

EDITORIAL

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Clinical innovation for neurodegenerative diseases

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Neurodegenerative diseases, including Alzheimer’s disease (AD), Parkinson’s disease, amyotrophic lateral sclerosis and Huntington’s disease, are devastating diseases, with huge unmet medical needs. Although it has been estimated that the pharmaceutical industry has already spent billions of US dollars on developing a treatment for AD, the output so far has been dismal. We, like many others, hope that this long history of failures will soon be replaced by success.

Whilst symptomatic treatments are valuable, especially those with clearly observable functional outcomes (e.g., L-DOPA in Parkinson’s disease), disease modification in terms of halting, slowing or preventing the evolution of neurodegenerative disorders remains the Holy Grail and no disease modifier product has yet been approved in any neurodegenerative disorder – with the possible exception of riluzole for amyotrophic lateral sclerosis. High cost, long timelines and low probability of success have led to reluctance by the pharmaceutical industry to invest in this area, despite the huge rewards that a successful treatments would reap [1]. Some companies have already opted to leave this area; others have decided to ‘reef the sail’. In contrast, publically funded efforts are growing. During the first decade of the 21st century, AD national plans were launched in a variety of different European countries. The US President signed the National AD Project Act in January 2011. The first European-wide Neurodegenerative Disease Research was launched in 2012. In 2013 the NIH total expenditure on AD research will reach an all-time high of US \$529 million.

A common belief is that public–private partnerships (PPPs) will generate breakthroughs in preclinical and clinical areas [2]. The Innovative Medicine Initiative (IMI) represents one such collaboration, which joins European governments and pharmaceutical companies together to speed up the development of better and safer medicines for patients. The IMI PharmaCog project was launched in 2010 and is already reporting data related to improved early preclinical and clinical experimental designs for predicting the cognitive properties of new drug candidates [101].

Complexity

The complexity of neurodegenerative diseases provides many challenges for drug discovery and explains many failures in recent Phase III trials. Our understanding of the pathophysiology of these diseases is still relatively poor. Moreover, the difficulty to deliver drugs to the brain, the lack of predictive ‘clinical’ animal models, the relatively insensitive clinical end points and the lack of validated biomarkers all present huge hurdles to developing a drug. Furthermore, the relationship between disease severity and progression, the high prevalence of concomitant diseases that interfere with pathophysiological processes and the **multiple medicines commonly taken by elderly patients can also contribute to the**

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complexity and variability in treatment outcomes [3].

Regulatory considerations

Whilst regulatory guidelines are sometimes considered to be hurdles, when used correctly they can be a very positive driver for productive research. For example, in their last concept paper on AD [102], the Committee for Medicinal Products for Human Use concluded that there is no need for revision of the guideline on AD medicines, but listed two major considerations for assessment of future clinical trials in AD: the change of diagnostic criteria and the potential use of biomarkers in different stages of drug development. It is important to note that precompetitive-PPPs and/or competitive PPPs (e.g. the Alzheimer’s Disease Neuroimaging Initiative and Coalition Against Major Diseases) have added significant value to both these considerations. During the interim period, whilst criteria and biomarkers are being developed, drug development will clearly continue and, as we learn more from clinical trials, the pharmaceutical industry will inevitably raise the bar and demand more stringently validated biomarkers.

■ **Human factor**

Another key component is to work to the strengths of academic and industrial partners and to build the right interactions. In this respect, there is a tangible shortage of clinical scientists and neurologists with drug development as a principal interest in academia. As such, few academic centers have developed high-level drug-development-oriented activities, including capability for rigorous Phase II and III clinical studies. Historically, there have been relatively few individuals who are energized enough to work effectively with industry to develop medicines. The challenges involved in fostering effective working relationships increased further with the recent closure of neurosciences R&D units and projects within the pharmaceutical industry. This has triggered the retraction of many CROs from the field of neuroscience.

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■ **Differentiation**

Pharmaceutical companies are looking to invest in drug discovery where they can see the best chance of making a medicine. Therefore, our community

needs to continuously deliver new confidence to the public and private decision makers, investors and scientists, to convince them that there is a tangible probability of success and to work smarter and more efficiently in a cost-constrained environment to deliver medicines that clearly benefit the patients suffering from a neurodegenerative diseases [4]. In this respect we should ask ourselves, ‘what is now being done differently from, and better than, what has been done before? What is the fundamental differentiation that will increase the probability of success?’

Proposal

■ **Ownership: competitive PPPs**

Precompetitive PPPs, such as IMI, have started to pave the way for cross-disciplinary collaborations in neurodegenerative diseases. Experience shows that having too many partners limits their relative engagement and effectiveness. A potentially better approach is to run a competitive PPP, in which participants are differentially rewarded based on their contribution. Specifically, new assets in development rather than on-the-market drugs should be used in the programs with well-defined costs, risks and reward sharing plans.

■ **A new clinical trial design**

In order to overcome the inherent limitations of discovery and clinical development in the neurodegeneration area, we recommend to rigorously apply the principle of ‘three pillars or cornerstones of survival’ [5], to generate evidence that the drug is delivered to the target site, that the target is occupied at the required level and that functional modulation of the target is achieved. The fourth cornerstone is to establish confidence that there is a disease-relevant, measurable pharmacological effect. To achieve this goal, we should develop an integrated approach for animal and human experiments, selecting evaluation methods that take in consideration target specificity and disease complexity.

A debatable strategy has been to use alternative diseases (e.g., orphan diseases) to neurodegenerative diseases as a ‘stepping stone’. However, this approach has not been particularly successful. Other approaches that have been adopted include:

- Evaluation of targets known for their role in other diseases and repurpose these through phenotypic screening;
- Focusing on diseases that could offer a more straight-forward development path;

- Exploring diseases that have been considered for potential symptomatic treatments (post-traumatic stress disorder, schizophrenia).

Classic drug development plans have so far led to many failures in neurodegenerative diseases. Paradoxically, negative predictive values for the failed trials have not been established. We believe that conducting classical middle-term Phase IIa and b trials does not increase confidence in moving candidate molecules forward, nor increase the Phase III studies probability of success. If we accept two more reasonable assumptions – first, that drug action is likely to start rapidly (≤ 3 months); and second, that there is a long latency before clinical efficacy – then the clinical development plan for neurodegenerative diseases should be revisited. We propose to run only a few short-term experimental medicine trials to address the four cornerstones. This should help in making decisions either to stop development early, or to bet on a higher probability of success and run a robust Phase IIa clinical trial that should comply with the second assumption of sufficient sample size, dosing duration and adequate, clinically meaningful end points for decision (or not) to enter a Commitment to Medicine Development.

Focusing on synaptic degeneration

Targeting molecular mechanisms underlying various neurodegenerative diseases has so far failed to demonstrate clinical efficacy. An alternative approach is to target synaptic repair mechanisms, because increasing evidence suggests that synapse loss – but not toxin accumulation – correlates with disease progression. Emerging evidence on BDNF regulation of synaptic functions and cognition, the impact of BDNF genotype on the endophenotypes

and the progress in tools to measure synaptic dysfunction in humans all suggest that the time is ripe to test the molecules that target mechanisms converging on synapses in the clinic. Based on these analyses, we propose a paradigm-shifting ‘synaptic repair’ strategy for neurodegenerative diseases.

■ **Training & ethics**

Organizing specific training in the field of neurodegeneration at the international level is now urgent. The aim is to reshape industry employees, who had up until now focused on other areas of neurology and psychiatry and to train them to be experts across disciplines [6]. Regulatory evaluation experts are also expected to be more involved at an earlier stage of clinical development. Academic researchers should integrate new approaches and tools in their practice. In order to increase PPPs efficiency, bridges between academia and industry have to be built [7].

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Protection of the subjects involved in clinical research and ethics should always be at the front of our minds. Recent analyses show that press and public barriers are clustered into four groups – lack of resources, administrative burden, relevance to the research and lack of interest [8]. This is of importance, especially when considering prevention trials in neurodegenerative diseases.

Financial & competing interests disclosure

O Blin, CH Davies and B Lu are GlaxoSmithKline employees.

O Blin’s interest declaration is publically available at www.sante.gouv.fr/declarations-publiques-d-interets-dpi-de-a-a-h.html. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

References

- 1 Schwab ME, Buchli AD. Plug the real brain drain. *Nature* 483, 267–268 (2012).
- 2 Vallance P, Williams P, Dollery CT. The future is much closer collaboration between

the pharmaceutical industry and academic medical centers. *Clin. Pharmacol. Ther.* 87, 525–527 (2010).

- 3 Dollery CT. The challenge of complexity. *Clin. Pharmacol. Ther.* 88, 13–15 (2010).
- 4 Cartwright ME, Cohen S, Fleishaker JC, McLeod JF, Musser B, Williams SA. Proof-of-concept: A PhRMA position paper with recommendations for best practice. *Clin. Pharmacol. Ther.* 87, 278–285 (2010).
- 5 Morgan P, Van Der Graaf PH, Arrowsmith J *et al.* Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival. *Drug Disc. Today* 17, 419–424 (2012).
- 6 Littman BH, Williams SA. The ultimate model organism: progress in experimental medicine. *Nat. Rev. Drug Disc.* 4, 631–638 (2005).

- 7 No author listed. Interview with Michael D Ehlers. *Trends Neurosci.* 35(5), 271–273 (2012).
- 8 Robillard JM, Federico CA, Tairyan K, Ivinson AJ, Illes J. Untapped ethical resources for neurodegeneration research. *BMC Med. Ethics* 12, 9 (2011).

■ **Websites**

- 101 The Innovative Medicine Initiative PharmaCog project. www.pharmacog.org
- 102 Committee for Medicinal Products for Human Use. Concept paper on no need for revision of the guideline on medicinal products for the treatment of Alzheimer’s disease and other dementias (2012). www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/03/WC500124534.pdf