Health Foundations Facilitate Translational Research Through Public-Private Partnerships

Diverse Funding Models and Integration Strategies

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Colophon

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The aim of the study was to examine and clarify the growing involvement of health foundations in public-private partnerships (PPPs) to facilitate translational research. The main outcome of the study reveals that health foundations, because of their patient focus, are positioned to inject a sense of urgency and a drive for collaboration into PPPs. Moreover, by focusing on the “Valley of Death” that many small pharma companies face around the proof-of-concept stage, investment from health foundations sufficiently de-risks promising treatment modalities to subsequently garner more traditional funds and development partners. This bridging allows health foundations to facilitate and expedite the translation of disease knowledge into an approved clinical application, thereby maximizing the use of health research evidence for the benefit of the patient. The question health foundations should be asking is not “Should we engage in PPPs?”, but rather “How can we best engage in PPPs?”. For a number of reasons, health foundations are positioned to occupy a key position in the translational research process and PPPs (focusing on cancer or other diseases). First, they possess important capital reserves that can be used to maximize the use of health research evidence for the benefit of the patient. Of course, health foundations do not possess the budgets of larger pharmaceutical companies, but it’s not only about the money. Health foundations can also provide the necessary clinical network and access to patients. They are in touch with the world’s leading academic experts who can help build understanding of the basic science, but who can also play a role in clinical trial design and evaluation. Moreover, a foundation joining a partnership facilitates the attraction of additional funding by, for example, generating appropriate exposure for the partnership. Therefore, health foundations considering engaging in PPPs need to be aware of:

What are effective and amenable partnership models for carrying out translational research in public-private partnerships, and how can health foundations participate to maximize the efficiency of this process?

Cancer is a leading cause of death worldwide, and is regarded as one of the most prominent and explicit forms of disease burden [Kaplan 2013]. The process of bringing new treatment modalities [for cancer] from “bench to bedside” has been described as a translation continuum in which disease knowledge is turned into a proven clinical application and eventually into medical practice [Drolet 2011].

Traditionally, basic research is performed by academic institutions, and applied research has generally been the domain of the private sector. In the last decade, the translation of basic scientific research into a potential treatment modality is increasingly being seen within “fully integrated discovery and development networks”. Within these networks, expertise and knowledge from academic parties, pharmaceutical companies and other stakeholders converge in one or more public-private partnerships. Although it has become evident that academia and industry need each other to effect substantive improvements in healthcare, the rules of the game for PPPs are fluid and ambiguous. Constructing an effective partnership between organizations with different values, interests and worldviews requires substantial effort and risk.
This report is sectioned into 3 main parts. The first part addresses the question "Why should health foundations engage in public-private partnerships?" by focusing on theoretical information on translational research and the rationale behind public-private partnerships. The second part addresses the question "What do health foundations do to engage in public-private partnerships?" by examining the strategy and operation of nine oncology and non-oncology health foundations. Finally, part 3 addresses the question "How do health foundations execute and implement their partnerships?" and involves discussing findings and showcasing details on PPP best practices, execution and implementation.

In general, an important objective of health foundations is to generate as much health research evidence in the therapeutic area of interest as possible. Traditionally, health foundations fulfilled this objective by investing in academic research institutions to support basic and translational research. This traditional funding role by health foundations is also described as the “Fund & Forget” model [Holmes 2012]. In the last decade, the efficiency and effectiveness of this approach has been increasingly questioned by patient advocacy groups, the public, but also by health foundations themselves [Faster Cures 2010]. Consequently, health foundations have started to reevaluate their way of funding, their role in translational medical research and their engagement with private for-profit entities in a PPP context.

Two independent dimensions were used to determine the existence and depth of interaction between health foundations and private for-profit entities in a PPP context: Portfolio and project management. Portfolio management entails the proactive decision making in regards to projects that are in line with the foundation’s strategy to advance translation of disease knowledge into a potential treatment modality. Project management entails the involvement in a project’s governance, development and advancement.

Taking these two dimensions into account, health foundations can adopt different roles in a PPP. Health foundations can adopt the traditional "Fund & Forget" role (F&F), which is characterized solely by financial contribution and no involvement in the governance or strategy of the PPP. Alternatively, "Select & Oversee" (S&O) is a more advanced funding role which allows health foundations to finance projects and act in a concierge or external advisor capacity (e.g. trouble-shooting). Health foundations can also choose to adopt the "Commit & Integrate" (C&I) role with the intention to manage their portfolio, but also to be a true development partner. Finally, the role of foundations that focus less on portfolio management, but which exhibit a high level engagement, is referred to as "Open & Integrate" (O&I).

The analysis revealed four health foundations (CFF, LLS, MJFF and CRUK) that fully adopted the Commit & Integrate role to advance the research process through partnerships. Two health foundations (TFF and AIRC) fulfill a role as a concierge facilitator (Select & Oversee), and have started to focus more on portfolio management and to facilitate the research environment. Initiation of new programs by health foundations that also target partnering with the private sector (venture philanthropy), was primarily driven by the fact that examination of their research portfolio revealed a lack of funded discoveries moving into the clinic [Gambrill 2007]. By leveraging their research budgets to address market failures in translational research, health foundations can effectively bridge the so-called Valley of Death, or funding gap, often seen in drug development.

The experience of these health foundations is that at the start of a venture philanthropy program, a considerable push is required, which with increased recognition eventually transforms into a pull from the private sector. Foundations make use of both scientific and business advisory committees in their grant-making process. Without exception, all intellectual property is left to the partner’s
control, but special clauses are part of the grant agreement to protect the investment in case development is halted for financial or other reasons. In addition, the majority of foundations require some sort of royalties as a potential return on investment. To control and govern their funding, foundations make use of milestone-driven grants that give foundations the possibility to cancel projects that demonstrate insufficient progress. Moreover, they are continuously kept in the loop on project progress and are seen as advisor or troubleshooter. A close comparison between the Cystic Fibrosis Foundation, deemed the “leading venture philanthropy organization” [Feldman 2012], and its British counterpart, Cancer Research UK, revealed that both foundations apply similar grant management, oversight committees and intellectual property procedures. Where they differ is in their investment plans and specific integration initiatives.

Much like PPPs themselves, a uniform blueprint for how health foundations should implement a PPP strategy does not exist. However, some key organization-specific characteristics have been identified that can be considered by health foundations that want to embrace a Commit & Integrate role for future funding [Chang 2010]. First of all, it is important to thoroughly comprehend the foundation’s background, internal organization and funding history, also known as a foundation’s “story of origin”. Apart from the internal organization, a central component of implementation is to map the various external stakeholders, in particular donors and patients, and the interest each group has in the foundation itself, but also the actual funding. Although a transition from a Fund & Forget role to a Commit & Integrate role may seem appropriate, expectations, wishes and goals that a health foundation wants to achieve should be matched with donor and patient expectations and wishes. It requires timely communication to stakeholders and the general public of the planned transition and the clear explanation of its necessity, added value and approach.

In conclusion, the outcome of this study reveals that health foundations represent a viable driving force for PPP collaborations. Health foundation-driven PPPs have the potential to maximize the use of health research evidence as they can be used to shuttle potential therapeutic modalities from basic discovery, through the translation continuum, to their end-target patients.
Introduction

Cancer is a leading cause of death worldwide [Farley 2008], and is regarded as one of the most prominent and explicit forms of disease burden, with broad consequences that go beyond individuals and their families, reaching the healthcare systems and economies of individual countries [Kaplan 2013]. The incidence of cancer continues to increase due to a multitude of factors, including unhealthy diets, smoking, the lack of exercise, environment and genetic susceptibility. Because of the global public health concern that cancer continues to represent, large investments have been made in oncology research to enhance understanding of the pathobiology and disease progression of cancer. A recent report by the London School of Economics (LSE) reveals that a total of 174 European and US public funding organizations spent close to €9 billion on oncology research during 2006-2007 [Kanavos 2009]. Apart from public funding organizations, there are a large number of private charities and health foundations supporting cancer research worldwide. Some focus on specific types of cancer while others assign priority to multiple types. Philanthropic funding in oncology is estimated at over €500 million in Europe and €230 million in the USA in 2007 [Kanavos 2009].

Due to the highly diversified nature of cancer, treatment has taken the form of multiple modalities, and includes surgery, classical chemotherapy, radiotherapy and targeted drugs against receptors and signaling pathways. Patients usually undergo a combination of these treatments. Due to the fact that each tumor’s genetic fingerprint is unique, cancer treatment is extremely difficult and therefore has the lowest success rate with the highest cost of development [Kanavos 2009].

The process of bringing new treatments from “bench to bedside” has been described as a translation continuum, where various resources, factors and areas of knowledge are involved in advancing from basic fundamental research to proven clinical application and eventually, medical practice [Drolet 2011]. In principle, basic research is being performed by academic institutions supported by public funding organizations and health foundations, such as The Netherlands Organization for Health Research & Development (ZonMw) and the Dutch Cancer Society (KWF). Traditionally, applied research generally has been the domain of private (for profit) companies.

However, over the past decade and for various reasons [Cockburn 2004], the role of large pharmaceutical companies within the pharmaceutical innovation field has been changing. It used to be the case that pharmaceutical companies would discover, develop and market their products internally, so-called “in-house competencies”. They would not outsource any part of their operations or research to specialized contractors who could do part of their job for them; instead they covered the entire R&D process by using their own resources. However, companies like Pfizer and GSK have moved away from this traditional “fully integrated discovery and development company” (FIDDCO) model towards one of open innovation that takes their competencies into account: late (phase II/III) clinical development and distribution of products. Consequently, discovery of potential new therapies, and subsequent pre-clinical and early (phase I/IIa) clinical evaluation, have become the domain of academic parties and small and medium-sized enterprises (SMEs).

The translation of basic scientific research into a potential treatment modality has transformed to fall under the auspices of “fully integrated discovery and development networks” (FIDDNET), in which expertise and knowledge from academic parties, large pharmaceutical companies, SMEs and other stakeholders converge in one or more partnerships [Croft 2005]. Thus, the R&D process is moving away from one pharmaceutical entity that handles everything internally to include a network of different entities, each contributing their own forte. As such, public-private partnerships (PPP),...
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Introduction
deeded the “hotbed” for interdisciplinary research, are increasingly considered an important instrument in expediting translational research in cancer [Luijten 2012]. The LSE report mentioned above reveals that 68% of oncology drug R&D projects in the US and 57% in the EU received joint funding in 2007 [Kavanos 2009].

However, one challenge that private-public partnerships face is the sustainability of funding. Due to the decade-long nature of drug development and research projects, PPPs stand to meet high attrition in their research budgets. As a result, partnerships need to expand their funding base to alternative financial entities. In addition, the rules of the game for public–private partnerships are fluid and ambiguous. Constructing an effective partnership between organizations with different values, interests and worldviews requires substantial effort and risk [Reich 2000].

Health foundations could play an important role in this process. Due to their financial contribution and their responsibility towards patients and public donors, they should be able to occupy a key position in the translational research process. This can be achieved by making translational medicine research and working in partnerships a priority [Holmes 2012]. It is clear that many foundations are recognizing their potential in this realm, and that they are ideally placed in the research field to make a difference [Feldman 2012].

Using nine oncology and non-oncology health foundations as examples, this study examined and clarified the interaction between health foundations and the public-private partnerships in which they are involved. The study specifically focused on the following research question:

What are effective and amenable partnership models for carrying out translational research in public-private partnerships, and how can health foundations participate to maximize the efficiency of this process?

This report utilizes a top-down approach which selects, deconstructs and appraises the importance of health foundations within the context of PPPs. It is the aim of this report to consolidate the characteristics of health foundations and the different funding and interaction mechanisms that can be applied to PPPs. This report is sectioned into 3 main parts. The first part addresses the question “Why engage in public-private partnerships?” by focusing on theoretical information regarding translational research and the rationale behind public-private partnerships. The second part addresses the question “What do health foundations do to engage in public-private partnerships?” by focusing on foundation-PPP interaction based on case analyses. This provides an overview of different strategies employed by health foundations. Part 3 addresses the question “How do health foundations execute and implement their partnerships?”, discussing findings and showcasing details on PPP best practices, execution and implementation.

In tandem with an internal evaluation, and discussions with KWF’s external advisory board and steering committee, the findings of this report should facilitate the discussion within KWF on its way of funding medical research and its future role in translational research.
Translational Research

Advancing discoveries from the bench to the bedside has been described by Drolet and Lorenzi as a “translation continuum”, because progression of knowledge requires various resources and actions [Drolet 2011]. Their proposed Biomedical Research Translation Continuum, depicted in Fig. 1, can be considered a further refinement of generally accepted translation models, in particular the “3 T’s” Road Map [Westfall, 2007; Dougherty, 2008]. The “3 T’s” Road Map basically explains the 3 translation periods or gaps that exist. Drolet and Lorenzi have renamed these gaps “translation chasms”, because they actually represent periods during which the necessary research and non-research activities must be conducted to bridge the four stages of research progress [Drolet 2011].

Translation chasm 1 (T1) represents the translation of basic science to humans. Bridging activities include evaluating biochemical findings in vitro and in animal models within the context of a potential medical application.

Translation chasm 2 (T2) represents the translation to clinical treatment by evaluating safety and efficacy using clinical trials.

Translation chasm 3 (T3) represents the translation to practice by implementing and adopting treatment modalities via medical guidelines and standards.

Having a model is only the starting point to understanding the translational process, and in no way properly reflects its actual complexity. A recent report from the American Academy of Arts and Sciences explains that a main challenge for today’s scientific endeavor is to “extract understanding from floods of disconnected data that threaten to swamp every discipline” [ARISE II, 2013; Yamamoto 2013]. Understanding how to advance discoveries from the bench to the bedside has become the subject of numerous studies and specific journals [Woolf 2008, Trochim 2011]. Contopoulos-Ioannidis et al. performed a study to better understand the efficiency of the translation of highly promising basic research into clinical experimentation [Contopoulos-Ioannidis 2003]. They found that the transfer rate of basic research into clinical use is low. Less than 25% of highly-promising biomedical discoveries, identified in the period 1979–1983, yielded published randomized clinical trials and less than 10% were established in clinical practice within 20 years.

1 David Satcher MD, PhD, Former U.S. Surgeon General [Monaghan 2001]
To allow the full exploitation of basic science into clinical utility, existing boundaries between scientific disciplines resulting from traditions, policies and bureaucracies have to be lifted [ARISE II 2013, Yamamoto 2013]. Such an endeavor requires integration along two separate, but intersecting planes. The first one calls for an increased level of collaboration between ICT, mathematics, and the physical and medical sciences to achieve the required “transdisciplinarity”. The second plane calls for an increased level of integration between major stakeholders involved in translational medicine: academia, government, private industry and not-for-profit organizations. The envisioned integration has to move beyond simple deal-making between public and private entities, and will require the establishment of policies and mechanisms that enable the convergence of expertise and knowledge from public and private stakeholders.

However, the public and private sectors play different roles in translational research. Public organizations, mainly academic entities, focus on technology PUSH [Fig. 2]. Their mark can be seen on the initial stages of the research continuum, namely, basic science discovery. The term “technology” encompasses, among other things, biochemical findings and new molecular entities, implying an invention which is pushed through R&D to the market without direct alignment to user need. Here, academic researchers and groups act based on curiosity and their passion for cultivating hypothesis-driven research. Crowley mentions the intrinsic level of unpredictability as an important, but also attractive characteristic of curiosity-driven research [Crowley, 2003]. He provided examples of important solutions to clinical problems that were derived from basic science that could never have been predicted at their outset, such as the successful treatment of leukemia and the clinical use of bisphosphonates [Crowley 2003].

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**Figure 2 – Public vs. Private Roles**
However, at the opposite end of the continuum lie the private entities, mainly industrial, which focus on market **PULL**. These private entities react to the needs of patients through market analysis, with the intention to maximize stakeholder satisfaction, shareholder value and product-market alignment. In principle, projects adopted by private entities fulfill low risk and high return on investment profiles.

Taking the varying positions of both public and private entities into consideration reveals that they are also interdependent [Chin-Dusting 2005]. Public academic organizations and private for-profit entities converge at the point of clinical trials. Public entities often provide the necessary access to patients, while private entities have industrial expertise and manufacturing capabilities. These capabilities are used to shuttle clinical trial findings to patients, for example as on-market drugs. Academic entities also regard private entities as “better managers” of risk as they employ a “results-driven” approach to project planning and implementation [Mitchell 2008]. Furthermore, they believe assets can be better utilized and end-services improved when private entities are involved. This is due to the large financial research budgets and economies of scale and scope that private entities enjoy [Bennet 1997].

On the other side, private industrial organizations require academic expertise for the de-risking of potential development projects prior to investment and for discovery research. Moreover, private entities regard public entities as loci of innovation and tacit knowledge which represent the root of their development projects. As stated by Crowley, “Academia and industry need each other to effect substantive improvements in health.”

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**Figure 3** – Role of Health Foundations

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**Public Technology Push**

Pathobiology & Disease Progression Model

Health Fund

Target Biology

Barrier

Funding + Empowerment

**Private Market Pull**

Patient

DC

eDC

Lead

Hit

Public (HF) Patient Focus

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**Figure 2** – Role of Health Foundations

**Figure 5** – Means Public Private Partnerships

**Figure 6** – Solution Translational Process

**Figure 7** – Portfolio Management
Without substantive collaborations between the two, maximum advances in healthcare for the US public are unlikely” [Crowley 2003].

Health foundations are starting to play a more pronounced role in the Biomedical Research Translation Continuum. An important aim of health foundations is to generate as much health research evidence in the therapeutic area of interest as possible. Traditionally, health foundations fulfilled their objective by predominantly investing in academic research institutions to support basic research focused on pathobiology, disease progression and target biology [Fig. 3, health funds]. This has been considered an acceptable approach for many decades. However, to maximize the use of health research evidence for the benefit of the patient, health foundations have also become more active in the space between research results and patient impact, i.e. by funding translational research [Fig. 3, patient focus]. This traditional funding role by health foundations is also described as the Fund & Forget model [Holmes 2012].

Recently the efficiency and effectiveness of the traditional Fund & Forget model has become the subject of considerable debate [Faster Cures 2010]. In particular, what is questioned is whether the Fund & Forget model actually facilitates the translation of research into patient benefits, or is it nothing more than a means of generating health research evidence. Consequently, health foundations have started to reevaluate their way of funding and their role within the Biomedical Research Translation Continuum.

To effectively maximize the use of health research evidence for the benefit of the patient, stronger engagement at the development side of the Biomedical Research Translation Continuum is required. As mentioned previously, strategic partnerships that bridge the gap between public and private entities stand to shuttle basic research results through the continuum to patients, and to address the dichotomy that exists between public and private funding.

As a result, health foundations are well-positioned to support or even participate in public-private partnerships and consequently effectively maximize the use of health research evidence for the benefit of the patient. To fully exploit their key position in translational research, health foundations can continue their central role in funding basic research, but also make the integration into public-private partnerships part of their funding strategy. They need to understand:

- What are effective and amenable partnership models for carrying out translational research in PPPs?
- How can health foundations participate to maximize the efficiency of this process?

Basically, health foundations have started to realize that they can be instrumental in creating a new driver for translational research: the patient focus, where obtaining maximum benefit for the patient is the main goal [FDA Voice 2013]. Health foundations possess large capital budgets that can be used to fund research projects of their choice. Their investments represent the sum of contributions made by the public and they have the intention of generating research evidence for patient impact.

In the next chapter, the concept of public-private partnerships is described in more detail, and different models are presented that health foundations can employ to support or integrate into PPPs.
As former NIH director Elias Zerhouni puts it, “The way forward in multidisciplinary research is to engage in predictive, personalized, preemptive and participatory medicine. For the creation of the optimal innovation climate that would allow for such a strategy, public-private partnerships have been proposed.” [Luijten 2012].

PPPs have been dubbed “win-win paradigms” [Bovaird 2004]. Due to their varying type and nature, there exists no consensus on an exact definition of a PPP. Van Ham and Koppenjan defined PPPs as “the cooperation of some sort of durability between public and private actors in which they jointly develop products and services and share risks, costs and resources which are connected with these products” [Hodge 2007]. This is just one definition. As already mentioned, the reality is that PPPs exist in many different shapes and forms and have been the subject of many studies [Luijten 2012; Hodge 2007; Monaghan 2001]. A recent review on the subject of PPPs reveals that most of these articles are based on anecdotal accounts of experiences in this area [De Pinho Campos 2011]. This makes it challenging to define a blueprint of a successful PPP. For example, PPPs can define completely different outcomes as successful. Some aim for the set-up and implementation of a successful research network, whereas other groups focus on the development of innovative treatment modalities [TREAT NMD].

That being said, within the context of healthcare, PPPs stand to usher in a number of added values. To begin with, they have proven to expedite translational research, moving compounds swiftly through R&D pipelines [Croft 2005]. Furthermore, PPPs are positioned to address the global prosperity gap by providing pharmaceutical entities with an alternative investment model for unattractive developing countries with low/middle purchasing power and return on investment [De Pinho Campos 2011]. Moreover, PPPs can address research gaps in global healthcare systems that have been formed by the fragmented nature of research investments.

Finally, PPPs are expected to strengthen health services and public healthcare education [De Pinho Campos 2011]. In simple terms, PPPs have the potential to make things happen that would not be possible in their absence and enable the exchange of valuable resources [Kaplan 2013].

In the healthcare sector, basically three main types of public-private partnerships have been described [De Pinho Campos 2011; Croft 2005]. This classification is based on the nature and goal of a PPP.

- **Product Development PPP:**
  
  In product development PPPs, the public entity provides basic discovery research to enable rational drug design, and houses the disease expertise. The private entity is responsible for the evolution of basic research to clinical trials and marketing of the product, and houses competencies to translate the research to patient use.

- **Portfolio PPP:**
  
  In portfolio PPPs, synergy is achieved through strategic selection of projects for effective collaboration. Public and private entities converge on the basis of complementary expertise and competencies for the purpose of successful teamwork and achievement of project goals under quicker project schedules.

- **Access PPP:**
  
  Access PPPs focus on increasing the accessibility of drugs and not their creation, as product development PPPs do. Eliminating disease burden is not limited to the development of effective treatments; instead it extends to stakeholder collaboration, efficient distribution systems and access to healthcare infrastructure. Furthermore, access PPPs focus on engaging with
policymakers to overcome obstacles in the distribution system of treatments. An example of an access PPP is The Children’s Vaccine Initiative, which is a collaboration between UNICEF, WHO, the World Bank, Rockefeller University and several industry players, aims to promote, coordinate and accelerate the development of new vaccines.

The motive behind engaging in any partnership generally emerges from one of two incentives. Organizations have a pre-established agreement or relationship and engage in collaborative activities, which eventually leads to a partnership. Alternatively, an organization might suffer from a deficiency in its expertise or capabilities and recognize the need for extramural resources like human capital, external tacit and explicit knowledge, finances or technology (Monaghan 2001).

In the healthcare context, motives behind engaging in PPPs are entity-specific. PPPs allow governmental bodies to reduce expenditures and deficit spending (Monaghan 2001). Hospitals and academic healthcare centers engage in PPPs as they can merge expertise to improve operating efficiencies, access new sources of capital, improve customer services and create opportunities for innovation. Finally, private businesses perceive PPPs as a tool to expand and access new and existing markets, potentially increase profits, optimize their use of capital investments and polish their brand equity by acting as good corporate citizens while promoting a positive public image.

The present research focuses on the potential benefit of the participation of health foundations in product development and portfolio public-private partnerships and the role they can or do play in the improvement of the quality and efficiency of these PPPs. A parameter of significant relevance here is the “level of integration of a health foundation in a partnership” (Fig. 4).

In order to qualify the “level of integration”, an international review of PPP performance, conducted by the Copenhagen Business School, suggested that PPPs are two-dimensional. “How are public and private actors engaged financially in PPPs?” and “How tightly organized are the public and private actors?” (Hodge 2007). Taking the latter into account, two different dimensions to qualify the level of integration of health foundations in PPPs can be distinguished.

**Figure 4** - Level of integration of a health foundation within a PPP context
First, a health foundation can participate on different levels in the portfolio management of a public-private partnership. Portfolio management entails pro-active decision making in regards to projects that are funded and added to the portfolio. It represents a calculated strategic direction and selective absorption of projects. On the integration scale, a high level of portfolio management (+) can take many forms, including the use of strict, clear selection criteria, the establishment of committees and boards that search for and assess possible research projects, or by accepting research proposals based on an invite-only system. Here, health foundations can create a clear view of their priorities, and maintain this direction by sifting through research proposals and extracting the ones that fit best with the portfolio strategy – or, maybe even better, by being actively involved in drawing up research proposals and recruiting the right public and private partners to execute the project nationally or even internationally. A low level of portfolio management (-) represents health foundations that do not actively select the projects they fund or interact with. Instead, they may choose to accept research proposals from entities that approach them without filtering their choices based on selection criteria or the assessment of a board.

The second dimension that defines the level of health foundation integration is whether or not they are involved in the actual project management of the projects executed by the PPP. Project management entails involvement in a project’s governance, development and advancement. Project management represents a conscious decision to work according to a specific method. When a health foundation is involved in the project management of a public-private partnership, it can influence or define the governance and policy of the partnership and the research that falls within its scope. A high level of project management (+) implies that the health foundation is actively involved in facilitating or advancing the research conducted in a PPP. Here, the foundation is involved in the managing of the process as well as the scientific content of its projects. A low level of project management (-) implies that foundations are only involved in the funding of their projects, and do not practice any form of process or project management.

Based on the two dimensions mentioned above, four roles can be distinguished that health foundations can play in a PPP context. Health foundations can adopt the traditional Fund & Forget role (F&F) [Holmes 2012], which is characterized solely by financial contribution and no involvement in the governance or strategic direction of the PPP. Here, they have low levels of portfolio and project management. Alternatively, Select & Oversee (S&O) is a more advanced funding role which allows health foundations to finance projects and act in a concierge or external advisor capacity (troubleshoot). Health foundations can also choose to adopt the Commit & Integrate (C&I) role, with the intention to be a crucial player in a FID^2NET business model. Finally, Open & Integrate (O&I) may be an option. It is similar to Commit & Integrate but differs by its low selectivity in projects. In this situation, health foundations (and their partners) are committed and fully integrated both financially and in the governance of a public-private consortium.

From a health foundation’s perspective, supporting or even integrating into a PPP represents a way to maximize the use of health research evidence for the benefit of the patient. It is important that a health foundation is aware of the different funding strategies available and of the types of PPPs it can support, in order to make a fully-informed strategic decision.
Health Foundations – PPPs in Practice

Having examined literature, it is clear that public-private partnerships are more than merely the sum of their parts. PPPs can offer diverse added values to health foundations, partnership participants and patients. At its core, a public-private partnership is a paradigm, a cluster of concepts and ideas on how public and private entities can potentially interact harmoniously. By stepping back and taking a holistic view of public-private partnerships, the connection between PPPs, health foundations and the translational process can be sketched (Fig. 5).

The problem in question lies with the increasing global disease burden of cancer. It remains a major challenge to shuttle the growing amount of basic discovery findings through the research continuum to their target points, namely, the patients. This is due partly to the lack of activities that bridge the translational chasms in the research continuum. As previously mentioned, public-private partnerships can mitigate the fragmented sources of funding and asymmetrical sources of research information by allowing diverse public and private entities to converge. In addition, the problem that cancer poses can be mitigated by engaging in the translational process. This process includes practicing translational research, establishing collaborative networks and infrastructures. As demonstrated in Fig. 5, public-private partnerships represent the means to engage in this translational process. By pooling and exchanging resources and expertise, PPPs stand to lower the learning curve for engaged parties, providing them with a significant competitive advantage. In turn, the establishment of PPPs can be facilitated by health foundations that operate in the interest of patients.

Health foundations do not possess the budgets of larger pharmaceutical companies; but it’s not only about the money. According to Chang, there are five additional value drivers that foundations add to a partnership [Chang 2010]. First, they can provide the necessary clinical network and access to patients [clinical network]. Second, peripheral players of strategic importance [CROs, clinical sites, animal testing facilities] can be “educated” and financed if necessary [supporting a cast of characters]. Third, because of their central position, foundations have relationships with

“Collaborations stretch dollars and make research projects possible.”

2 Gambril 2007, Venture Philanthropy on the Rise, Volume 14, issue 06

Figure 5 – Health Foundations – PPPs in Practice
and access to the world’s leading academic experts who can facilitate understanding of the basic science, but who can also play a role in clinical trial design and evaluation ([access to the best science]). Fourth, as already mentioned, foundations help attract additional funding to a partnership, for example by bringing appropriate exposure to the partnership ([good housekeeping seal of approval]). Finally, foundations put great emphasis on collaboration and information sharing. Where confidentiality is an issue, for IP or trade secret reasons, the foundation can act as a central hub ([knowledge management and collaboration]). How much value is created through any of these five value drivers, however, is difficult to determine, and depends for a large part on the intensity of partner engagement.

Although health foundations can act as facilitators of PPPs, they are not homogenous in what projects they fund or how they fund them. When it comes to what they fund, health foundations have multiple treatment modalities to choose from, including drug development, diagnostics and innovative approaches (immune response modifiers, surgery and radiotherapy). In this report, health foundations seem to invest predominantly in drug development; however, innovative therapies and diagnostics are certainly not irrelevant. In particular, with the rise of personalized or stratified medicine, the borders between medicinal products and diagnostics appear to become less strict. Health foundations may choose to invest in diagnostics as the market becomes more attractive. The numbers of oncology drugs that have so-called companion diagnostics (CDx) coupled to them are increasing. It has been estimated that up to 80 new targeted cancer drugs set for 2018 will be combined with companion diagnostics ([Jorgensen 2013]). Furthermore, although the return on investment is lower than that for drugs, there is no requirement for lengthy clinical trials, allowing products to get to the market faster ([Batchelder 2006]).

Despite the fact that the number of new CDx are expected to increase, reimbursement schemes for CDx are significantly lower than those for drugs, making the field risky for investors that cannot cover the cost of development ([Desiere 2013]). Here, health foundations can play a role in de-risking the diagnostics field by cooperating with interested partners and pooling financial and non-financial resources:

“Partnerships are key in the regulatory approval and commercial launch of CDx. The infrastructure for developing and obtaining approval of a CDx rarely exists within the same corporate entity” ([Love 2012]).

As mentioned before, health foundations continue to fulfill their traditional role of funding basic research, but at the same time some of them have started to engage directly with for-profit private entities within a PPP context. The main objective of this study is to clarify what are effective and amenable partnership models for carrying out translational research in a PPP constellation, and how health foundations can participate to maximize the efficiency of this process. As such, the traditional role of funding basic research, although rightly acknowledged as the cornerstone to advance understanding of disease pathobiology, is considered outside the scope of this study. An in-depth analysis of how some of these health foundations are moving beyond traditional funding models was therefore the starting point of this study.

In order to examine the nature and operation of health foundations in practice, nine health foundations and their PPP interactions were selected for appraisal. These include three non-oncology and six oncology foundations:

- Leukemia & Lymphoma Society (LLS)
- Cancer Research UK (CRUK)
- Breakthrough Breast Cancer (BBC)
- Terry Fox Foundation (TFF)
- Cystic Fibrosis Foundation (CFF)
- American Cancer Society (ACS)
Health Foundations Facilitate Translational Research Through Public-Private Partnerships

- Michael J. Fox Foundation (MJFF)
- Italian Association for Cancer Research (AIRC)
- Wellcome Trust (WT)

The MJFF, CFF and WT are not cancer-focused, while the remaining six cases either focus specifically on one type of cancer or on multiple types.

Cases were selected from literature [Kavanos 2009; Gambrill 2007] based on representativeness, content and the following selection criteria:

- Involvement in translational (cancer) research
- Substantial level of income (> €20 million)
- Involvement in high-impact health projects
- Foundations based in Europe and the United States

Each health foundation was subjected to an examination of its strategic affinity. Strategic affinity is a combination of two measures. First, the level of integration, which as previously mentioned encompasses the level of portfolio and project management. Second, strategy, which includes the initiatives and activities put in place to interact in a PPP context (where applicable). Strategic affinity, therefore, indicates whether a health foundation practices Commit & Integrate, Select & Overseer, Open & Integrate or Fund & Forget.

Although health foundations may apply the same integration model, each health foundation possesses unique features that distinguish it from others. In order to provide a line of comparison, we apply descriptive measures that profile each health foundation against the other. These include a health foundation’s research affinity, resources and organizational character. Research affinity describes on what level of translational research and what research modality a health foundation focuses on. Resources describe the funding budget and in-house R&D capacity available to a health foundation. Organizational character is used to provide insight into a health foundation’s orientation. This includes its country of origin, goal, income, business model and engagement in private funding. These measures stem from various scientific publications that describe important and relevant characteristics of public-private partnerships [Kanakoudis 2007; De Pinho Campos 2011; Monaghan 2001; Mitchell 2008].

The results, conclusions and statements presented in the next chapter in a condensed format are solely based on the qualitative assessment of publically available and accessible data. This data includes scientific literature, annual reports, grant agreements and contracts, press releases, website information, the International Cancer Research Partnership (ICRP) database and, in some cases, financial statements. It is important to mention that the amount and type of information available per foundation is not homogeneous across the case list. Details available for one foundation may not be publically accessible for the other, which translates into a limitation in this study. Detailed case analyses and overall results, including tables and examples, can be found in the appendix.
Case Analysis – Strategy

Based on the analysis performed, the chosen health foundations occupy different positions within the integration matrix. As demonstrated in Fig. 6, they are grouped into the four categories.

Category 1 represents health foundations acting as development partners which practice Commit & Integrate. These health foundations have high levels of portfolio and project management. Furthermore, they directly interact with partners. This category includes the Leukemia & Lymphoma Society (LLS), Cancer Research UK (CRUK), Cystic Fibrosis Foundation (CFF) and the Michael J. Fox Foundation (MJFF).

The Leukemia & Lymphoma Society (LLS) focuses on financing and supporting project development PPPs & access PPPs. LLS uses its Therapy Acceleration Program (TAP) to integrate with its partners. TAP allows LLS to assist its partners with investigational new drug applications (IND) in gathering proof of concept data, testing, registration and marketing of new treatments. TAP consists of different divisions, each with its own mandates for expediting R&D. The Academic Concierge Division partners with specialized CRO service providers that have a wide range of preclinical expertise which can be contracted if needed. This division also assists in the gathering of FDA-required documentation prior to the commencement of clinical trials. If an LLS-partner then advances to clinical trials, LLS also has a portfolio of additional biotech and pharmaceutical affiliations at its disposal for further support. The TAP program also houses the Biotechnology Accelerator Division which strategically selects programs for LLS to invest in. Programs must be developing novel anticancer therapies and are expected to yield net results that will enable LLS to raise additional funding.

Figure 6 - Level of integration of examined health foundations in a PPP context
Cancer Research UK (CRUK) focuses on project development PPPs and portfolio PPPs. CRUK uses its specialized in-house Drug Development Office (DDO), which has 30 years of expertise in early-phase oncology trials, to integrate with its partners. The DDO allows CRUK to conduct its own in-house research while still engaging in extramural funding as a foundation. The DDO manufactures and formulates small molecules and biological therapies. It consists of the Bio-therapeutic Development Unit (BDU) and the CRUK Formulation Unit. Both are used to develop and manufacture biological agents to be used in DDO clinical trials and testing by partners. Due to the DDO’s state-of-the-art manufacturing facilities, extensive experience and formidable track record, it is considered to be the “one-stop-shop” solution for companies that are funded by CRUK and involved in early-phase oncology therapy development. As a result, the DDO represents CRUK’s proactive involvement in projects. It also represents CRUK’s active portfolio management. The DDO exclusively searches for partners requiring pre-clinical and early-phase clinical studies.

The Cystic Fibrosis Foundation (CFF) focuses on project development PPPs. The CFF has established the Cystic Fibrosis Foundation Therapeutics (CFFT) branch to manage and interact with its funded partners. The CFFT recognizes that it does not possess billion-dollar research budgets and consequently leverages its position by applying a "venture philanthropy" approach. Early-stage research is invested into de-risking the field for other interested parties who can continue research beyond the Valley of Death. To integrate with its partners, CFFT has created the Therapeutics Development Network (TDN) which is composed of multiple clinical care centers that have culminated experience in the design and conduct of clinical trials. These centers streamline the clinical trial process for CFF partners. Contributions made by the CFFT are considered “investments”, and therefore the CFFT expects a return on investment from funded drug development projects. If the drug achieves on-market status, then CFFT proceeds to collect the returns and cycles back to its pipeline for re-investment. In addition, the TDN houses the Research Development Program (RDP) which serves as a “core supply center” that shares tools and resources and disseminates information among researchers globally. The CFF has established a total of eleven RDP centers in which it acts as an external expert advisor that serves a troubleshoot function. These centers allow partners to bypass the learning curve by up to 6 months, by providing access to validated assays at their CRO affiliations or by pairing partners with experts in pharmaceutical development. With regards to portfolio management, the CFF funds projects on a matching basis between preclinical development and initial clinical trials, only funding projects that demonstrate potential for advancement through the translation continuum.

The Michael J. Fox Foundation (MJFF) focuses on project development PPPs and has established The Partnering Program. The goal of this program is to foster formal and official channels for partnerships. Named “Charting the Course”, the first stage of this program is to approach world leading specialists to map and maintain an encompassing view of the field to identify promising projects. The second stage is the “Selection Process”, where its scientific staff reviews potential research opportunities. In the third “Research Process” stage, the foundation tries to fund quickly, within 2 months. Here, the MJFF has a team of in-house researchers and business-trained project leaders that collaborate with partners to advance and steer projects at all levels of the translation continuum. The final stage, designated “Capitalizing on Results”, gives MJFF its unique character as it appropriates returns from its own and external researchers. The MJFF actively strives not to cannibalize the efforts of other for-profit companies that may compete for financial, scientific or collaborative resources. It is adamant on de-risking...
the field and, as a result, the MJFF does not derive any revenue stakes or intellectual property from research projects. The MJFF is focused on critical collaborations that yield regulatory approval and on-market status for therapies.

Category 2 represents health foundations acting as concierge facilitators which practice Select & Oversee. These health foundations have high levels of portfolio management, and levels of project management that fall between that of C&I and F&F. They include the Terry Fox Foundation (TFF) and the Italian Association for Cancer Research (AIRC).

The Terry Fox Foundation (TFF) focuses on access PPPs by indirectly interacting with projects. TFF has established the Terry Fox Research Institute (TFRI) to fund and interact with projects. With regards to project management, the TFRI is not directly involved in the strategic advancement of funded projects. The foundation does not provide stage-specific development support nor does it act as an external advisor. Instead, it has established so-called “TFF nodes”, which are centers used to aggregate research projects and pool resources. Within these nodes, TFF has enlisted management entities to help supervise its research projects. This is based on milestone-driven goals for continued funding. It is not solely a financial contributor, nor is it a development partner. When it comes to portfolio management, the TFRI applies strict multi-level selection criteria. Also, TFRI accepts project proposals by invitation-only from institutions that are signatories to its TFRI Node Memorandum of Understanding for cooperation. Furthermore, projects are only funded if they are involved in tumor-site specific translational cancer research. Among TFF’s partners, this study could find no evidence of direct engagement with private for-profit entities, unlike the AIRC. However, TFF is included in this study as it is a clear representation of a Select & Oversee role with its accompanying integration initiatives. A private for-profit relationship cannot be ruled out; TFF may interact with private for-profit entities through its public grantees, but determining this would require further investigation efforts, possibly in the form of interviews, beyond the scope of this study. TFF’s indirect method of interaction is therefore regarded as a limitation in this study.

The Italian Association for Cancer Research (AIRC) focuses on access PPPs, interacting directly with projects and providing financial support exclusively to national research projects. It also focuses on facilitating the environment around projects. The AIRC plays no role in project governance or strategic management; however, it does strive to disseminate knowledge for its funded project partners. This is done by facilitating access to information generated from national and international cancer studies and research activities, which is achieved by providing access to its publication system and website “Fondamentale”. The funding of national cancer research projects is based on extensive appraisal by a rotating Scientific Committee of national experts and 350 foreign experts. This process takes nine months; selected projects are innovative, have substantial expected patient impact, are feasible, and have been proven by preliminary results.

Category 3 represents health foundations acting as financial contributors which practice Fund & Forget. These health foundations have low levels of portfolio and project management. They include the American Cancer Society (ACS) and Breakthrough Breast Cancer (BBC).

The American Cancer Society (ACS) is a globally-oriented not-for-profit entity with a virtual research model that utilizes a sponsorship role to advance cancer research. It funds research institutes such as The Scripps Research Institute and the Salk Institute for Biological Studies. It has a total research budget of $107 million [2012] and focuses on all research modalities and on all the translational chasms [T1-T3]. The ACS is not involved in active project management, and...
projects are funded on a minimally-selective procedure. This procedure involves the suggestion of an extramural Grant Council based on societal objectives and available funds for allocation.

**Breakthrough Breast Cancer (BBC)** is a charity organization located in the United Kingdom which focuses on funding innovations that can increase the pace of detecting cancer and developing effective treatments for all primary breast cancer types. Its efforts are based on a 10-year commissioned plan. Funding focuses on drug development, innovative approaches and diagnostics research modalities. BBC does not fund projects on a selective basis; rather it establishes **BBC Research Units** in national universities that receive financial support. It also does not engage in project interaction, neither as a facilitator nor as an involved project partner.

Category 4 is comprised of the Wellcome Trust, which has a low level of portfolio management and a high level of project management. It acts as a **nonselective partner utilizing Open & Integrate.**

**The Wellcome Trust (WT)** does not apply strict selection criteria for its funded projects. The only prerequisites for funding are that projects should focus on public health research and infectious or tropical diseases. When it comes to project management, the WT utilizes research centers of excellence to integrate with its partners. These centers house research capacities, facilities and resources, which serve to disseminate knowledge through publication, to facilitate the research environment by providing a pool of resources, and to provide in-house research capacities to support funded projects.

To summarize, when it comes to funding translational research, this study revealed that all health foundations examined invest in all three translational chasms (T1-T3). Furthermore, the analysis revealed that two health foundations (ACS and BBC) that exhibit low levels of integration still continue to fulfill their role as financial contributor. Two health foundations (TFF and IACR) have moved beyond their role as financial contributor, and have started to focus more on portfolio management by acting as a concierge in an external advisory capacity. Finally, four health foundations (CFF, LLS, MJFF and CRUK) have fully adopted the Commit & Integrate model, providing corroborative evidence that health foundations have indeed started to shift from a traditional funding organization to an organization that provides the necessary investments to address the market failures in translational research.

Here, it is important to stress the difference between Select & Oversee and Commit & Integrate. The defining characteristic of Select & Oversee is the fact that it is used to **facilitate the research environment.** In contrast, Commit & Integrate which is used to **advance the research process.** This is reflected in the health foundations’ integration initiatives. Select & Oversee requires the establishment of research nodes and knowledge dissemination platforms, while Commit & Integrate requires the establishment of centers of expertise, partnership divisions and in-house R&D competencies. By looking at the profile of each health foundation, it can be seen that the four health foundations employing Commit & Integrate generate substantial yearly revenue, which allows them to establish costly centers of expertise and R&D facilities. However, health foundations practicing Fund & Forget or Select & Oversee generate substantially less revenue and consequently possibly cannot establish the same initiatives. In this sense, from a financial means perspective, S&O serves as an alternative to CBI. Such foundations use their lower level of revenue to establish less costly integration initiatives.
**Select & Oversee**

**Project Management**
1. Geographically strategic [inter]national nodes
2. Knowledge dissemination platform
3. Enlist specialized management entities
4. Milestone-driven goals for continued funding

**Portfolio Management**
5. Rotating committee of [inter]national experts to assess projects
6. Establish a memorandum of cooperation to evaluate proposals by invite only

**Commit & Integrate**

**Project Management**
1. Centers of [clinical] expertise
2. Clinical patient divisions for increased enrollment
3. Partnering division
4. Establish in-house R&D capabilities

**Portfolio Management**
5. Create Global Research Map
6. Scientific Advisory Council for selective funding of projects

*Figure 7 – Comparison between Commit & Integrate and Select & Oversee*
Commit & Integrate in Practice – Execution

When examining the different integration strategies employed by health foundations and the difference between their integration initiatives, it is relevant to examine why health foundations are shifting to more integrated methods of interaction. Here, Gambrill provides important insights into the motivation of three out of four of these foundations to make the shift towards a Commit & Integrate role [Gambrill 2007].

Looking at their research portfolios, health foundations realized that solid progress was made on the academic and discovery research side, but in terms of translating the discoveries and getting more things into the clinic a lot of things were not happening. At the same time, however, they realized that blind and non-strategic funding of translational research would not solve this problem. A new mode of strategic funding and partnering was required which could be applied and controlled. Therefore, foundations reevaluated their granting mechanisms and started new programs that also target partnering with the private sector [Feldman 2012; Potts 2011].

Although health foundations continue to award most of their available funding to academia, they also position themselves strategically at points within the Biomedical Research Translation Continuum [Gambrill 2007]. An important positioning is to address the Catch-22, or the so-called Valley of Death, that most biotech start-up companies face. If these organizations cannot demonstrate proof-of-concept for their treatment modality, then they cannot attract funding; but without the necessary capital, they cannot demonstrate proof-of-concept. It is believed that strategic funding by health foundations in this area can sufficiently de-risk promising treatment modalities to garner more traditional funds and development partners. Moreover, foundations in general tend to provide non-dilutive capital to PPPs, which does not require the sale of a company’s shares – a setup uniquely relevant to a small, private company.

This clarifies why certain health foundations have adopted the Commit & Integrate role – to leverage what they perceive as their added value to a partnership on top of their financial investment. However, perhaps a more important question is how do or how can health foundations organize their investment or venture philanthropy endeavors. To be more specific:

> How are projects being sourced and selected [decision making]?
> How do health foundations control and govern their funding [governance]?

With the aim to enhance understanding of the interface between disease-focused foundations and the private sector, Chang provides a very extensive overview of how CFF, LLS and MJFF and eight other health foundations have addressed these questions [Chang 2010]. To start with, three important aspects of Commit & Integrate model are identified:

> Employment of proper risk management tools
> Each commitment should be accompanied by a suitable level of project management and governance
> Prior to commitment, details about the next steps in the development process should be known

With regard to sourcing and selection of projects, it is not surprising that all of the health foundations regard both investigators [academia] and companies [private sector] as sources for partnering. Interestingly, initial focus at the start of a venture philanthropy program is to build recognition and scientific credibility with potential private partners. Part of this endeavor is to identify tangible rewards to incentivize partnering. The experience is that at the start, programs require a considerable PUSH from the foundation, but with increased recognition this eventually transforms into a PULL from the private sector.

As mentioned before, health foundations provide knowledge and access to the best science for their specific disease[s] or disease
groups. To maintain a continuous grasp on the current state of affairs, foundations frequently engage with various stakeholders in annual gap analysis sessions to review both short term and long term priorities.

All foundations studied here made use of both scientific and business advisory committees in their grant-making process. The former first reviewed the scientific risk and robustness of proposals, which was followed by a due diligence assessment by the business group, comprised of venture capitalists, industry professionals and entrepreneurs.

The primary means of grant-making was a milestone-driven grant, consisting of an upfront payment plus one or more subsequent payments. Consequently, ongoing dialogue with partners to discuss and reach agreement on the milestones, payment schedules, IP and sharing of scientific know-how was an important part of the grant-making process.

Without exception, all intellectual property is left by the foundation to the partner’s control, the reason being that this will serve as a valuable incentive for private partners to accelerate development of treatment modalities. However, to protect the considerable investments health foundations make, a so-called interruption license is part of the grant agreement. What this means is that if for any reason development is halted (e.g. due to financial insolvency), IP and scientific know-how are transferred to the health foundation, which can then find a new development partner.

Employment of other more sophisticated investment vehicles, like options, warrants and equity, are the exception rather than the rule. Equity is particularly regarded by foundations as high risk for financial and PR reasons.

Most partnerships start at 1-2 years, but an option to extend is not uncommon and reveals the intent to build a sustainable partnership. Finally, the majority of health foundations required some sort of royalties as a potential return on their investments. The actual level of funding varies considerably, but a range of $100 thousand to $1 million seems to be most common.

With regard to how health foundations control and govern their funding, all foundations are kept in the loop on project progress and are used primarily as advisor or trouble-shooter. Day-to-day activities are left for the partners to decide. Frequent updates consist of informal monthly updates or more formal annual meetings with the aim to discuss current or potential bottlenecks, deliverables and future activities.

As already mentioned, the use of milestone-driven grants provides health foundations with an important tool of control. It is not uncommon that health foundations cancel projects because of lack of sufficient progress. The majority of health foundations allow extension or cancellation of the project by a partner. Of course, in case of project cancellation, the aforementioned interruption clause plays a central role to protect the interest of the health foundation.

All foundations investigated preferred not to take a seat on their partner’s board, but preferred to co-chair some sort of oversight committee. This avoids the sensitive issue of generating a potential conflict of interest and unduly mixing power and control. Readel makes a strong case based on a number of scholars’ opinions that “the risk of such conflicts of interest is heightened when a member of a disease advocacy group is placed on a for-profit company’s board of directors” [Readel 2013].

Having examined the strategies adopted by each health foundation and having highlighted the overall practices for interaction, we now move to details on how health foundations implement their partnerships at an operational level.
Commit & Integrate in Practice – Implementation

Although the research presented in the previous chapter provides a thorough and deep understanding of why and how health foundations operate via a Commit & Integrate model, there are some limitations that may hamper the translation of the results to the Dutch situation. For one, the CFF, MJFF and LLS are all three US-based health foundations, and important cultural differences may exist with regard to venture philanthropy between the US and Europe. Moreover, all three health foundations more or less focus on delivering treatment modalities for a single disease. This does not mean that developing a treatment modality for such a disease is regarded as straightforward. It does, however, imply that the dynamics around decision making [sourcing, selection and crafting of PPPs] may be different from health foundations that focus on developing treatment modalities for multiple diseases, like KWF or Cancer Research UK. Perhaps by coincidence, the ACS, which is here classified as a financial contributor [Fund & Forget] did propose an in-house venture philanthropy arm, but decided to pull out for reasons that are unclear [Chang 2010]. On the other hand, Cancer Research UK has fully embraced Commit & Integrate in relation to PPPs. Moreover, CRUK, being a European-based foundation, allows us to examine how European counterparts operate and organize their role and commitment to PPPs. This can provide valuable insight for European health foundations with regards to the day-to-day management of funded partnerships. The analysis presented here is based on, among others, grant and partnership terms and agreements that are publicly accessible. It should be noted that it is not specified whether these agreements may vary between for-profit and non-profit grantees or partners. Furthermore, we were interested in information regarding logistics, such as number of FTEs assigned to PPP engagement, size of investment and the return on investment, but such details were in general not readily available in the public domain or were not up to date [Gambril 2007]. Retrieval of this level of detail will require further research, which will include interviews, but is considered beyond the scope of the current project.

As an alternative, the Cystic Fibrosis Foundation, deemed the ”leading venture philanthropy organization” [Feldman 2012], and its British counterpart Cancer Research UK, have been chosen for a direct comparison to better understand the implementation of partnerships at an operational level.

Integration Initiatives

Both CFF and CRUK established their first integration initiatives around the same time. CFF established 11 Research Development Program (RDP) centers in 1982, while CRUK established its Drug Development Office (DDO) in 1980. In 1990, CRUK expanded its DDO to include its Bio-therapeutics Development Unit (BDU), while in 1998 CFF created its Therapeutic Development Network (TDN) of centers as successors to its RDP centers [expanded to a total of 80 centers by 2009]. Although no details could be found on CRUK’s DDO centers, CFF’s TDN centers dedicated $33 million in 2010, $41 million in 2011 and $57 million in grants in 2012. Through its successful venture philanthropy model, the CFF affiliate, CFF Therapeutics, received royalty payments of $54 million and $156 million in 2010 and 2012, respectively. Royalties originated from two FDA-approved treatments [Cayston® and Kalydeco®] that were developed with CFF support.

It was found that both foundations apply similar grant management, oversight committees and intellectual property procedures. Where they differ is in their investment plans and integration initiatives. While CRUK centers provide in-house R&D, CFF centers provide clinical expertise. Though there is no mention of this in CRUK’s records, in 1994 CFF made use of a “policy entrepreneur”, Robert Beall. Beall is considered by CFF to be the key force behind its shift from Fund & Forget to venture philanthropy. A policy entrepreneur can use his/her political connections,
resources and persistence to promote a position, in this case, venture philanthropy [Feldman 2012]. Although a policy entrepreneur has not been mentioned by other CBI foundations, further investigation through interviews may shed light on its significance and whether it can be extrapolated to other foundations.

Grant Management and Progress Updates

Funded partners are required to submit scientific reports at the end of each installment period to be reviewed by CRUK’s scientific committee or CFF’s scientific advisory council. Both CFF and CRUK reserve the right to audit any funded account at the partner’s institution in relation to its administration and accounting. Both require chief investigators of funded projects to provide progress reports, based on CRUK’s Scientific Milestone Review (SMR) and CFF’s milestone development goals for continued funding. CFF makes use of external advisory committees responsible for evaluating these progress reports.

Boards Involved in the Funding Process

Both foundations make use of oversight committees. Taking a seat on their private partner’s board is not explicitly mentioned in grant agreements. CRUK has established two committees that are responsible for funding decisions, each with its own range of funding and remit. The Science Committee is responsible for the oversight, review, and management and funding of research grants for projects that focus on biomarker research and drug discovery. The Clinical Trials Award and Advisory Committee is responsible for reviewing and funding cancer clinical trial projects. Both committees are overseen by CRUK’s Scientific Executive Board (SEB), which is responsible for the development and implementation of CRUK’s scientific strategy. CFF makes use of coordinating centers that include a steering committee, an independent monitoring board, an external advisory committee and a scientific advisory council. These centers are responsible for proposal assessment and all relevant funding procedures. Peer-reviewed, milestone-driven mechanisms are used to evaluate research projects for continued funding.

Intellectual Property

When it comes to intellectual property, CRUK has established Cancer Research Technology (CRT), a wholly owned subsidiary, which acts as the technology development and commercialization arm of CRUK. Any intellectual property resulting from the collaboration between CRUK and its funded partner automatically and immediately vests with the partner, termed “funded intellectual property”. Partners, however, grant CRUK non-exclusive license to use the intellectual property for non-commercial research. In the event that CRUK wants to gain ownership of the resulting intellectual property, it formulates a request and the funded partner is allowed to negotiate with CRT. If negotiations are fruitful, CRT enters into a Technology Transfer Agreement (TTA) with its funded partner. CFF, on the other hand, has established CFFT, the Cystic Fibrosis Foundation Therapeutics. According to CFF’s grant agreements, CFFT “co-owns” intellectual property rights with its private partners. Partners are required to pay CFFT tiered royalties based on the net sales of the product. Furthermore, CFF reserves the right to implement an interruption license in cases where the capabilities of its partner are compromised.

Tailored Investment Plans and Grant Schemes

Following approval from the evaluation committees, CRUK establishes the type of grant to be awarded. Grants are grouped into three categories based on CRUK’s reporting requirements [see appendix] and last up to 3 years. CFF adopts a different approach; it establishes the type of grants based on the type of research. Basic research can be awarded up to $90,000 per year for a 2-year
period, while clinical trials receive $100,000-$225,000 per year for up to 3 years.

**Human Resources**

Apart from external stakeholders who may feel uncomfortable with a change in funding strategy, the process of embracing a Commit & Integrate model may also result in considerable internal tensions. These tensions can be fed by mistrust towards the private sector, discussion about financial resources, and its distribution between basic research, translational research and clinical studies. Commit & Integrate may also require foundation staff with other competencies to run the grant-making process. These tensions need to be mitigated. For example, CRUK applies “induction” measures. These measures are used to ensure effective people management to foster a culture of research integrity. New project leaders are given management courses to improve or rejuvenate their skills. Furthermore, informal retreats and workshops are encouraged in order to share experiences and promote development.
Clear cut, one-size-fits-all blueprints cannot be applied to all PPPs because of their sensitivity to context, including the type of partners and research involved. PPPs are multidimensional and multi-level phenomena that require precise appraisal and consideration before deciding how to interact with them. Taking that into consideration, Chang provides some key organization-specific characteristics that can be considered by health foundations that want to embrace a Commit & Integrate model for future funding [Chang 2010]. It may serve as a guide for further discussion and consideration. These characteristics include a stakeholder analysis to distinguish the various relevant parties and their interests, such as donors and patients. With regard to sources and uses of funds, Chang outlines how a health foundation’s expectations, wishes and goals should be aligned with donor expectations and wishes. This may require timely and effective communication to donors and/or the general public of the planned transition, with clear explanations of its necessity, added value and approach. The same applies to managing the expectations of patients. In addition, Chang uses the phrase “Where is the science at?” to describe how decisions on grant allocations in the drug development process should largely take into consideration the level of understanding of the underlying disease pathobiology. Finally, a foundation’s story of origin is important. While some may have a strong and long history of traditional grant-making, others need to gain traction and set up specific subsidiaries to generate a legal and cultural firewall between themselves and their subsidiaries.

To conclude, lengthy therapy development projects coupled with a growing disease burden represent a problem faced by a multitude of players, including academic research centers, private research institutes and hospitals. The solution to this problem is translational research, and public-private partnerships are the tool to facilitate and expedite it. Our study reveals that the question health foundations should be asking is not “Should we engage in public-private partnerships?” but rather “How can we best engage in public-private partnerships?” Players focused on patient benefit, such as health foundations, are gaining a larger role in research, one that goes beyond the traditional Fund & Forget model. Although their research budgets are not comparable to those of pharma players, they can leverage their position by de-risking the field, providing facilitative services and, in some cases, contributing with their own in-house research.

Final Remarks

It is interesting that health foundations find themselves in a unique paradox. On the one hand, they need to raise money and interest from public donors. On the other hand, creating patient value from interaction with private for-profit entities can also be questioned as not operating in the public’s best interest. One thing is clear, though: nowadays, proof of concept is not enough to secure continued funding, which puts patient benefit at risk. And this so-called “funding gap” is what health foundations can address.

In conclusion, it is important to realize that health foundation-driven PPPs stand to inject a sense of urgency and collaboration into research and development. These PPPs provide the means to advance potential therapeutic modalities in the translation continuum and thereby maximize the use of health research evidence for the benefit of the patient.
# Abbreviations

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<tr>
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<td>ACS</td>
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<td>AIRC</td>
<td>Italian Association for Cancer Research</td>
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<td>BBC</td>
<td>Breakthrough Cancer Research UK</td>
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<td>CBI</td>
<td>Commit &amp; Integrate</td>
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<td>CF</td>
<td>Cystic fibrosis</td>
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<td>CFF</td>
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<td>CRUK</td>
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<td>DC</td>
<td>Development compound</td>
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<td>eDC</td>
<td>Exploratory/early development compound</td>
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<td>F&amp;F</td>
<td>Fund &amp; Forget</td>
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<td>FID²CO</td>
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<tr>
<td>MJFF</td>
<td>Michael J. Fox Foundation</td>
</tr>
<tr>
<td>NBE</td>
<td>New biological entity</td>
</tr>
<tr>
<td>NCE</td>
<td>New chemical entity</td>
</tr>
<tr>
<td>PoC</td>
<td>Proof of concept</td>
</tr>
<tr>
<td>PoP</td>
<td>Proof of principle</td>
</tr>
<tr>
<td>PPP</td>
<td>Public-private partnership</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>Research &amp; development</td>
</tr>
<tr>
<td>RDP</td>
<td>Research Development Program</td>
</tr>
<tr>
<td>S&amp;O</td>
<td>Select &amp; Oversee</td>
</tr>
<tr>
<td>SMEs</td>
<td>Small and medium-sized enterprises</td>
</tr>
<tr>
<td>TFF</td>
<td>Terry Fox Foundation</td>
</tr>
<tr>
<td>WT</td>
<td>Wellcome Trust</td>
</tr>
<tr>
<td>ZonMw</td>
<td>The Netherlands Organization for Health Research and Development</td>
</tr>
</tbody>
</table>
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Please note: The last accessed date for website links used for CRUK and CFF agreements in this report was between 04-09-2013 and 18-10-2013


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# Appendix

## Table 1: Interaction details

<table>
<thead>
<tr>
<th>Health Foundation</th>
<th>Strategy</th>
<th>Level of Integration (Portfolio / Project)</th>
<th>Role</th>
<th>Integration Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Cancer Society</td>
<td>- Fund projects based on the suggestion of an in-house Extramural Grant council which suggests projects based on society’s objectives and available funds alignment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-/-</td>
<td>Financial Contributor</td>
<td>Fund &amp; Forget</td>
</tr>
<tr>
<td>Breakthrough Breast Cancer</td>
<td>- Establishment of Research Centers and Units in national universities that receive financial support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-/-</td>
<td>Financial Contributor</td>
<td>Fund &amp; Forget</td>
</tr>
</tbody>
</table>
| Terry Fox Foundation                  | - Establishment of Terry Fox Research Institute to oversee the selection of funding projects. Projects are selected and funded based on strict multi-level selection criteria  
- Establishment of national research nodes that serve as “convergence points” for conducted research  
- The supervision of funded research projects by applying milestone-driven goals with no direct involvement in the achievement of those goals |
|                                       |                                                                           | +/-                                       | Concierge (Facilitator) | Select & Oversee      |
| Italian Association for Cancer Research | - Funding of national cancer research projects based on extensive appraisal by a rotating Scientific Committee of national experts and 350 foreign experts  
- No direct project involvement however, the AICR focuses on the dissemination of relevant cancer research results and knowledge conducted by national and international levels for its partners |
|                                       |                                                                           | +/-                                       | Concierge (Facilitator) | Select & Oversee      |
| Cystic Fibrosis Foundation            | - Practices Venture Philanthropy to de-risk early stages of research  
- Provides financial support based on a matching basis between potential preclinical and clinical development  
- Milestone driven goals are applied for the supervision of funded projects  
- Establishment of a therapeutic development program that selects lucrative projects  
- Therapeutics Development Network: Health fund acts an expert external advisor providing troubleshoot and guidance for partners that are involved in clinical trials |
<p>|                                       |                                                                           | +/-                                       | Development Partner    | Commit &amp; Integrate    |</p>
<table>
<thead>
<tr>
<th>Organization</th>
<th>Approach</th>
<th>Development</th>
<th>Commit &amp; Integrate</th>
</tr>
</thead>
</table>
| Michael J. Fox Foundation            | - Selective funding of projects based on appraisal by a team of in-house key experts  
- Pro-active selective funding of projects that have the potential to de-risk the research landscape  
- Partnering Program: close collaboration between MJFF’s in-house researchers and business trained project leaders at every stage of research continuum | +/+         | Development Partner Commit & Integrate |
| Leukemia & Lymphoma Society          | - Supports public & private research entities financially  
- Establishment of a Therapy Acceleration Program (TAP) for selective funding and project integration  
- Project integration is achieved using as subdivision of the TAP known as the Academic Concierge Division [Integration Initiative]  
- Strategic affiliations with specialized CROs and Pharma entities | +/+         | Development Partner Commit & Integrate |
| Cancer Research UK                   | - Support public & private research entities financially  
- Support research through multiple Cancer Centers of Excellence  
- National partnerships with national cancer research community  
- International partnerships with industry entities | +/+         | Development Partner Commit & Integrate |
| Wellcome Trust                       | - Nonselective approach to filling portfolio  
- High project management achieved using centers of excellence, in-house R&D and knowledge dissemination platforms | -/+         | Nonselective Partner Open & Integrate |
<table>
<thead>
<tr>
<th>Health Foundation</th>
<th>Year of Establishment</th>
<th>Country of Origin</th>
<th>Goal</th>
<th>Total Revenue (2012)</th>
<th>Business Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Cancer Society</td>
<td>1913</td>
<td>US</td>
<td>Support new drug development to combat CF and improve patient quality of life</td>
<td>$925 m</td>
<td>Globally-oriented not-for-profit entity characterized by its sponsorship role and its virtual research model</td>
</tr>
<tr>
<td>Breakthrough Breast Cancer</td>
<td>1989</td>
<td>UK</td>
<td>Focusing on innovations that can increase the pace of detecting cancer and developing effective treatments for all primary breast cancer types</td>
<td>£18 m</td>
<td>Charity organization utilizing a hybrid business model that focuses on in-house competencies and extramural partnerships based on a 10-year commissioned strategy plan</td>
</tr>
<tr>
<td>Terry Fox Foundation</td>
<td>1988</td>
<td>Canada</td>
<td>Improving the outcomes of cancer research for patients through a highly collaborative, team-oriented, milestone-based approach that enables global translational research</td>
<td>26 m CAD</td>
<td>Virtual institute utilizing a not-for-profit model to foster highly oriented collaborative efforts</td>
</tr>
<tr>
<td>Italian Association for Cancer Research</td>
<td>1965</td>
<td>Italy</td>
<td>Dedicated to fostering and expanding cancer research in Italy by targeting promising research initiatives</td>
<td>€165 m</td>
<td>Virtual nonprofit model with a strong emphasis on portfolio management</td>
</tr>
<tr>
<td>Cystic Fibrosis Foundation</td>
<td>1955</td>
<td>US</td>
<td>Advancing and facilitating cancer research through funding</td>
<td>$298 m</td>
<td>Not-for-profit voluntary entity utilizing venture philanthropy</td>
</tr>
<tr>
<td>Michael J. Fox Foundation</td>
<td>2000</td>
<td>US</td>
<td>Finding a cure for Parkinson’s disease by facilitating the development of improved therapies and focusing on clinical applications</td>
<td>$88 m</td>
<td>Private research funder utilizing a portfolio approach for optimized partnership alignment with a strong industry inclination</td>
</tr>
<tr>
<td>Leukemia &amp; Lymphoma Society</td>
<td>1949</td>
<td>US</td>
<td>Proactively advance diagnosis and treatment of blood cancer through strategic funding</td>
<td>$305 m</td>
<td>Virtual model using a portfolio approach at the development stage</td>
</tr>
<tr>
<td>Cancer Research UK</td>
<td>1902</td>
<td>UK</td>
<td>Focusing on areas of unmet needs, investing in innovative opportunities, strengthening current competencies</td>
<td>£493 m</td>
<td>Hybrid business model that funds partnerships and collaborative efforts selectively and strives to enhance its in-house competencies</td>
</tr>
<tr>
<td>Wellcome Trust</td>
<td>1936</td>
<td>UK</td>
<td>Achieving extraordinary improvements in human and animal health by focusing on supporting breakthrough research, the application of research and embedding medicine into culture</td>
<td>£242 m</td>
<td>Global nonprofit charitable foundation that funds research with minimal selection and is highly focused on asset allocation and risk management</td>
</tr>
</tbody>
</table>

1 Figure from 2010
2 Excluding Net realised and unrealised gains on investments of £1,485 m
<table>
<thead>
<tr>
<th>Health Foundation</th>
<th>Total Research Grants Awarded [2012]</th>
<th>Research Modality</th>
<th>Level of Translational Research T1 T2 T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Cancer Society</td>
<td>$107 m</td>
<td>- Drug development</td>
<td>T1 T2 T3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Innovative approaches</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Diagnostics</td>
<td></td>
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<tr>
<td>Breakthrough Breast Cancer</td>
<td>£10.4 m</td>
<td>- Drug development</td>
<td>Information not available</td>
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<tr>
<td></td>
<td></td>
<td>- Innovative approaches</td>
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<tr>
<td></td>
<td></td>
<td>- Diagnostics</td>
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<tr>
<td>Terry Fox Foundation</td>
<td>4.5 m CAD&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- Drug development</td>
<td>T1 T2 T3</td>
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<td>- Innovative approaches</td>
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<td>- Diagnostics</td>
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<tr>
<td>Italian Association for Cancer Research</td>
<td>€77 m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>- Drug development</td>
<td>T1 T2 T3</td>
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<td>- Diagnostics</td>
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<tr>
<td>Cystic Fibrosis Foundation</td>
<td>$87 m</td>
<td>- Drug development</td>
<td>T1 T2 T3</td>
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<td>- Innovative approaches</td>
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<td>- Diagnostics</td>
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<tr>
<td>Michael J. Fox Foundation</td>
<td>$55 m</td>
<td>- Drug development</td>
<td>T1 T2 T3</td>
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<td>- Innovative approaches</td>
<td></td>
</tr>
<tr>
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<td></td>
<td>- Diagnostics</td>
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<tr>
<td>Leukemia &amp; Lymphoma Society USA</td>
<td>$68 m</td>
<td>- Drug development</td>
<td>T1 T2 T3</td>
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<td>- Innovative approaches</td>
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<td>- Diagnostics</td>
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<tr>
<td>Cancer Research UK</td>
<td>£332 m</td>
<td>- Drug development</td>
<td>T1 T2 T3</td>
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<td>- Innovative approaches</td>
<td></td>
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<td></td>
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<td>- Diagnostics</td>
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<tr>
<td>Wellcome Trust</td>
<td>£511 m</td>
<td>Information not available</td>
<td>Information not available</td>
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</table>

<sup>1</sup> Research funded through Terry Fox Research Institute. Excluding funding of Canadian Cancer Society, International cancer research organizations and Canadian Institutes of Health Research (Total 15-16 m CAD)

<sup>2</sup> Figure from 2010
Detailed Case Analyses

CASE 1: Leukemia & Lymphoma Society

According to the following analysis, the Leukemia & Lymphoma Society (LLS) practices a high degree of both portfolio and project management and consequently applies a Commit & Integrate funding model. As a health foundation, it can be characterized as a development partner.

The Leukemia & Lymphoma Society (LLS) is based in the United States and was founded in New York City in 1949 by Rudolph and Antoinette de Villiers following the death of their son Robert who suffered from leukemia. Originally known as the Robert Roessler de Villiers Foundation, in 2000 it was changed to the Leukemia & Lymphoma Society in 2000 to reflect the organization’s encompassing focus on all types of blood cancer. Since its establishment, the LLS has funded in excess of $600 million of research. The LLS proactively strives to advance the treatment of blood cancers through strategic funding efforts. It funds private entities including contract research organizations, pharmaceutical companies, research institutes and biotech firms. An example is the Beckman Research Institute of the City of Hope, Valor Biotherapeutics and Celator pharmaceuticals. Furthermore, it utilizes a virtual model that does not enjoy any in-house product development facilities. Instead, it achieves its goals through funding external research facilities.

LLS has a total research budget of $68 million, with $305 million in revenue (as of 2012). LLS focuses on drug development projects and supportive diagnostics on the T1, T2 and T3 levels, targeting the entire translation continuum.

LLS’ strategy focuses on financing and supporting project development and access PPPs. In the absence of any subsidiary, LLS directly interacts with projects. This is achieved by setting up a Therapy Acceleration Program (TAP). Besides financial support, this integration initiative allows LLS to assist clinical investigators and companies in gathering proof of concept data and in the complete testing, registration and marketing of new treatments. TAP consists of three divisions, each with its own mandate for expediting research and development. The Academic Concierge Division partners with companies that manufacture clinical-grade materials, technology platforms and CRO service providers. The expertise of these entities lies with preclinical medicinal chemistry studies, including toxicology, pharmacodynamics and pharmacokinetics (PK/PD). As a result of LLS’ affiliation with these specialized entities, it is in a prime position to support partners with their investigational new drug (IND) applications. In addition, the concierge division can also assist in the gathering of FDA-required documentation prior to the commencement of clinical trials. If an LLS partner then advances to clinical trials, LLS also has a portfolio of additional biotech and pharma affiliations at its disposal for further support.

The TAP program also houses the Biotechnology Accelerator Division which strategically selects programs for LLS to invest in. This division identifies projects developing novel anti-cancer therapies (prevention, diagnostic or treatment of blood cancer) as potential candidates. Candidates seeking funding will need to demonstrate the following:

- Therapeutic potential of its drug candidate
- Capabilities of its management and scientific staff
- Financial strength
- Freedom to operate, including intellectual property protection
- Well-designed regulatory and commercialization strategies

Furthermore, the Biotechnology Accelerator Division selectively funds projects that are expected to yield net results that will enable LLS to raise additional funding to support the testing, registration and marketing of
new therapies. Finally, the Clinical Trials Division focuses on access PPPs, aiming to increase patient enrollment in blood cancer trials by assisting patients in finding clinical trial studies that are in their community or familiar proximity.

An example of LLS’s Therapy Acceleration Program is its partnership with Celator Pharmaceuticals for the phase 2b clinical study of CPX-351 [Cytarabine:Daunorubicin] liposome injection. This partnership represents a T3 research bridging activity. LLS provided paramount financial support in the form of $5 million and aided in the establishment and design of Celator’s phase 2b multicenter, randomized open-label clinical trial which spanned 35 sites in the US, Canada, France and Poland. Findings demonstrated positive trends in overall patient survival and complete remission rates in patients with an unfavorable risk profile.

“The findings presented at ASH demonstrate that CPX-351, through the targeted delivery of a consistent and synergistic ratio of cytarabine and daunorubicin, results in improved clinical outcomes compared to standard salvage therapy,” stated Dr Cortes. “Enhancing the clinical benefit of the two most active drugs we have against AML gives us the potential to take an important step forward in AML therapy.”

http://www.celatorpharma.com/new/pr_20111212.html
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CASE 2: Cancer Research UK

According to the following analysis, Cancer Research UK practices a high degree of project and portfolio management. As a result, it applies a Commit & Integrate funding model. Furthermore, as a health foundation it can be characterized as a development partner.

Cancer Research UK (CRUK) is based in the United Kingdom and is the world’s largest independent cancer research charity. It was formed in 2002 through the merger of the Cancer Research Campaign and the Imperial Cancer Research Fund with the aim to focus on areas of unmet needs. It operates under a hybrid business model which invests in innovative research opportunities while simultaneously striving to strengthen in-house drug development competencies. The target of its private funding is research institutes, such as the Wellcome Trust Sanger Institute. It is dedicated to supporting research scientists achieve translation in their research.

CRUK’s strategy focuses on project development and portfolio PPPs. CRUK interacts with projects indirectly through established subsidiaries. CRUK has a specialized in-house Drug Development Office (DDO) which has 30 years of expertise in early-phase oncology trials. CRUK has the ability to extramurally fund research projects but also conducts its own internal research. It has the ability to manufacture and formulate small molecules and biological therapies. The DDO represents an integration initiative and consists of the Biotherapeutic Development Unit (BDU) and the CRUK Formulation Unit. The BDU is used to develop and manufacture biological agents to be used in DDO clinical trials. Agents include antibodies, plasmid DNA, recombinant proteins and viral vectors. The CRUK Formulation Unit is also responsible for supplying new therapies for testing; however, it is the product of an external partnership with the University of Strathclyde, Glasgow.

Due to the DDO’s state-of-the-art manufacturing facilities, extensive experience and formidable track record, it is considered to be
the “one-stop-shop” solution for companies that are funded by CRUK and involved in early-phase oncology therapy development. The DDO thus represents CRUK’s initiative to be proactive in the involvement of projects. It also represents CRUK’s active portfolio management. The DDO exclusively searches for:

- Preclinical and early-phase clinical studies
- Projects requiring preclinical development, including safety toxicology, drug manufacture and formulation
- Early phase II proof of principle studies focusing on the use of biological endpoints
- Non critical path studies on agents in active commercial developments

An example of CRUK’s DDO initiative is its partnership with the Wellcome Trust Sanger Institute. This partnership focuses on modeling resistance to anaplastic lymphoma kinase inhibitors and exploring novel therapeutic strategies. Anaplastic lymphoma kinase (ALK) has been identified as a critical oncogenic kinase in multiple cancer types, including non-small cell lung cancer (NSCLC), neuroblastoma and anaplastic large-cell lymphoma (ALCL). Novel ALK inhibitors already exist in early phase clinical trial pipelines, however the probability of relapse due to resistance is expected to be high. As a result, CRUK and the Sanger Institute have partnered up to screen a wide range of alternative kinase inhibitors using a high-throughput cancer cell line screening platform developed by CRUK’s DDO. Furthermore, CRUK’s Formulation Unit will be responsible for the manufacture of cell lines representative of the clinical population. This research effort represents a T1 translational research activity and findings stand to benefit a number of patients who engage in targeted therapy against activated kinase. This project has been in progress for 3 years and is part of a funding project that focuses on nine institutes, with an overall budget of £37 million.


http://www.cancerresearchuk.org/prod_consump/groups/cr_common/@abt/documents/generalcontent/cr_049656.pdf

CASE 3: Terry Fox Foundation

According to the following analysis, the Terry Fox Foundation practices a high degree of portfolio management. It is not directly involved in the governance of funded projects. The foundation does not provide stage-specific development support nor does it act as an external advisor. It has established nodes to aggregate research projects and has enlisted management entities to help supervise and direct its research projects based on milestone-driven goals for continued funding. It is not solely a financial contributor, nor is it a development partner. As a health foundation, it can be characterized as a concierge (facilitator) that Selects & Oversees.

The Terry Fox Foundation (TFF) is located in Canada and was founded by Terry Fox, who was diagnosed with bone cancer above his knee. Having experienced the suffering of cancer patients first-hand, he decided to run across Canada to raise money for cancer research, therefore starting the now-yearly “Marathon of Hope”. The foundation purposefully tries to improve the outcomes of cancer research through a collaborative, milestone-based approach to enabling translational research. It operates as a not-for-profit, virtual institute to foster highly focused collaborative efforts. The TFF does not fund private entities; instead, it focuses on public research institutes affiliated with academic research centers and universities. The foundation dedicates $20 million (CAD) to Canadian-based research per year and has raised over $600 million worldwide for cancer research.
The TFF aims to fund 12 million CAD yearly in translational research focused on drug development, innovative approaches and diagnostics on the T1 and T2 levels. As of 2012, it had funded 4.5 million CAD. Furthermore, TFF focuses on access PPPs by indirectly interacting with projects. The TFF has established the Terry Fox Research Institute (TFRI) to supervise the foundation’s cancer research projects by collaborating with multiple organizations experienced in the management of research projects. These organizations include the Canadian Cancer Society (CCS) and the Canadian Institutes of Health Research (CIHR). In addition, the foundation has established a number of strategically placed research “nodes” that serve as convergence points for national researchers. Geographically-dispersed nodes around the country allow hospitals, cancer organizations and universities to establish unprecedented collaborative teams with the focus of translational research. The supervision of funded projects is conducted by the TFRI and is based on applying milestone-driven goals with no direct involvement in the achievement of those goals.

The TFRI selects projects for funding based on strict multi-level selection criteria. Moreover, the TFRI accepts project proposals by invitation-only from institutions that are signatories to the TFRI Node Memorandum of Understanding for cooperation. Furthermore, projects are only funded if they are involved in tumor-site specific translational cancer research.

The TFRI exclusively searches for projects with measurable impact that:
- Reduce the number of individuals diagnosed with cancer
- Improve the quality of life or survival of patients being treated for a particular cancer

An example of the TFF’s Select & Oversee role can be seen in its Non-Hodgkin’s lymphomas (NHL) research project, named “Defining the molecular correlates of disease progression, treatment failure and prognosis in non-Hodgkin’s lymphomas”. This project is housed within TFRI’s British Columbia node which consists of the BC Cancer Agency and the University of British Columbia. Initially this node provided research tools, facilities and financial funding for research projects that studied manipulated genes in follicular lymphoma. The initial study focused on the genetic changes that occur which lead to diversity in clinical outcomes. Having established that, the node has strategically chosen to pursue translational research projects in the area of heterogenic patient outcomes. Previously undiscovered genetic abnormalities in lymphoma cells provide new targets for treatment. The extension of the discovery project will provide additional focus on large B cell lymphoma which is incurable in 30-40% of lymphoma patients.

http://www.tfri.ca/programs/foundation_programs.asp
http://www.tfri.ca/about/
https://www.icrpartnership.org/viewProject.cfm?pid=715112&SHID=14914

CASE 4: Cystic Fibrosis Foundation

The Cystic Fibrosis Foundation practices a high level of portfolio management. Its project is best characterized by its application of venture philanthropy. It has established business relations with biotech and pharmaceutical players to share risk and to provide financial support and expert facilitative advice. Based on the analysis, the CFF applies a Commit & Integrate model. As a health foundation, it can be characterized as a development partner.
The Cystic Fibrosis Foundation (CFF) is based in the United States and has the goal to advance cancer research through managing drug discovery and development alliances. It utilizes a not-for-profit virtual model that links investors with private biopharmaceutical companies, including Pfizer.

When it comes to research, the CFF funded $87 million as of 2012. Drug development, innovative approaches and diagnostics all fall under the research umbrella of CFF and they span the entire translation continuum, T1, T2 and T3.

The CFF has established the Cystic Fibrosis Foundation Therapeutics (CFFT) branch to manage funded projects. The CFFT focuses on project development PPPs and achieves this by applying the concept of venture philanthropy. CFF was the first disease-focused foundation to fully apply this model in bringing a drug to market. Unlike traditional charity grants, venture philanthropy regards funding as an investment. This involves entering into contractual agreements with global top-tier and innovative pharmaceutical companies. The CFFT has created the Therapeutics Development Network (TDN) which is composed of multiple clinical care centers that have culminated experience in the design and conduct of clinical trials. The goal of this initiative is to streamline the clinical trial process for partners funded by the CFF. This is facilitated, among other mechanisms, by cutting lengthy recruiting times for trials by providing access to CFF’s care centers and patient registry. Moreover, the clinics include an independent monitoring board and a scientific advisory council that are familiar with the clinical development of drugs for cystic fibrosis and which supervise the entire process. Supervision includes peer-reviewed, milestone-driven mechanisms to evaluate research projects for continued funding. CFFT expects a return on investment from funded drug development projects. If the drug achieves on-market status, then CFFT proceeds to collect the returns and cycles these back to its pipeline for reinvestment. Return on investment comes in the form of royalty payments based on net amount of sales or a multiple of its original investment. In addition, the TDN also houses the Research Development Program (RDP) which serves as a “core supply center” that shares tools and resources and disseminates information among researchers globally. The CFF has established a total of eleven RDP centers in which it acts as an external expert advisor that serves a troubleshoot function. Through regular advisory meetings, CFFT assists in resolving project obstacles. In addition, the CFFT allows partners in funded projects to bypass the learning curve by up to 6 months by providing access to validated assays at its CRO affiliations or by pairing partners with experts in pharmaceutical development.

CFF’s venture philanthropy approach focuses on investing in the early-stages of research in order to de-risk the field for other interested parties which can continue the research. CFF recognizes that it does not possess billion-dollar research budgets, however it leverages its position by targeting the most risky stage in the drug development process, the “Valley of Death”. A thirteen-fold increase in research investment can be seen between the years of 2000 and 2008 by disease-focused foundations applying venture philanthropy, with approximately $90 million invested in biopharmaceutical companies. Within a partnership, CFF is regarded as a research pioneer, fundraiser, advocate and caregiver. As a research pioneer, it is involved in producing innovative research for the drug development process and funding innovative opportunities; as a fundraiser it fosters funding support; as an advocate it maintains awareness and press coverage of cystic fibrosis; and finally, as a caregiver, it helps patients get access to information and care. Moreover, CFF also applies part of its resources to funding development and validation programs for new technology platforms. This is achieved using its Technology Access Program.
With regards to portfolio management, the CFF funds projects on a matching basis between preclinical development and initial clinical trials, only funding projects that show the potential for advancement through the translation continuum.

The essence of venture philanthropy lies within the formation of partnerships as stated by Feldman [Feldman 2013] between academic researchers and industry firms. An illustrative example of CFF’s venture philanthropy model is the development of the drug Kalydeco. Kalydeco was the manifestation of a research alliance and commercialization agreement between CFF and Aurora Biosciences. In 2000, CFF provided $30 million in funding and $17 million on a provisional milestone-achievement basis. According to the terms of the agreement, Aurora was responsible for identifying and developing 2-3 new drug candidates over a five-year timespan.

“The important science that CFF has funded over the years in university labs and medical centers has created new opportunities for therapies. To convert these opportunities quickly and efficiently into compounds that can be tested in the clinic requires skill sets, technologies and expertise that may be beyond those in the basic research lab. These are the capabilities Aurora brings to this partnership” – Stuart J.M. Collinson, Chairman, CEO and President of Aurora

200,000 compounds were screened in the process of identifying potential compounds, and compound VX-770 showed unprecedented therapeutic benefits in phase 2 clinical trials. In January 2012, Kalydeco [VX-770] received FDA approval and was the first drug to address the underlying cause of cystic fibrosis, targeting 4% of patients. In the course of Kalydeco’s and its complementary combination treatments, CFF contributed a total of $75 million. It stands to earn royalties which it will reinvest in future research.

CASE 5: Michael J. Fox Foundation
According to the following analysis, the Michael J. Fox Foundation (MJFF) exhibits a high level of portfolio and project management. It provides financial support and actively engages in collaborative partnerships in the disease and drug development pipeline. The foundation is characterized by the rapid deployment of financial resources and expertise. The MJFF applies a Commit & Integrate model and, as a health foundation, can be characterized as a development partner.

The Michael J. Fox Foundation (MJFF) is based in the United States and was established by actor Michael J. Fox in 2000. Since then, it has become the largest global non-profit funder of Parkinson’s disease research, with $350 million invested to date. The MJFF has the goal of finding a cure for Parkinson’s disease by facilitating the development of improved therapies and clinical applications. It is a private research funder that uses a highly oriented portfolio approach and enjoys strong alignments with research institutions and private industry players, including Envoy Therapeutics. In 2010, the MJFF launched the first large-scale clinical study on Parkinson’s biomarkers based on a five year, $45 million plan.

The MJFF had total revenues of $88 million and allocated $55 million to research (as of 2012). It focuses on drug development, innovative approaches and diagnostics on the T1, T2 and T3 levels.

The MJFF focuses on project development PPPs and has established The Partnering Program. In the absence of any subsidiary, the MJFF directly interacts with projects. The goal of this program is to foster formal and official channels for partnerships. Named “Charting the Course”, the first stage of this program is to approach worldwide leading specialists to map and maintain an encompassing view of the field and identify research fields that are promising for Parkinson’s disease [Potts 2011]. These meetings
directly lead to funding and collaborative efforts. The second stage is the “Selection Process” where its scientific staff reviews potential research opportunities. In the third “Research Process” stage, the foundation tries to fund quickly, within 2 months. Here, the MJFF has a team of in-house researchers and business-trained project leaders that collaborate with project partners at all levels of the translation continuum, including top therapeutic targets. The final stage of “Capitalizing on Results” gives the MJFF its unique character as it appropriates returns from its own and external researchers.

The MJFF actively strives not to cannibalize the efforts of other for-profit companies that may compete for financial, scientific or collaborative resources. It is adamant on de-risking the field and, as a result, the MJFF does not derive any revenue stakes or intellectual property from research projects.

The MJFF is focused on critical collaborations that yield regulatory approval and on-market status for therapies. An example of the MJFF’s collaborative strategy includes the MJFF’s funding of biotech entity Proteotech, which was in the early development of a therapeutic compound for Parkinson’s disease. The MJFF provided 4 years of funding and the project yielded positive results, which primed the recruitment of Avid Radiopharmaceuticals to advance the project. Proteotech was then able to secure a funding deal for its therapeutic program with GSK.

The MJFF is highly selective in its funding of high-risk/high-reward projects. An in-house team of experts comprised of science and business-oriented individuals proactively searches for projects that complement the world’s largest Parkinson’s research portfolio, prioritizing projects that ensure a strategic course. These projects revolve around:

- Research exploring specific therapeutic approaches that could contribute to the development of improved Parkinson’s disease treatments
- Research to develop tools and resources that will help accelerate the development of Parkinson’s disease treatments

**CASE 6: Italian Association for Cancer Research**

The Italian Association for Cancer Research (AIRC) was founded in 1985 and has gradually expanded to include 17 national committees with 1.8 million members. The AIRC is dedicated to fostering and expanding cancer research in Italy by targeting promising research initiatives and creating a system to inform and improve public awareness. The AIRC utilizes a virtual non-profit model with a strong emphasis on portfolio management. The AIRC has funded a total of 487 oncology research projects and provided €77 million in funds in 2010.

The AIRC’s focus is on innovative approaches on the T1, T2 and T3 levels.

The AIRC interacts directly with funded projects and focuses on access PPPs. The AIRC provides financial support exclusively to national research projects. The AIRC plays no role in project governance or strategic management, however it does strive to disseminate knowledge for its funded project partners. This is done by facilitating access to information generated from national and international cancer studies and research activities. This is achieved by providing access to its publication system and website “Fondamentale”.

The funding of national cancer research projects is based on extensive appraisal by a rotating Scientific Committee of national...
experts and 350 foreign experts. This process takes nine months, and selected projects are innovative, have substantial expected patient impact, are feasible, and are proven by preliminary results.

CASES 7 and 8: Breakthrough Cancer Research and the American Cancer Society
Both cases 7 and 8 exhibit low portfolio and project management and consequently are considered to apply a Fund & Forget model in which they act simply as financial contributors with no involvement in the strategic selection nor the governance and management of projects. They are straightforward sources of non-dilutive capital and can be characterized as financial contributor health foundations.

CASE 7: Breakthrough Breast Cancer
Breakthrough Breast Cancer (BBC) is a charity organization located in the United Kingdom which focuses on fostering collaborative efforts and partnerships based on a 10-year commissioned strategy plan. It focuses on drug development, innovative approaches and diagnostics research modalities. BBC does not fund projects on a selective basis; rather it establishes BBC Research Centers & Units in national universities that receive financial support. It also does not engage in project interaction, neither in a facilitating nor in an involved-partner manner.

CASE 8: American Cancer Society
The American Cancer Society (ACS) is a globally-oriented not-for-profit entity with a virtual research model that utilizes a sponsorship role to advance cancer research. It funds private research institutes such as The Scripps Research Institute and the Salk Institute for Biological Studies. It has a total research budget of $107 million and focuses on all research modalities on the T1, T2 and T3 levels, with $925 million in revenue (as of 2012). The ACS is not involved in active project management, and projects are funded via a minimally-selective procedure. This procedure involves the suggestion of an extramural Grant Council based on societal objectives and available funds for allocation.

CASE 9: Wellcome Trust
The Wellcome Trust (WT) does not apply strict selection criteria for its funded projects. The only prerequisites for funding are that projects should focus on public health research and infectious or tropical diseases. When it comes to project management, the WT utilizes research centers for excellence to integrate with its partners. These centers house research capacities, facilities and resources. These sources serve to disseminate knowledge through publication, facilitate the research environment by providing a pool of resources, and provide in-house research capacities to support funded projects. The Wellcome Trust had funded £511 million in 2012 in research projects due to additional donations and fundraising efforts.

In the last five years, the Wellcome Trust has strived to integrate with and support its projects beyond only financial investment. According to their annual report, “During the last five years, we have introduced several new approaches to our grant making.” WT’s “strategic awards” initiative supports large, ambitious programs that have the potential to apply technology transfer to enable practical applications of funded research. The Wellcome Trust has also launched initiatives to enable individual and institutional research capacity in low and middle-income countries. “We will provide talented and innovative researchers with the freedom and resources that they need to generate the discoveries that are essential to overcome these challenges. Our funding philosophy is to support the brightest researchers at all stages of their careers and to create the environments that they need for their research. We will support a wide range of activities to accelerate the application of research that can benefit health. We will maximize opportunities to engage diverse audiences with medical science and the questions that science raises for society.”
CRUK Agreements – Additional Details

Grant Management and Progress Updates

Partners funded by CRUK are required to submit scientific reports at the end of each installment period to be reviewed by CRUK’s scientific committee. Furthermore, an interim reconciliation report is required at three-year intervals and at the end of the grant period. CRUK reserves the right to audit any CRUK-funded account at the partner’s institution in relation to its administration and accounting. CRUK also requires chief investigators of funded projects to provide progress reports based in on its Scientific Milestone Review (SMR), subject to review by the relevant funding committee. If it is deemed that satisfactory progress has been made in compliance with the terms and conditions of the award with a satisfactory high standard of research, then CRUK provides further funding.

Regular meetings are held to discuss and scrutinize research projects. CRUK’s primary tool against scientific misconduct and shortcoming is its peer review system which is based on five types of meetings. These include student, individual-lab, group leader, interdisciplinary and department/institute-wide meetings.

All grants awarded to partners are subject to terms and conditions set by CRUK. CRUK reserves the right to amend these terms and conditions from time to time, but must make these changes abundantly clear to partners. That being said, CRUK holds the right to withhold or suspend grants with immediate effect and terminate grants with a 2 month notice.

Both committees are overseen by CRUK’s Scientific Executive Board (SEB), which is responsible for the development and implementation of CRUK’s scientific strategy.

Intellectual Property

When it comes to intellectual property, CRUK has established Cancer Research Technology (CRT), a wholly owned subsidiary, which acts as the technology development and commercialization arm of CRUK.

Any intellectual property resulting from collaboration between CRUK and its funded partner automatically and immediately vests with the funded partner, termed “funded intellectual property”. The partner does however, grant CRUK non-exclusive license to use the intellectual property for non-commercial research (alone or with third parties). In the event that CRUK wants to gain ownership of the resulting intellectual property, it formulates a request and the funded partner is allowed to negotiate with CRT. If negotiations are fruitful, CRT enters into a Technology Transfer Agreement (TTA) with its funded partner.
In cases where CRUK does not enter into a TTA with its partner, the partner is obliged to grant CRUK access to the resulting research for non-commercial research. Furthermore, funded partners reserve the right to identify any funded intellectual property as having potential for translation to the benefit of the patient and commercialization. In this case, partners notify CRUK within 30 days before the publication or presentation of any results. At CRUK’s request, the dissemination of research results can be delayed to establish intellectual property protection. Partners cannot grant third parties the right to exploit funded intellectual property that has not been transferred to CRUK. When it comes to third parties interacting with funded intellectual property, CRUK must always give consent. In the case that CRUK has been bypassed and funded intellectual property is exploited commercially without CRUK’s consent, the funded partner must transfer 60% of all gross income to CRT without the deduction of taxes and costs incurred.

**Tailored Investment Plans and Grant Schemes**

Following approval from the evaluation committees, CRUK establishes the type of grant to be awarded. Grants are grouped into three categories, based on the reporting requirements of CRUK. These include:

- **Type A – annual awards**: Projects such as clinical trials require scientific review on an annual basis. Partners granted type A awards will need to engage in scientific milestone reviews and provide research update reports.

- **Type M – multi-year awards**: Projects based on programs or personal awards are expected not to yield significant scientific outcome within 12 months and, consequently, assessment of progress is done at longer time intervals. Partners granted type M awards will need to engage in scientific milestone reviews at the end of 3-year intervals and provide research update reports on a yearly basis.

- **Type F – full duration awards**: Projects based on small grants are expected not to yield significant scientific outcomes during early stages and therefore require assessment at the end of the grant period. Partners granted type F awards will need to provide yearly research update reports only.

Having established the type of grant to be awarded, CRUK establishes a single and fixed indexation rate to be applied to all subsequent installments. Indexation rates are static for the duration of the grant period. In the event that clinical and translational research projects face delays, CRUK must be notified in writing, and approval for additional funding must be requested. CRUK then considers longer activation periods for the grant and assesses possible delays at 3-month intervals.