
Foreword to Volume 6

The attrition rate in the clinical development of new chemical entities (NCEs) has increased over time, in spite of escalating funds allocated to research and development. Less than 10% of all NCEs succeed in effectively treating some clinical symptom. NCEs develop to treat central nervous system (CNS) disorders, together with oncology, exhibit the greatest attrition of all. One can argue that the major explanation for this lack of success is the complexity of the biological mechanisms underlying CNS indications and our lack of understanding of the aetiology of these disorders. Therefore, it is essential that an early assessment of compound efficacy in Phase II is sought. Most marketed CNS drugs modulate G-protein-coupled receptors (GPCRs) or protein transporters associated with the major neurotransmitters in the brain. It is only recently that molecular research led to the identification of novel targets implicated in neurodegenerative conditions. Many of these targets are intracellular and require specific approaches to assess drug efficacy, since many of these mechanisms cannot be directly monitored through non-invasive means in human subjects. The CNS drug development process is most likely to be successful, the more similar the human and animal models are to one another. For this reason, focusing on specific genetic conditions (for which the aetiology is known) as a way to assess drug efficacy and safety might lead to a more rapid evaluation of specific mechanisms.

The *major challenge* for CNS drug discovery is the lack of understanding of the human biological mechanisms underlying the various stages of these diseases. Considerable more effort needs to be placed on investigating whether the human biology supports specific target hypotheses underlying novel drug discovery campaigns. Non for-profit Foundation and Government researchers are much more likely to work with early symptomatic patient populations, and it is essential that specific hypotheses are investigated before clinical development. In addition, to expedite the development of clinical lead molecules for early human studies, a few critical domains are worth highlighting as having a major impact in the evaluation of novel chemical series. These are: advances in ADMET (absorption, distribution, metabolism, excretion, and toxicity), and specifically in understanding interactions with the major drug efflux mechanisms present at the blood–brain barrier, computer modelling of drug–target interactions and crystal structure aided drug design and the development of on-target occupancy endpoints to understand the

pharmacokinetic/pharmacodynamic (PK/PD) relationship for a given molecule: the necessary occupancy to determine a suitable therapeutic window between efficacy in a given biological mechanism and potential side effects.

It is likely that drugs developed to treat one condition might be beneficial for other indications. This evokes a sense of hope that the efforts in developing new treatments will have broad impact from a medical and societal standpoint. This book highlights different approaches to mitigate the cellular processes thought to be affected regardless of which animal model (typically disease-specific) is first used to identify lead clinical candidates. In essence, it is my belief that disease animal models should be selected for any given target based on the molecular similarities to the human condition. In the context of lead evaluation, argue that an animal disease-specific model might not be necessary. Rather, a *mechanism* model, based on a proximal and specific readout for a specific target, allows researchers to quickly screen through potential leads and establish a PK/PD correlation as rapidly as possible. Once a suitable lead is identified, costly and lengthy experiments can be conducted with the disease model. In some instances, the most faithful disease models in terms of pathology or molecular changes require many months of drug administration. Therefore, the utilization of mechanism models to identify clinical leads is essential.

Neurodegenerative disorders have been typically grouped based on pathological findings and neurological symptoms. They are generally characterized by a slow symptom progression, adult or juvenile onset, specific neuronal vulnerability, and the presence of aggregated proteins identified as inclusion bodies after histological analysis. They all share age as the major risk factor, and in most cases (a notable exception being Huntington's disease, HD) have a mixed aetiology from a molecular perspective. While in all cases, familial forms of these disorders have been documented, and these account for a small percentage of all reported cases. For example, in spite of the broad incidence of Alzheimer's disease (AD) and Parkinson's disease (PD), only between 1% and 5% of all cases display a Mendelian inheritance pattern.

The existence of familial cases prompted a strong emphasis in the research community to identify the molecular basis for these disorders. These efforts have largely been successful in identifying the genes causative for the various conditions. For instance, mutations in amyloid precursor protein (APP) were identified in the case of AD; Huntingtin in the case of HD; α -synuclein, DJ-1, LRRK2, and Pink1, among others, for PD; TDP-43 and SOD1, among others, for amyotrophic lateral sclerosis (ALS); and SMN-1 for spinal muscular atrophy (SMA). Because of this, clinical development strategies have shifted from the application of drugs developed to treat the symptoms of the disease (traditionally investigated through a re-purposing of existing psychotropic molecules developed for psychiatric conditions), to strategies aimed at modulating the main biochemical mechanisms thought to be affected by these proteins. This, thus far, has also proven unsuccessful from a clinical

standpoint, as no effective new treatments have yet been identified. However, many are in clinical development.

In spite of their broad prevalence in the general population, neurodegenerative diseases are very inefficiently treated. Some of the challenges in drug discovery can be ascribed to the fact that most causative genes for neurodegenerative disorders cannot be targeted through traditional pharmacological means. In spite of more recent efforts to develop molecular therapies to eliminate expression of the mutated proteins, the majority of current clinical development strategies are aimed at “restoring” normal neuronal or glial function based on the cellular mechanisms now thought to underlie the toxic effects that arise from the mutant proteins.

There are some important commonalities in the molecular mechanisms thought to underlie these disorders. Many of the genes identified through positional cloning as causative of these set of disorders encode proteins that were shown to aggregate in *in vitro* and *in vivo* models and form the pathological inclusions traditionally used to diagnose these diseases. This was unexpected and argued that perhaps the propensity of these proteins to aggregate or form multimeric species had direct relevance to their toxic properties. In addition, many of the cellular mechanisms identified as being affected in rodent models for these diseases (generated through genetic means by introducing a mutant gene) show perplexing similarities. Among the mechanisms identified, mitochondrial disturbances, deficits in axonal transport and synaptogenic mechanisms, autophagy, protein folding, and transcriptional dysregulation are affected in all these diseases. Therefore, there is typically a convergence of strategies being developed to treat these disorders. A caveat in all of these approaches is the fact that, with the sole exception of HD and SMA, the aetiology of these disorders is mixed, and the majority of cases originate without much evidence for mutations or deregulation of the pathways linked to the mutant proteins which cause the familial (typically of earlier onset and faster progression) cases.

The converging field of synaptic dysregulation and transcriptional adaptations to changes in neurotransmitter tone is exemplified by the alterations known to exist in terms of key transcriptional effector molecules, such as histone acetylation and cAMP response element-binding protein (CREB) signalling. In this regard, two chapters are dedicated to the development of isotype selective modulation of phosphodiesterase (PDE) inhibitors to modulate neurotransmission (through effects on cAMP signalling) and transcriptional modulation (Chap. 2), and to the identification of subtype-specific inhibition of histone deacetylases (HDACs; Chap. 1). The large repertoire of various enzyme subtypes found in mammalian neurons is a key factor in the development of effective treatments, without significant side effects already identified for non-subtype selective small molecule modulators of these classes of key enzymes needed for normal brain function. The main challenge here is twofold: to identify which enzymes need to be specifically targeted for

each indication (as signalling in neurons is localized to specific domains coupled to selective signal transduction mechanisms); and to develop early measures of target engagement and efficacy in clinical trials through imaging studies or other measures to monitor changes in brain activity in response to a drug effect, such as quantitative electro-encephalogram (EEG). The initial findings for potential efficacy in neurodegeneration for the HDAC inhibitors originated from studies using non-selective molecules, which had significant toxicities associated with them after prolonged administration in animals. The effects of these molecules in various cognitive rodent models and in pathological analysis encouraged neuroscientists to try to identify class-selective molecules with good brain exposure, of increased potency and with fewer peripheral side effects. Similarly, the early clinical data surrounding rolipram (PDE4 inhibitor) in treating depression and displaying a pro-cognitive effect, together with many converging aspects of cAMP cascade deficits in various disease models, prompted the development of very specific active site inhibitors for this broad family of signalling molecules. Some of the recent advances in the development of selective brain penetrant PDE inhibitors are highlighted in Chap. 2, with an emphasis on cognitive enhancement for AD. However, many of these molecules are likely to exhibit activities beneficial to other neurodegenerative conditions, and are currently being tested for other indications in animal models.

In terms of synaptic biology, a key finding is the vulnerability of specific neuronal populations that die selectively in the various disorders. Presumably, this vulnerability will eventually be found to originate from the specific role of each mutated protein within these cells, or to the properties of the neuronal and glial cells found in the circuitry affected in each disorder. In essence, the spectrum of clinical symptoms used to define these diseases can be largely explained by the pathological findings of neuronal death and gliosis affecting the relevant circuitry. A key approach for treating these disorders is therefore based on improving the function of the circuits affected in each disease, and specific neurotransmitter modulators are being developed based on the cells most affected by each condition.

Within synaptic modulation, one of the predominant hypothesis common to all neurodegenerative conditions is the specific vulnerability of neurons to deregulated calcium signalling, and specifically calcium signalling mediated by glutamate receptors. This theory, termed *excitotoxicity*, is far from proven, but appears common to many of these disorders. Excessive or extrasynaptic calcium entry has become one of the major strategies for the treatment of neurodegenerative diseases. In the case of ALS, riluzole, the only approved drug for this disease, is a sodium channel blocker thought to modulate excessive calcium entry. Chapter 3 specifically reviews the theory of excitotoxicity and abnormal glutamate signalling mostly in the context of Alzheimer's disease, although similar principles (and drugs) are relevant to other indications. Indeed, many of these are currently in clinical development for

various CNS disorders. For instance, both memantine (an NMDA receptor antagonist) and mGluR5 antagonists are in clinical development for PD and HD. However, the essential role for glutamate signalling in brain function makes this a difficult mechanism to modulate with an acceptable therapeutic window. The complexities in glutamate signalling in various circuits affected in these disorders require a deeper investigation of the changes during disease progression in human subjects, to better predict whether a specific drug might lead to clinical improvement.

Other strategies aimed at the indirect modulation of glutamate, acetylcholine and other major neurotransmitter systems that are being prosecuted, which might be associated with more tolerable adverse effects. For instance, the role for metabolites of the kynurenine pathway (a product of tryptophan degradation), shown to be neuroactive and specifically altered in human subjects and animal models for some diseases, is described in Chap. 4. This novel approach to modulate synaptic transmission through a specific modulation in key metabolic enzymes (such as kynurenine mono-oxygenase or KMO; kynurenine amino transferase or KAT) highlights some of the new avenues taken by industry experts to uncover novel methods for treating these difficult diseases. Chapter 4 focuses on the development of KMO inhibitors specifically for HD. However, changes in kynurenine metabolites have been reported in many neurodegenerative indications. In addition to the role of kynurenine pathway metabolites in synaptic transmission, this pathway has been implicated in the modulation of the immune response, a biological area of active investigation to decrease neuronal cell death.

Finally, Chap. 5 highlights recent developments in the treatment of SMA. The genetic cause of this disease is well understood (lack of expression of the gene SMN1 due to a missense mutation), and current efforts are aimed at enhancing expression of a gene, SMN2, which can act to compensate for the loss of the SMN1 gene. This chapter illustrates the strength of focused efforts on overcoming the cause of the disease, through various means. All share in common the utilization of cellular and animal models focused on understanding the effects of novel molecules in increasing expression of SMN1. Similarly, in HD and familial models of AD and PD, a specific emphasis on demonstrated genetic contributions to the disease is key to develop novel drugs with a well-validated biological principle. In the case of other, genetically heterogeneous disorders (AD, ALS and PD), the applicability of such strategies rests perilously on the assumption that similar biological principles will apply in idiopathic cases where the cause of the pathology is unknown. Overall, the various approaches highlighted here serve to illustrate new directions in CNS drug discovery, and leads to an emphasis in a deeper understanding of the molecular causes for these disorders as a more efficient way to overcome the inherent difficulties in treating, or preventing, neurodegeneration.

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