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Science & Society

Steps towards Collective Sustainability in Biomedical Research

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The optimism surrounding multistakeholder research initiatives does not match the clear view of policies that are needed to exploit the potential of these collaborations. Here we propose some action items that stem from the integration between research advancements with the perspectives of patient-advocacy organizations, academia, and industry.

There is hope about the growing collaboration in biomedical research between academia, industry, and patient-advocacy organizations. Declarations of intents and partnerships have been launched and capital has been invested in large multistakeholder efforts (e.g., the European Union's Innovative Medicines Initiative) and in smaller programmes (e.g., the Collaborative Network Awards of the Progressive Multiple Sclerosis Alliance) that, despite their size, have been capable of attracting the interest of hundreds of researchers in dozens of international networks.

Despite the reasons to be optimistic, including the flow of resources and the different models that exist for collaboration, some concern is emerging about the ability of these partnerships to evolve in a coordinated and productive manner and whether these partnerships can match patients' needs [1,2]. In the face of these concerns, suggestions have been put forward, ranging from models of collaboration in specific diseases [3] to measures to improve the impact of philanthropy [4].

While all these suggestions provide precious inputs, they still do not ensure that Multistakeholder Research Initiatives (MSRIs) will deliver their full potential and advance over time with the commitment of all relevant stakeholders. As put forward in the setting of social-ecological systems [5], and by recent calls for proposals (e.g., the H2020 SWAFS-05-2017 call for proposals: *New Constellations of Changing Institutions and Actors*), collaborative initiatives still present challenges that call for innovative solutions.

As patients' representatives, researchers, and experts in business ethics, we have been involved in collaborative efforts (often together), and have been confronted with the difficulties of sustaining and advancing research through traditional models. Based on our experience, we here suggest some new action items that integrate scientific progress and stakeholders' perspectives, toward achieving a collective impact of MSRIs. We also propose that the step that needs to be taken to implement these or other items is to invest in the development of a 'science of collective sustainability' that identifies and accompanies those actions that are most relevant for all the stakeholders, individually and as a group.

The main neurodegenerative diseases can exemplify the difficulties that clinical research faces in some conditions more than in others. Their pathophysiology is a complex interplay between neurodegenerative and inflammatory processes, with different cell types involved; the diseased tissue is very difficult to access; clinical course is often slow; and appropriate experimental models are frequently missing. These factors are responsible not only for the difficulty in identifying 'druggable' targets, but also for the lack of satisfactory outcome measures and reliable biomarkers that may accelerate the clinical evaluation of basic science acquisitions. Furthermore, it is difficult to fully understand why any given therapeutic attempt has failed (positive biological effects, on a given type of insult, may be overruled by other mechanisms of damage not targeted by the single treatment). To overcome the above issues, a series of *in vitro* and *in vivo* models have been created in the attempt to recapitulate aspects of human central nervous system (CNS) pathophysiology. Sophisticated neuroimaging and neurophysiology techniques have been developed. However, none of these attempts has proven to be a 'game changer' and there is no trial design that promises to improve both trial duration and consistency of the results.

Now that molecular mechanisms, shared in common across multiple diseases, are being increasingly described [6,7], new opportunities may come from a new integration between the above approaches and research on other, often 'underserved', diseases. Among the 'underserved' diseases, we find conditions that 'simplify' the above-mentioned problems, either because the pathophysiology is less complex and better understood (e.g., diseases that primarily affect a single cell type, such as Nasu-Hakola disease for microglia or Alexander's disease for astrocytes, or the neuropathological similarities between Niemann-Pick disease and Alzheimer's disease), or because the affected tissue is more accessible (as in peripheral nervous system conditions), or because the disease course is faster (e.g., in neurological paraneoplastic diseases). Clinical trials in these diseases may unveil a biological efficacy that may

be more difficult to demonstrate in more common CNS diseases, where different types of damage converge. Interestingly, this is even truer for symptomatic therapies (often overlooked but of paramount importance for patients), where shared mechanisms can be successfully targeted in different diseases [8].

Unmasking the positive effects of a treatment on single disease processes would also enable the rational construction of combination therapies, possibly the only approach that, in the short/medium term, may be able to combat the different types of damage that characterize the more common diseases.

On these bases, encouraging coordinated clinical research initiatives referring to diseases that share pathophysiology at different levels of complexity might be a new objective for patient organizations.

Collaboration may bring several advantages: 'companion clinical trials' may be imagined where trials in common diseases are flanked by trials in 'simpler', underserved diseases, selected according to shared pathophysiological principles. Developing therapies across different diseases may also help develop the economies of scales that may promote the industrialization of rare disease therapy development [9]. Moreover, clinical false negative results may be better understood, while positive results may de-risk industrial investments and be perceived as more reliable by regulatory authorities. At the same time, this would offer a chance to patients with diseases that rarely happen to be the object of properly designed and conducted clinical trials. Finally, any initiative that raises awareness about rare/underserved diseases, among those who routinely deal with more frequent disorders, might reduce the probability of diagnostic errors that all too often occur in qualified clinical settings.

To capture these opportunities (summarized in Figure 1), the adaptation of patient advocacy to biomedical research will require a step in its evolution. The growing understanding of how common principles in pathophysiology are shared should convince patient-advocacy organizations to look beyond one's own illness and share resources according to shared biology (the development of a common classification system to uniformly identify priorities across diverse funder types and research portfolios will be key to finalize the process). This would also coordinate well with

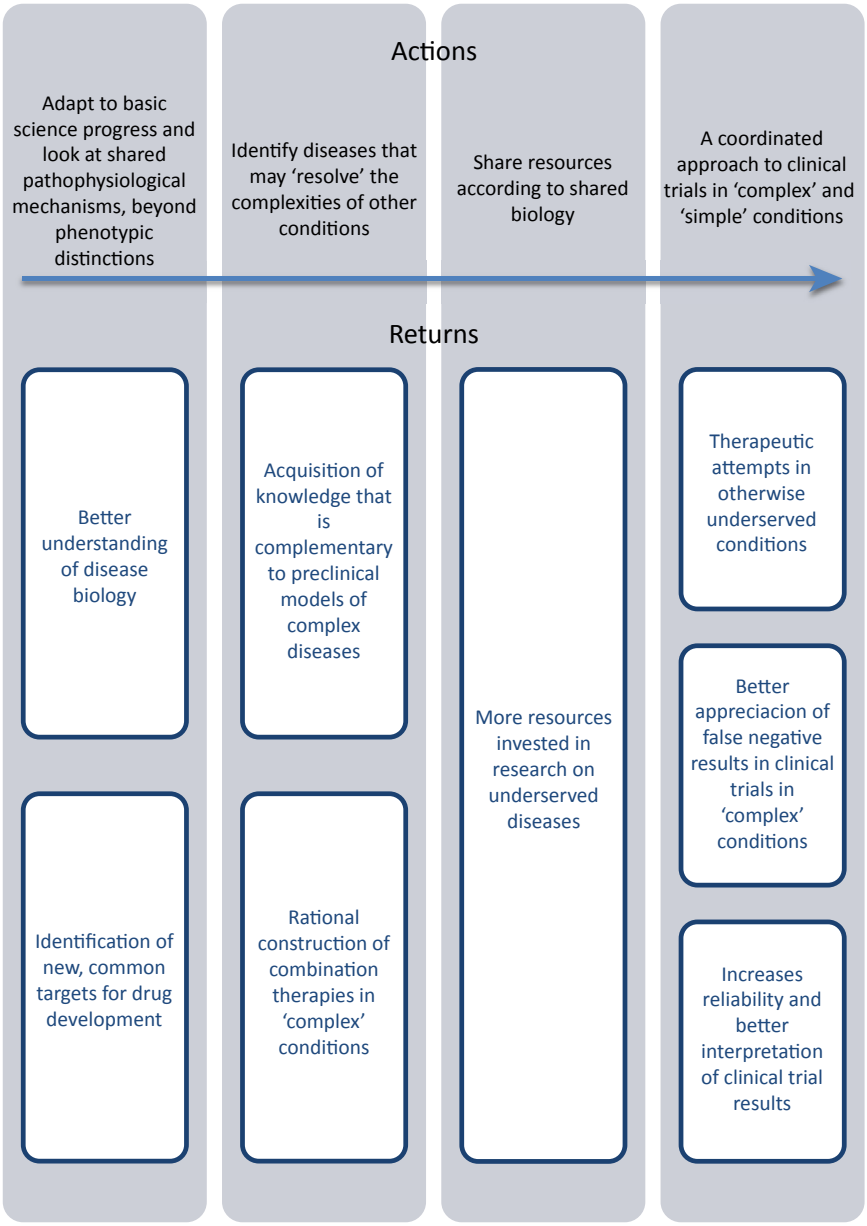

Figure 1. Sequence of Concrete Actions and Returns That Are Relevant for all the Stakeholders, Individually and as a Group.

Box 1. Collective Actions to Unlock the Potential of Repurposing

So far, repurposing (i.e., finding new therapeutic indications for existing compounds) has not delivered its full potential. In the hands of academia and patient-advocacy organizations it generates new knowledge but not the financial return to sustain the transition from phase 2 to registration trials. Conversely, industry has a high success rate in registering chemically modified, repurposed compounds but, often, it does not improve the 'old' drug to a point that justifies the increase in healthcare costs.

There are good reasons (in our opinion still not fully realized by current MSRI) for companies, academia, and patients to act jointly in the field.

It is in the companies' interest to sustain patient-advocacy organizations and academia in implementing early-phase repurposing trials with innovative designs and biomarkers (because of the huge investments, these kind of 'experiments' are hardly feasible in a traditional drug development process).

It is in the interest of patients and academia to advocate for policy changes that incentivize companies to generate intellectual property by testing new dose levels, drug combinations, and routes of administration. These approaches are more likely to advance treatments compared with strategies that, presently, are less 'challenging' and, therefore, more frequently adopted (e.g., chemical modifications of the 'old' compound).

companies evaluating the same drug in different diseases (e.g., laquinimod in multiple sclerosis and in Huntington's disease; repurposing, Box 1).

Like other goals in MSRI, the policies presented in this article are collective action problems that need sustainable and innovative solutions. It will be difficult to achieve the suggested objectives/advancements without investing in the development of new models of collaborative and sustainable research governance ('a science of collective sustainability'). These are difficult tasks (as the reduction in preclinical deals between industry and academia seems to reflect [10]) but could be facilitated if all the stakeholders maintain the same perception of patients' priorities.

A strong focus on patient-oriented research is already at the root of different ongoing MSRIs. The remaining challenge is that stakeholders have to contribute jointly negotiated solutions to common action problems (mission), while advocating their own return of investment. No single blueprint exists for how to meet this challenge. 'Shared measurements of impact' are among the tools that may, in practice, facilitate this process [11]. However, conventional metrics in biomedical research are not normally designed to represent different claims of different stakeholders [12]. Insights are emerging from recent research that have stimulated discussion on the need for more participatory forms of research governance and the need to revisit some of the foundational elements of the Collective Impact Model ('movement building' or, as spelled out by Al Etmanski and Vickie Cammack, two celebrated social innovators, 'act like an organization but think like a movement' [13]). Building on this vision, a Collective Impact Research Framework could be adopted by each research initiative, according to its mission: 'when a measure becomes a target it ceases to be a good measure' [14]. This may head toward better and participatory decision making of the relevant stakeholders in the design of the agenda (Community Aspiration), funding programmes and evaluation procedures (Strategic Learning), and policies (High Leverage Activities and Inclusive Community Engagement). Within this framework, an Integrated Accountability Model (IAM) [15] applied to MSRIs in four different dimensions (efficacy, excellence, efficiency, and social) is a prospective model to be implemented at the start of a research initiative, engaging stakeholders in defining metrics in a bottom-up approach, rather than a single performance assessment system. The IAM model conveys a balanced 'sustainable' way to deliver an integrated report, thanks to processes of stakeholder empowerment along the whole framework.

Within this frame, in measuring the impact of the research in health research organizations, it is fundamental to consider patients as key stakeholders throughout the entire measurement process. The development of practices, methodologies, and measures for patient engagement deserves attention, resources, and structures in which these strategies are made operative and new professionals are trained.

In a time of considerable progress, basic science advancements offer opportunities for the development of new therapies. However, to really move the field forward, basic science progress should also stimulate innovative policies and actions that may reshape and streamline collaboration in clinical research. These will need to be applied and prospectively adapted to changes, to ensure that the best possible collective impact is maintained over time, for all the stakeholders involved.

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Spotlight

Fatty Acid Oxidation Regulates the Activation of Endothelial-to-Mesenchymal Transition

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The molecular mechanisms underpinning the process of endothelial-to-mesenchymal transition (EndMT) are mostly unknown. Recently Xiong and colleagues explored for the first time the metabolic changes associated with the activation of the mesenchymal program in endothelial cells, and found that reprogramming of fatty acid oxidation pivotally regulates EndMT.

EndMT is the cellular transdifferentiation program by which endothelial cells acquire mesenchymal features, including loss of cell–cell junctions and the acquisition of a fibroblast-like morphology and gene expression profile. Originally described as being physiologically important for the formation of the heart valves [1], EndMT was subsequently discovered to be important in the pathological setting of cardiac fibrosis [2], and eventually as a key driver of many different pathologies [3–5]. Features of EndMT have been mainly inferred by analogy from the process of epithelial-to-mesenchymal transition (EMT), and very limited knowledge is available about the molecular mechanisms uniquely defining EndMT [6].

A recent publication by the group of Toren Finkel has now identified metabolic alterations that accompany the activation of the EndMT program [7]. Metabolic profiling of human pulmonary microvascular endothelial cells (HPMVECs) stimulated to undergo EndMT by combined treatment with TGF-β1 and IL-1β revealed a marked reduction of endothelial fatty acid oxidation (FAO) following cytokine stimulation. This metabolic change was characterized by an early rapid decline in the level of carnitine *O*-palmitoyltransferase 1 (CPT1A), a rate-limiting enzyme located in the outer mitochondrial membrane whose function is indispensable for mitochondria-dependent β-oxidation of long-chain fatty acids. Exogenous overexpression of CPT1A was able to block the induction of EndMT following TGF-β1 plus IL-1β treatment, whereas inhibition of FAO by shRNA-mediated CPT1A silencing was sufficient to activate the EndMT program by potentiating endogenous TGF-β signaling. In search for potential molecular mechanisms explaining the observed FAO-dependent modulation of EndMT, the authors found that cytokine induction of EndMT resulted in low levels of acetyl-CoA. Modulating the levels of acetyl-CoA by either acetate supplementation or pharmacological inhibition resulted, respectively, in the suppression or activation of TGF-β-induced EndMT. The study also showed that the capacity of acetyl-CoA to function as a sensor for EndMT susceptibility is exerted by post-translationally controlling SMAD7, a potent inhibitor of TGF-β signaling. In fact, the authors demonstrated that acetyl-CoA, and hence FAO, are required to induce SMAD7 acetylation and consequently to maintain its stability, therefore promoting the suppression of TGF-β signaling. To validate the physiological relevance of these *in vitro* findings, Xiong and coworkers generated a mouse model to genetically target FAO specifically in endothelial cells by crossing mice carrying the *Cpt2* conditional knockout allele with VE-cadherin Cre^{+} mice. Consistent with the data collected from the human endothelial cell lines, primary lung endothelial cells isolated from $Cpt2^{E\text{-}KO}$ mice displayed reduced acetyl-CoA levels and constitutive activation of the TGF-β-associated SMAD signaling, which could be reverted by acetate supplementation. *In vivo* endothelial inhibition of FAO caused a marked thickening of the heart mitral valve and, consistent with the known role of EndMT during heart development, lineage-tracing analysis confirmed that this phenotype was a consequence of increased EndMT in $Cpt2^{E\text{-}KO}$ embryos. In adult mice, increased incidence of endothelial cells undergoing mesenchymal transition was detected in organs