

Small Molecule Therapies For Motor Neurone Disease and Other Neurodegenerative Diseases

Prof Ron Grigg, University of Leeds

NON-CONFIDENTIAL SUMMARY

Background. Motor Neurone Disease (MND) – an Orphan Disease.

MND is a group of related diseases that affect the motor neurones in the brain and spinal cord causing their selective premature death. The motor neurones control voluntary actions such as speech, chewing, swallowing, movement of all limbs and breathing. The majority of patients are rapidly immobilised and die from respiratory failure within one to five years. The disease has no impact on intellect, memory, sight, hearing, taste, smell or sensation. MND has an incidence of ~2/ 100,000 and a prevalence of 6-8/ 100,000 in most countries. In the UK approximately 5,000 patients have MND at any time point and approximately 1,200 die from the disease each year. The only drug licensed for MND, riluzole, currently sells in the region of \$100 million annually and prolongs survival for an average of 2 months. The high cost of drug development when set against the relatively low predicted return from subsequent sales to a small group of patients dissuades large pharmaceutical companies from MND drug development. Thus it is termed an orphan disease. The UK financial burden of neurological diseases will double to £35 Bn a year by 2026.

Technical Progress. Our YEF program uses cutting edge catalytic cascade chemistry allied to advanced scientific software to design and synthesise promising MND drug lead compounds and to take these through to patenting and clinical trials. We have developed novel catalytic cascade processes allow us to assemble multi-target directed or multivalent ligands (MTDLs) drugs. This is crucial for MND because it is a multifactorial disease and it is clear from the dismal MND clinical trial results over many years that single target drugs should no longer be considered as drug candidates for this complex disease. Cascade processes involve loading all the reactants together in one reactor and the first reaction then creates or releases the functionality for the second reaction to occur and so on. This approach integrates exceptionally well with the challenge of creating MTDL drugs as each individual chemical building block can be separately tuned to ensure maximum performance at the sites causing the diseases. Promising in vitro data showing excellent reduction in oxidative stress has been obtained in collaboration with Professor Pam Shaws group at Sheffield. Targeting oxidative stress will have broad applicability to different subgroups of MND, including sporadic disease as well as familial subtypes caused by known genetic mutations, for example in the SOD1 gene. Furthermore elucidating the mechanisms that underlie the diseases will facilitate the development of neuroprotective and neurorestorative drugs where, for example, both neurones and synaptic junctions retain or are restored to smooth functioning. Mouse models that will permit in-house screening of drug candidates are being set up in Leeds with Dr Silka Saha.

Commercialisation. A draft patent has been written and awaits installation of a neurorescue element in the drug candidates and in vivo data.