Shijun Zhang, Ph.D., a professor in the Department of Medicinal Chemistry at the VCU School of Pharmacy, likes to think both big and small. He finds joy and fulfillment in the discovery and engineering of tiny molecules that may lead to an effective treatment for Alzheimer’s disease.

More than 5.8 million Americans are living with Alzheimer’s disease, and experts predict that number will soar to nearly 14 million by 2050. The neurodegenerative disease is the sixth leading cause of death in the U.S., and it affects millions more loved ones who often provide care for family members who receive the heartbreaking diagnosis. “Alzheimer’s disease is a devastating condition that desperately needs effective treatments to help patients and their caregivers,” Dr. Zhang said. “Our technology may provide a new direction in developing novel compounds to fight this disease.”

Emerging research suggests that chronic inflammation may be linked to the buildup of cellular debris that causes neurological dysfunction in Alzheimer’s patients. Armed with that knowledge, Dr. Zhang is researching how to disrupt inflammation responses, which over time lead to degeneration as the disease progresses. By turning off inflammation proteins, Dr. Zhang hopes he can help the body protect the neural pathways that normally are ravaged by the disease.

PREPARED FOR THE CHALLENGE

Dr. Zhang was trained as a medicinal chemist with a specialty in disorders of the central nervous system. His postdoctoral research focused on designing opioid-receptive molecules that could help reduce abuse and addiction by targeting opioid receptors. The skills he built on that project, he said, translated directly to his work at VCU Health on Alzheimer’s. Currently, he is pursuing two promising lines of research in the development of treatments for Alzheimer’s disease.

“In medicinal chemistry, we do a lot of chemical synthesis,” Dr. Zhang said. “If you know how to design, how to synthesize, how to analyze and test compounds, these common skill sets can be applied to any field.”

His interest in Alzheimer’s began after engaging with research on the disease that underscored both the severity and scope of the problem. Knowing there was no treatment or cure inspired him and piqued his interest. His love of teaching brought him to the VCU School of Pharmacy, where he built his lab and research focus around Alzheimer’s disease. Dr. Zhang’s training provided expertise in creating bivalent components, or two linked molecular structures designed to target different types of receptors. In his postdoctoral work, he developed structures to address problems with opioid addiction through receptor signaling, and Dr. Zhang saw potential for application to the problem that now captivates his attention. “I want to see whether I can use a similar strategy to tackle the problems involved in Alzheimer’s,” he said.

THE TRADITIONAL APPROACH

Dr. Zhang’s research to develop treatments for Alzheimer’s disease includes both a targeted drug discovery path and a traditional drug discovery path. In the traditional discovery approach, his team built off research on the neuroprotective properties of melatonin, the sleep hormone, and curcumin, a chemical component of turmeric that gives the spice its bright yellow color. Previous studies have shown that these natural products have properties that decrease neuroinflammation. One challenge is that the bioavailability, or how much of the substance enters circulation in the body, is poor for curcumin. Knowing that both naturally occurring substances have efficacy at combatting Alzheimer’s disease risk factors provided Dr. Zhang and his team with a starting point for building a new molecule based on the structural components of each. His lab engineered small molecules based on a chemical framework constructed with components from both melatonin and curcumin. Dr. Zhang’s team also tested these novel compounds with the goal of evaluating their effectiveness in cell models, including whether the compounds could cross the blood-brain barrier and if the delivery method of the compounds could ensure enough of the drug was present to have a positive result. The new molecular structure would address various risk factors in the brain with a new mechanism of action. Eventually, they hope to move this research into clinical trials.

“We tested these compounds in our Alzheimer’s disease cell model and it’s very promising,” Dr. Zhang said. “When you compare to melatonin or curcumin, it’s better and...
much more neuroprotective.” He and his team have also progressed through various tests to ensure it penetrates the blood-brain barrier. In tests, they also observed improvements in the pathology and in cognition, which was a promising development.

Based on earlier studies, his lab continues to craft new analogs of these molecules in order to improve the scaffolding created by combining structural elements of curcumin and melatonin. The new compounds are evaluated based on how protective they are against risk factors for Alzheimer’s disease and whether they can cross the blood-brain barrier to provide enough of the drug needed to be effective. Those factors will help determine which drug candidates move into potential clinical trials. Dr. Zhang’s research was supported in part by funding from the Alzheimer’s and Related Diseases Research Award Fund, which was established by the Virginia General Assembly to stimulate innovative investigations into Alzheimer’s disease, and that support has been critical for helping advance the work to develop and test potential treatments.

TARGETING HIS APPROACH

Dr. Zhang’s additional research into remedies for Alzheimer’s includes a promising line of work to develop small molecules that function as inhibitors for neuroinflammation. The project initially started with the heart. He and a graduate student working with a cardiovascular lab in the VCU School of Medicine were developing small molecule inhibitors targeted to a specific inflammasome, NLRP3. This NLRP3 protein complex is part of the body’s innate immune response. In many ways, it functions like a home security system. Once the body detects invasions, like a pathogen, the NLRP3 complex assembles and acts as a dispatcher, signaling the body to produce cytokines, such as interleukin 1 beta (IL1ß), which play an important role in signaling cells in various ways during inflammation.

Additional research has shown evidence that the NLRP3 protein complex plays a role in the development of neurogenerative disorders when the immune response becomes out of balance and chronic inflammation occurs. The NLRP3 protein complex is important to regulating balance in the inflammatory response, which research literature suggests is a contributing factor in the development of Alzheimer’s disease. The National Institutes of Health awarded Dr. Zhang a grant to explore the creation of inhibitors that could prevent or stop the progression of Alzheimer’s disease by blocking the overactivation of the NLRP3 inflammasome.

“When we started this research, we noticed the involvement of the inflammasome, which is critical, especially as the first barrier in the host system,” Dr. Zhang explained. “We want to see whether we can address what role this NLRP3 protein complex has in the development of Alzheimer’s disease by designing different chemical tools. And on the other side, eventually we want to know whether we can develop some drug candidates from molecules that target the inflammasomes.”

With that knowledge, Dr. Zhang and his team soon engaged in repeatedly building and testing small compounds to address the NLRP3 inflammasome complex. In the evolving process, Dr. Zhang and his lab are engineering and testing molecules for their effectiveness at inhibiting the protein. The molecules themselves are also tools. Dr. Zhang said, for better understanding the role the protein complex plays in the development of Alzheimer’s. Their tests confirmed how effective the molecules were by measuring decreases in the byproducts of NLRP3 inflammation.

“From here, Dr. Zhang’s team ran countless tests of potential compounds to see how they affected the amount of chemical byproduct produced as part of the body’s immune response. Through this screening, they confirmed that the appropriate protein complex was targeted and that their compounds decreased the output of inflammation responses linked to the development of Alzheimer’s disease. They also assessed how the compounds would be absorbed in the body and whether they would successfully penetrate the blood-brain barrier. For Alzheimer’s patients, long-term treatment is expected, so his lab is looking to design a solution that can be orally ingested.

Multiple rounds of testing yielded compounds that met Dr. Zhang’s requirements for effectiveness. In particular, the team measured cognitive improvements when using compounds designed to curb the inflammasome complex. Dr. Zhang’s hope is to take compounds from his research into clinical trials. Right now, his team continues to evaluate the pharmacokinetic properties of the compounds and to confirm the toxicology aspects of each compound to ensure the potential treatments are safe for use.

“It’s exciting — when you get to testing and see improvements in cognition,” Dr. Zhang said. “This is really promising. We’re confirming our hypothesis and seeing results.” The team has amassed a significant library of compounds and data to support preclinical studies and intends to pursue funding for the work ahead. That support will be critical, Dr. Zhang said, for fueling a discovery process that is ongoing. “As we think about future clinical studies, we may need a better molecule, so we’d go back and continue building and testing candidates for this particular application,” he explained.

Shijun Zhang, Ph.D., a professor of medicinal chemistry in the VCU School of Pharmacy, created a new chemical scaffolding that used structural elements found in curcumin, which gives turmeric its bright yellow color, and the sleep hormone melatonin. Both naturally occurring molecules have been observed to help reduce inflammation linked to Alzheimer’s disease progression. In testing, Dr. Zhang’s novel compounds proved to be more effective than curcumin and melatonin at decreasing neuroinflammation associated with Alzheimer’s disease.

Photo: VCU University Marketing

The team is eager and excited to pursue this research, with the goal of advancing toward clinical trials and ultimately, Dr. Zhang hopes, a treatment option that can provide hope for patients and loved ones affected by Alzheimer’s disease.

If you would like to be a part of advancing the next breakthrough in discovering treatment options for Alzheimer’s disease, please visit www.MCVFoundation.org.

Go directly to the Give Now button and select the “Pharmacy Current Fund” from the dropdown menu and note this research project on the form.

5. J.G. Walsh, Daniel Muruve, and Christopher Forrest. Inflammasomes in the CNS.