MOK kinase drug discovery for the treatment of neuroinflammation

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Abstract: MOK (MAPK/MAK/MRK overlapping kinase) is a serine/threonine kinase consisting of 419 amino acids and a calculated molecular weight of 48 kDa. It shares modest similarities with members of the mitogen-activated protein kinase (MAPK) superfamily[1]. Recent studies[2][3] have shown that MOK kinase plays a key role in regulating neuroinflammation by influencing the activation of microglia—immune cells in the brain—and contributing to neuronal damage in neurodegenerative diseases such as amyotrophic lateral sclerosis. MOK kinase is thus emerging as a promising target for neuroinflammation treatment.

Along with SgK494, MOK kinase is one of only two human kinases known to contain an endogenous nucleophilic cysteine in the gatekeeper position. Its activity can potentially be inhibited using covalent inhibitors that feature an electrophilic warhead capable of selectively binding to this cysteine via a covalent bond.

This project is structured in three phases: 1) computational studies will be conducted to identify molecules that interact with MOK kinase; 2) selected molecules will be synthesized and characterized; 3) biological assays will be performed to evaluate the ability of these compounds to modulate the target and achieve a therapeutic effect on neuroinflammatory processes.

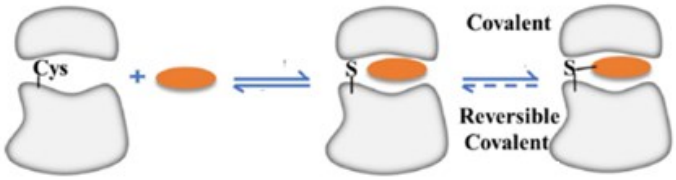

Figure 1: Mechanism of action of covalent inhibition[4]

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