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Chemical Biology of Infectious Disease
NIH Center for Biomedical Research Excellence
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**COBRE Proposal Letter of Intent**

June 14, 2018

**Eligibility criteria**

I will start as an assistant professor at the Department of Medicinal Chemistry, School of Pharmacy, University of Kansas, on July $29^{th}$, 2018. I have previously not held any externally funded, peer-reviewed grants from Federal or non-Federal sources.

**Nature or focus of the research**

Prion protein, PrP, represents a unique infectious disease vector. It is an abundant protein whose precise role in brain is not completely understood. When mutated, PrP undergoes a conformational change and induces other PrP proteins to adopt the same conformation. The aberrant conformation starts the process of aggregation of PrP particles into large agglomerates that are toxic to neurons. Certain variants of mutated PrP have been unequivocally implicated as causal agents of fatal familial insomnia, a disease that is the final stage of a process that begins with improper folding of PrP. Genetic studies also indicate this protein as the main culprit of the disease and suggest that lowering the amount of PrP in non-symptomatic mutation carriers slows down the progression of the disease.[1]

There are now studies under way that are attempting to lower the amount of PrP by sequestering the PrP mRNA through a complementary oligo-nucleotide interference. Ability to degrade PrP by a small-molecule protein binder (through one of protein degradation methodologies available today, i.e. von Hippel-Lindau tumor suppressor-recruiting or cereblon-recruiting chemical inducers of proximity) presents a unique therapeutic opportunity in this important area.

This proposal will look at PrP's ability to bind copper and other heavy metals as a starting point to design selective small molecule binders. These binders can then be elaborated into "recruiters" for protein ubiquitylation and subsequent destruction via protein degradation machinery. Exploring the metal-binding ability of PrP will also shed new light on its basic function and may also present a chemical explanation for the toxicity of PrP aggregates in brain. Clear answer to why protein aggregates would lead to massive death of neurons is still eluding the researchers. Consideration of metal, and particularly copper, homeostasis in brain and the ability of transition metals to "catalytically" oxygenate carbon–hydrogen bonds[2] in brain lipids and neurotransmitters will provide a molecular mechanism-of-action piece of this puzzle.

**COBRE CBID Core Labs utilization**

This project would rely heavily on protein expression and assay development through the Chemical Biology for Infectious Diseases core labs. Specifically, PrP protein (native or isotopically-enriched) will need to be expressed and purified for binding studies based on NMR. Assays that measure the behavior of PrP in cellular environment would need to be developed. Understanding the ligating ability of the unstructured region of PrP would require sophisticated modeling in collaboration with the Computational Chemical Biology core.

**References**

[1] Adriano Aguzzi and Anna Maria Calella. Prions: Protein Aggregation and Infectious Diseases. *Physiological Reviews*, 89(4):1105–1152, oct 2009.

[2] Tong Xiao, Cheri M. Ackerman, Elizabeth C Carroll, Shang Jia, Adam Hoagland, Jefferson Chan, Bao Thai, Christine S. Liu, Ehud Y. Isacoff, and Christopher J. Chang. Copper regulates rest-activity cycles through the locus coeruleus-norepinephrine system. *Nature Chemical Biology*, jun 2018.

Sincerely yours,

Zarko Boskovic