Cancer Drug Logs Early Success as Alzheimer’s Treatment

BrightFocus Grantee Leads Drug Repurposing Effort

Current BrightFocus grantee, Stephen Strittmatter, MD, PhD, and his team of researchers from Yale report early success using a still-experimental cancer drug known as saracatinib to treat Alzheimer’s disease in mice, and they have completed a successful Phase 1 safety trial in humans with Alzheimer’s disease.

The work leading to clinical trials was supported by BrightFocus and the federal New Therapeutic Uses program launched in 2012 by the National Center for Advancing Translational Sciences (NCATS) at NIH. The program matches scientists with pharmaceutical compounds that have undergone significant research and development by industry, including safety testing in humans, to test potential ideas for new therapeutic uses.

With his BrightFocus grant, Strittmatter is investigating prion proteins and the spread of Alzheimer’s plaques in the brain. A protein called Fyn kinase plays a central role in how amyloid beta clusters damage brain cells. Saracatinib targets the same protein, and in cancer trials, it had cleared several key steps in the drug development process. This gave the research team a head start in their Alzheimer’s research.

Four weeks after administering saracatinib to mice with Alzheimer’s-like symptoms, the mice showed complete reversal of spatial learning and memory loss. Examination of their brains showed that the characteristic Alzheimer’s-related loss of synapses (junctures where signals pass from (Continued on page 3)
BrightFocus Advances Knowledge of Inflammatory Factors in Alzheimer’s

Removing TREM2 Quells Inflammation and Disease Progression in Mice

Research published in the March 2015 issue of the *Journal of Experimental Medicine* (JEM) by senior author Bruce Lamb, PhD, of the Cleveland Clinic, describes the surprising – even counterintuitive – role that a genetic trait associated with the immune system might play in Alzheimer’s disease.

Lamb’s lab has investigated a genetic variant of an inflammatory factor known as TREM2. It presents dramatically elevated risk not only for Alzheimer’s disease, but for other neurodegenerative diseases as well, including frontotemporal dementia, Parkinson’s disease, and amyotrophic lateral sclerosis (ALS). However, in some studies TREM2 served beneficial functions, including to encourage an anti-inflammatory response.

Lamb, along with co-authors BrightFocus 2013-14 grantee Crystal Miller, PhD, of the Cleveland Clinic and Taylor Jay of Case Western Reserve University, examined what might happen when TREM2 is removed from mouse models with Alzheimer’s disease pathologies. Among their findings, they discovered:

- TREM2 increases with age in the brains of Alzheimer’s disease mice.
- Inflammatory factors decrease and anti-inflammatory factors increase in TREM2-deficient mice.
- TREM 2 expression is increased on immune cells surrounding amyloid-beta deposits.

Another finding, a direct outgrowth of this BrightFocus-supported project, was that TREM2 cells in Alzheimer’s disease mouse models expressed high levels of inflammatory cells in response to immune signaling. If this finding is proven, it speaks volumes about the protection resulting from TREM2 deficiency, according to these authors. They speculate about mechanisms by which TREM2 deficiency might impede inflammatory activity in the brain and hypothetically inhibit the growth and/or toxicity of plaques and tangles, with some targets possibly attainable through the blood. Gaining control over these speculative mechanisms could have the power to retard Alzheimer’s disease and possibly other neurodegenerative disorders associated with TREM2.

President’s Corner

No Time to Lose: The Race to Cure Alzheimer’s Disease

The number of people developing Alzheimer’s each year is staggering. Today more than 5 million Americans are struggling with this disease. By 2050, that number is expected to more than double.

In this issue of *Alzheimer’s Disease Research Review*, you’ll read about work that is helping us to gain on this devastating disease.

From the important research advancing knowledge of inflammatory factors, to the time-saving collaboration between researchers and drug manufacturers in repurposing drugs, we are focused on moving forward in this fight. Studies on the biological factors surrounding this disease allow researchers to concentrate their work on potential treatments that will reverse or delay the deterioration of mind and body of those with Alzheimer’s.

BrightFocus is optimistic about research results and ongoing efforts. They inspire us to continue on in this fight. We hope you’ll stand with us. Your generous support is crucial to our work to fund promising research and provide vital public education.

Thank you for partnering with us in our mission to stop this dreadful disease.

Stacy Pagos Haller
President
Plaque-Fighting Drug Passes Early Clinical Test in Humans

Aducanumab Will Proceed to Phase 3 Trial

This spring a Cambridge, Mass.-based biotech company reported success in an early clinical trial of its Alzheimer’s drug, aducanumab, with “better than expected” results. Individuals treated with aducanumab had a significant reduction in amyloid and symptoms of cognitive impairment were slowed compared with untreated controls.

These trial results, while promising, are among the earliest attempts to test aducanumab in humans and have to be viewed with caution. Phase 1 trials are deliberately small and narrow in scope, designed to assess safety and establish safe dosing levels for promising agents as they head out of the starting gate. Aducanumab appears to be safe, although side effects were reported at higher dosing levels. These concerns will be analyzed further in data from this trial, and from phase 3 trials up ahead, which the company has announced it will pursue.

Phase 3 trials are considered the gold standard proof of clinical effectiveness, and are meant to test a drug’s effectiveness over time in the patient population it’s designed to treat. If successful, these trials typically lead to a drug’s approval by the U.S. Food and Drug Administration, at which point companies are free to market their product for specific conditions under a brand name.

Anti-amyloid agents currently represent the nearest, best hope of taking Alzheimer’s treatment to a new level, where it’s possible to do more than achieve mild improvement in symptoms. These complexly designed biologically-active drugs have earned the title of potential “disease-modifying” agents because they’re believed capable of slowing down the disease and delaying onset of symptoms, including memory loss and cognitive decline.

Results of the first phase 3 clinical trials of solanezumab, an anti-amyloid agent, suggested the drug might be beneficial in subgroups who had very early Alzheimer’s. Reisa Sperling, MD, of Harvard, who received a 2010-14 BrightFocus grant for her amyloid imaging research, is helping to lead the large Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Study (A4) trial, which uses PET imaging to confirm physical signs of early disease followed by treatment with solanezumab. The A4 trial is currently recruiting patients at dozens of sites in the United States and internationally.

Cancer Drug (Continued from page 1)

one neuron to another) had been fully restored. The treatment also reduced several other Alzheimer’s-related biochemical changes in the mice and did not appear to be toxic.

Typically, it can take a decade or longer from the discovery of a therapeutic target until drug discovery techniques pan out and an experimental compound is ready to enter a Phase 2 human clinical trial to establish dosing levels and test its effectiveness. Thanks to BrightFocus funding and NCATS’ New Therapeutic Uses program, Strittmatter and his team were able to hasten the process and complete animal and preclinical safety studies in less than two years.

To learn more about clinical trials, visit brightfocus.org/clinicaltrials
Brain Food
Meet Another Healthy Recipe Contest Winner!

Roxie C. shared her recipe for Confetti Quinoa Pilaf and became a winner in our Healthy Recipe Contest. A diet that includes plenty of whole grains, fruits and vegetables while limiting sugar and fat can reduce the incidence of many chronic diseases, like Alzheimer’s. Roxie’s recipe is a great dish to incorporate into your healthy lifestyle.

Confetti Quinoa Pilaf

Ingredients

1 cup quinoa
1/4 cup frozen yellow corn kernels, thawed
1/4 cup frozen green peas, thawed
1 dozen cherry tomatoes, halved (color of your choice)
1/4 cup grated carrot
1/4 cup chopped red bell pepper
1 green onion, minced
1/2 cup sliced cooked green beans
2 Tbsp. pistachio nuts
2 Tbsp. toasted slivered almonds

Directions

1. Cook the quinoa according to package instructions.
2. Place in a large mixing bowl along with the next 10 ingredients.
3. In a small saucepan combine the rest of the ingredients; gently heat till hot and well blended.
4. Toss with the quinoa mixture to evenly coat.
5. Spoon onto a platter and serve. Serves 6-8.

Enter to Win! The Next Healthy Recipe Contest Starts Soon

What’s your favorite healthy recipe? Share it with us and you could be a winner in our next Healthy Recipe Contest! Winning recipes will be published in upcoming issues of Alzheimer’s Disease Research Review. For details, visit our website: brightfocus.org/recipes.