Identifying Nrf2 target pharmacodynamic and potential diseasemodifying transcriptional changes by RNA sequencing

Challenge: Use RNA-Seq transcriptomic profiling to demonstrate that an NRF2 activator compound BIO-1619928 is pharmacologically active in the CNS of the Distal Hypoxia Medial Cerebral Artery Occlusion (DH-MCAO) mouse model of stroke.

Solution: RNA-Seq data analysis was performed on ipsilateral and contralateral brain cortex isolated from DH-MCAO animals 7 days after injury, and animals were treated with either vehicle or 30 mpk BIO-1619928, an NRF2 activator small molecule (A). RNA-Seq profiling revealed

1. a 9584 gene (FDR<0.05) neuroinflammatory signature in ipsilateral cortex of the DHMCAO stroke mice compared to sham-surgery animals (B, C)
2. a 500 gene signature (FDR<0.05) in BIO-1619928 treated animals compared to the vehicle treatment group.
3. The 500 gene signature showed significant NRF2 gene up-regulation (eg OSGIN1; D), as well as partial dampening (down-regulation) of neuroinflammatory pathways, including a number of microglialexpressed genes (eg TREM2).

Impact: RNA-Seq revealed robust proximal pharmacodynamic activity of BIO-1619928 in stroke mice cerebral cortex, and also unexpectedly revealed modulation of key neuroinflammatory pathways. These data may help the NRF2 program gain reentry into the pre-clinical drug discovery pipeline.