

# DRUG DISCOVERY, DESIGNING CHEMISTRY AND PHARMACEUTICAL ANALYSIS &

# BIOBETTERS AND REGULATORY AFFAIRS

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**Eric Ka Wai Hui**

ArmaGen Inc., USA

## Treatment of human lysosomal storage disorders with Blood-Brain Barrier penetrating IgG-fusion proteins

The majority of lysosomal storage disorders affect the brain. Enzyme replacement therapy does not treat the brain, because recombinant enzymes are large molecules that do not cross the Blood-Brain Barrier (BBB). BBB-penetration of enzyme therapeutics is enabled by re-engineering the recombinant enzyme as bi-functional IgG-enzyme fusion protein, wherein the IgG domain targets specific endogenous receptor-mediated transporter within the BBB, such as the insulin receptor. Brain penetrating IgG-enzyme fusion proteins have been engineered for Hurler Mucopolysaccharidosis (MPS) Type I (MPSI), Hunter MPSII, metachromatic leukodystrophy, Sanfilippo MPSIIIA and Sanfilippo MPSIIIB, and validated in Rhesus monkey *in vivo* and in human fibroblasts in culture. Brain uptake in non-human primates approximates 1% of Injected Dose (ID) per brain. This level of brain uptake is able to replace between 20-100% of endogenous enzyme activity in brain. Confocal microscopy shows that these brain penetrating IgG-enzyme fusion proteins target lysosomal compartments in human fibroblasts, reducing accumulation of sulfated glycosaminoglycans. Bio distribution of the IgG-enzyme fusion protein, as compared to enzyme alone, has been evaluated with whole body autoradiography in Rhesus monkeys. Although enzyme alone does not penetrate the primate brain, there is global uptake of the IgG-enzyme fusion protein throughout the brain of the non-human primate. Conversely, there is comparable uptake of either the enzyme alone or the IgG-enzyme fusion protein by peripheral tissues. The data are consistent with comparable uptake of either the IgG-enzyme fusion protein or the enzyme alone in peripheral organs mediated by the Mannose 6-Phosphate Receptor (M6PR), which recognizes the enzyme domain of the fusion protein. However, the M6PR is not expressed at the BBB. Brain penetration of the fusion protein is mediated via the IgG domain of the fusion protein, which targets the BBB insulin receptor. Successful development of a BBB-penetrating platform is transformational for MPS diseases as well as broader CNS/neurological conditions. Neurocognitive function, somatic effects and safety of a phase II proof of concept clinical trial in Hurler MPSI pediatric patients will be discussed. This represents the first in human clinical trial of a fusion protein engineered to cross the BBB.

### Biography

Eric Ka Wai Hui is a Principal Investigator at ArmaGen, Inc., a biotech company focused in the development of biotherapeutics for the brain. Dr. Hui joined ArmaGen in 2008 following 10 years of academic experience in molecular biology of neuroscience. His responsibilities have been instrumental in the development of ArmaGen's extensive product pipeline, including potential biotherapeutic treatments for mucopolysaccharidosis, stroke, Alzheimer's disease and Parkinson's disease. Dr. Hui has a Ph.D. in Microbiology and Immunology, and he has published numerous papers in his field.

[ehui@armagen.com](mailto:ehui@armagen.com)

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