EMBO Molecular Medicine

# A meeting of minds: Overcoming roadblocks in the development of therapies for neurodegenerative disorders

Neurological and psychiatric disorders continue to intrigue and perplex the clinical and scientific world. Neurodegenerative conditions follow a relentless course, causing increasing disability as they progress, and ultimately, early demise. Despite intensive basic and clinical research, progress has been painfully slow, with not a single treatment developed to slow or limit the progression of any of the many neurodegenerative disorders. This includes some of the most common diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD), as well as other equally debilitating conditions such as amyotrophic lateral sclerosis (ALS). So why has progress been so slow?

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There is no denying that neurodegenerative disorders are complex, but the discovery of several genes causing rare familial forms should have provided vital clues to jumpstart our understanding of neuronal dysfunction and disease pathogenesis, and hence to develop therapies. Each new discovery of a gene linked to neurodegenerative disease is hailed as a major breakthrough and widely anticipated to lead to improved treatment. However, subsequent advances have generally been disappointingly slow. For example, mutations in genes such as the amyloid precursor protein, causing AD (Goate et al, 1991); Cu/Zn superoxide dismutase (SOD1) in ALS (Rosen et al, 1993); and Huntington in Huntington's disease (HD) (Huntington's disease collaborative research group, 1993) were uncovered more than 15 years ago. Since then, despite several thousands of research articles, these advances are yet to be translated into therapies of any proven benefit to patients.

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The reasons are multifold. Many of the disease-causing genes so far unearthed are largely uncharacterized; their functions are obscure. The laboratories making these discoveries have often lacked the expertise to uncover the functions of proteins and/or have failed to establish effective interactions with basic researchers who might be able to provide this. Similarly, basic researchers have been slow to react and move their research towards the newly uncovered genes.

Another problem is that new genes are often unrelated to an existing framework of understanding of pathogenetic mechanisms. How do they relate to other known causative genes of the same disease? Do they operate in the same or different pathways? For example, it is unclear how mutations in the recently discovered ALS genes—encoding RNA-binding proteins TDP-43 and FUS (Lagier-Tourenne & Cleveland, 2009)—fit into our understanding of ALS based on extensive previous work on SOD1 biology. Another example is how PINK1 and LRRK2—the protein-kinase-encoding genes associated with PD—interplay with other proteins implicated in this condition, including the natively unfolded protein, α-synuclein and the ubiquitin E3 ligase, parkin (Abou-Sleiman et al, 2006).

Another stumbling block has been an over-reliance on mouse genetic models, which for the most part have not faithfully replicated the human pathology and phenotype. In many cases, mimicking of human disease mutation in mice yields little or no neurodegenerative phenotype, as demonstrated by the parkin and PINK1 knockout models (Goldberg et al, 2003; Kitada et al, 2007). In other cases, where severe phenotypes are observed, success has also been limited. For example, despite the use of the R6/2 mice containing the polyglutamine repeat expansion in exon 1 of the Huntington gene (Mangiarini et al, 1996) in more than 200 studies, our understanding of the Huntington protein function remains extremely limited, with little prospect of a treatment. Additionally, although model systems may trigger valuable new lines of investigation, a major concern remains whether mice, or other genetic models such as fruitflies and worms, are suitable for modelling human disease in view of their vastly shorter lifespan compared to humans, as well as significant systems level differences in brain physiology.

What then is the way forward? In answering this question, it is perhaps instructive to compare the state of the neurodegeneration field today with that of cancer a few years ago, when

mutations in many diverse unlinked genes—encoding GTPases (*e.g.* Ras), phosphatases (*e.g.* PTEN) and kinases (*e.g.* growth factor receptors, PI 3-kinase, LKB1)—had been discovered in a variety of tumour cells. The key advance came with the positioning of virtually all of the proteins encoded by these genes within a couple of interconnected signalling networks – the PI 3-kinase–mTOR and the ERK MAP-kinase pathways. These control growth, proliferation and cell survival. More importantly, it is now clear that most of the mutations lead to activation of these pathways, causing the uncontrolled growth of tumour cells. These advances have resulted in a seismic shift in our understanding of cancer and laid bare the way forward in therapeautic treatment strategies – the targeted inhibition of the PI3-kinase/mTOR and ERK pathways. Some of the most anticipated outcomes of ongoing clinical trials relate to anti-cancer therapies that inhibit these pathways, including PI 3-kinase inhibitors (GDC9401); dual mTOR–PI 3-kinase inhibitor (NVP-BEZ235); and the MEK inhibitor (AZD6244/ARRY-142886). All hold great promise for anti-cancer efficacy in the future.

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In comparison, there is far less cause for optimism in ongoing trials on neurological and psychiatric diseases. The list of genes for which the function remains unknown (*e.g.* α-synuclein, amyloid precursor protein, Huntington), and the enzymes of known function but unknown physiological pathways (*e.g.* SOD1, PINK1, LRRK2, Parkin) is likely to continue to grow apace as powerful genetic screening methods are undertaken to uncover disease mutations. Pharmaceutical companies have traditionally held back from investing in therapy development in these areas due to confusion in the literature and a lack of ideas on which key targets could slow disease progression. Crucial to the field will be an increased focus on defining pathways to which these disease-causing genes belong. Understanding the functions of the entire pathway(s), as well as the effects of the mutations on these networks, will also be vital. This will arm the pharmaceutical industry with the knowledge to identify clear targets and chemical strategies to mitigate the effects of mutations.

That said, experience in the cancer field shows that even this level of understanding is not always enough to convince the pharmaceutical industry to tackle a pathway. Success will also be dependent on validating the physiological roles of pathways and using genetic models to show proof of how they become dysregulated in disease *in vivo*. For example, if a mutation in one gene that causes neurodegeneration is shown to activate a pathway, then a hypomorphic mutation suppressing the downstream target should effectively repress the pathway and prevent neuronal dysfunction or death (provided, this can be assayed in a mouse model). In the cancer field, these types of strategies have been invaluable in validating the PDK1 (Bayascas et al, 2005) and AMPK (Huang et al, 2008) protein kinases as key nodes of the PI 3-kinase–mTOR pathway, as well as stimulating research to develop PDK1 inhibitors or AMPK activators as anti-cancer therapies.

A glimmer of hope in the search for a disease gene-related signalling pathway in psychiatric disease comes from the recent finding on the Disrupted in Schizophrenia 1 (DISC1) gene. Disrupted by a chromosomal translocation in a Scottish family with a high incidence of major depression, schizophrenia and bipolar disorder, DISC1 functions to regulate GSK3 in the Wnt-β-catenin signalling network (Mao et al, 2009). GSK3 plays major roles in the development of the brain. The fact that DISC1 regulates the GSK3β-β-catenin signalling pathway explains how alterations in this pathway may contribute to the causes of psychiatric disorders. Significantly, the authors of the study suggest that drugs inhibiting GSK3, or other components of the Wnt–β-catenin signalling pathway, may be of clinical use in the treatment of depression, schizophrenia and bipolar disorder. GSK3-inhibiting lithium has been used for many years in the clinic to treat bipolar disorder (Thase & Denko, 2008) and more specific inhibitors of GSK3 have been developed by pharmaceutical companies, mainly to lower blood glucose levels in the treatment of diabetes (Medina & Castro, 2008). It would be fascinating to test whether these new-generation GSK3 inhibitors have the potential to supersede lithium in psychiatric disorders.

> *» The closer and more concerted efforts of clinicians and basic researchers – the very premise of EMBO Molecular Medicine. «*

Clearly, an influential factor in overcoming obstacles in the progress of neurodegenerative research lies in the closer and more concerted efforts of clinicians and basic researchers – the very premise of EMBO Molecular Medicine. Key to this research will be elucidating the signalling pathways that are disrupted by mutations causing neurodegenerative disease. We hope that this Journal will become a forum for researchers to publish major advances in these areas and facilitate the development of therapeautic strategies based on sound biological understanding of the molecular mechanisms of the disease.

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