Development of Glutamate Carboxypeptidase and System x_c^- Inhibitors for the Treatment of Neurodegenerative Disorders

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The past decade has seen a tremendous rise in academic drug discovery activities and in novel shared-risk partnerships between academic institutions and Pharmaceutical companies. Two examples of collaborative academic drug discovery projects will be reviewed. Glutamate carboxypeptidase II is a membrane-bound peptidase that cleaves the abundant neurotransmitter N-acetyl-aspartyl glutamate NAAG, liberating glutamate. New orally available GCPII small molecule inhibitors and novel delivery mechanisms have been developed and shown to be efficacious in neurological and psychiatric disorders wherein abnormal glutamate transmission is presumed pathogenic including MS cognition, stroke, schizophrenia, neuropathic pain, and drug addiction. System x_c^- is a Na^+-independent amino acid transporter that couples the export of intracellular L-glutamate with the import of extracellular L-cystine. Excessive glutamate release via system x_c^- in activated microglia has been shown to play a significant role in brain cancer and broad range of neuroinflamatory diseases. To date, there are no selective and potent small molecule system x_c^- inhibitors modulators available. We developed a high throughput screening assay and in collaboration with Eisai, Inc., screened their high-quality corporate compound library to identify novel system Xc^- inhibitors. Structure activity studies with the identified hits are underway at Johns Hopkins. This shared risk partnership may pave the way for new model of industrial-academia drug discovery collaborations.