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Public-Private Partnership: A New Engine for Translational Research in Neurosciences

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We have made little recent progress developing effective new treatments for neuropsychiatric and neurodevelopmental disorders. Novel molecular mechanisms have been identified, but have not translated into the clinic. We suggest an alternative: combinations of treatments targeting different aspects of final common pathways in biologically defined clinical subgroups. This will require integrated translational neuroscience and international public-private partnerships.

Hundreds of millions of people worldwide suffer from neuropsychiatric and neurodevelopmental disorders that are severe, enduring, and come at a very significant cost. Whereas brain disorders associated with aging, i.e., dementia and Parkinson's disease, are widely recognized as priorities to be urgently addressed by industries, public institutions, and charities, less attention is paid to neurodevelopmental disorders such as autism (autism spectrum disorders [ASDs]), despite their high prevalence and impact on society. ASDs comprise a family of highly genetic, heterogeneous, neurodevelopmental disorders characterized by deficits in social interaction and communication, and by unusual repetitive behaviors. Around 1% of all children suffer from ASDs, making them more common than childhood cancer, juvenile diabetes, and pediatric AIDS combined. Thus, an estimated three million patients in the European Union (EU), 1.5 million patients in the United States (US), and tens of millions of patients worldwide are affected by ASDs.

As for all neuropsychiatric/neurodevelopmental disorders, we should have made more progress in reducing the disease burden of ASDs. Basic neuroscience is in its "discovery heyday" of potential molecular mechanisms underpinning a large number of disorders, and major investments have been made in the EU and the US to understand how the brain works in health and disease (e.g., the Human Brain Project and the NIH Brain Initiative). Yet it is still unclear whether and/or when these large-scale research endeavors will translate into new therapies. We suggest that the challenges and the potential solutions include a complex interaction between knowledge of disease biology together with the way science, industry, and regulators are organized.

Scientific challenges for most neuropsychiatric/neurodevelopmental disorders include disease heterogeneity, biological/clinical overlap between disorders, and absence of reliable disease biomarkers. Most of these disorders also likely have a large number of causative (and disease-modifying) mechanisms that impact a smaller number of final common pathways. Moreover, we will need to modulate pathophysiology in people who have had a brain disorder (or are at ultra-high risk for developing one) for many years/decades. Hence, besides the complex scientific challenges to be addressed for the identification of molecular mechanisms that may provide therapeutic targets, it is essential to develop innovative tools to assess the efficiency of therapeutic interventions, to delineate the patient populations that will benefit from them, and to intervene at a stage where the brain changes are reversible. Furthermore, lessons learned in other difficult disease areas such as cancer suggest that the most effective therapeutic strategies in ASDs will be based on combinations of treatments that target different aspects of final common pathways over a relatively long time period. This is illustrated by recent evidence that the pathophysiology of ASDs may include a combination of GABAergic and inflammatory mechanisms acting at different developmental time points (Voineagu et al., 2011).

Basic neuroscience also faces political/cultural challenges to being more rapidly (and cost-effectively) translated into treatments. Current funding mechanisms understandably mainly support grants that are relatively short term and narrowly focused. Also, many neuroscientists (1) do not work in multidisciplinary groups, (2) are not trained to seek a "translational" application for their work by structuring experiments that will lead to treatments that can gain regulatory approval, (3) (incorrectly) assume that if they identify a mechanism it will then be "picked up" by industry and developed into a treatment, and/or (4) do not apply the stringent rigor in compound testing as done in industry. Perhaps most importantly the experimental models typically employed by basic scientists (including those in industry) mainly investigate one potential causative mechanism and at one time point. This approach misses the most likely causative and clinical scenarios (interacting causative mechanisms with differing effects across development, and the interaction with other treatments already being prescribed for very commonly associated mental health comorbidities). In other words, how likely is it that a treatment targeting one molecular mechanism, tested in rodents at one developmental time point, and piloted in small groups of medication-free individuals with a clinical disorder, is going to work in "real-world" populations of

clinically (and biologically) heterogeneous individuals, who typically are of varying ages, already receiving a variety of different medications, and suffering from very common comorbidities (such as intellectual disability, depression, anxiety, or ADHD) that are all associated with biological variation and impact on outcome?

Facing this complexity, the pharmaceutical industry is reluctant to invest in research and development on disorders such as ASDs, and especially to conduct the costly large-scale, long-term clinical trials that are needed to move therapeutic approaches forward. Moreover, this commercial reluctance is reinforced because the key parameters to demonstrate drug efficacy are not established, the regulatory environment is uncertain, and the overall risk of failure is very high. These legitimate concerns should be urgently addressed, since recent important advances have generated new hopes for pharmacological intervention in ASDs. First, promising drug targets have been identified, and perhaps especially the metabotropic glutamate (Williams, 2012) and GABA-A receptors (Han et al., 2014). Second, there is evidence in a mouse model of ASDs that neuronal alteration can be reversed after completion of brain development (Baudouin et al., 2012). Third, recent evidence suggests that certain genetic mutations might be used to stratify ASD patients early in development (Bernier et al., 2014). And fourth, the potential for biomarkers to further aid clinical stratification has emerged from neuroimaging, eye tracking, and electrophysiological studies (including adults; see Ecker et al., 2010).

In order to take the best advantage of this recent progress, pharmaceutical companies organize collaborative efforts at different levels. Above all, major companies active in the field recognize that neuroscience may prove to be a privileged area for noncompetitive research, and so they will likely benefit from joining forces with each other, and academia, to address some of the most difficult challenges related to ASDs. As an example, by sharing their experience and pooling data from 34 previous trials with antipsychotic agents in schizophrenia, five companies working with academic partners produced evidence that (by focusing on relevant symptoms and paying attention to gender balance) it is possible to significantly reduce both the number of patients and the duration of observation to demonstrate drug efficacy (Rabinowitz et al., 2014). Collaboration between industry and academia is also expanding beyond the usual bilateral agreement between a single company and a given university. For instance, the building of large public-private consortia is increasingly driven by novel research strategies based on the collection and management of large data sets, the so-called ''big data'' approaches, which might revolutionize research in neurosciences (Manji et al., 2014).

In ASDs, the consortium EU-AIMS launched by the Innovative Medicines Initiative (IMI) represents the most important public-private partnership driven by pharmaceutical companies in the field of autism. IMI launched in 2008 as a joint undertaking between the EU and the European Federation of Pharmaceutical Industries and Associations (EFPIA). IMI's goal is to speed up the development of, and patient access to, safer and more effective medicines in fields as diverse as diabetes, medicines safety, clinical trial design, and the assessment of real-life effectiveness of new treatments. With a total budget of over EUR five billion for the period 2008–2024, IMI is the world's biggest public-private partnership in health; it forges collaborations between researchers in industry, academia, small- and medium-sized enterprises, patient groups, regulators, and others involved in health research and healthcare. In most cases, IMI projects are inspired and driven by industry. IMI enables the ''open innovation'' approach by acting as a neutral third party, providing impartial advice and guidance and ensuring that the interests of all project partners are respected when it comes to issues such as governance and intellectual property.

EU-AIMS was launched in 2012 (Murphy and Spooren, 2012) and has been one of the most successful of the 50 IMI projects launched to date, both in terms of scientific output and interactions between the different stakeholders including the European Medicines Agency (EMA), FDA, and patient advocates. For instance, Autism Speaks, the world's leading autism science and advocacy organization, supports EU-AIMS both scientifically and financially in developing large-scale biobanks and data repositories.

EU-AIMS brings together overlapping themes to underpin new drug discovery for ASDs. This reflects our belief that neither ''top-down'' clinical and translational studies, nor ''bottom-up'' model system analysis, can impact on ASDs alone. Rather, we need to integrate proven technologies around (for example) animal models and PET, together with new approaches (e.g., fMRI, and multiomics to identify candidate biomarkers, and induced pluripotent stem cells for drug screening). These integrated approaches are also applied to targets for clinical populations that encompass at-risk infants, children and adults with ASDs, and nonautistic individuals with genetic abnormalities that may be informative (e.g., those with synaptic gene defects). Our strategy, therefore, employs synergistic experimental work packages (WPs) bringing together animal model and patient studies to progress new translational approaches to ASDs. Together, the aim of these WPs is to deliver new validated assays, both in vivo and in vitro, that aid our understanding of etiology and deliver tractable platforms for drug discovery in ASDs (Figure 1).

To date, we have linked cellular deficits to systems-level abnormalities and ASD-relevant behavior by creating a centralized repository of rodent models with high construct and face validity that are shared by all partners. For instance, we recently showed that Nlgn3 knockout mice (a model for ASDs) display a convergent pathophysiology with fragile X syndrome, which could be genetically (Baudouin et al., 2012) and pharmacologically rescued. To translate findings from animals to humans (and back) we have already developed new translational neuroimaging stratification techniques (Ecker et al., 2013), PET ligands, rodent touchscreen tests, and behavioral assays. For example, we reported structural and functional candidate biomarkers that are specific to ASDs (i.e., not found in other neurodevelopmental disorders such as ADHD) or that vary between males and females with ASDs (Lai et al., 2013). Also, our proof-of-concept studies showed abnormalities in striatal glutamate concentration in both rodent models and adults with ASDs that are linked with abnormal