

EVALUATION REPORT OF PHD DISSERTATION

Thesis: Tau proteins cooperatively assemble into cohesive envelopes that protect microtubules against severing enzymes

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The dissertation submitted by Valerie Siahaan, titled "Tau proteins cooperatively assemble into cohesive envelopes that protect microtubules against severing enzymes," presents a remarkable journey through cutting-edge scientific research and is delightful to read through. The work unravels the regulatory functions of tau proteins with a blend of new discoveries and future textbook-forming knowledge.

Tau, an intrinsically unstructured microtubule-associated protein, localizes to the axonal microtubule bundles in neuronal cells and regulates microtubule stability and axonal transport. Tau-tau interaction is necessary for forming cohesive envelopes around microtubules, which act as a protective sheath regulating accessibility to associated proteins. Malfunction of tau and its detachment from axonal microtubules are hallmarks of tauopathies, including Alzheimer's disease. However, the mechanisms underlying tau's regulatory functions remain largely unknown.

Valerie Siahaan's dissertation systematically explores these mechanisms with outstanding scientific rigor. Through a series of innovative experiments, Siahaan elucidates the formation and regulation of tau envelopes, shedding light on their protective functions. Her work has led to several high-impact publications in journals such as Nature Cell Biology and Nature Chemical Biology, underscoring the significance of her findings.

Valerie Siahaan's dissertation achieves several key breakthroughs by characterizing the distinct binding modes of tau on microtubules using in vitro reconstitution and TIRF microscopy. Her research reveals that tau envelopes assemble cooperatively, with tau molecules adding to the envelope boundaries and exchanging dynamically with molecules in solution. Siahaan demonstrated that tau envelope formation induces local microtubule lattice compaction, which governs their cooperative binding mode and influences access to other microtubule-binding proteins. The study also shows that tau envelopes block kinesin-1 transport while allowing other motors to pass through and protect microtubules from severing by katanin. Furthermore, Siahaan found that tau phosphorylation decreases envelope formation and destabilizes existing envelopes, linking phosphorylation to

decreased microtubule stability and providing insights into neurodegenerative disease mechanisms.

Valerie Siahaan's dissertation comprehensively describes the cooperative binding mode of tau proteins, forming adaptable protective envelopes on microtubules that influence intracellular transport and protein interactions. The discussion part is very thorough and demonstrates visionary thinking and conceptual integrity of the PhD candidate. The insights gained from this work not only enhance our understanding of cellular transport and microtubule stability but also provide a foundation for further research into the organization of cytoskeletal processes. The dissertation's high standards of scientific writing, rigorous data interpretation, and logical progression make it an exemplary piece of research.

In summary, Valerie Siahaan's dissertation represents a groundbreaking contribution to the field, characterized by technical rigor, innovative methodologies, and significant impact. The dissertation meets high standards of scientific writing and presentation and offers an insight into the formation of the next generation scientific leader. Given its depth of research, influential publications, and potential for future contributions to the field, I strongly recommend it for acceptance.

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Specific question:

Valerie Siahaan's work has introduced a series of unresolved questions and inspired avenues for future research. The intriguing phenomenon of tau crosslinking, which spans from freely diffusing individual tau proteins and the formation of reversible tau envelopes to the irreversible tau fibrils and tangles regulated by phosphorylation, has profound implications. What is the current level of understanding or the relevant hypotheses regarding the chemical mechanisms underlying tau-tau crosslinking at the level of projection domains, and could other parts of the protein also be involved?