

MIND Matters

SPRING 2021

SPECIAL FEATURE

What are monoclonal antibodies?

Scientists are exploring ways to leverage the power of antibodies to help in the fight against Alzheimer's disease. But what is an antibody? Antibodies are a type of protein made by our immune system to help defend against disease. They work by recognizing a foreign body like a virus and signaling the immune system to destroy it. Antibodies can also be made in the laboratory for use as treatments. Monoclonal antibodies recognize foreign invaders in a single location and are already used to treat a variety of diseases from rheumatoid arthritis to some cancers.

Since the early 2000's, researchers have been studying whether immunotherapies, including monoclonal antibodies, could be effective treatments for Alzheimer's disease (AD). The first monoclonal antibody tested in human clinical trials, bapineuzumab, slowed the accumulation of amyloid plaques in the brains of people with AD but did not affect cognitive decline and the trials were stopped in 2012. To date, over a dozen different antibodies have been examined in human trials for AD. They differ in where they attach on the target protein and in the type of protein they target.

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Monoclonal antibodies are proteins made in the lab that act like our immune system and fight off harmful pathogens.

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Dear Friends of UCI MIND,

Spring has sprung and there is much to look forward to. COVID-19 infections remain low in Orange County. We are grateful to our colleagues from UCI Health who have done an incredible job of caring for people during the pandemic and navigating us toward an end through well-organized vaccination programs. We are planning resumption of our pre-pandemic research activities. The campus has reduced restrictions on in-person research while maintaining essential safety parameters. There is a collective sense of eagerness to “catch-up” on work delayed by the pandemic. This will include UCI MIND’s signature study, the longitudinal study of the Alzheimer’s Disease Research Center, and exciting observational research by renowned investigators such as Dr. Dan Nation (p 4). Research involving investigational treatments (clinical trials) has continued through the pandemic and we’re anticipating new trials to begin soon. A decision is imminent from the Food and Drug Administration about the potential approval of Biogen’s aducanumab—a monoclonal antibody against the beta amyloid protein (p 1).

As we’ve outlined before, this decision has produced controversy and consternation in the field. Whatever the decision, readers can expect that UCI MIND will be ready to answer questions about “Where do we go from here?” And we’re especially excited to answer these questions and more when we resume in-person community educational programs, which we hope to do soon. Dr. Megan Witbracht (p 7) will help lead these efforts, filling the void left by the departure of Chelsea Cox, who will begin graduate studies in the fall. Community education remains a mainstay of our work and is supported by myriad partnerships with Orange County organizations and remarkable leaders such as Carol Choi (p 5) and Joan and Don Beall (p 6). These individuals have enabled new efforts to further UCI MIND’s mission. We are grateful to them and eager to get back to normal.



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Many monoclonal antibodies are currently being tested for efficacy in human clinical trials. Illustration by Björn Öberg

For example, some antibodies target the tau protein in neurofibrillary tangles while others target the amyloid beta protein in neuritic amyloid plaques. Several monoclonal antibodies are currently being tested in human clinical trials including solanezumab, gantenerumab, aducanumab, donanemab and lecanemab (the “mab” at the end of name means “monoclonal antibody”). Some, such as solanezumab, bind to soluble amyloid beta in the brain and reduce the free form of the protein. Others, such as aducanumab and lecanemab, appear to reduce or even remove amyloid plaques from brain tissue.

Data released from Biogen’s Phase III trials of aducanumab and Eli Lilly’s Phase II trial of donanemab have suggested that some of these monoclonal antibodies may have a disease modifying effect in symptomatic AD. While Biogen is currently seeking FDA approval (a decision is expected in June 2021), Eli Lilly is in the process of conducting a Phase III trial of donanemab to test if the drug is safe and effective in a larger group of people. Results from multiple trials of Eli Lilly’s solanezumab and Roche’s gantenerumab have been mixed but there is recent evidence suggesting that the drugs may be most effective when used at higher doses and earlier in the disease process. A Phase III study of solanezumab

Since the early 2000’s researchers have been studying whether immunotherapies, including monoclonal antibodies, could be effective treatments for Alzheimer’s disease (AD).

in preclinical AD (older people who are cognitively unimpaired but have evidence of AD brain changes) called the A4 Study is ongoing and is expected to be completed in 2022. The AHEAD Study is a new trial here at UCI that will test lecanemab in preclinical AD. Read more about this study in our past newsletter at mind.uci.edu/summer2020.

Approval of any disease modifying treatment for AD would dramatically change the landscape of clinical care and Alzheimer’s research. Yet none of the drugs tested have been shown to stop or reverse disease progression. These drugs also carry risks and inconveniences. Most antibodies require at least monthly infusions and careful tracking for safety. In other words, even with any new FDA approval, there will still be need for safer, more convenient, and more effective drugs. Nonetheless, progress is being made and important milestones may be on the horizon.



How does heart health impact the brain?



Q&A with UCI MIND faculty member, Daniel Nation, PhD, Associate Professor of Psychological Science in the UCI School of Social Ecology. He earned his PhD in clinical health psychology from the University of Miami and completed residency in neuropsychology and a postdoctoral fellowship training in biological psychiatry and neuroscience at UC San Diego. Dr. Nation's research examines the role of vascular factors in cognitive decline and Alzheimer's disease with an aim to improve early detection and identify targets for potential new therapies.

How are our hearts and brains connected?

Nation: They're actually quite intimately connected. The brain requires tons of blood flow, much more than most other organs in the body. So, the supply of blood coming from the heart and the blood vessels is very important for brain function. It's thought that the brain has up to 400 miles of tiny micro vessels that provide nutrients to brain cells to keep them functioning normally, and

so this means it's very important that the vessels stay healthy in order for the brain to stay healthy.

What is the "blood brain barrier" and why is it important to Alzheimer's research?

Nation: The brain is a special organ that has to keep a special environment to allow for communication between brain cells. For that signaling to work properly, the brain has to be sealed off from the blood, which is a different type of environment. So, a bunch of cells wrap the brain to protect it, and if that barrier breaks, blood vessels begin to leak into the brain tissue. Researchers think this could trigger the degeneration of the brain, similar to what we see in Alzheimer's disease and other forms of dementia. In fact, in a series of major studies we have recently discovered that the memory centers in the brains of older adults will actually show leakiness in the vessels. It seems to be an independent process that contributes to memory decline in older adults, separate from the sticky amyloid proteins that build up in the brain as part of Alzheimer's disease.

What is your lab learning about cardiovascular contributions to Alzheimer's disease?

Nation: Our research is focused on the functioning of the blood brain barrier and how micro vessels help clear waste products

from the brain and help provide nutrients to brain cells. We have two main projects that we're very excited about. The first involves new technology to help us better study these micro vessels in the brain. We're using this technology to see if we can detect early blood vessel problems in cognitively healthy older adults to try to identify at a very early stage those who may be at risk for future cognitive impairment. Our second project is studying whether stem cells in the blood that naturally support and protect vessels are also preventing people from developing cognitive problems. Again, with an eye toward finding people who have a deficiency in those stem cells. We hope this will lead to treatments that could target deficient cells and help protect vessel health in older adults.

What are your next steps?

Nation: Right now, we're working on identifying these very early biological markers that help identify blood vessel dysfunction. After we identify people with no cognitive problems but abnormalities in blood vessels, we need to tailor treatments to fix those abnormalities and hopefully prevent or delay cognitive decline. This work will lead to clinical trials of a totally new approach from what is currently being done. I think that will be exciting and hopefully lead to some positive results.

Carol Choi named District 74 Woman of Distinction

Entrepreneur-philanthropist and UCI alumna Carol Choi ('85) was named among the 74th Assembly District 2021 *Women of Distinction* by Assemblywoman Cottie Petrie-Norris. The annual recognition occurs each March in honor of Women's History Month to recognize women "who have shown extraordinary work, mentorship and leadership."

For those fortunate enough to know and work with Carol, this honor comes as no surprise. Carol embodies leadership through service on several committees at UCI, including as a University Trustee.

Additionally, Carol serves as Board Chair of the Korean American Alumni Chapter, whose Founding President Alexander Kim now serves as District Director for the 74th District.

At UCI MIND, Carol has been instrumental in our work to engage the Korean American community in research. She facilitated a partnership between UCI MIND and the Somang Society, which is committed to serving aging Korean Americans. Under the leadership of Boon Ja Yoo, president of the Somang Society, this partnership has built new bridges between the Asian



Philanthropist Carol Choi photographed by Steve Zylius/UCI

American Pacific Islander (AAPI) community and research efforts at UCI MIND.

We join the many voices of the Anteater community to congratulate Carol Choi on this well deserved honor and look forward to working with her, Alex, President Yoo and others to continue to enhance community relationships.

Thank you to our donors



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UCI MIND & REMIND to launch inaugural Beall Scholar Program



UCI MIND's trainee-led organization, REMIND (Research & Education in Memory Impairments & Neurological Disorders), consists of predoctoral and postdoctoral leaders committed to mentorship and collaboration in the field of neurodegenerative disease research. To improve treatment and care for diverse communities impacted by Alzheimer's disease and related disorders, there is an urgent need to nurture a diverse future workforce of scientists and healthcare providers dedicated to solving this health crisis.

In an effort to address this need, UCI MIND and REMIND have partnered with philanthropists Joan and Don Beall to launch the inaugural *Beall Scholar Program*. The program will engage diverse students from local high schools in research and education on Alzheimer's disease and dementia to inspire future academic and career choices in STEM (Science, Technology, Engineering and Mathematics). The program will select 10-15 eleventh graders for a week-long summer session of interactive educational seminars, tours, and panels led by REMIND trainees and UCI MIND faculty members. The program aims to provide skills and experiences that enhance students' opportunities when applying to college, especially for majors focused on aging, neuroscience, and healthcare.

REMIND CO-CHAIRS



UCI MIND welcomes new Associate Director of Education

UCI MIND is excited to welcome Megan Witbracht, PhD, to lead community outreach and education programs for the Institute. Dr. Witbracht joined UCI MIND in 2015 to manage regulatory processes for the Alzheimer's Disease Research Center (ADRC). For the past three years, she has worked closely with the Outreach, Recruitment and Engagement (ORE) Core of the ADRC, led by Joshua Grill, PhD, to conduct independent research on recruitment and retention to Alzheimer's disease clinical trials.

Dr. Witbracht completed her PhD in Nutritional Biology from the University of California, Davis and her postdoctoral training at the USDA Western Human Nutrition Center in Davis. She replaces Chelsea Cox, who has served as Associate Director of Education for UCI MIND since 2015. Chelsea will be starting a PhD program in Health Behavior and Health Education at the University of Michigan School of Public Health in the fall where she will study implications of sharing Alzheimer's disease risk information.



Megan Witbracht, PhD (above) moves into the role previously held by Chelsea Cox, MPH, MSW (below).



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