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Nonprofit foundations spur translational research

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Every year, hundreds of promising basic discoveries in the pharmacological field are lost and will never have a chance to be exploited for patients due to difficulties in clinical translation. This is especially true for most neurodegenerative disorders lacking disease-modifying therapies. Here we present the current scenario and our vision of a 'collective-impact' multistakeholder approach to expedite the development of new drugs.

Call to action: patients need new therapies

Despite progress in innovative therapies for several human diseases, approaches to mental and neurological disorders remain comparatively disappointing. In Europe, the burden of brain disorders was €798 billion in 2010 [1]. Other Western countries such as the USA, Canada, and Japan face similar challenges. In this scenario, the market for drugs is enormous. However, for the degenerative forms of these disorders, such as Alzheimer's and Parkinson's diseases, and progressive multiple sclerosis (MS), no disease-modifying drugs are yet available. One reason is that, in this area, R&D tools are mostly unproven. These include: (i) predictive experimental disease models; (ii) markers to assess the activity of drug candidates on targets; (iii) surrogate measures and biomarkers to detect disease initiation and progression; and (iv) sensitive and robust clinical measurements. Drug developers must make large bets on putative drug targets and perform clinical trials before knowing whether their faith has been well placed. Because of this (and because of the intrinsic chronic features of these diseases), clinical trials have been extraordinarily expensive and often unsuccessful. In the past 10–15 years, pharmaceutical companies (Pharma) have concentrated efforts and investments mainly on less risky 'low-hanging fruits', contributing to the so-called 'innovation crisis' [2,3]. To meet the challenge, it is mandatory to revitalize innovation and become far more effective in building relationships along the entire drug-discovery and -development pathway with all involved stakeholders including, academia, government and regulatory agencies, patient and health foundations, biotechnological companies (Biotechs), and Pharma [2].

New companies and academia as sources of innovation

Starting in the 1990s, Biotechs based on innovative ideas mostly coming from academia started developing drugs for still-unmet medical needs. Of 252 new drugs approved by the FDA between 1998 and 2007, about half came from Biotechs or academia [4]. Now, due to diminished early-stage venture capital for Biotechs and reduced public funding to academia, these two actors do not often have the required resources to sustain innovation. Moreover, due to growing early-stage research costs, Pharma and venture capitalists have started focusing on the late, Phase II/III stages of clinical research [3]. As a consequence, a translational gap, often referred to as the 'Valley of Death' [5], appears between Pharma on the one hand, waiting for de-risked programs, and Biotechs/academia on the other hand, doing all they can to move their programs across the Valley.

How to fill the translational gap: the role of foundations

To foster the discovery of new therapies, nonprofit health organizations and patient foundations have taken a growing role in intervening at distinct levels in the R&D process. For example, health and patient foundations have often represented a major funding source for disease-specific basic research [2]. In 2012 alone, patient and health foundations distributed approximately US$1.5 billion in the UK and USA ([6], see Table S2). This has represented a meritorious mechanism to keep innovation alive, as reflected by increasing numbers of high-impact-factor breakthrough publications on disease-related basic research. For example, the Italian MS Society (AISM), through its foundation (FISM, http://www.aism.it/index.aspx?codpage=intro_aism_fism_eng) has long been investing in research (€47.4 million in the past 24 years). In 2013, €6.3 million devoted to research of excellence in MS has generated 140 scientific publications with a mean impact factor of 5.9. Sometimes, to accelerate innovation, foundations have adopted a successful 'orphan-disease' approach. In orphan diseases, once a research program has identified a new potential therapeutic target, financial support mechanisms for further preclinical and clinical development dissipate quickly. To solve this problem, in a similar manner to the National Institutes of Health (NIH) (see, for example, the Therapeutics for Rare and Neglected Diseases program [7]), some patient organizations for neurodegenerative diseases have created funding mechanisms to cover every step from target identification to the first human clinical trials (see below and, for example, [8–10]).

Foundations have also started building on the development of appropriate performance metrics for researchers (invention disclosures, patents, licenses), and applying a milestone-driven and go/no-go decision approach.

Academia often lacks drug-discovery assets such as expertise, tools, and equipment. Foundations and nonprofit entities can provide academics with the right translational

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assets to meet requirements for a 'druggable' target and support preclinical/clinical database generation and data sharing to be mined for key tools such as biomarkers. For example, the NIH have created the Molecular Libraries Program and the National Chemical Genomics Center, with a screening capacity equivalent to that of major Pharma. Many patient foundations have become indispensable partners in the clinical research enterprise by developing, refining, and validating clinical end points for their diseases [8]. Examples of such foundations and efforts include Fast Forward, created by the National MS Society (USA), as well as the work of the Michael J. Fox and Alzheimer's Drug Discovery foundations.

Multistakeholder initiatives

We believe that the translational gap can be bridged only by promoting multidisciplinary and integrated efforts among all relevant stakeholders. In multistakeholder initiatives, representatives from different sectors work around a common theme (i.e., to develop new therapies for patients' benefit). However, so far, stakeholders have mostly acted as independent entities through a traditional silo-type model, according to which academic discoveries are transferred to Biotechs or directly to Pharma (Figure 1B). In this scenario, to help fill the translational gap, health and patient foundations have started adopting strategies characterized by increasing involvement in projects' governance, development, and advancement (project management) and by proactive decision making about the projects that are funded (portfolio management) [6] (Figure 1A).

The traditional 'fund-and-forget' model is characterized solely by financial contributions to academia. According to this model, the main criterion for project selection is scientific merit, and foundations adopting this model take a more distant role in portfolio and project management ('investigator-driven' approach). The efficiency and effectiveness of the fund-and-forget model in facilitating the translation of health research into patient benefit is increasingly being questioned [6]; however, as mentioned above, in our experience this behavior helps to keep innovation alive in disease-related research.

With the 'select-and-oversee' approach, foundations are driving the portfolio by selecting research topics while taking a more distant advisory role in project management. This behavior has been adopted to support Biotechs focused on the preclinical and clinical development of neuroprotective and myelin-repairing molecules, to make projects more attractive for Pharma and to support the clinical development of orphan stem-cell therapies (http://www.mesems.org/index.php?lang=eng).

The 'open-and-integrate' approach is focused on project management. Foundations work also with other funding

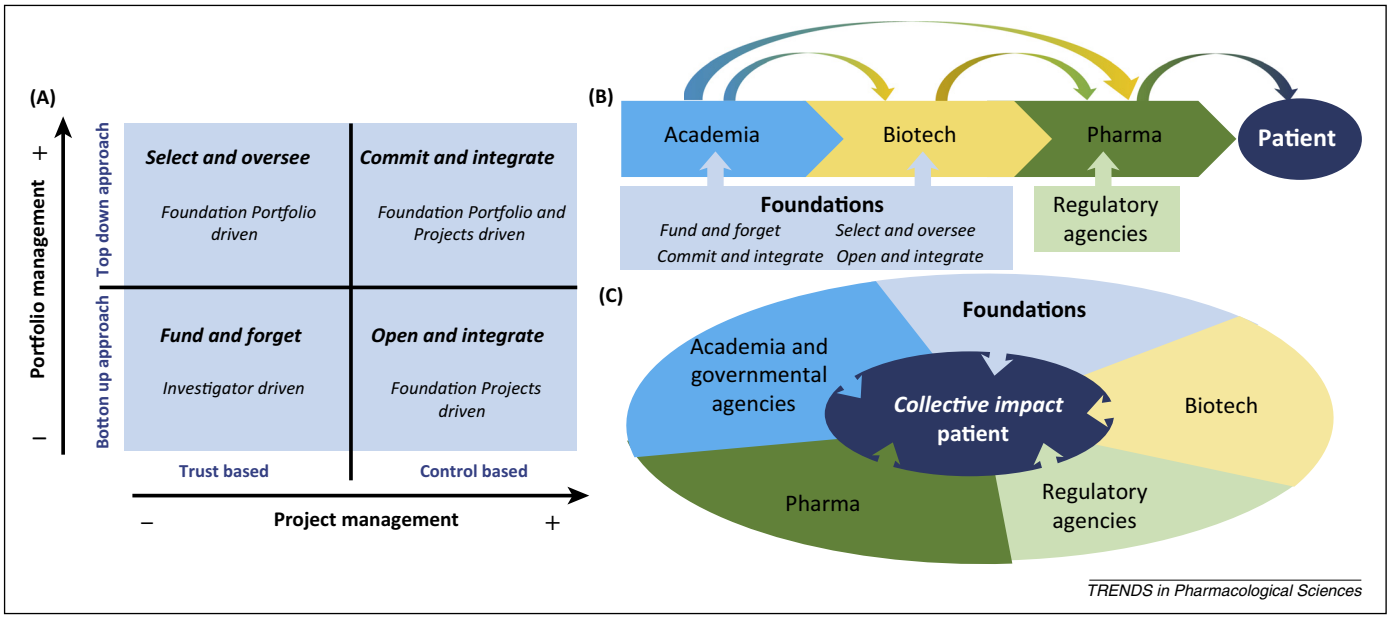

Figure 1. The changing role of health and patient foundations in the discovery and development of innovative medicines. **(A)** Interaction models for health organizations and patient foundations, including two dimensions: the degree of portfolio management and the degree of project management. Foundation behaviors are also classified according to the models described in the European Research Area Board Report 2009 (http://ec.europa.eu/research/erab/pdf/erab-study-high-risk-high-gain-2010_en.pdf) that are indicated for each model in the parentheses below. 'Fund and forget': Investigator driven in nature and characterized solely by financial contributions to academia (bottom-up and trust-based approach). 'Select and oversee': The portfolio is driven by foundations (top-down and trust-based approach). 'Open and integrate': Foundations also work with other funding agencies to sustain key research infrastructures and resources to develop and advance projects. Characterized by high-level engagement with for-profit organizations (bottom-up and control-based approach). 'Commit and integrate': Foundations are actively involved in the development and management of both portfolio and projects in collaboration with other key stakeholders (top-down and control-based approach). This model has led to remarkable results, like ivacaftor (Kalydeco™) to be used in combination with lumacaftor (VX-809) for people with cystic fibrosis (currently in Phase III clinical trial; a New Drug Application to the FDA is expected by the end of 2014 for review, with possible approval in 2015). Adapted from [6]. **(B,C)** Multistakeholder initiatives. (B) Traditional silo-type model of drug discovery and development, in which innovative discoveries are transferred from academia (often lacking the appropriate translational assets) to biotechnological companies (Biotechs) and then to pharmaceutical companies (Pharma) (or directly to Pharma). Foundations can support academia and/or Biotechs by using the various described funding strategies. (c) Proposed 'collective-impact' model, according to which stakeholders apply a shared-resources and shared-risks approach. In both models, representatives from different sectors work to achieve the same goal: to develop new therapies for patients' benefit. However, in the collective-impact model, a *sine qua non* condition is that, besides being connected to each other (see 'commit and integrate'), all parties involved in expediting the discovery of new drugs have a return of investment (ROI). A backbone organization (infrastructure) coordinating all partners' activities is believed to be necessary for the implementation of the latter model [14].

agencies in sustaining key research infrastructures and resources to develop and advance projects and ensure that the outputs of research are preserved and shared. In our experience, this model has started securing the right translational assets and supporting preclinical/clinical database generation and new clinical endpoints for diseases [8].

Finally, with the 'commit-and-integrate' model, which is leading to several highly significant successes (Figure 1A), foundations are actively involved in both portfolio and project management, in collaboration with other relevant key stakeholders (multistakeholder initiatives). In Europe, a relevant example of a multistakeholder initiative is the Innovative Medicines Initiative 2 (IMI2), which, as part of the Horizon 2020 Program, will bring together Pharma, public laboratories, small/medium-sized enterprises, patient groups, and regulatory agencies with the goal of delivering the right treatment to the right patient at the right time for priority diseases (http://www.imi.europa.eu/content/imi-2).

Multistakeholder initiatives in MS

MS is a demyelinating disease and the most common cause of neurological disability in adults. The disease starts with a relapsing–remitting (RR) course and evolves to a progressive phase characterized by the accumulation of irreversible damage. While major progress has been made in RRMS [9], treatment for progressive MS remains comparatively disappointing. Based on this need, a collaboration was convened by volunteer and staff leaders from several MS societies to expedite the development of disease-modifying therapies [10]. We believe that this is a unique example of a multistakeholder initiative. For the first time, the Progressive MS Alliance (http://www.progressivemsalliance.org/) is connecting the world's leading academics, clinicians, industry, and MS organizations to tackle priority areas to make real breakthroughs in progressive MS. In an unprecedented manner, through associations that represent them worldwide, patients are asking the MS community to share knowledge and to leverage global resources toward the common goal of accelerating the development of new therapies for the 1 million people living worldwide with progressive MS.

FISM is using all of the above-described models in an integrated manner toward innovative treatments and MS-centered care. FISM has long been investing in disease-relevant academic research through active management of progressive MS portfolio opportunities and projects. G protein-coupled receptor 17 (GPR17) represents an interesting example. Academic research had shown that this receptor is expressed by myelin-forming oligodendrocyte precursors (OPCs). Levels of GPR17 are increased at sites of brain injury, indicating its involvement in damage and/or repair [11,12]. GPR17 genetic, pharmacological, and biotechnological inhibition impaired OPC maturation, suggesting a role in myelin repair. Its druggability is precedence based, since GPR17 belongs to the G protein-coupled receptors family. *In silico* modeling and virtual screening, followed by pharmacological *in vitro* confirmation, identified synthetic ligands to be tested in MS [13]. FISM is now working with academia in implementing a multistakeholder model to develop proprietary GPR17 ligands with the desired patient-centered focus.

The collective-impact multistakeholder model

So far, most multistakeholder initiatives have lacked shared measurements of impact and supporting infrastructures to enable true alignment of efforts and accountability of results. To secure future successes, multistakeholder initiatives will have to be further sustained by fostering a collective-impact approach, in which, besides being deeply coordinated, each party also has its return of investment (ROI) aligned with the common goal of developing effective therapies for patients (Figure 1C). In this model stakeholders will apply a shared-resources and shared-risks approach focused on clearly defined outcomes and a common goal.

In the case of the social ROI (SROI), five key conditions are needed for collective-impact projects: (i) common agenda; (ii) shared measurements to track performance; (iii) mutually reinforcing activities; (iv) continuous, open communication among nonprofits, corporations, and governmental agencies; and (v) a backbone organization (i.e., an infrastructure with specific skills in project and data management, in facilitation and communication) supporting the entire initiative and coordinating actions [14,15].

Certainly this model is ambitious and challenging, since it requires a transparent and collective approach. It also has several potential limitations, one of which is the difficulty of quantifying SROI, which is meant to measure extrafinancial value relative to invested resources. However, some benefits (as well as some outcomes) cannot always be monetized. Conversely, one of the dangers of SROI is that parties may focus on monetization without following the rest of the process. Moreover, to avoid choosing inappropriate indicators, each party must be clear about its mission and values and understand how its activities change the process. Last, but not least, SROI needs considerable effort and is time and resource intensive [14].

By working with all stakeholders, we envisage that additional relevant ROIs may still have to be developed and believe that, to pave the way for breakthrough medicines, the collective-impact multistakeholders model deserves attention and investment.

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