Building a Neuroscience Drug Discovery Platform

N.R. Mirza, T. Rosenstock, L. Jagger, J. Cooper, R. Hjerpe, S. Vickers, T. Phillips

Sygnature Discovery, BioCity Nottingham, NG1 1GR, UK

m.mirza@sygnaturediscovery.com

Neuroscience encompasses a wide range of diseases, ranging from neurodevelopmental, neurological, and psychiatric. Judicious choices need to be made establishing a neuroscience drug discovery platform (NDDP). Having considered multiple factors, Sygnature Discovery have initially focussed on 4 key pillars to underpin our NDDP: **Disease agnostic mechanisms**: notably in neurodegeneration, but also in other disorders, common pathogenic mechanisms are involved and so we have focussed our efforts on developing assays demonstrating mitochondrial dysfunction, excitotoxicity, lysosomal and proteosomal biology, the latter closely tied to our expertise in targeted protein degradation; **Neuroinflammation**: this is a hot topic across neuroscience and we have developed assays of microglial dysfunction utilising multiple endpoints (e.g., cytokine levels, gene expression, phagocytosis). We complement this with ex-vivo assays using human blood donor cells, and recently an in-vivo LPS assay in rodents where we measure cytokines in blood, brain, CSF and complement with measures of microglial activation and broader neuroinflammatory markers. **Biomarkers:** critical for early translation of target engagement and/or disease biology we extensively utilise in-vitro cell-based systems, ex-vivo radioligand binding, microdialysis, and brain and biofluid biomarkers (including Tau, various phospho-tau species, Aβ40/42, Nfl) to build confidence in an asset/project. **Neuroplasticity**: approval of esketamine in TRD and emerging understanding of psychedelic drugs indicate neuroplastic changes might be relevant to their therapeutic actions. We use in-vitro outgrowth, ex-vivo ballistic dye labelling with confocal microscopy, and ex-vivo SV2A radioligand binding to better understand neuroplasticity. These 4 pillars are complemented by (i) an ethos to humanise the DD process wherever feasible (e.g., iPSCs, PBMCs etc); and (ii) an extensive in-vivo pharmacology capability focussed on behavioural and ex-vivo measures of efficacy and safety, including use of transgenic animals. Our NDDP is underpinned by core industry principles of achieving multiples of target exposure, evidence of on-target binding, and PK/PD, with a multidisciplinary team of over 200 scientists across Bioscience, DMPK, and in-vivo Pharmacology.