Investing in translational research to produce clinical, commercial and financial outcomes: Current and future mechanisms

A White Paper for CIRM by Steve Dickman and the team at CBT Advisors

Cambridge, MA, April, 2013

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Executive Summary

The transition of promising research ideas from the research lab to clinical application has become more challenging, despite increases in funding for both discovery research and late-stage product development. The so-called "venture gap," that is, the near-disappearance of venture capital from the translational funding arena, has exacerbated the problem. Dealing with this critical need while advancing the cause of patients who could benefit from new therapies has become a focus for CIRM and many other government agencies and non-profits.

From the current unsettled situation, a "new normal" is likely to soon emerge. Gradually, the old structures are being replaced with new and potentially more robust funding mechanisms.

This white paper was commissioned by the California Institute for Regenerative Medicine (CIRM) in order to explore some recently adopted mechanisms for translational research funding and to better inform its strategic planning.

The paper first creates a framework by looking at the underlying interests and cash flows involved in translation. Then the paper describes twelve approaches and evaluates the pros and cons of these approaches on their own merits and for CIRM. Finally, the paper provides some specific input for CIRM regarding which aspects of these approaches can be adopted as CIRM considers its own path forward in this area.

Expecting a return on investment is a relatively new concept for agencies historically involved in grant funding of innovation. Doing so aligns a funding body with other investors in translation. Either venture capital or venture philanthropy approaches achieve this goal. Contract research organizations (CROs) are able to add value at an early stage in the process. CROs offer an attractive alternative or add-on to traditional venture funding. A securitized "megafund" for biotech innovation is an attractive concept but there is little evidence that this will be a practical approach.

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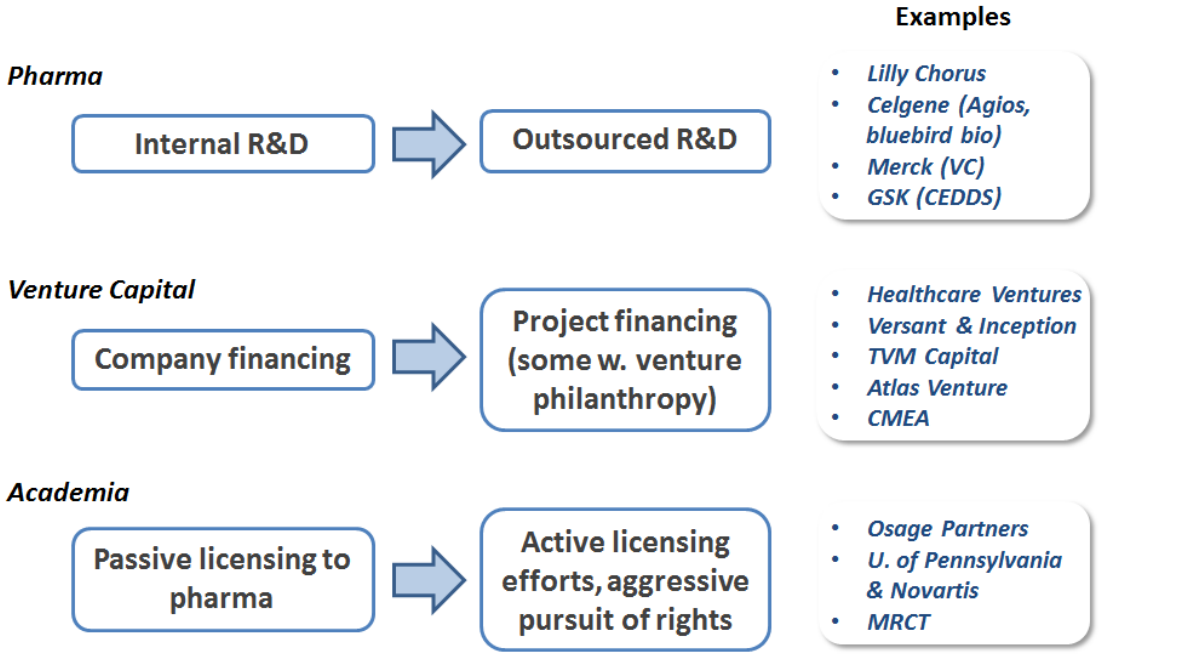
1. Introduction

The methods and structures for the funding of translational medicine projects have reached a crossroads. The more or less stable ecosystem built around traditional venture capital that existed from roughly 1990 until 2007 has begun to collapse under the weight of poorly performing venture funds. The "venture gap" has become a mantra for those lamenting the absence of reliable sources of financing for speculative projects exiting academia but not yet ready for pharmaceutical industry partnerships.

From the current challenging situation, a "new normal" is likely to soon emerge. Gradually, the old structures are being replaced with new and potentially more robust funding mechanisms.



Graphic: CBT Advisors

Fig. 1: Three parallel transitions

This white paper was commissioned by the California Institute for Regenerative Medicine (CIRM) in order to explore some recently adopted mechanisms for translational research funding.

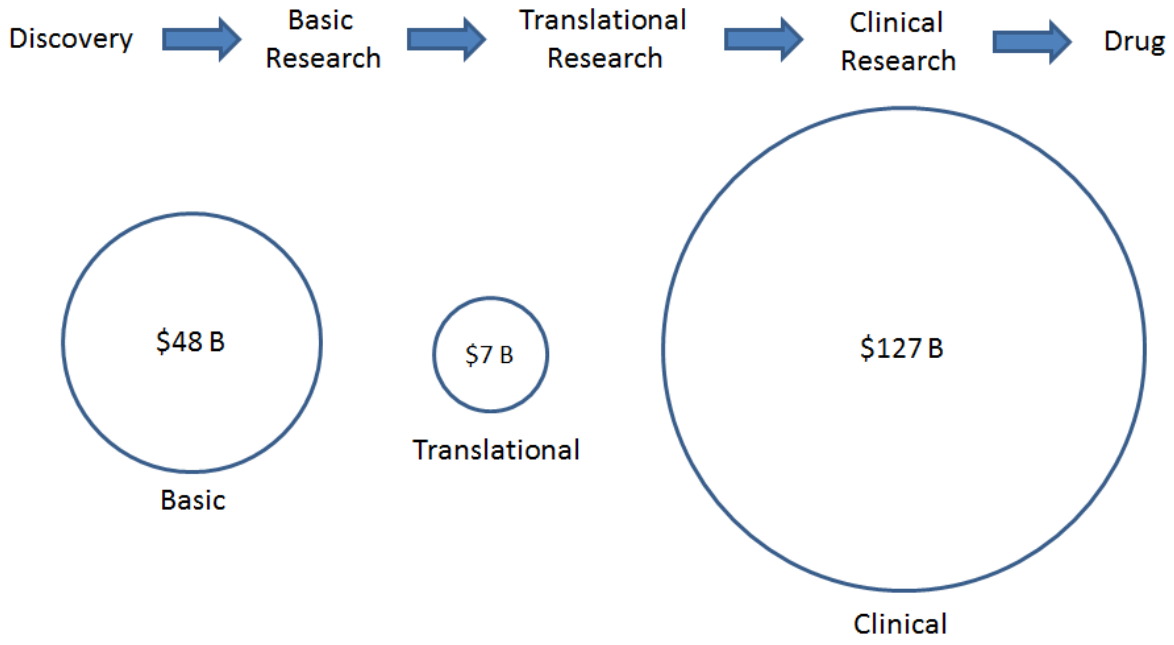
The paper will examine some of the new structures arising in translational funding and assess their advantages and disadvantages. Given the rapidly changing mix of institutions involved in translation and given the experimental nature of some of these efforts, this analysis should be considered a snapshot of a quickly evolving ecosystem.

The white paper is organized as a main section and an appendix. In the main body of the white paper, the evolving situation for translational funding and its likely further development will be described. Twelve approaches to the translational funding gap were chosen. Each one was researched, described and evaluated according to some basic criteria. Summaries of these evaluations appear in the main body of the white paper.

An appendix will describe each of the approaches and evaluate them in greater depth.

2. The current dilemma: translation in transition

Translation is what has to happen for a basic research discovery to become a useful therapy. Another term for translation is moving discoveries "from bench to bedside." There is a painful awareness in government, academia and industry that translation has lagged while both basic research and clinical development have surged ahead. Rough figures assembled by Andrew Lo and his team at MIT indicate that basic biomedical research in the United States garners $48 billion a year and clinical research $127 billion whereas translation receives only $7 billion (Fig. 2).[1]



Due to limited funding for translational research, it has become a "Valley of Death" that impedes R&D.

Data: http://www.fastercures.org/assets/Uploads/FixesInFinancingPub.pdf. *The $7 billion figure includes $584m/year from the NIH SBIR program (2011), $400m/year from angel investors (2011), and $6b from venture capital (2011). Sources Cited By FasterCures: Research!America, National Institutes of Health, CB Insights, National Venture Capital Association, Center for Venture Research. Graphic: CBT Advisors*

Fig. 2: Translation as a "Valley of Death"

Translation has fallen short in two important ways: there is both a dearth of money, especially compared to the amounts of money spent on basic and later-stage clinical research; and there is a deficit in light of the medical, commercial and societal need for improved therapies. Finding ways to overcome the former while addressing the latter is

[1] Fernandez JM, Stein RM, Lo AW. Commercializing biomedical research through securitization techniques. Nat Biotechnol. 2012 Oct;30(10):964-75.

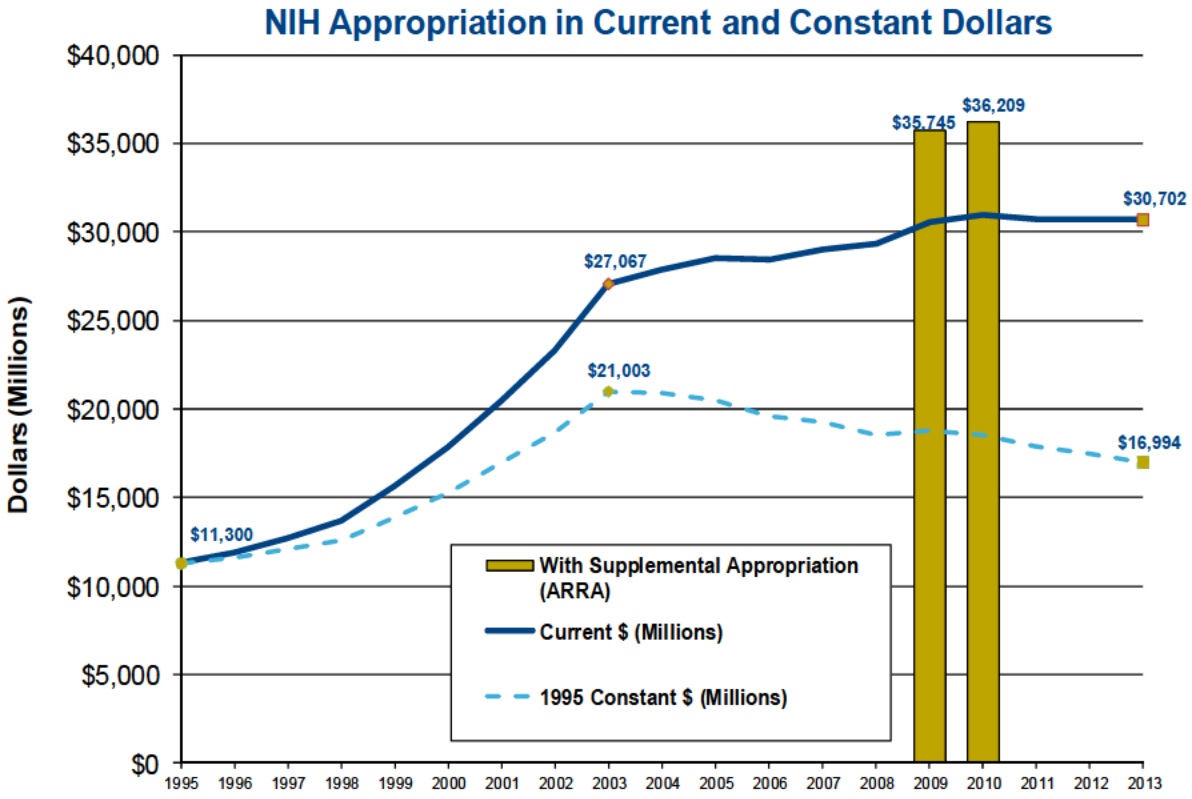
in the interest of CIRM and many other groups looking at new mechanisms of funding translation.

The last twenty years have seen an unprecedented surge in funding for basic research. The NIH budget has increased by a factor of three in twenty years[2] (from $10.3 billion to nearly $31 billion in 2012, as measured in actual dollars, not inflation-adjusted – see Fig. 3). Yet despite recent decisions raising the amount of funding for translation, most of this funding goes to basic research. This choice to stick to pre-translation research might well make sense from a purely financial point of view. According to (NIH), eighty to ninety per cent of research projects fail before they ever get tested in humans.[3] But the absence of funding leaves a painful gap.

On top of that, NIH budgets have plateaued lately and, with the sequester, they might soon even begin to shrink. That has made granting committees conservative, to the detriment of some of the riskier translational efforts that NIH-funded scientists and physicians may wish to take.

[2] http://www.nih.gov/about/almanac/appropriations/part2.htm

[3] National Institutes of Health. 2009. "NIH Announces New Program to Develop Therapeutics for Rare and Neglected Diseases," http://www.nih.gov/news/health/may2009/nhgri-20.htm



Data and graphic: FASEB

Fig. 3: Big increase in the NIH budget over 20 years

The massive financial success of the pharmaceutical industry, one of the most profitable industry sectors in the world, has not improved the picture for translation. Indeed, pharmaceutical companies have become very conservative themselves, stung by patent expirations and rapidly increasing costs of late-stage development and regulatory approval. In addition, pharmaceutical companies have become painfully aware that their R&D efforts have fallen short in terms of productivity. Most pharmaceutical companies have therefore scaled back internal R&D, to the detriment of translation.[4]

A 2011 research paper by the non-profit organization FasterCures explored the reasons for this dilemma. It stated that "translational and clinical research … are more difficult and expensive to conduct than basic research because they often involve complex organisms (i.e. animal models, humans) living in multifaceted environments." Such

[4] FasterCures white paper" Crossing over the Valley of Death," released February, 2011 http://www.fastercures.org/assets/Uploads/VOD-TranslationalResearch2.pdf.

projects become exponentially more costly as they approach animal and human proof-of-concept studies. The projects are de-risked, but this comes at a large cost.[5]

[5] Ibid.

3. A drop in venture funding creates a gap

Between NIH-funded basic research (and its equivalent in other countries outside the United States) and pharmaceutical-industry-funded clinical research, there used to be a translation booster called "venture capital." But in contrast to the increase in spending seen in basic research and the steady or increasing funding devoted to pushing drugs across the finish line and onto the market, venture funding for translation has suffered dramatically in the last five to seven years, to the point where the lack of funding for translation has widely come to be called the "venture gap."

Calling the current lack of translation resources a "venture gap" is a bit of a misnomer. Venture funding was never going to be the main solution to the translation challenge. With its tight coupling to financial outcomes and its dependence on external factors such as risk tolerance by big investors and taxation policy imposed by governments, venture capital investment was at best going to serve as a vehicle for a small minority of projects with particularly strong scientific founders or existing pedigrees from pharma (e.g. molecules spun out of pharmaceutical companies for strategic reasons).

But during the period from roughly 1998 to 2008, venture funds were able to raise unprecedented amounts of money and then turn around and pour them into more translational projects than they had ever funded before. To say the results of this endeavor were mixed would be giving venture capitalists too much credit. Caught up in agency issues (as identified much later by outside observers such as the Kauffman Foundation[6]) and driven to raise ever-larger funds, some venture investors raised too much money and put it to work in too many unpromising projects. The outcome of this behavior – and the complicity exhibited by the venture capitalists' limited partners – was described in piquant fashion in the 2012 report by the Kauffman Foundation.[7] Before about 2008, the difficult truth was obscured by the unusually high returns that these venture funds earned in the "bubble" years of 1999 to 2001. But the combination of the worldwide financial crisis of 2008 and the maturation of funds raised in the 2000-2001 time frame, yielding negative ten-year results, opened the eyes of investors who have harshly cut back on their allocations to venture funds and forced many venture funds into shutting down or changing their investment models.

The turndown in the ability to raise new funds in the 2009-2013 time frame has forced even very good venture funds into much more resource-limited approaches. There are a few exceptions to this trend, especially Third Rock Ventures in Boston, which still builds old-fashioned early stage biotech companies some of which tackle translation. Third

[6] www.kauffman.org/uploadedFiles/vc-enemy-is-us-report.pdf
[7] Ibid.

Rock Ventures recently announced[8] that it had raised a third fund, its largest one yet, of some $516 million. But the traditional venture capital model has been greatly diminished and many fewer projects are able to obtain financing this way.

All in all, despite strong financial performance of the pharmaceutical industry and despite large secular increases in NIH and other basic research funding compared to five or ten years ago, translation remains a big and challenging bottleneck.

[8] http://www.xconomy.com/boston/2013/03/25/third-rock-reloads-with-516m-new-fund-looks-to-start-16-new-cos/

4. Specific challenges within translational research

A number of specific challenges exist within translation. Any effort to improve translation of new therapies to market will have to address some or all of these challenges. The efforts toward greater adoption of stem cell and regenerative medicine technologies supported by CIRM have made much headway including some progress in translation. However, the initial $3 billion allocation to CIRM, while a large amount of money, was not intended to support full clinical development all the way through Phase 3 trials and registration. It is worthwhile to consider both traditional and non-traditional approaches to meeting this challenge. They include:

- Whether to and how to co-invest in IP alongside academic institutions and inventors
- How to fund creation of necessary but expensive tools for drug development
- How to select the most translation-worthy projects
- How to work with pharma
- How to ensure that projects funded in the translation phase are taken forward into later-stage development and marketing

Above and beyond these general challenges, CIRM faces some additional challenges in bringing forward projects in the stem cell and regenerative medicine areas:

- Reluctance of some pharma companies to invest in innovative but more risky therapeutic approaches
- Few case histories of regulatory approval due to the novelty of the field
- Absence of a single disease state around which to focus donors or partners

It is beyond the scope of this white paper to advise CIRM on how to address all of the challenges and obstacles described above. But it is our hypothesis that most if not all of these challenges can be overcome and that the result could be a robust, sustainable mechanism that supports CIRM's mission of funding worthwhile research in the stem cell and regenerative medicine fields. Given the nascent stage of many of the translation efforts described below, it is not possible to say that a clear path exists. But by observing the achievements and strategies taken in the approaches described below, CIRM can draw valuable lessons on how to proceed should it decide to move in this direction.

5. Within the challenges, seeds of a solution

In its 2011 research paper[9], FasterCures broke down the challenges inherent to all translational research, a category which in our view necessarily includes regenerative medicine, into four key aspects:

- Lack of funding
- Lack of technical expertise
- Lack of incentives
- High risk of failure

The challenges to funding translation have been examined above. The other three challenges, daunting though they may be, point the way to some potential solutions.

- **Lack of technical expertise**. The process of translation is both science- and technology-intensive. Specific expertise is required on both the target side (biology) and the molecule side (chemistry of small or large molecules). When cell therapies or tissue-engineering therapies are considered, the technical demands are equally high but the availability of expertise to address them is much lower. Development of all types of therapies requires deep knowledge of the patient populations and any inherent clinical, financial or societal challenges in addressing those patients. Any proposal to bridge the translation gap must address the need for high-level technical input. **And any organization that can bring significant technical expertise will have an inherent advantage.**

- **Lack of incentives**. The high degree of uncertainty involved in translation requires that those involved in the process be both incentivized to the upside if the therapies work and protected on the downside if they fail. In our view, the former has been one of the chief disappointments of NIH-funded clinical studies and their counterparts in other countries: the absence of a positive feedback loop in the event that studies deliver positive results. Follow-on funding, pharmaceutical industry licensing deals and financial returns are frequently lacking due to the way in which trials were conducted. Therefore, the best-quality individuals working on the thorny challenges of translation are typically found in the private sector, in pharma or biotech, not in academia. And the latter – lack of downside protection – is one of the challenges inherent to starting and maintaining venture-backed biotech companies. At least in the traditional model, the risk of failure threatens not just the employees in the company that is trying something daring but also the venture capitalists themselves and even their investors, all the way up the chain. **Finding a model for funding translation**

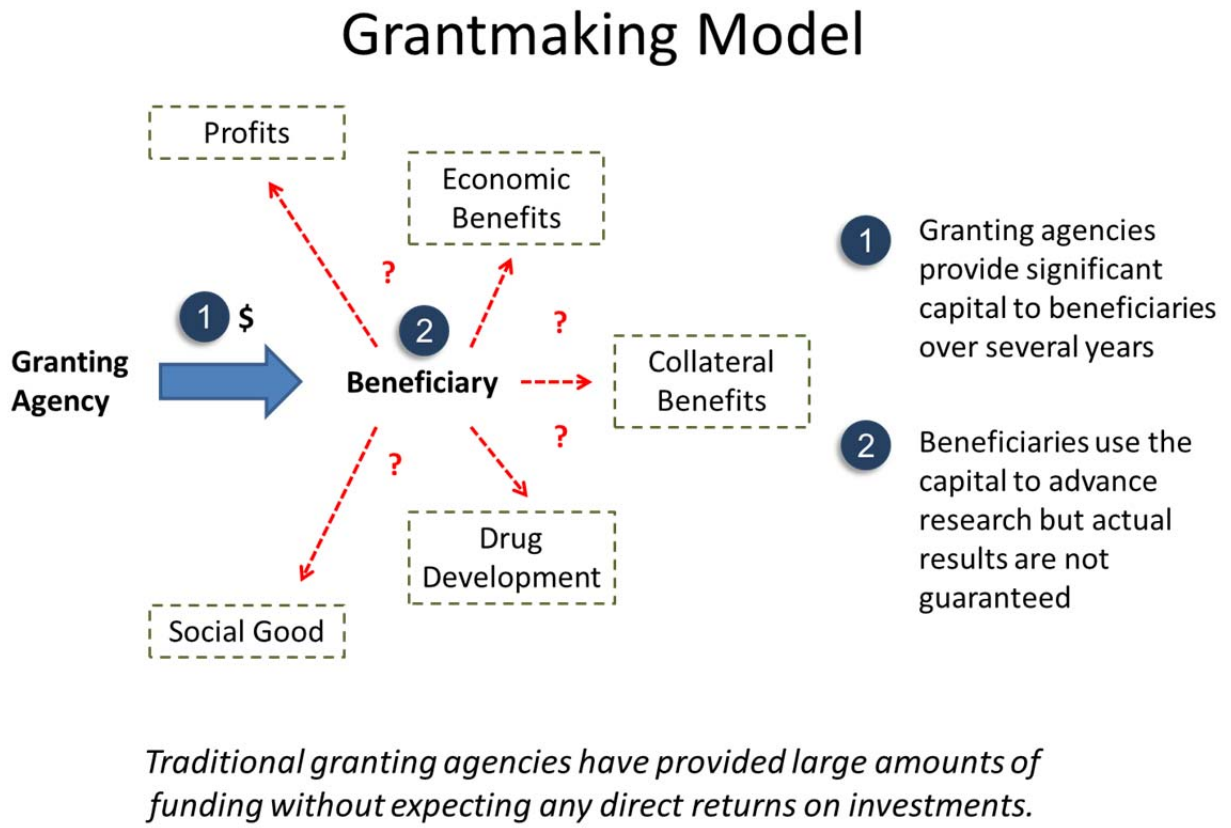
[9] http://www.fastercures.org/assets/Uploads/VOD-TranslationalResearch2.pdf

without creating new, risky biotech companies will be favored in today's markets.

- **High risk of failure.** This is related to the previous point. In what context is it all right to fail? Even if the perceived degree of difficulty is very high, say, in developing a new therapy for Alzheimer's disease or ALS, two notoriously tough clinical challenges, there can be a nearly irreversible stigma – not to mention a financial disincentive – attached to individuals taking on these risks who do not succeed. Therefore, the most functional approach to new and large medical challenges has to involve some sort of portfolio in which high risk in some projects is offset by lower risk in others. **An entity that is broad-based enough to pursue projects at differing levels of risk is going to have a built-in advantage.**

6. Interests and cash flows: A framework for looking at the funding of translation

As the team evaluated various mechanisms of research funding, we realized that the interests and cash flows involved could be reduced to simple graphics, facilitating discussion. The following figures illustrate our view of four fundamental approaches toward funding translation. Each will be accompanied by a paragraph or two of explanation.



Graphic: CBT Advisors

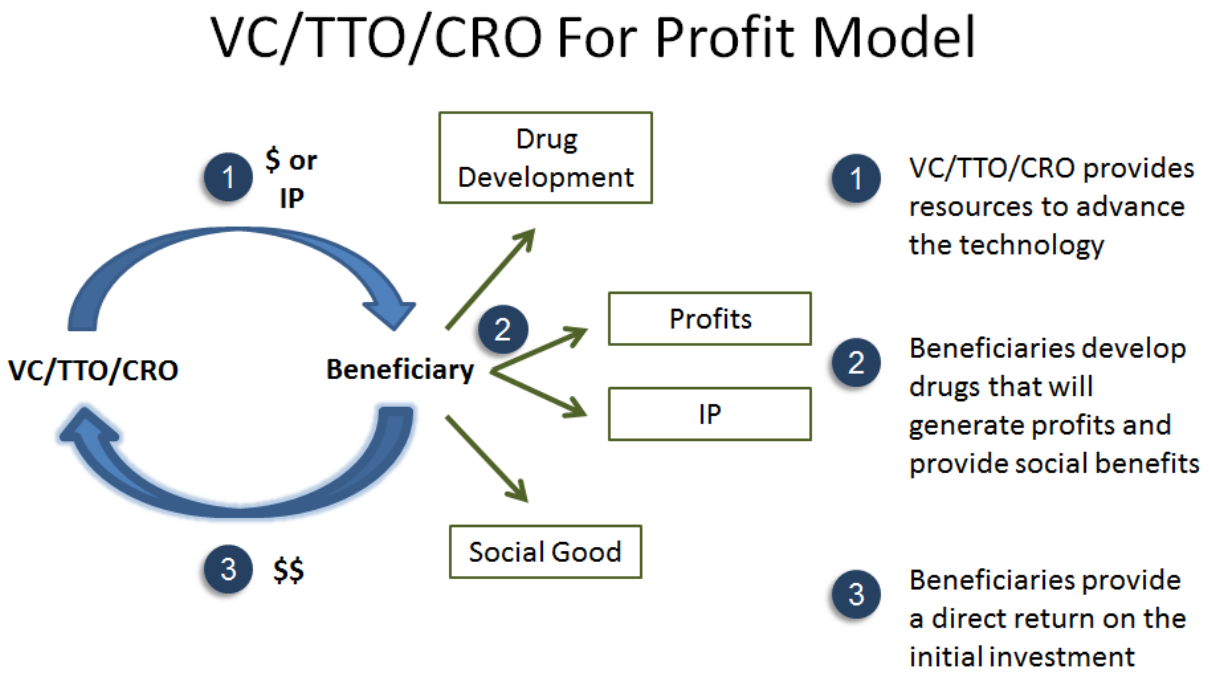
Fig. 4: Grantmaking has traditionally been a one-way proposition

As shown in Fig. 4, the traditional model of grantmaking – whether pursued by federal agencies like the U.S. National Institutes of Health or the Medical Research Council (UK) or by state agencies such as CIRM – have traditionally not expected a return on investment. The money flows one way. Collateral benefits are supposed to then flow from the beneficiaries' use of the money. This method may have worked reasonably well for funding basic research (though even that proposition has been the subject of

some dispute). However, experience has shown that when this method is used to fund translation, it runs into some challenges.

Recognizing this deficit, NIH has recently put $480 million into its Clinical and Translation Science Center (CTSC) Awards, and another $500 million in a National Centers for Advancing Translational Sciences (NCATS). These grants are supposed to be much more targeted than basic-research funding. The outcomes of these granting programs are not yet clear.

A new granting agency model has emerged in the context of regional economic development. The economic benefits referenced in Fig. 4 can include job creation, tax revenues and other downstream effects of the establishment and growth of drug development companies in a particular geography. One example of such a regional entity is CIRM itself, of course. Another one is the Massachusetts Life Science Center (MLSC; http://masslifesciences.com/). MLSC was established in 2007 and as of 2012 has disbursed or committed $302 million in grants to academic organizations and medical centers; investments in and loans to life sciences companies; and grants for capital projects such as incubators and manufacturing facilities. These grants are virtually all traditional “one-way” grants with no mechanism for a direct financial return on the state’s financial investment. Therefore, MLSC was not considered in greater depth as a potential role model.

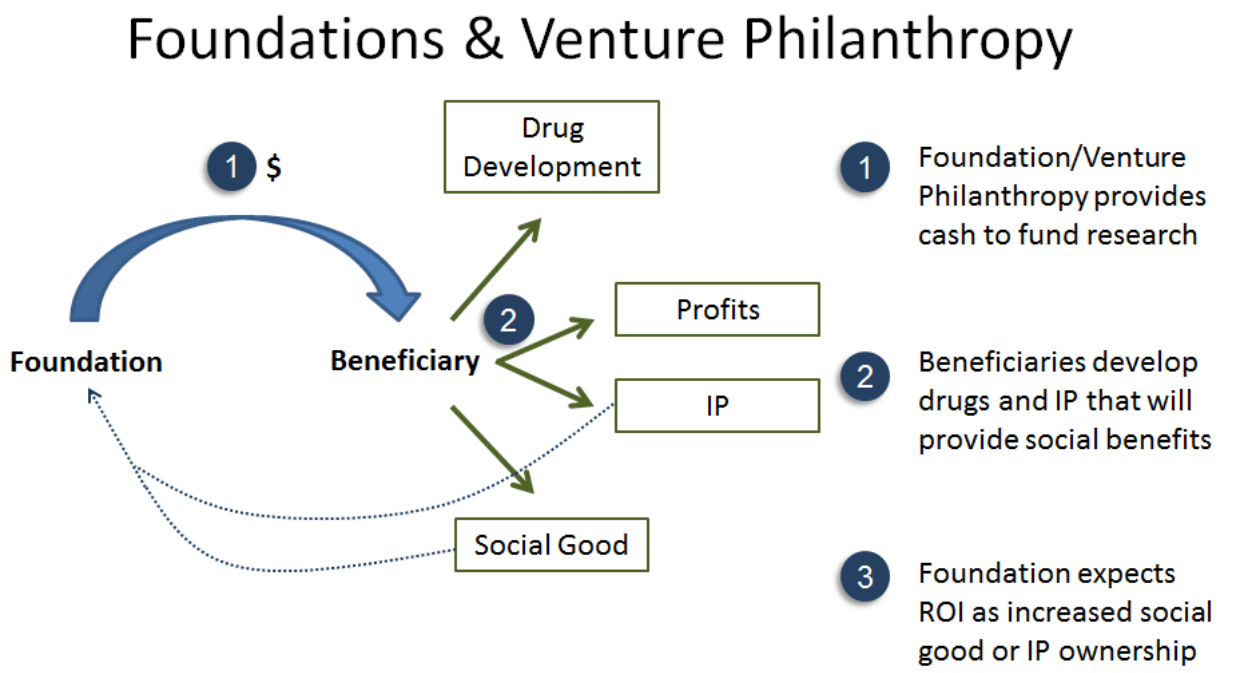


Graphic: CBT Advisors

Fig. 5: Investors in translation expect a financial return

Figure 5 shows the idealized version of the for-profit model of investing in translation. Venture funds (to the extent that they invest in translation), tech transfer offices and the newcomers, contract research organizations, are putting in money or intellectual property or both in return for a financial return on investment. Other positive developments usually occur in the process, including the social good that comes from new therapies reaching the market as well as additional intellectual property. But the main purpose of these models is to generate revenue.

Recently, some new approaches to for-profit, translational investment have emerged. These will be treated in more detail in the summaries of the approaches below. In particular, Syncona, a new venture-like entity in Great Britain, has emerged as an especially innovation-focused and long-term venture-type investor. Although Syncona has not yet made investments into translation, it is in a particularly good position to do so given its large fund size, ability to attract co-investment and especially its long-term focus. Another emerging example of a novel, for-profit approach is that of Evotec AG, a contract research organization in Germany that has begun to strike partnerships with some of the biggest-name research universities in the United States

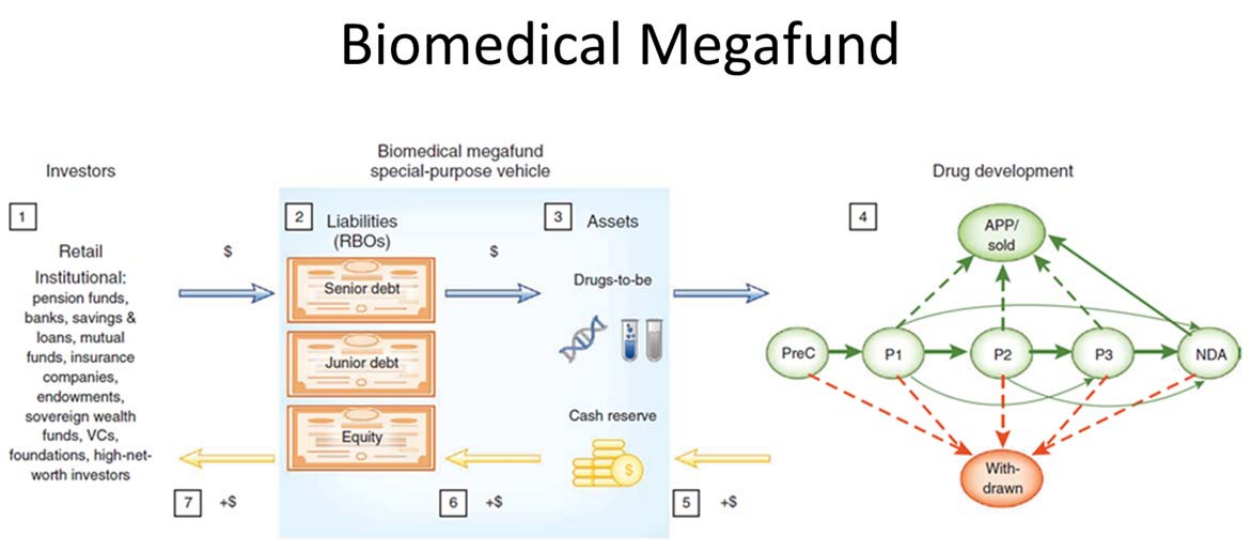


Graphic: CBT Advisors

Fig. 6: Venture philanthropy efforts blend granting with for-profit mechanisms

Over the past fifteen years, venture philanthropy (Fig. 6) has emerged as a "win-win" method of supporting translation inside biotech companies. Typically practiced by charitable foundations focused on specific diseases, venture philanthropy provides sizable amounts – usually in the millions of dollars – to fund specific drug or therapy discovery or especially drug or therapy development programs inside for-profit biotech companies. The companies derive the bulk of any profits generated from these endeavors but foundations are usually in a position to make back some multiple of their initial investment and, in addition, to realize a tangible therapeutic benefit to those who suffer from the disease in question. CIRM has pursued a similar model, particularly in its Disease Team research awards.[10]

[10] http://www.cirm.ca.gov/our-funding/research-rfas/disease-team-research-i; http://www.cirm.ca.gov/our-funding/research-rfas/disease-team-therapy-development-iii



Graphic: Nature Biotechnology

Fig. 7: The "megafund" concept of Prof. Andrew Lo

Figure 7 shows the business structure of a biomedical megafund special-purpose vehicle as described in Andrew Lo's article on that topic published in Nature Biotechnology on 30 September 2012.[11] In this model, funds are raised from retail or institutional investors (1) through the capital markets issuance (2) of various types of debt and equity. These funds are invested in molecules being developed to cure, in this case, cancer (3). Some funds are reserved to pay for later clinical development costs and, if required, to cover the first few periods of coupon payments. The portfolio of drugs is developed over time (4). At any time a compound can be discontinued or move to the next or subsequent phases, based on the results of the trials. It is also possible that compounds can be sold before their FDA approval for marketing if it is necessary to monetize them to cover some of the fund interest or principal payments. Any compound that is approved for marketing as a new drug is sold to a biopharmaceutical company. At the end of the life of the fund, all remaining compounds in the portfolio are sold (5). After bondholders are paid back (6), the residual cash is used to pay back the equity holders (7). VC, venture capitalist; RBO, research-backed obligation; PreC, preclinical; P, phase; NDA, new drug application; APP, approval.

[11] http://www.nature.com/doifinder/10.1038/nbt.2374

7. Specific approaches in brief

a. Grantmaking (One-Way) Models

Examples of grantmaking models we considered were **Catapult** (UK); **MaRS Innovation** (Canada); and the **European Lead Factory**.

1) Cell Therapy Catapult (United Kingdom)

OVERVIEW

Cell Therapy Catapult is part of a new UK network of seven technology and innovation centers. The Catapult centers are part of a government initiative that focuses on innovation and pre-commercial development in order to promote and accelerate growth of "high value development activity" in the UK. In creating CT Catapult, the UK government has recognized that small- and medium-sized enterprises (SMEs) represent the majority of cell therapy companies. These companies face challenges with technological, regulatory and strategic uncertainties. CT Catapult will address these challenges by provide SMEs with enabling infrastructure and expertise (i.e. clinicians, technologies, regulatory bodies, etc.) to speed up product development and market entry.

CHARACTERISTICS

- Public sector
- Not sustainable
- Not intended to be profitable or even to return capital
- Not focused on IP ownership
- An expression of the UK government's industrial policy that is meant to support UK business

ADVANTAGES

- Provides a mechanism to lower risk to regional businesses and increasing competitiveness
- Shares cost burden equally among government, academia and industry

CHALLENGES

- No proven role model

- Arguably less valuable in life sciences; model has been deployed more often in information technologies where manufacturing and enabling technologies loom larger

2) MaRS Innovation (Canada)

OVERVIEW

Based in Toronto, MaRS Innovation (MI) was created in 2008 to offer early-stage funding, management, mentorship and IP strategy protection for inventors in MaRS Innovation's membership institutions. The creation of MI was driven by the Canadian federal and Ontario governments to support innovation. This led to MI receiving a $15 million[12] grant over the course of five years from the Networks of Centres of Excellence for Commercialization and Research (CECR) to act as a commercialization agent for the intellectual property created by their member institutions. MI also received $15 million from its member institutions. In the fall of 2012, MI received a further $15 million from Ottawa to create the Centre for Commercialization of Regenerative Medicine (CCRM). MI has also worked with Ontario to provide 'superseed' money, ranging from $20,000 to $50,000 per project for very early stage commercialization initiatives. MI's involvement has resulted in support and relationships with large companies such as Merck Frosst, IBM and Johnson & Johnson.

CHARACTERISTICS

- Not for profit
- Essentially a tech transfer initiative with support for its 16 member institutions and spinout companies
- Focused across all technology areas, not just healthcare
- Not likely to be sustainable – will depend short-term on government funding and long-term on marketplace success of inventions (still very tenuous)
- Recently set up a Centre for Commercialization of Regenerative Medicine
- 12 healthcare companies spun out since 2008, no big winners
- Based in Toronto and most projects come from there
- Similar to Ascenion (Germany), MRC Technology (UK)

ADVANTAGES

[12] These are Canadian dollars. The Canadian dollar and the US dollar have been at rough parity for the last few years.

- Bundles the IP and assets from multiple institutions, potentially making it easier to find partners
- Could lead to catalytic investment into useful platforms and tools for regenerative medicine e.g. stem cell banks, databases etc.
- One company, ApneaDx, received seed funding from Johnson & Johnson; another received Series A venture money from VC sources as well as Qiagen
- In 2012, an early validating partnership was signed with Baxter ($1 million). Baxter and MaRS Innovation will identify investment opportunities emerging from well-validated scientific research discoveries within MaRS Innovation's sixteen member institutions. Baxter will provide up to $1 million in funding over a three-year period to support promising individual projects based on their positive due diligence, which will be leveraged with financial support from MaRS Innovation.[13]

CHALLENGES

- Will require continued infusions from government until inventions turn a profit
- Amounts of money (less than $50 million over five years) quite small
- Does not offer pharma industry relationships "baked in." Each relationship with pharma has to be built from scratch. Little evidence of success as yet.
- Capital markets in Canada not large enough to carry local biotech companies to proof of concept studies

3) European Lead Factory

OVERVIEW

Funded by the Innovative Medicines Initiative (IMI), the European Lead Factory (ELF) is a "pan-European platform for drug discovery" that will allow academia, industry, SMEs and patient organizations to work together and advance novel scientific research. The world's largest public-private partnership in health, IMI supports collaborative research projects between industry and academia in to order to accelerate development of new treatments for patients. By using an open innovation approach to crowd-source research, IMI hopes that ELF will allow key stakeholders in the drug development process (especially academia and pharma) to share knowledge and IP.

With participants such as Bayer, Janssen (Johnson & Johnson) and other big pharma companies (for full participant list, see appendix), ELF has a well-established molecular library. In total, the seven large drug partners will contribute at least three hundred thousand compounds, while academics and other collaborators will contribute

[13] http://marsinnovation.com/2012/10/baxter-and-mars-innovation-form-strategic-partnership/#.UWXDeLWLaSo

about two hundred thousand other compounds. Using a selection process that evaluates compounds based on "novelty, diversity potential, innovative design, synthetic tractability and other criteria," small and medium-sized companies (SMEs) and academic institutions will first establish high quality compound libraries. With high throughput screening (HTS), industrial-scale screening can be used to further identify potential molecules and drugs. With this approach, ELF hopes to improve the biological properties of existing molecules and increase the diversity of biological targets pursued by companies (especially those that are poorly represented in current libraries).

CHARACTERISTICS

- Not for profit but meant to be self-sustaining
- Well-funded through the European Union Framework Programme 7
- A mechanism in place to protect IP if any is discovered

ADVANTAGES

- Participation of seven big pharma companies lends credibility
- Compound library is large enough to be valuable
- Access to more targets would be valuable for drug discovery
- Risk-sharing between public and private entities can encourage participation

CHALLENGES

- No structure like this has been shown to work
- Next steps are unclear after molecules are identified
- How will key stakeholders benefit if new IP is discovered?

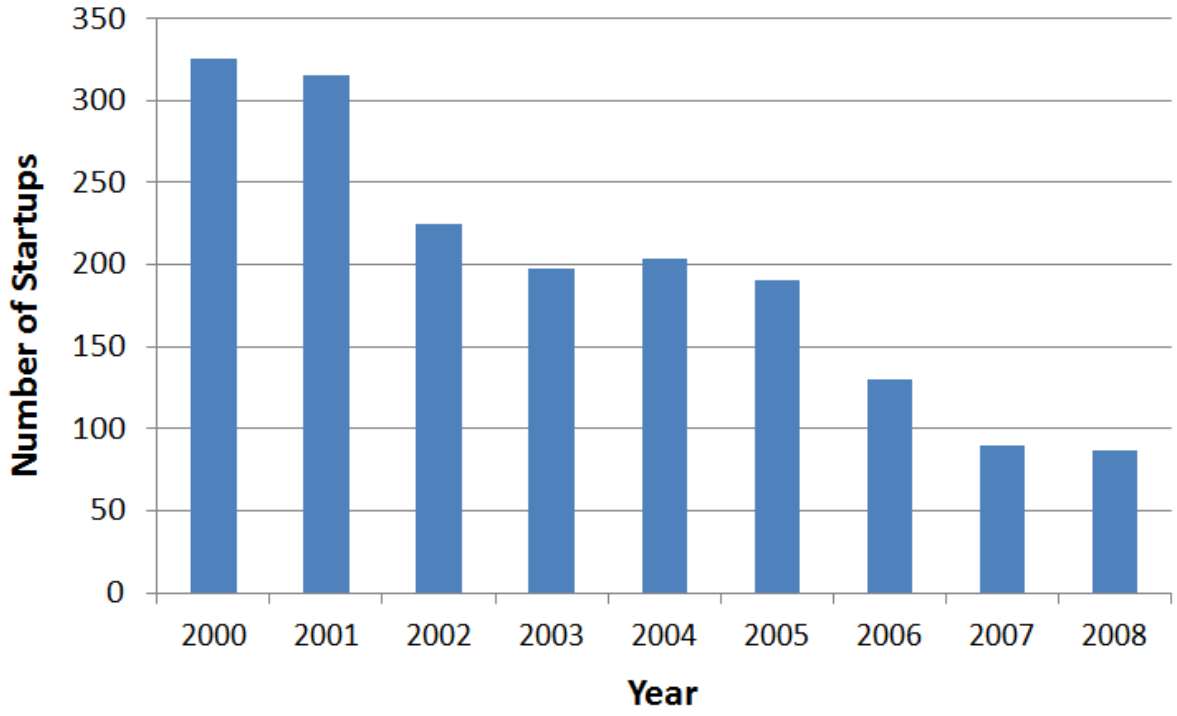
b. For-profit models

Among for-profit models we considered include **venture-backed project financing, Syncona, Osage** and **Evotec**. Traditional technology transfer offices are additional for-profit vehicles worth considering. We chose one technology transfer office, **MRC Technology**, that has begun operating a small CRO.

4) Venture-backed project financing

OVERVIEW

Venture-backed project financing or "asset-based financing" represents a new trend in the venture capital world. In the old paradigm, IPOs were liquidity events and venture firms were incentivized to build companies that made viable IPO candidates. Even if each company did not possess a full, rich pipeline of product candidates, as long as its lead candidate and perhaps the second program were considered viable, bankers and retail investors had no trouble paying for the chance to own the shares and wait for success. This all began to change in the aftermath of the post-bubble market downturn of 2001. Retail investors stopped paying premiums for these companies, rightly objecting to being charged for the "company" aspect of what was really a portfolio of assets. By 2008, when the financial crisis hit, any IPOs that occurred either happened after a company had started receiving revenue from its products or it occurred at a price that left venture investors investing alongside IPO investors and hoping to exit later. So venture investors dramatically slowed their investment in companies (see Fig. 8).



Data: BioCentury. Graphic: CBT Advisors

Fig. 8: The startling decline in the number of biotech startups[14]

This diminishment of what had once been the main exit route for venture-backed biotech investments left venture capitalists to find new models with which to finance

[14] Graphic adapted from "Life in the New Ecosystem," lead article in Back-to-School Issue, BioCentury: The Bernstein Report on BioBusiness, Sep. 14, 2009, p. A2.

promising early-stage candidates without taking undue risk. The "project financing" or "asset-based financing" was one of the results of their search. Under this model, a venture investor sets up a holding company for one or more assets. The investor assembles a stable of drug development experts and hunts for drug candidates within academia; within the pharmaceutical industry (e.g. in the form of spinout molecules); or within biotech, including in the VC firm's existing portfolio. Once some promising early assets are identified, single financial entities are set up within the holding or separately and the VC invests into those entities with the expectation of realizing an exit once the entity has reached a certain, probably clinical, milestone such as Phase 2 proof-of-concept data. Many variations on this model are possible involving earlier assets funded to earlier milestones (e.g. lead identification) or multiple assets bundled to mitigate risk and handed off to development teams incentivized to advance the whole package.

CHARACTERISTICS

- For-profit model run by venture firms
- VCs develop assets projects instead of (or in addition to) companies
- Widely adopted in the transition away from traditional VC funds
    - Atlas Venture
    - CMEA
    - Healthcare Ventures
    - Index Ventures
    - TVM Capital
- Creates single-asset entities managed by a VC holding company
- The point is to earn venture-like returns on $150 million to $250 million exits on $12 million to $15 million project financings
- Requires staff of drug discovery and development experts on retainer or on payroll
- Popular among some pharma companies e.g. Eli Lilly & Co.
- Focus on developing specific products or technologies rather than building successful companies
- Products/ technologies can be sold at any time during life cycle to generate cash
- VCs have control over sale, licensing and management of IP

ADVANTAGES

- Modular approach allows precise deployment of capital ("capital efficiency")
- Fitting model for a capital-constrained, low-IPO environment
- Assets can be selected on a case-by-case basis, leading to stringent criteria
- Funding to drug development milestones (lead compound, safety data, efficacy data) provides greater control

- Outsourcing in principle eases cost of obtaining meaningful data (though in some cases, costs may be higher due to heavy use of expensive consultants rather than less expensive management team members)
- Reduces overhead from setting up full-fledged operating companies
- Allows VCs to fund only "top priority" programs, one per company, rather than funding a pipeline of five or more programs within a company; one of those five will be the fifth-best and hence probably not worth funding
- Makes shutdown of projects easier
- Allows projects to be funded by individual VCs rather than syndicates

CHALLENGES

- Untested over the long haul
- Makes VCs a surrogate for drug development execs – not necessarily an area of expertise for them
- Very dependent on contract research organizations to meet key milestones
- Hard to appropriately incentivize staff members used to receiving options in companies
- Less downside protection for staff in the event that a project fails to meet a milestone
- Giving pharma (e.g. Lilly) control in the form of opt-in rights makes it hard to raise VC money and hard to obtain the best projects

5) Syncona Partners: An evergreen fund seeking to bridge the venture gap

OVERVIEW

Founded in 2012 by the Wellcome Trust, Syncona Partners is an independent subsidiary of Wellcome Trust and operates as an evergreen investment company. Syncona provides financial resources to companies and individuals that advance the Wellcome Trust's vision of improving human and animal health through biomedical research. Syncona identifies, supports and develops technologies that will revolutionize the healthcare market of the future.

According to its web site,[15] Syncona aims to hold investments in a small number of significant, profitable businesses around the world that are transforming the healthcare markets. In particular, Syncona will finance early- and late-stage companies in the healthcare fields of devices, therapeutics, diagnostics and information technology.

[15] http://www.synconapartners.com/strategy/

Syncona will invest as a majority investor or as part of a syndicate; investments will range from £1 million ($1.52 million) to £20 million ($30.4 million) per company. Syncona will support partner organizations as they grow and succeed in order to create long-term, sustainable healthcare businesses.

With just a few forward-looking investments, Syncona has the potential to set a new tone in VC investing.

CHARACTERISTICS

- For profit
- Evergreen entity with nominal 20-year horizon
- Structured as an operating company rather than a VC partnership
- £200 million ($304 million) initial size
- Invests across all life sciences
- Backed by Wellcome Trust, a large and credible UK granting agency
- Partners are all experienced VCs with high credibility
- Sustainable in principle
- IP-focused – Syncona invests in traditional companies that own their own IP
- Looking for long-term investments
- International mandate with focus on Europe (London-based)
- Launched officially in January 2013

ADVANTAGES

- Wellcome Trust is a valued brand
- Opportunity to see lots of early science, fine tune its judgment
- Compared to traditional financial VC, Syncona has multiple advantages
    - Longer timeline to exit
    - Ability to invest in early science pre-translation
    - Able to do early-stage investing across multiple areas including interdisciplinary ones
    - Single limited partner, no need for external fund-raising
    - Implied commitment for more financing
- Compared to traditional corporate VC, Syncona has several advantages
    - Unfettered by the interests and goals of a single pharma or life sciences company
    - Not subject to the pressures on corporate executives or the demands of the balance sheet

CHALLENGES

- Finding co-investors

  - Most financial VCs' time horizons are much shorter than Syncona's
  - Most corporate VCs are more oriented to their own parent companies' pipelines
  - Fund structure as a company could lead to a lack of alignment with co-investors
- New fund – needs to establish a brand of its own
- Having a single limited partner is always a risk. Wellcome Trust has pulled the plug on funds in the past e.g. September Ventures
- Some skeptics say that a long time horizon disincentivizes fund managers from acting quickly. Syncona's compensation scheme is not public but it has to have been designed in a sensitive manner in order to avoid agency issues highlighted in the May, 2012, Kauffman Foundation report.[16] One such issue was general partners raising too many venture funds in too short a time period. The Kauffman Foundation was itself a limited partner in many venture funds. During the 1998-2008 time period, the report noted that some venture firms raised multiple funds in a short time period in order to "stack" management fees instead of seeing each fund through to achieving at least some early returns. This lack of aligned interests between limited partners and general partners was one of the reasons the report identified for poor performance of VC funds during that time period.
- May be limited to European investments (though Syncona is screening investments from North America)

6) Osage University Partners: A venture fund aligned with universities

OVERVIEW

A $100 million venture fund, Osage University Partners (a sister fund to Osage Venture Partners) uses the "Participation Rights" of academic institutions to generate returns. Universities and research institutions primarily generate returns if their IP becomes developed into a drug through licensing fees, royalties and equity. As equity holders in start-ups, academia also has the Participation Right to maintain its ownership via future financings (and benefit from further success of the technology), but few have exercised such rights because they lack the cash and expertise.[17] Osage Partners bridges this gap by providing capital and expertise in investments on behalf of universities and research institutions.

[16] http://www.kauffman.org/uploadedFiles/vc-enemy-is-us-report.pdf
[17] http://www.elsevierbi.com/Publications/Start-Up/18/3/Schools-Rights-Are-Investment-Grade-At-Osage-University-Partners?elsca1=custom&elsca2=rss&elsca3=%3Fsource%3DSTART-UP

As a first-mover with this unique approach, Osage Partners has established key relationships with 50 academic/ research institutions to ensure the success of their model. Osage Partners' exact formula of payout to its partners is unknown, but seems to vary depending on the organization. In addition to forming connections with TTOs, Osage Partners has positioned itself to strategically engage key stakeholders in industry and in the venture community. As such, Osage Partners has established a strong business network to facilitate their future investments.

Although Osage Partners' approach provides value to previously useless "Participation Rights," it may be quite some time before a return can be made on the initial investment. As a result, Osage may have to invest in companies that will guarantee returns. With more than 2,000 licensed technologies and 225 "investable" companies, it may be difficult for Osage Partners to evaluate the best investments that will ensure returns. Osage Partners may have to forgo funding viable, longer-term early-stage projects and instead fund late-stage projects that yield a guaranteed short-term return.

CHARACTERISTICS

- New venture fund that generates returns based on the "Participation Rights" of academic and research institutions
- Currently has 23 portfolio companies with 14 in the life sciences (goal of 30-35 companies total)
- Investments limited to companies and technologies that have direct ties to its 50 university partners
- Typical investments are non-dilutive and range from $0.5 million to $2 million
- Rewards are aligned: partners whose spinouts contribute returns to the fund receive a larger portion of returns

ADVANTAGES

- First-mover advantage. Osage is the first VC to implement such a model and has established connections with 50 partners already. It will be difficult for another VC to find another 50 partners who are as reputable and well-established though there are opportunities to partner with the largest universities.
- Sizeable amount of initial funding ($100 M). Plans for a second fund are already in the works.
- Opportunity to make an impact: as TTOs become understaffed due to the financial crisis (increased number of inventions, yet same operating budgets)

CHALLENGES

- Limited budget of $100 million: leads to questions about where future funding will come from and the status of companies should the funding fall short.

- Negotiations for the participation of TTOs might be complicated
- Too early to evaluate success. Osage estimates that the first fund won't be repaid before a second fund will be raised (in 2014 or 2015).
- Difficult to form partnerships with academic institutions that already have strong TTOs (i.e. Harvard, MIT)
- Limited to co-investment opportunities; Osage is rarely the lead investor. This limits Osage's influence.

7) University-CRO Partnerships: Evotec in Partnership with Major Research Universities

OVERVIEW

Evotec, which calls itself a "drug discovery alliance and development company," is evolving beyond its original identity as a CRO. Headquartered in Hamburg, Germany, Evotec currently has over 500 scientists. In 2011, Evotec had revenue of €80.1 million ($104.1 million) and operating income of €5.2 million ($6.76 million). Evotec has drug discovery alliances with several large pharmaceutical companies.

Contract Research Organizations (CROs) assist pharmaceutical and biotech companies by providing clinical study and trial support so that those companies can reduce fixed costs and hire the appropriate expertise on every drug development project. Evotec has differentiated itself by becoming more involved in early-stage development by partnering with research organizations and obtaining some ownership of the technology that they are developing.

Evotec recently struck[18] a new partnership with Yale University. Under the terms of the deal, Evotec and Yale together will choose projects out of Yale laboratories and then help Yale to transform this early research into late preclinical and IND-ready assets. That, in turn, should create more value in licensing deals with pharma or in company spinouts. Evotec's role is to give input into study conditions; bring in highest-quality biological assays and chemical matter (e.g. libraries of small molecules); design and then complete initial pre-clinical studies; and package the assets for later clinical development within pharma. Evotec has the option to license any technologies developed. All costs and revenues are shared between Evotec and the academic institution.

[18] http://www.evotec.com/article/en/Press-releases/Evotec-and-Yale-University-form-Open-Innovation-Alliance/2372

The partnerships between Evotec and academic institutions are extremely innovative, given the fact that, historically, most university projects have been too early to attract serious pharmaceutical industry interest. Furthermore, most pharma deals have not resulted in significant up-front payments to university researchers or their universities. Most of the value in these partnerships was left to the back end, and pharmaceutical companies were not compelled to advance products based on the partnered technologies. Universities had little or no recourse in that situation and university licensing offices, with some exceptions, have typically not been very good at navigating those challenges.

CHARACTERISTICS

- For profit
- Turns university research projects into partnerable assets
- Focused on early to late preclinical development
- Sustainable in principle
- IP-focused
- International
- Began only recently – first public announcement in 2012
- Promises to help fill the “venture gap” in preclinical development

ADVANTAGES

- Novel approach – positive reception in the trade press
- Evotec has expertise in both biological and chemical aspects of drug development
- Evotec has deep experience dealing with pharma as customers – claims to know what pharma needs and wants
- Strong bargaining position and professional negotiation when assets are good – leads to unprecedented deals as in the case of Harvard/Janssen
- Highly reputed universities among the early partners (Harvard, Yale) lend credibility
- Compared to traditional licensing, this model offers a potentially much greater return to universities and university researchers on their early technologies
- Partners the clinical development with pharma, allows each sector to do what it is strongest at
- Offers universities an attractive way to add value to assets that would otherwise be too early to partner
- Evotec is driven by profit motive – a strong motivation
- Evotec has limited resources and will focus sharply on viable projects

CHALLENGES

- Most of the Evotec work force located in expensive Europe, not inexpensive India/China; this might be a disadvantage
- Each university will want its deal to be structured differently, which may be time-consuming to negotiate
- Evotec has a small market capitalization. If it does not make enough money in its core business, these partnerships and the model they represent could be endangered
- Deal with Harvard driven by a personal relationship between Evotec CSO and Prof. Doug Melton. Can this be replicated?
- Remains unclear if Evotec will be able to add enough value to satisfy universities or if Evotec will have to forward integrate into clinical drug development?

8) MRCT (UK Medical Research Council Technology)

OVERVIEW

Founded in 1999 as a follow-on to three prior UK tech transfer agencies, MRCT is the exclusive technology transfer agent (commercial arm) for the UK Medical Research Council (MRC), and it also acts as a technology transfer charity and company.

One of the world's most successful IP transfer companies, MRCT adds value to new technologies through patent protection, creative licensing of IP and partnered research with MRC institutes. By leveraging its unique role as an intermediary between academia and pharma, MRCT has developed tremendous expertise in managing IP and advancing translational medicine. Involved in more than twelve major drug discoveries and the formation of more than eighteen start-up companies, MRCT has developed an exemplary IP-focused approach .

In the 2009-10 fiscal year, the MRCT received a budget of £375m ($592.5 million) from the MRC Institutes. At the start of 2010, total licensing income generated by MRCT was over £500 million ($790 million) since inception.

CHARACTERISTICS

- Classic TTO with a laboratory of its own that produces proof-of-concept data and partners the resulting packages with pharma/biotech
- Parent organization (MRC = Medical Research Council) is focused on life sciences only, giving greater focus to MRCT
- Strong positive association and positive returns from monoclonal antibody therapeutics and related enabling technologies (Humira, Avastin) and affiliated companies (Cambridge Antibody, Celltech, Domantis)

- Employs seventeen chemists in its own laboratory. Scientists and managers recruited from pharma
- Identifying new drug discovery projects from other geographies, not just MRC (similar to Evotec)
- Over twenty drugs on the market came through MRCT
- Recently spun out a highly successful startup, Heptares, based on more than three years of research funded by MRCT and pharma (Pfizer)

ADVANTAGES

- MRC is a premier research institution
- Long track record lends great credibility
- Strong, professional management
- IP ownership gives MRCT the luxury of self-funding
- Can take on extremely risky projects since no shareholder will lose equity if a project fails
- Own lab (CRO) activity gives MRCT the flexibility to source projects from outside MRC as well as inside
- Unlike many TTOs, no aversion to starting a company (rather than selling a license to industry) if that is warranted

CHALLENGES

- Large operating budget not (yet) covered by income from licenses and shares
- Uncertain if there will be room for MRCT to play a more active role in holding and managing shareholdings in small companies spun out of MRC
- Success may encourage MRCT managers to want to create a private, for-profit company. That would put MRCT in conflict with MRC.

c. Foundations and Venture Philanthropy

Venture philanthropies in general will be considered and Fast Forward, an innovative partnership between a foundation (the US National Multiple Sclerosis Society) and a single pharmaceutical company (Merck Serono) will be reviewed in greater detail.

9) Venture Philanthropy (e.g. JDRF, ADDF, CFF)

OVERVIEW

Venture philanthropy "takes concepts and techniques from venture capital finance and high technology business management and applies them to achieving philanthropic goals."[19] In life sciences, venture philanthropy (VP) is mostly practiced by disease foundations that raise funds from donors and deploy some of those funds in partnerships with biotechnology and pharmaceutical companies. Venture philanthropies have become a considerable funding source for biotechnology research over the past 15 years. They are differentiated from these foundations' previous therapy development efforts in that venture philanthropies typically attach conditions to their grants to incentivize progress, rather than providing general funding for discovery research. These conditions hold a researcher or company accountable for further developing the funded programs or else having to pay back the money.

Importantly, venture philanthropies enter the funding process with the explicit goal of making money, if not necessarily as much as they would in a for-profit setting. This goal aligns VP investors with pure financial investors such as venture capitalists. That alignment can play a critical role in making a funded company maintain focus on funded programs. The crowning measure of VP success – "doing well by doing good" is exemplified in the Cystic Fibrosis Foundation's (CFF) ten-plus-year-funding relationship with, first, Aurora Biosciences and then subsequently with its acquirer Vertex Pharmaceuticals, which eventually yielded Kalydeco, the successful marketed drug from Vertex. The many millions of dollars of returns on the Aurora/Vertex investment helped the CF Foundation to enter into what we believe is the largest VP deal in history together with Pfizer in 2012.[20] In that deal, CFF is providing $58 million over six years to fund pre-clinical research on potential CF therapies.

Venture philanthropy is especially useful for crossing the proverbial "Valley of Death" between target validation and Phase 2 proof-of-concept data.[21] VP can provide

[19] http://en.wikipedia.org/wiki/Venture_philanthropy

[20] http://www.cff.org/aboutCFFoundation/NewsEvents/2012NewsArchive/11-19-CFFT-Announces-Pfizer-Agreement.cfm

[21] http://opinionator.blogs.nytimes.com/2011/05/02/helping-new-drugs-out-of-academias-valley-of-death/

validation, funding and expertise to programs that otherwise might languish inside academia or biotech.

CHARACTERISTICS

- Not for profit but strongly aligned with for-profit efforts
- Able to draw on donations from disease foundations
- Focused on specific disease areas
- Sustainable in principle
- Has a claim on IP in funded companies
- Began many years ago (1980s) and greatly increased over the last 5-7 years
- Supported by FasterCures, an effective non-profit
- Promises to help fill the "venture gap" in preclinical development

ADVANTAGES

- Significant success stories (e.g. Kalydeco in cystic fibrosis; more than thirty drugs moving through the clinical development pipeline in 2011, a big increase over 2001[22]) generate publicity, which in turn creates a "positive feedback loop" driving new donations
- Increases degree of focus within biotech companies on specific disease programs
- Offers the possibility of smoother patient recruitment and market feedback due to the foundations' close contact with the affected populations
- Committed to generating cures more than profits)

CHALLENGES

- Has not been shown to work yet very much outside of disease-focused entities
- Much greater impact if tens of millions can be deployed – not every foundation can generate that much money
- Without the right network/ connections, it can be difficult to bring together pharma, academia, non-profits and negotiate funding, IP, etc.

10) Fast Forward, LLC: Accelerating Commercial Development/Innovation Fund for Multiple Sclerosis

OVERVIEW

Fast Forward, LLC was founded in 2007 as a not for profit organization and a subsidiary of the National Multiple Sclerosis Society. Fast Forward's stated goal is to "Dramatically

[22] http://digitalcommons.kennesaw.edu/cgi/viewcontent.cgi?article=1486&context=etd

increase the number of potential drugs in the development pipeline (resulting in more therapies)." Fast Forward aims to do this by means of funding and collaboration with academia and biotechnology/pharmaceutical companies. In addition, Fast Forward will provide leveraged funding to early-stage companies and academic groups preparing to start a company or license technology. Fast Forward has two funds from which it makes grants: the General Fund ($30 million) and the Collaborative Fund ($30 million including a $19 million collaboration with Merck Serono).

The General Fund program is attractive to both academics and pharmaceutical and biotech companies. The Collaborative Fund program resembles those programs covered in the venture philanthropy section above. We still question how likely it is that large pharmaceutical companies outside of those who invest in the fund would be interested in these programs.

CHARACTERISTICS

- Not for profit but VC-like in its aims and mechanisms
- Has funded thirteen companies including established private and public biotechs
- Does not own IP
- Earns milestones and royalties from commercial projects
- Created by the US National Multiple Sclerosis Society
- Successfully partnered with Merck Serono for $19 million

ADVANTAGES

- Strong expertise regarding multiple sclerosis – a true differentiator
- Venture-like model emphasizing commercial success factors e.g. management, additional capital
- Considerable amount of money raised through philanthropy ($30 million plus at least another $11 million)
- Provides insight and expertise to Merck Serono that could create more effective competition among pharmaceutical companies

CHALLENGES

- Fast Forward's exclusive ties to Merck Serono could limit its opportunities
- Concerns exist that project failure could lead to financial losses at FF since the organization has no apparent IP and no "clawback"[23] right
- A decision by Merck Serono not to license the project could lead other pharmaceutical companies to question that program's value

[23] http://www.answers.com/topic/clawback

d. Other programs

The bold proposal from Prof. Andrew Lo put forward in the October, 2012, issue of Nature Biotechnology is unlike any other funding mechanism ever suggested for drug development. It covers all stages of research, from basic research through translation to late-stage clinical development and commercialization. It proposes to use securitization (familiar from the U.S. mortgage crisis of 2007-2008) to balance the returns of the later stages of development against the risks of early-stage development.

The description of FasterCures, which could be of considerable utility to CIRM, is also included here.

11) A securitized "megafund" for drug development

OVERVIEW

Lo's proposed cancer "megafund" is a single, $30 billion entity that will fund a large number of biomedical programs (i.e. $200 million *each* for 150 programs). The model will invest in a large, diversified portfolio of early stage cancer research programs and finance programs through securitization (debt) and equity. Although each individual program has a high risk of failure, bundling them together and especially combining early-stage and later-stage projects results in much lower risk. Furthermore, the large size of the megafund reduces risk through diversification and would in principle attract capital from both risk averse and risk-seeking investors. As a result, a megafund could in principle fill the gap in translational medicine by funding more early-stage research programs.

CHARACTERISTICS

- For profit
- Relies on securitization (a la US mortgage market) to distribute risk
- Idea published in *Nature Biotechnology* 2012; no fund entity as yet
- Has spurred some discussion among funders of translation

ADVANTAGES

- Sustainable in principle
- Unusually strong ability to smooth out the risks involved in life sciences investing
- Long time horizon and momentum due to sheer size of the fund

CHALLENGES

- Novel, never been tried

- A lot of big and small concerns to overcome
- Royalty funds are already diversifying and might eventually cover most of the positive aspects of the proposed megafund

12) FasterCures: Non-profit supporting venture philanthropy

OVERVIEW

Founded in 2003, FasterCures is a non-profit think tank (part of the Milken Institute) based in Washington, DC, that aims to improve the efficiency and effectiveness of the medical research system. FasterCures is not a granting agency. Rather, it works both on its own and together with non-profit organizations on research policy (i.e. with NIH and FDA), new technology development that advances research (i.e. EMR, biobanks), innovative R&D models (i.e. non-profit and pharma collaborations), and new financing mechanisms. In order to speed up the time from discovery to drug, FasterCures offers several high-impact programs that stimulate innovative collaborations, increase patient engagement, improve research process and policy, and facilitate greater access and more strategic allocation of capital.[24]

As non-profits have become more active in funding research, FasterCures has played a pivotal role in facilitating the process. FasterCures helps non-profits fund research and provides them with an opportunity to de-risk assets for further development by pharma. Through "The Research Acceleration and Innovation Network," FasterCures has organized a community of 55 organizations that fund half a billion dollars in R&D each year to universities, early stage biotech and pharma[25]. Meanwhile, FasterCures' Philanthropy Advisory Service informs philanthropists of promising research opportunities. FasterCures has also featured novel funding models in its monthly case study series.

CHARACTERISTICS

- Non-profit, self-described "action tank"
- Independent from pharma, VC, academia, etc.
- Consists of several programs that address the entire drug development process
- Serves as a community-builder for research
- Focused beyond just R&D, also regulatory approval & reimbursement

[24] http://www.fastercures.org/About/what.php
[25] http://www.fastercures.org/traininventory/

ADVANTAGES

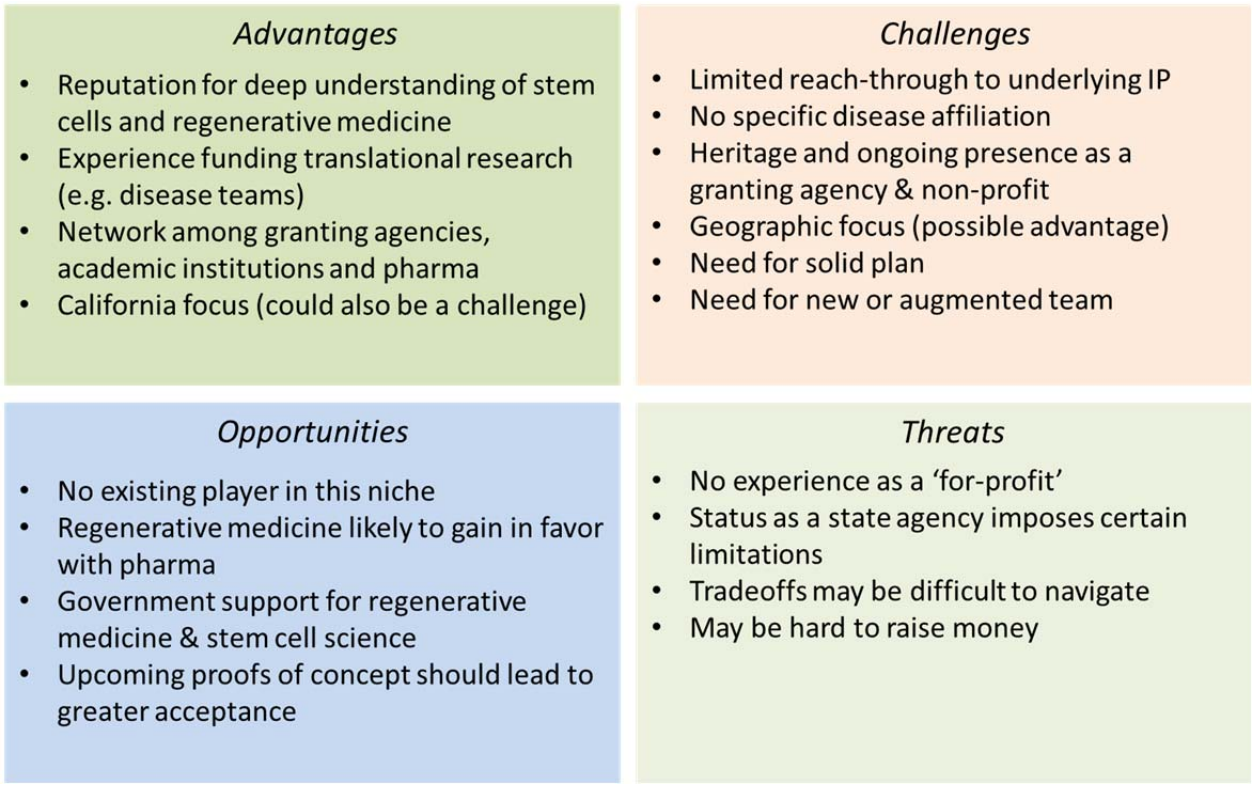
- Affiliation with Milken Institute assures high profile
- Strong connections with key stakeholders (doctors, patients, non-profits, pharma)
- Reputation for success; positive media image
- Unbiased patient-centric approach
- Helps bridge the "Valley of Death" by finding funders for research that VC/ pharma considers to be too risky and by motivating the funders to adopt best-practices

CHALLENGES

N/A

8. Pros and cons: what will work best for CIRM

When we looked at CIRM's current status as a high-quality granting agency engaged in funding both basic research and translation in the exciting area of regenerative medicine, we came up with the SWOT analysis shown in Fig. 9. This shows a simplified version of our view of where CIRM has advantages and where it has challenges in considering a transition to an even greater focus on funding translation.



Graphic: CBT Advisors

Fig. 9: The CIRM opportunity summarized

Although it is early days for most of the approaches to translation described here, CIRM can learn much from the experience of others in planning additional translation efforts of its own. CIRM funds translation already, of course, in its Disease Team Research grants. But some of the most promising mechanisms e.g. venture-like financing or conducting CRO-like contract research are more readily available to true "for-profit" entities.

As a thought experiment, we went through each of the approaches we covered in this analysis and evaluated which ones had delivered value as measurable by the generation of marketed products and the positive impact on patients' lives. We realized in carrying out this evaluation that most of the approaches described here are too early to have brought products to market, although there are some notable exceptions.

Kalydeco, the cystic fibrosis product marketed by Vertex Pharmaceuticals, was the product of not only pharma-driven drug development but also of funding and advice from the Cystic Fibrosis Foundation. Similarly, multiple antibody therapeutics have come to market with the help of MRC Technologies.

But by and large, the earlier-stage the efforts are, the less evidence there is of that level of success. So we shifted our focus to a "surrogate marker:" the level of interest in and commitment of pharmaceutical companies to the model. As measured by this standard, a number of the approaches described here have begun to achieve success.

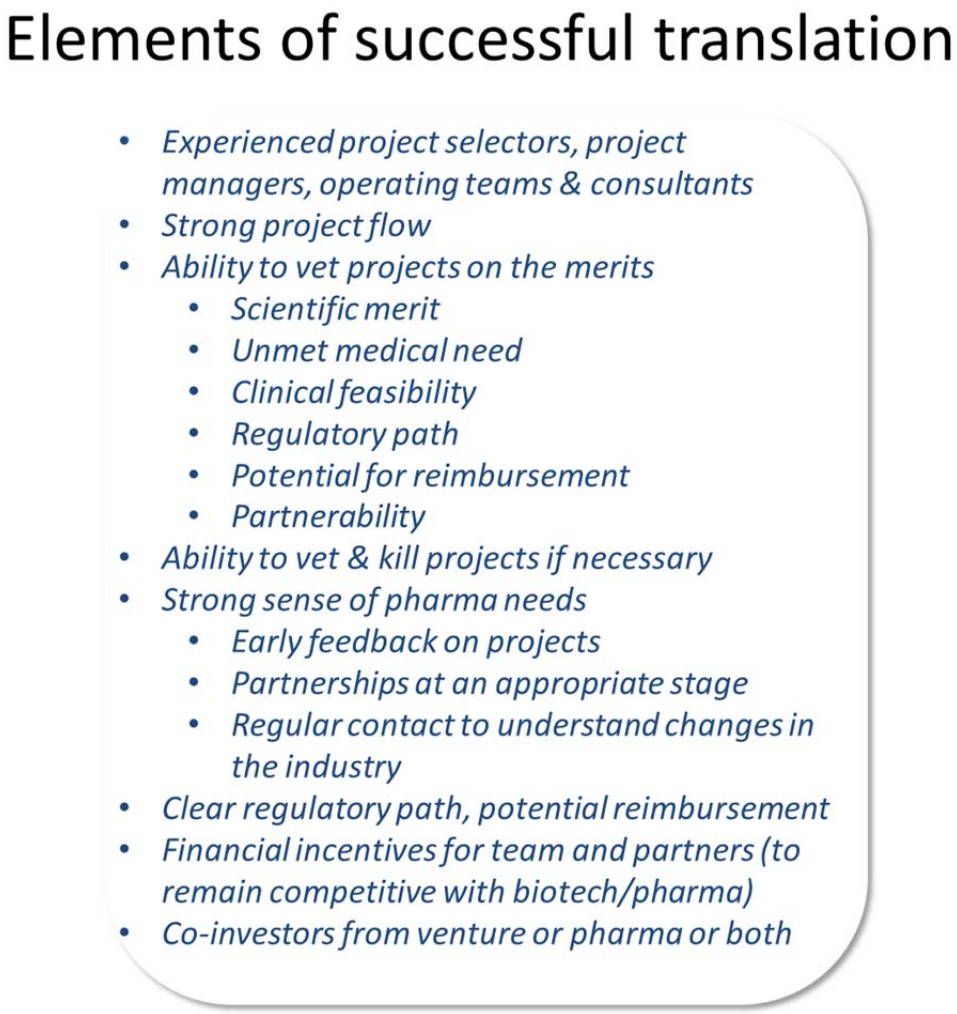


Fig. 10: All of these elements are achievable in multiple models: venture capital, venture philanthropy, asset-based financing, CRO partnerships. Some elements are very compatible with granting agency models (vetting, project flow, pharma interaction) whereas other elements may be less compatible (e.g. hiring operating teams, securing co-investment, providing biotech-like financial incentives). By managing some internally and outsourcing others, an experienced granting agency such as CIRM could expand further into funding translation.

In revisiting the list of challenges in section 3, we can begin to use these examples of success to illustrate how CIRM could overcome the expected challenges and build a viable, long-term funding structure for translation in regenerative medicine.

- **Lack of funding.** Raising funds either from donors, the government or private investors could be pursued. The challenge for CIRM will lie in leveraging its reputation for scientific expertise, project management and broad industry ties while not risking that reputation by venturing too far off its initial path. This will be a topic for much future consideration. The key achievement will be sustainability. It should be noted that only those approaches that can achieve a return on their investments in the space can be considered sustainable. Granting models do not work sustainably and even the CRO models such as MRC Technology have not yet proven themselves sustainable. Only the venture-like models and the proposed megafund would seem to offer true sustainability and here, too, there is not enough of a track record to say for sure that this would work.
- **Lack of technical expertise.** CIRM has already built a reputation as one of the premier if not the premier granting agency in the world for stem cells and regenerative medicine. That reputation will alleviate many of the startup challenges facing other approaches. In this regard, CIRM already resembles the more high-profile venture philanthropies mentioned here e.g. Cystic Fibrosis Foundation, the National Multiple Sclerosis Society and the Juvenile Diabetes Research Foundation. In the remaining years of the original CIRM funding, that reputation will improve even further.
- **Lack of incentives.** As stated above, finding a model for funding translation without creating new, risky biotech companies will be favored in today's markets. The asset-backed venture capital approach described here is a role model in this regard, ostensibly offering a better risk/reward to the investor once certain criteria have been fulfilled. Those venture funds that have teamed up with pharmaceutical companies as investors (Index Ventures, notably, with GSK and J&J, but also TVM Capital with Lilly) are giving themselves an even better chance of finding projects that would later be of interest to pharmaceutical companies but other funds may be just as successful.
- **High risk of failure.** Three of the approaches have explicitly addressed the high level of risk inherent in translation. In an interview with CBT Advisors, the MRCT head of business development said that MRCT seeks out projects that have higher levels of risk than a pharmaceutical or biotech company could typically tolerate.[26] Intractable targets, novel chemistries, challenging animal models – these are the building blocks of innovation and they are all the more favored in an environment of embracing risk. Syncona Partners decided to create an "evergreen" fund structure with a nominal 20-year lifespan as a way to get outside of the limitations of traditional venture funding. And Evotec has brought its hands-on drug discovery and development expertise to bear on both selecting projects to focus on those most likely to succeed, then adding even more value to them (at Yale) and advancing existing molecules of interest (at Harvard).

[26] Michael Dalrymple personal interview with Steve Dickman, CBT Advisors, 8 March 2013.

Through our analysis of FasterCures' approach and by engaging with their executive Melissa Stevens on a panel at a biotech / pharma partnering conference, CBT Advisors formed a very positive opinion of this organization. Thus, in addition to using the success examples as pointers, CIRM would be well advised to engage with FasterCures in a review exercise. In carrying out such an exercise, CIRM would follow in the footsteps of many high-quality foundations and non-profits and benefit from FasterCures' vast expertise. That was the value of considering FasterCures as one of the approaches.

Figure 10 enumerates many of the success factors that would go into a translational medicine program. All the elements listed are achievable in multiple models: venture capital, venture philanthropy, asset-based financing, CRO partnerships. Some elements are more compatible with granting agency models (vetting, project flow, pharma interaction) whereas other elements may be less compatible (e.g. hiring operating teams, securing co-investment, providing biotech-like financial incentives). By managing some internally and outsourcing others, an experienced granting agency such as CIRM could expand further into funding translation.

Two words about pharma. First, this report did not engage heavily in approaches that pharma itself is taking, for example in its partnerships with universities. This was done on purpose, since one of the success criteria we defined for the approaches we studied was "has pharma bought in yet?" and if pharma is driving one or another of these processes, then by definition that criterion has been fulfilled. In another external or internal project, it would be relevant for CIRM to investigate exactly how pharma is directly engaging with universities and see if the learnings in other technology areas can be applied to therapies based on stem cells and regenerative medicine. See also the recommendations in the concluding section of this report.

Second, the pharma industry is still principally focused on finding small-molecule or biologic therapies to treat diseases of heterogeneous populations. Some pharma companies are shifting into a more "personalized-medicine" approach, usually in conjunction with cancer therapy. An example of this is Novartis' 2012 partnership with the University of Pennsylvania to pursue personalized T cell therapies for cancer.[27] Other examples include gene and cell therapies beginning to be adopted by big pharma and biotech companies. For instance, Celgene partnered in March, 2013, with privately held bluebird bio of Cambridge, Massachusetts, to find stem cell-directed gene therapies in cancer.[28] But by and large, the pharma industry does not (yet) see how to make the amount of money it is used to making from small molecules and biologics.

This divided attitude and expectation of the pharmaceutical and biotech industries is a two-edged sword for a forward-looking non-profit like CIRM. On one hand, it would be reassuring and potentially catalytic if a pharmaceutical company could be found that

[27] http://www.uphs.upenn.edu/news/News_Releases/2012/08/novartis/

[28] http://www.businesswire.com/news/home/20130321005275/en/bluebird-bio-Announces-Global-Strategic-Collaboration-Celgene

would take the lead in a new CIRM effort to carry out translation. On the other hand, in our experience at CBT Advisors, innovation often happens in a more natural and unencumbered way when it happens *outside* of pharma's purview. Bringing it to them later, after the initial ideas have matured and taken shape, is almost guaranteed to bring greater financial upside to the developer.

For all of these reasons, it would be most advantageous if CIRM could find a way to position its efforts in the direction of venture capital or venture philanthropy investing, either in the traditional, company-building mode or, more likely, in the new, asset-based financing mode. The high status and the implied reach of a venture capital or venture philanthropy fund, not to mention its ability to raise capital, would be highly desirable for CIRM, especially in the years before high-profile regenerative medicine therapies reach the market in significant numbers. A lot more can be said about adopting the more constructive elements of a venture capital or venture philanthropy approach. Much has been learned in the industry over the past ten years and that experience is available for sale or for rent.

Evolving in the direction of venture capital would address one of the challenges CIRM faces in setting out in a new direction, namely, what to do about intellectual property (IP). Unlike MRCT or other tech transfer organizations, CIRM never had access to the underlying IP in the projects it funded, even the more translation-oriented ones. Obtaining access to this IP would be very problematic given the ownership position of inventors, universities and companies. But if CIRM became a funder of first resort for companies spun out of the academic institutions, or even a prime mover, perhaps together with a venture fund or pharmaceutical company, in founding companies that owned the IP inherent in promising regenerative medicine projects, CIRM could then follow a venture capital-like or venture philanthropy-like model in pushing these projects toward clinical outcomes and commercialization.

Such an evolution would not be trivial. The lack of reach-through to IP is included in the "challenges" section of the SWOT analysis in Fig. 8 for a reason. CIRM has achieved its reputation as a highest-quality granting organization without having access to intellectual property. Neither CIRM itself nor those who have dealings with CIRM are accustomed to CIRM exercising the leverage of a venture investor as it interacts with the rest of the translational funding ecosystem. Such a shift would have to be managed carefully and reconciled with CIRM's mission. There are not only brand and reputational challenges involved in this evolution. There are also large potential upsides, that is, a move towards venture capital or venture philanthropy investing could be broadly rewarded in both financial ways and in terms of benefits to society. CIRM will have to weigh these tradeoffs and engage in serious deliberations in order to arrive at the appropriate balance between being a granting agency (with few or no strings attached to its grants) and thinking more like an investor.

9. Conclusions and Recommendations

The field of translation is moving faster than ever toward new structures. This movement has created many opportunities. Regenerative medicine offers a very promising area in which to apply some of these structures. It is nascent enough and exciting enough to offer tremendous promise; at the same time, cell therapies and tissue engineered solutions are approaching or achieving clinical proof of concept in enough areas that it is easier than ever to anticipate broad-based success in the future. The basic research breakthroughs in stem cell research, such as the creation of induced pluripotent stem cells (iPS cells), are equally if not more encouraging in this regard.

In making recommendations to CIRM for how to proceed in this exciting area, we feel it is important to strike a balance. On the one hand, we want to urge CIRM to move forward quickly in exploring and embracing some of the new mechanisms. Much research is available for next-step translation and nothing will be gained from delay. On the other hand, jumping too quickly into an ill-considered structure would squander an otherwise very promising, indeed unique, opportunity. There is only one CIRM and it has carved out an influential and important role in supporting the best stem cell and regenerative medicine research. Any next step must uphold this strong tradition and allow CIRM to continue to function as a grant-maker for early-stage and precompetitive research.

The recommendations we choose therefore center more on “further study” rather than “immediate action.”

Recommendations

- ***Talk*** to a few key existing partners in academia, granting agencies and non-profits in a formal or informal benchmarking exercise
- ***Talk*** in a systematic way to pharma
    - Learn which pharma companies are most interested in regenerative medicine and which models will work best for them
    - Establish and maintain lasting relationships that will benefit CIRM and regenerative medicine research regardless of CIRM’s own structure
    - Determine if more than one pharma company is interested in similar elements
    - Learn who else in the space is trying to figure out a translational model and begin to keep tabs on those groups (“competitive intelligence”)
- ***Begin*** to identify an anchor investor or anchor donor for a new possible fund structure
    - For-profit (investor)
    - Non-profit (donor)

- ***Examine*** business models that have been used to deliver cell therapies, tissue engineering and other regenerative medicine approaches. Become an expert on these business models. This expertise will be an asset both in discussions with pharma as well as with investors, donors and other stakeholders.
- ***Do nothing*** to jeopardize CIRM's existing positive relationships with the state of California and other key stakeholders.
- ***Try*** to obtain financing for additional grants beyond the initial CIRM mandate
- ***Get input*** from FasterCures
    - Access to FasterCures' own knowledge and insight
    - Access to other non-profits that have moved in a similar direction
- ***Make*** key decisions early on regarding disease focus and geography
- ***Determine*** if and how a CRO model could work (very IP-driven)
- ***Consider*** what fits best with existing CIRM structures.
    - California focus both a strength and a liability: stem cell research is international
    - The nature of CIRM as a state agency is perhaps the biggest weak point – has to be addressed politically and cleared up as soon as possible or raising money will be unnecessarily challenging
- ***Set up*** a structure for translation in a well-defined relationship to CIRM's granting activities

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