Alzheimer’s studies first to use new mouse models that can bridge gap between preclinical research, clinical trials

University of Nebraska Medical Center researchers' novel mouse model of Alzheimer’s disease enables study of how human-like immune system interacts with disease

OMAHA, NE, UNITED STATES, April 9, 2025 /EINPresswire.com/ -- In a landmark study, researchers at the University of Nebraska Medical Center developed a novel mouse model of Alzheimer’s disease that, for the first time, enables the study of how the human immune system interacts with Alzheimer’s pathology.

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> *Howard Gendelman, MD*

Pravin Yeapuri, PhD, R. Lee Mosley, PhD, and Howard Gendelman, MD, of the UNMC Department of Pharmacology and Experimental Neuroscience led the investigative team.

The models, developed at UNMC, were described in two recently released papers, one in Alzheimer’s & Dementia: The Journal of the Alzheimer’s Association, and another in Neuroimmune Pharmacology and Therapeutics, a journal created and developed by Dr. Gendelman at UNMC with the Society on NeuroImmune Pharmacology.

These models facilitate translational research, bridging the gap between preclinical research and human clinical trials, particularly in developing next-generation neuroprotective therapies.

“Prior mouse models commonly used for disease prevention and therapeutic interventions to ameliorate Alzheimer’s are significantly limited in their ability to reflect the natural disease course,” Dr. Mosley said. “While these models show cognitive improvement with experimental treatments, they have a poor track record of human clinical trial success.”

For example, Dr. Mosley said past vaccine studies targeting amyloid plaques were adequate in mice but caused severe immune reactions, leading to brain swelling in human trials. “These failures reflect a deeper issue,” he said. “The models lack the complexity of the human immune and genetic landscape.”

“While CRISPR-engineered mouse models have helped us accurately knock in Alzheimer’s-related genes, they miss key features like widespread neuronal loss and neuroinflammation,” Dr. Gendelman said. “Our new models go much further. They show robust neuronal degeneration and can be reconstituted by the human immune system. This opens the door to studying how human immune cells respond to human Alzheimer’s-related proteins, something no previous model could do.”

Dr. Gendelman said this overcomes the major limitations of earlier models, which relied on non-physiological gene overexpression and lacked human immune components.

Howard Gendelman, MD, chair of the University of Nebraska Medical Center Department of Pharmacology and Experimental Neuroscience

The team used CRISPR-Cas9 knock-in technology to knock in early-onset familial Alzheimer‘s-associated genes while preserving replicate human gene expression patterns, thus more accurately reflecting the true disease.

“These new models are critical to our recent work on T cell-based immunotherapies,” Dr. Yeapuri said. “They let us test how the human immune system responds to Alzheimer’s immunotherapies in a disease-relevant environment. That’s a significant leap forward.

“These models now allow us to simulate human clinical trials in mice equipped with a human immune system, enabling the study of regulatory T cells, tau pathology and neurodegeneration in a physiologically relevant context. They also support testing antibody-based therapies in a system that closely mirrors human biology."

Dr. Gendelman emphasized the new platform set the stage for future clinical trials, which his team has been working toward for decades. “With these tools in hand, we’re closer than ever to developing therapies that work in people,” he said. “The future of Alzheimer’s treatment is finally within reach.”

Other contributing investigators to the papers included:
- Saurav Bhattarai, Rana Kadry, Roshan Sapkota, Shefali Srivastava, Mohit Kumar, and Emma Foster, students at the UNMC Department of Pharmacology and Experimental Neurology;

• Jatin Machhi, PhD; Yaman Lu; Susmita Sil, PhD; Chen Zhang, PhD; Prasanta Dash, PhD; Larisa Poluektova, MD, PhD; and Santhi Gorantla, PhD, senior scientists and faculty at the UNMC Department of Pharmacology and Experimental Neurology; and
• Tsuneya Ikezu, MD, PhD, former UNMC Department Pharmacology and Experimental Neurology faculty and now at the Mayo Clinic.

About UNMC
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