Development of assay systems to aid in the fight against chronic neuroinflammation

Alison Holiday, Sarah Whipple, Scarlett Turner, Ian Winfield, and Trevor Askwith.

Inflammatory responses are critical for survival during instances of infection and injury. However, aberrant inflammation is implicated in a variety of neurodegenerative, cardiovascular, autoimmune, and metabolic diseases. Due to the presence of the blood brain barrier, the CNS has a separate immune state to the rest of the body and can initiate its own neuro-inflammatory response through microglia rather than macrophages. Due to the poor repair mechanisms of the CNS, immune responses must be terminated to maintain homeostasis. Persistent insult, or inadequate termination, leads to chronic neuroinflammation, a continuous and self-exacerbating cycle, cell damage and ultimately death. Chronic neuroinflammation has been identified as a driving force in many brain pathologies including dementias, traumatic brain injury and stroke. Drugs that inhibit abnormal inflammatory responses (e.g. NLRP3 inflammasome inhibitors) have thus become highly sought after due to their potential to modulate multiple disease-states. To aid development of more efficacious drugs, Domainex are developing a suite of assays to enable screening of compounds against inflammatory and neuro-inflammatory targets. These include chemotaxis, phagocytosis and inflammasome assays using both macrophages (differentiated THP-1s) and iPSC-derived microglia. Here we present data pertaining to, inhibition of the inflammasome pathway with MCC950, initiation and inhibition of immune-cell chemotaxis, and microglial phagocytosis using *S. aureus* pHrodo bioparticles.