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A glycated core of Neuropathology

What causes intractable neurological disorders such as Alzheimer's, Parkinson's and ALS? Are they primarily signal transduction pathologies? Forms of amyloidosis? Do they arise from rogue neuroinflammation? There is ample evidence for any of these etiologies, yet no single disease model has achieved clinical breakthroughs. Perhaps we must view these effects (protein dysregulation, aggregation, autoimmune dysfunction, etc.) as symptoms rather than root causes, and dig a bit deeper to identify a common pathological origin in order to discover better countermeasures.

Findings from recent publications hint at a plausible nexus for these etiologies. Specifically: 1) exposure to advanced glycation end-products (AGEs) impairs structural, enzymatic and signaling performance of various proteins, 2) AGEs tend to accelerate amyloid-related protein aggregation, and 3) glycated proteins trigger sustained inflammatory response. Much of this insight derives from studying peripheral diseases such as lupus, diabetes, arthritis, Crohn's, etc., but a compelling CNS link comes from the fourth observation that: 4) glycated proteins disrupt VEGF function, producing microvasculature that, in the choroid plexus epithelium, degrades the blood brain barrier. Taken together, this suggests a core molecular basis, amenable to structural biological characterization of the basis for how

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advanced glycation end-products may alter protein folding and function, hyper stimulate complement-related immune response, and produce small neurotoxic protein oligomers.

This talk will assess key observations in the neuropathology literature and apply structural biological concepts to rationalize them, en route to a framework for unraveling how glycation phenomena can help to unify disparate etiologies, and how the unified etiologies may be therapeutically exploited.

Speaker Biography

Gerald Lushington is a co-founder of TheraPeptics, LLC, a startup effort focused on applying artificial intelligence and bioinspiration for developing novel peptide formulations for antimicrobial, anticancer and immunotherapeutic medicines, as well as for a variety of analytical and diagnostic technologies. His other key biomedical interests include antiviral protease targeting and neuropathic mechanistic studies. His primary technical specializations are in informatics, modeling and visualization as applied to a diverse range of chemical and biological foci. He is Editor in Chief of the journal Combinatorial Chemistry & High Throughput Screening (Bentham Scientific) and serves on editorial boards of numerous other journals. He completed his PhD at the age of 26 years from the University of New Brunswick in Canada. He has over 200 publications that have been cited over 4100 times, amounting to an H-index of 35.

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