DEPARTMENT OF MOLECULAR AND CELLULAR BIOLOGY
HARVARD UNIVERSITY

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Evaluation of: Zhiyuan Wang

Course Description:
The Molecular Biology of Memory and Memory Diseases (MBMMD) Research Course guides students to develop the mindset of a research scientist. Students learn to ask questions, not simply to absorb answers. The curriculum emphasizes creative thinking as the means to ask and answer one's own questions. Students then devise experiments to answer their questions and prove hypotheses. To that end, the course teaches how to design and interpret experimental data. Some of the major discoveries of modern biology are used as models of scientific thinking, experimental design and, in some cases, to illustrate the serendipity that is common in scientific discovery. The course also introduces a suite of core technologies for genetic manipulations, genomic and gene expression analyses, and is especially focused on technologies applied to studies of the nervous system. Examples include methods for analyzing synapse and neural circuit function, such as calcium and voltage fluorescent imaging and electrophysiology, as well as techniques for controlling neural activity, such as optogenetics and chemical genetics. Advanced microscopy is also covered, including methods such as super-resolution and fluorescence microscopy. With knowledge of the technical tools and the 'art and craft' of experimental design, students are prepared to join research laboratories and pursue independent research projects.

Course research projects address important basic and clinical questions in neuroscience, such as mechanisms of memory formation, epigenetic transfer of memory and behavior between generations, and causes of neurological diseases such as Alzheimer's Disease. Students have the opportunity to explore topics of their own choosing. Students are identify a research question on the basis of significance and tractability and to approach the question by forming a sound hypothesis. They design experiments and anticipate findings that answer questions and resolve hypotheses, accomplishments that are reviewed in final presentations and written research proposals. The research projects allow students to explore a specific topic deeply, to gain experience in developing and describing a research plan, all skills that prepare them careers in research and other pursuits in which creative and logical thinking are necessary to succeed.

Evaluation of: Zhiyuan Wang

Zhiyuan Wang was an outstanding student in the Molecular Biology of Memory and Memory Diseases Course this past summer. He demonstrated a strong ability to reason quantitatively about the mechanisms underlying extracellular-vesicle-mediated tau propagation in Alzheimer's disease. His research proposal focused on a difficult and highly specific problem: how to identify the proteins that physically tether pathological tau filaments to the luminal membrane of brain-derived extracellular vesicles.

The central strength of Zhiyuan's proposal was its phenotype-first logic. He recognized that a protein associated with tau or extracellular vesicles is not necessarily a tethering protein. A genuine tether should allow normal tau filament formation and extracellular-vesicle secretion while specifically reducing the physical attachment of tau filaments to the vesicle membrane. He therefore proposed an initial cryo-electron tomography checkpoint, or "Gate-0," to ensure that the experimental model actually reproduced the end-tethered tau phenotype before any screening began. This was an excellent example of using structural evidence to establish the validity of a biological model.

Zhiyuan designed a sophisticated chemical-biology screening pipeline using tag-free P301S tau, Alzheimer's disease-derived paired helical filament seeds, and large extracellular vesicles. He proposed scaling vesicle production in hollow-fiber culture and separating large vesicles by density and size. The screening would combine enzyme-inhibitor libraries with cell-permeable peptides designed to disrupt candidate protein interactions. Complementary membrane-stripping procedures would distinguish transmembrane or lipid-anchored tethers from peripheral adaptor proteins.

His proposal was especially strong in the way it tied each experimental result to a specific mechanistic interpretation. A three-dimensional filter would combine cytotoxicity measurements, free-versus-bound tau quantification, phospho-tau analysis, and tau-seeding assays. Candidates would then be classified as tethering factors, extracellular-vesicle formation factors, or cargo-sorting factors. Zhiyuan understood that all three classes could produce an apparent loss of tethering, and he designed the experiments to distinguish among them. He further proposed endogenous gene editing, a 2 × 2 knockout and drug-occlusion design, wild-type rescue, and quantitative correlative light and electron microscopy involving more than 1,000 vesicles.

The in vivo component provided an important functional endpoint. Zhiyuan proposed comparing extracellular vesicles produced by control, tether-disrupted, and rescued cells after hippocampal injection into tauopathy models. Reduced AT8-positive tau spread after tether disruption, followed by restoration after rescue, would connect the molecular tethering mechanism to pathological propagation. He also thoughtfully considered alternative outcomes. A negative protein screen could indicate lipid- or RNA-mediated anchoring, while failure to block propagation could suggest that tethering protects cargo without controlling its release.

In the shared presentation, Zhiyuan was responsible for the second technical approach. His section presented the cargo model, structural admission checkpoint, chemical-biology screen, matrix-based filtering, cryo-electron tomography, and in vivo confirmation. This was a masterful presentation that made clear how his approach complemented the genetic and proteomic strategies developed by other members of the group. The organization was coherent, and the experimental criteria were presented with unusual precision. The organization and design of the slide presentation was outstanding.

Overall, Zhiyuan demonstrated excellent biological reasoning and a rare ability to design experiments in which alternative explanations are anticipated in advance. He combined structural biology, chemical biology, quantitative analysis, and animal experimentation in a coherent framework. His work revealed a strong sense of originality, scientific maturity, and considerable potential for advanced research in Alzheimer's disease and molecular neuroscience.



Samuel Kunes
Professor

Grade: A+