Chapter 15
Creating ROI: Return on Innovation-the Partners Model

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New Technology Must Be Translated into Products to Benefit Patients

Healthcare Customers Expect Innovation to Improve Care and Cost-Effectiveness

Multiple complex challenges create an increasing demand for better and more cost-effective healthcare solutions. Many healthcare markets increasingly include aging populations with multiple chronic diseases, cancer, and obesity to name a few very expensive challenges. US healthcare system expenditures for chronic disease management annually exceed $1 T and for management of diabetes, heart failure, and chronic obstructive pulmonary (COPD) alone, costs are $367B [1]. Furthermore, healthcare inflation, increasing regulatory requirements, higher liability for patient safety, and an evolving NIH emphasis of basic over translational science all provide additional barriers to innovation by academic medical centers (AMCs) and their interactions with industry. Ironically however, at the same time, AMCs are expected to lead in the innovation process by addressing all of these modern challenges in healthcare.

In fact, the public expects AMCs to lead in innovation partly because of their dominant and critical role in US healthcare delivery and partly because they rely

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heavily on public funding intended to enable discovery in the biomedical sciences. In 1980, the Bayh-Dole Act granted title to intellectual property (IP) generated by inventions funded by the federal government to universities, small businesses, and nonprofit organizations, which further solidified the role of AMCs in biomedical science and healthcare innovation [2]. Academic institutions that emphasize innovation as important in their mission have made efforts to promote entrepreneurial cultures in their investigator communities, which collaborate with startup, pharmaceutical, and medical device companies to translate their academic inventions into commercial products for the benefit of society.

The relationship between AMCs and industry has resulted in increasingly defined but evolving professional and institutional conflict of interest policies. These policies are intended to protect against perceptions and realities of potential harms and abuse derived from financial incentives held by inventors and their academic institutions [3, 4]. Previous policies had been designed to avoid conflict by simply prohibiting these interactions [5, 6]. Increasingly, these evolving policies are being designed to recognize the benefits of public-private collaboration and to permit opportunities for these interactions while still maintaining patient safety and actively managing to minimize risk of bias and abuse introduced by these financial incentives.

Professional and institutional conflict policies have been crafted to accomplish a balance between the support of the innovative process and protections from any potential or actual harm. Previously, the balance had been tilted, without restraint, toward risk aversion by the institution prohibiting any support for innovation from healthcare industry suppliers who listen to voice of the customer in the market.

Currently many AMCs have taken critical steps to evolve their critical role to promote this translational process - one example has been the adoption of a “rebuttable presumption” approach. Although the institutional policies set conservative presumptions for faculty behavior regarding potential conflicts, administrative processes are beginning to review applications to better understand any potential conflicts and to allow the faculty to rebut these presumptions on a case-by-case basis. These applications request a waiver of one or more aspects of the presumption (i.e. rebuttal of the presumptions). If the faculty’s rebuttal argument is convincing, a waiver may be allowed. In these cases, institutional management plans are typically initiated to monitor any real or potential conflicts by the faculty member in their developing relationship with industry or further development of their inventions.

Discovery and Invention Are Not Innovation Until They Reach the Market

Before embarking on innovation, a deep understanding of the unmet need is critical for ultimate success. From the innovator’s perspective, the customer voice requires considerable work to clearly identify the problem that is being solved and to understand how each constituency in the healthcare system perceives the problem.

A clinician may be the end user of the product, but the purchase decision is made by the provider institution and they will be sensitive to the payer's willingness to reimburse. Clinicians are also not monolithic in their interpretation of an innovation's merit. It is a challenge to define a single solution to simultaneously meet all relative customer's needs. For example, in the field of bone marrow transplantation, even for cancer, there is little agreement among oncologists that the transplanted bone marrow cells should be purified to be cancer-free although this might be considered by some to be an obvious requirement.

Once a need is identified, which addresses a sufficiently large market that would justify the commitment of resources, it will be necessary to ensure that the technological challenges are understood well enough to be confident that these challenges can be overcome within a timeframe that is realistic. Ideally, technical challenges can be mitigated using institutional funding, perhaps even using federal funds, as a preamble to company creation. The more that the risk of the commercial proposition can be reduced prior to approaching potential investors, the easier it becomes to raise capital to create a venture for product development.

If the invention addresses a well-defined need that is significant enough to be worth solving and the technological risks are sufficiently understood and overcome, then investors can make a judgment as to whether, just because one can, a product development program should be pursued based on the invention, (i.e. Will the effort be worth it?). It is best to "fail fast" before too much effort and money has been spent for naught. An inventor or inventors who are so focused as to not be willing to walk away when confronted with reality could become a red flag to institutions and any potential investors. Frequently, the ultimate successful products from startup companies have not been the company's initial concepts but are altered versions that may not even resemble those concepts from the starting point.

There are many barriers to success in the market even if sufficient, initial financial investment has been garnered. Often timing is an important consideration – if a target innovation is too far ahead of customer awareness of the needs being addressed, adoption will be exceedingly delayed and revenue will be exhausted as subsequent investors lose patience. The challenge then becomes to prepare the market by educating customers to their value proposition. This is particularly challenging if the innovation is not a direct substitute with extra benefits for a product the customer is already using. The best combination is for the innovation to be an obvious improvement that customers would immediately understand and promptly switch to adopt. This requires careful planning and selection of the invention from the very beginning to ensure it will meet the needs of the market when it launches years after it was initiated.

Consider an example from our experience: a lab-on-a-chip diagnostic test for staging HIV disease in low-resource field settings. The technology was designed to determine if a patient's current therapy is working based upon thresholds for CD4 T-cell count. These T-cell counts would guide the decision to change treatments at the point of care. Over the multi-year course of the product development process, the market shifted to quantitative viral load rather than T-cell counts, making the

innovative technology for a hematologic analysis no longer relevant despite the elegance of the solution.

On the other hand, the timing can be late by introducing a product whose value proposition is minimally better than the current product, which addresses the same or very similar need. In this case, the startup company product is competing on terms other than its exclusivity to adequately address a need. This problem becomes compounded when the competing product is marketed by a large, well established company with a tremendous advertising and marketing budget, sales force, and established customer base. The option for the startup is to compete based upon price, which means the startup must maintain a very low cost of goods, inventory, distribution, and customer support. Because of this very minor advantage to its value proposition, the startup's product becomes a commodity. Typically, venture investors shy away from investment in products that will become commodities because of their highly restricted return on investment, particularly when compared to the return on investment for a therapeutic.

An ideal innovation solves the well-defined need using well-understood technology (i.e. no eureka moment required) before formation of the company. Even after these conditions are met, there are multiple business challenges that remain, providing significant risk for a successful execution of the company. These include: regulatory, marketing, sales, competition, supply, distribution, manufacturing, and market adoption, to name a few, and any of these can contribute risk to ultimate business success. Invention can only be accepted as an innovation after it experiences an ultimately successful introduction of the product into the market.

Only Companies Can Supply Products, Not Hospitals or Professional Practices

Companies are in the business to compete and commercialize products by achieving the rights to sell products, to create barriers for others to sell the same or comparable products based upon regulatory approval, to organize the marketing and sales force identifying customers for these sales, to enable and ensure that these products are sold and reimbursed, to maintain an inventory of products, and to provide long term customer support among many other company activities. The company maintains and supports the product sales and distributions either directly or by using original equipment manufacturers (OEMs), distributors, or other vendors. Hospitals and professional practices can develop and support protocols and practice guidelines but in general, they do not routinely replace the many company activities for a successful innovation; those activities are most appropriately handled by a commercial entity.

The biomedical industry has evolved to a point where pharma and medtech practice an "open innovation" model in which companies seek out invention from academic wellsprings of discovery. Suppliers and manufacturers can fill their development pipelines by in-sourcing early stage programs from researchers and

their host institutions who offer new and novel biological and clinical insights. This should be viewed as a healthy "ecology" in which the cooperating parties bring complementary expertise and resources to bear on important problems of commercial relevance ultimately for the benefit of public health.

Clinicians-Scientists Are Well Positioned to Find Solutions to Unmet Needs

Clinicians and scientists in academic medical centers routinely see clinical problems whose current solutions fall short of satisfaction by either the patient or the practitioner. Often, they are also in a position to ask "why" do we treat these conditions in this manner and "could there be better solutions" based on more recent scientific or technology advances? This creates a fertile environment for potential invention leading to innovation. There is a competitive advantage to the AMC setting that derives from the juxtaposition of practitioners of clinical medicine, basic science, engineering, and technology, who can provide solutions, with the clinicians, who are on the front lines of patient care (Fig. 15.2). The required clinical and technological interaction is promoted by the co-location of laboratory and clinic where collaborations can be initiated by encounters in a seminar, a grand rounds presentation, or in the cafeteria [7]. As is often the case, the training embodied in an MD/PhD graduate can converge the problem-solution capability in multiple of these domains within the same individual.

The benefits of clinician-scientist interaction can occur within an AMC's own investigator community, but it is equally productive when it happens through industry-academic cooperation. These creative encounters are promoted through conference participation, sponsored research agreements, industry-funded grant programs, crossover hiring, journal publication, and patent application filings to name a few examples.

Limitations of Traditional Tech Transfer Model

Bridging the Development Chasm Between Invention and Innovation

By far, the risk of failure because of the chasm between invention and actual achievement of innovation (e.g. commercialization) can be reduced by the many features mentioned above including: a greater understanding of the actual market need, the technology challenges, the clinical problem, the regulatory barriers, the scale-up challenges, the competitive landscape, the payment or reimbursement challenges, and a multitude of other more complex features related to successful

development of a business startup (Fig. 15.1). This is just to mention a few of the challenges that create chaos and result in failures of what otherwise might be rational innovation in healthcare and medicine. One approach to reduce these risks is to remain in an incubation mode within an AMC while understanding and defining each of these risks and developing management strategies to mitigate them. This approach is easier to accomplish for devices and diagnostics rather than therapeutics. In this continuum, there is an advantage to begin with the clinical problem and to then explore technological options to create a meaningful solution within the AMC environment before venturing out into a startup company.

Although this can be a rational approach to increase the likelihood of success to cross this chasm, funding and managing the many challenges for academic incubation is also daunting. Over the past decade or more, there has been an increasing appreciation for a mutual interest shared between entrepreneurial young surgical scientists and their respective AMCs and universities. In many ways and increasingly, it is better understood that one of the most important missions for AMCs is to create better diagnostics, which are more accurate and contain greater informational content. These better diagnostics would be a tremendous benefit for patients. Furthermore, more effective, less invasive, and more cost-effective therapeutics also can and should be developed. Both challenges have increasingly become the responsibility of AMCs to lead.

Traditionally, AMCs that are able to justify the overhead expense to support a tech transfer function to handle the complexities of IP management. They manage the process of obtaining patent protection and creating license arrangements. These are complex agreements with companies who use those rights to protect their com-

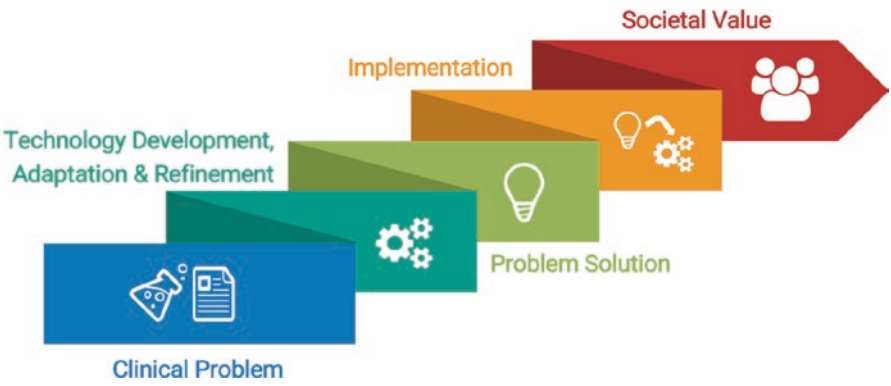

Fig. 15.1 Narrowing the gap between research and clinical translation. Generally, the ideal approach begins with an understanding of the clinical problem with an insightful concept of a step change improvement in the current treatment or diagnostic paradigm. Exploration of technologies that might be refined and/or adapted to enable this invention should follow creating a prototype for a potential solution to the perceived problem. Implementation is complex with staged clinical trials with regulatory implications using the well-developed diagnostic or therapeutic. Ultimately, if the business challenges are overcome, societal value is created, and innovation achieved

Fig. 15.2 The AMCs benefit from multiple interactions that occur routinely within its hospitable environment. Many of these interactions are leading to an increase in developmental collaboration between clinicians, scientists, engineers, and those within industry. This synergy takes place between the clinicians, who have firsthand knowledge of clinical medicine; the scientists and other investigators, who understand the basic sciences of a disease or disorder; and the engineers and scientists who develop the technologies. Together this can lead to the development of new and adapted innovations that help to overcome those problems previously not conceived. Often multiple of these domains are being addressed by a single individual who possesses both MD and PhD credentials

petitive position after a substantial investment to bring a product through regulatory approval and market introduction, which typically may take many years. Some of the more successful institutions have created a substantial stream of royalty revenue from these licensing activities. Most of those license agreements originate with startup companies who invest the time and capital to create a marketable product [8]. Typically, the new company (NewCo), will then be acquired by an established market player who wishes to acquire the rights to sell the proven innovation through their established product distribution channels.

Dearth of Funding Sources for Translational R&D

A most serious challenge to innovation arises from the dearth of funding available for these early development activities. Although there is generally a tremendous desire to support innovation leading to significant translational successes, it is very uncommon to encounter programs that consistently accomplish these goals. From the investor's perspective, commitment of funding requires trust and an intrinsic faith that the organization they are supporting has the ability and credibility to create commercial value starting from laboratory prototypes and very early model concepts. From the inventor's perspective, it is rare to encounter an environment that supports this freedom to embrace risk and to reach forward to create new paradigms in devices, diagnostics, and therapeutics.

Due to the current risk averse environment particularly in the public domain (i.e. National Institutes of Health), innovation is limited to incremental and often very small advances beyond current state of the art. These advances are frequently inadequate to address the many serious challenges that are encountered in modern medicine. Newer and more effective models are needed to more adequately address this increasing gap.

A New Experiment: Academic Venture Capital

Founding of Partners Innovation Fund

Partners HealthCare System (PHS) was created as an integrated healthcare delivery network anchored by the Massachusetts General Hospital and the Brigham and Women's Hospital. The combined annual research budget exceeds $1.5 billion today generating more than 250 issued patents per year (Fig. 15.3). The technology transfer function was a well-established and high functioning professional operation that returned significant income to the parent organization from its out-licensing activities. An additional critical factor is that the Boston venture capital community is highly developed and productive largely due to the density of sources of IP and technical talent that is the primary driver of any new company created in the life sciences.

The monetization of the invention pipeline in the academic sector has traditionally been limited to early stage licensing of preclinical IP assets. The wealth generated by commercialization of these inventions is largely captured in the form of equity appreciation that benefits the shareholders of these new enterprises founded upon core IP from the AMCs. Tech transfer offices have demonstrated foresight by making share grants part of the financial consideration for license rights packaged with the customary milestone payments and sales royalties [9]. The equity grant is usually small (<10% after first financing) and is subject to dilution in subsequent rounds.

The combined scale of Partners HealthCare System has made it possible to consider non-traditional options to increase the licensor's participation in future product economics. The hospitals have made a decision to expand the tech transfer operation by creating an intramural venture capital function managed by an experienced team of investment professionals. The motivating principle was to join the financing syndicate as co-investor with the same rights, risks, and upside potential that venture capital firms assume when they commit to a new enterprise.

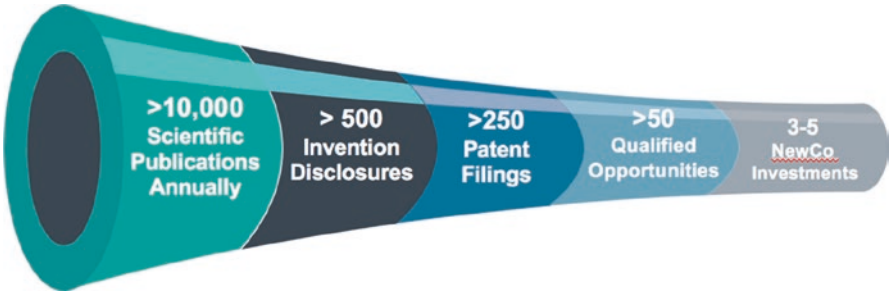

Fig. 15.3 The pipeline of new venture opportunities available to PIF originates from the large knowledge base generated by the PHS investigator community-at-large. The conversion from science to technology to IP to venture creation is a highly reductive process that requires high volume of input to create market worthy innovation

Fund Design, Structure and Operations

Starting with an initial stake of $35 million committed capital, drawn on demand from the hospitals as limited partners, the Partners Innovation Fund (PIF) was incorporated as a Limited Liability Corporation (LLC) in 2008. The fund is governed by a board of managers comprised of the participating hospital CEOs and the system CFO. The fund is strictly limited to consideration of opportunities that contain IP licensed from one or more of the PHS investigator communities.

One of the most important founding principles was to maintain a high standard of objectivity in the evaluation and analysis of investment decisions. The fund management team established a rigorous due diligence process conducted in a manner consistent with standard protocols of the venture capital industry. An external board was established to review all investment recommendations from the fund management team – by this mechanism, decisions are insulated from lobbying forces arising inside the institution. The review board is comprised mostly of executives from the biomedical industry and independent venture capital funds who serve on a *pro bono* basis.

By 2017, PIF had funded more than 30 startups. As expected in the early stage life science sector, there have been more losers than winners across the whole portfolio, but careful risk management continues to deliver highly favorable net returns to date for the hospital limited partners. So much so that the hospitals made the decision to increase their capital commitment and expand the portfolio. Further acknowledging that success, PIF has responded to outside expressions of interest to participate in the investment activities by creating a second fund comprised of investors unrelated to the PHS hospitals, including several major healthcare manufacturers. The second fund, PIF II is managed as a "side car" vehicle by the same management team in tandem with the original core fund. The initial hospital-owned fund was structured as an "evergreen" fund in which dividends, as available, are periodically issued to the limited partner hospitals. PIF II differs in that there is a 10-year lifetime to liquidation, which is the industry standard. The total capital under management has grown to $171 million from the original stake of $35 million.

Relationship with Investigators

PIF recognizes the special nature of its relationship to the hospitals' investigator community. As a "related party", PIF takes responsibility to educate and nurture potential innovators who have no prior experience or training in product development or entrepreneurship. That occurs through specially designed educational outreach programs as well as individual consultation. The goal is to identify homegrown opportunities of high commercial potential and to guide the inventors on a path to successful investment. A form of rubric has been developed that is shared with

inventors with the goal to impart an understanding of the thought process by which investors and ultimately customers evaluate new product offerings. Often this reveals a difference of opinion between the inventor and evaluator, but the aim is to bridge understanding and win respect for PIF as a trusted advisor [10].

PIF does not assert any exclusivity on access to IP developed at PHS. Inventors are free to utilize their own connections to pursue their own path to market. The goal of PIF is to serve the system as another option for realizing "return on innovation".

Conflict of Interest Policy and Practice

PHS hospitals are governed by the Harvard University, and particularly the Harvard Medical School, conflict-of-interest policies and these policies also apply to PHS venture fund activities. Hospital faculty and staff inventors who may hold founders as well as investor equity ownership in startups are prohibited from holding simultaneously management positions in their related startups. However, they are allowed to serve as paid consultants, and they may serve on the board of directors under management plans.

Many potential conflicts arise because of interest to further develop IP in the inventor's or investigator's laboratory using funds from the startup or the licensee. If the newly formed company or licensee elects to sponsor research in the investigator's, clinician's, or inventor's laboratory, then a conflict of interest discussion is created. Furthermore, and in addition to the investigator, clinician, or inventor, the institution also can find itself conflicted if the company plans to conduct clinical research at any of the investing hospitals while the fund holds equity in the company or the clinician or inventor plays an active role in this research or its publication. This can be problematic particularly in surgical device development programs when the inventor is often the preferred choice for first clinical deployment of the prototype instruments. These perceived, potential, or real conflicts are currently reviewed and managed by the various PHS hospital or affiliate institution's Committees on Conflict of Interest in collaboration and cooperation with the Harvard Medical School's Standing Committee on Conflict of Interest and Commitment.

Key Lessons Learned

The academic venture fund experiment is in progress, but interim findings can be inferred though not proven. These are some retrospective observations that can be offered for others who are considering their own attempts at institutional venture fund creation.

- To be a successful self-sustaining fund, decisions on investment opportunities must be judged on commercially relevant criteria. External validation should come from objective market-based inquiry into customer value proposition, realistic

assessment of product economics, and confirmation from respected co-investors. Despite the relationship that exists between inventor and institution, the investment decision-makers must remember that they are analysts and not advocates.
- Despite their aspirations, inventors are not likely to be the optimal managers for a venture-backed startup. Loss of control to investors is very difficult for inventors to accept but it is the reality of the fundraising process, particularly at the earliest stage of emergence from the AMC laboratories. Professional management trained by the experience of product commercialization is essential to the success of the enterprise.
- It is possible for academic venture funds to maintain a double bottom line of mission and return on investment. A disciplined approach to investment decisions can support the creation of innovations with societal benefits while returning revenue to the host institution for re-investment towards more innovation.

Summary

The potential for AMCs to achieve powerful innovations in twenty-first century healthcare is tremendous given the superb advances made in the physical sciences, genomics, proteomics, metabolomics, imaging medicine, and many other related fields within the last century. The broadening role for AMCs in innovation and development of new devices, diagnostics, and therapeutics has driven an evolved approach in our academic organizations. This shift is moving the field from a risk averse posture, to one that is more supportive and facilitating for translational medicine and its commercialization. The approach by many of the AMCs appears to be expanding from their prior role focused on basic patient care to that of a greater commitment to facilitate invention and innovation for the future of advanced medicine. Many AMCs with a proficient entrepreneurial culture have become actively engaged in the innovation process by not only providing a nurturing entrepreneurial technology transfer environment, but also through exploring their own early venture investment opportunities. These opportunities come not only from simple advisory and collaborative roles, but from ones that provide institutional investment in these new ventures coupled with substantial professional development for the future success of the "NewCo" and/or any inventions. Evolving AMC programs to nurture and grow innovation in the field is critical to creating a better future for patient care, while also supporting the development of clinicians, scientists, and institutions in the twenty-first century of healthcare.

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