

The Alzheimer's Prevention Initiative (**API**) announced the first-ever prevention trial in cognitively healthy individuals who are destined to develop Alzheimer's disease because of their genetic history. This groundbreaking study—the first to investigate whether an anti-amyloid treatment can stave off the disease—will span two countries and help launch a new era of prevention research in the urgent fight against Alzheimer's.

This is a huge effort combining the talents and resources of the top organizations in the field of Alzheimer's research. Collaborators include powerhouses such as the National Institutes of Health (NIH), Banner Alzheimer's Institute (BAI), University of Antioquia in Colombia and Genentech, a member of the Roche Group.

The \$100 million trial is the cornerstone of the new API international collaborative. The API was formed to accelerate the evaluation of promising but unproven prevention therapies. It will study an experimental anti-amyloid antibody treatment called crenezumab in approximately 300 people from an extraordinarily large extended family in Colombia, who share a rare genetic mutation that typically triggers Alzheimer's symptoms around age 45. The trial will also include a smaller number of individuals in the United States. The API team will collaborate with researchers from the NIH-supported Dominantly Inherited Alzheimer's Network (DIAN) to identify and recruit the U.S. participants.

The trial is designed to determine whether the drug can reduce participants' chances of developing the disease's disabling and irreversible symptoms, preserve memory and thinking abilities, and slow the progression of Alzheimer's biomarkers. Drs. Eric M. Reiman and Pierre N. Tariot from the Phoenix-based BAI lead the broader initiative, and they also will be leading the trial in close cooperation with Genentech's research and clinical team and a Colombian team headed by Dr. Francisco Lopera of Grupo de Neurociencias de Antioquia at the University of Antioquia. Together, these three groups designed the study with input from other prominent scientists and NIH and regulatory officials.

If crenezumab is shown to sustain memory and cognition in people certain to develop Alzheimer's, prevention trials could be designed to test it and other anti-amyloid drugs in a larger segment of the population. If the treatment's effects on brain imaging and other biological measurements of the disease are shown to predict its clinical benefit, the study could establish a much more rapid way to test future therapies.

Dr. Reiman, BAI Executive Director, said,

“We are grateful for the chance to evaluate such a promising prevention treatment.”

“We have tried to design the study in a way that might bring the field closer to ending Alzheimer's before another generation is lost.”

The study will be supported with five-year NIH funding expected to total \$16 million, as well as a BAI commitment of \$15 million in philanthropic funds. Genentech will contribute the major share of funding, in addition to providing study drug and clinical and operational expertise integral to the design and conduct of the study. Given the importance of the trial, data and findings will be shared publicly after its completion to help the entire Alzheimer's research community find faster ways to test promising prevention therapies.

Richard H. Scheller, PhD, Executive Vice President, Research and Early Development at Genentech, shared his excitement. He commented,

“Genentech is very excited to be a part of this landmark effort.”

“If the study demonstrates that we can prevent the disease in this special group of patients, it may pave the way to preventing Alzheimer's in the general population.”

About 5.4 million Americans are living with Alzheimer's today, a number expected to top 7.7 million by 2030. Globally, the disease and other dementias are expected to affect nearly 66 million by then.

The study represents a marked shift in researchers' approach to detecting, treating and ultimately preventing Alzheimer's. Many in the clinical and scientific community believe that by the time memory begins to slip and confusion and other thinking problems emerge, too much damage may already have occurred for some treatments, such as those focusing on amyloid, to

be effective. They suspect that these potential therapies must instead be started before the onset of symptoms.

BAI researchers already have shown how advanced brain imaging, biomarkers and other measurements can identify and track subtle Alzheimer's-associated changes in healthy people at genetic risk for the disease many years before its first clinical signs appear. They proposed using these tools in a prevention trial that would not require a lengthy wait for those symptoms.

The new study will test what is often called the amyloid hypothesis, which suggests that accumulation of the protein amyloid in the brain plays a key role in the progression of Alzheimer's disease.

Preclinical studies indicate that crenezumab, an antibody therapy that Genentech is developing in collaboration with Swiss biotech company AC Immune SA, works by binding to amyloid proteins and clearing them from the brain. It has been studied in both healthy individuals and people with Alzheimer's and currently is being evaluated in a Phase II clinical study in patients with mild to moderate symptoms. No significant safety issues have been detected to date. The drug was selected for this prevention trial with guidance from an expert advisory panel.

Dr. Lopera is "in the trenches" at Medellín. There, he has followed generations of the families since the early 1980s. He explained,

“The trial represents big hope for the people here.”

“For those with the genetic mutation, it is a chance to modify their destiny. For those who are not carriers, it is a chance to save loved ones. They all want a far different future.”

Among the Colombian as well as U.S. participants, crenezumab will be administered to individuals 30 and older with normal cognitive function. Participants in the double-blind, placebo-controlled trial will receive an injection of crenezumab or placebo at set intervals for up to five years. Researchers will use advanced imaging techniques, cerebrospinal fluid tests and

sensitive cognitive measures to monitor whether the accumulation of amyloid and other tell-tale proteins in the brain is reduced, whether brain size and function is maintained, and, most importantly, whether mental performance is preserved.

To avoid signaling the genetic status of participants, most of whom do not want to know if they have the mutation, the study will include relatives who are non-carriers and will receive the placebo.

Dr. Tariot, BAI Director, stated,

"We are cognizant of the responsibility that we face, not just to the scientific community but to the families who will be involved in our work."

"Yet the possibilities ahead are tremendous. If this approach to fighting Alzheimer's is successful, it has the potential to transform all future prevention and treatment research and to herald the beginning of the end of this devastating disease."