually being plugged. However, to keep pace with leading biotech markets, sustained action is critical.

Amid the slowdown in biotech markets, continued governmental support is needed, and innovative financing can help to crowd-in alternative sources of capital that are more aligned with biotech development timelines. This report describes two models that can supplement existing funding schemes as reserve mechanisms should extra financing be needed in the future.

FL equity funding will help to de-risk biotech investments for private investors and, ideally, crowd-in reputable lead investors who inspire and guide the rest. VP is best suited for high-risk, high-reward projects and can set the rules of the game to spur the necessary mindset changes.

Beyond financing, each model also seeks to address the commercialization talent needed to drive biotechs forward. On this front, the Institute hopes that its annual high-level convenings, such as its Asia Summit in Singapore and Global Conference in Los Angeles, can connect key stakeholders, drive pivotal collaborations, and improve health and well-being.

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