

THE *Current*

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Clinical Trials for Alzheimer's Disease Preventative Drug to Begin Early 2013

After an announcement by federal officials approving clinical trials for the drug Crenezumab, researchers searching for a way to treat Alzheimer's Disease are gearing up for a rare study that will allow them to test a therapy for a genetically predestined disease -- before its onset.

"This is really incredible," said UC Santa Barbara neuroscientist Ken Kosik, who is the Harriman Professor of Neuroscience Research in the Department of Molecular, Cellular & Developmental Biology, and co-director of the Neuroscience Research Institute. He, along with several other Alzheimer's experts in the United States and Colombia, will be conducting the five-year, \$100 million study, starting early next year.

The scientists will be drawing their study participants from a large family in Medellín, Colombia. It's a family of about 3,000, with the unfortunate distinction of coming down with the disease early in life — onset begins at around 49 years of age. Unlike the kind of Alzheimer's that strikes late in life, this particular form has been traced to a specific genetic mutation.

"Almost everybody, if they have the mutation, gets the disease like clockwork," said Kosik, who first met with members of the family in the early 1990's, just after

starting his work with Alzheimer's as an assistant professor at Harvard University. His interests led him to Bogotá, where he met Francisco Lopera, the Colombian neurologist who told him of the family, and who is another lead researcher on the study.

At the time, there was the interest in starting treatment and research, but the country was in upheaval, caught between political insurgents, drug cartels, and internal armed conflicts. Pharmaceutical companies were reluctant to invest or participate in any trials.

Two decades later, not only has turmoil in the country decreased, but the thinking toward treatment of Alzheimer's Disease has shifted from cure to prevention, paving the way for studies such as this one.

"When the brain is severely damaged with full-blown Alzheimer's disease, it's very hard to treat. There's already been a lot of damage and you can't replace the neurons that have died," said Kosik.

About two years ago, Kosik received a call to do this study from colleague Eric Reiman, executive director of the Banner Alzheimer's Institute in Phoenix and another lead researcher. At that time, several Phase 3 trials on what was hoped to be a viable treatment for sufferers of the disease had failed, forcing the neuroscientists to rethink their approach.

What is unique about this opportunity, said Kosik, is that the population being studied is a relatively homogenous group. Family members have the same genetic mutation, the same rural background, similar diets, and activities.

"They have said over and over that this disease has been such a burden to them, that they want to participate in a clinical trial," Kosik said.

The study involves testing candidates for the genetic mutation, taking a record of baseline conditions, administering either the medication or a placebo over a period of time, and monitoring the subjects' progress. In this double-blind trial, neither the subjects nor the investigators will know which subjects have the mutation, or which ones receive the drug or the placebo. A third party will handle that information.

Additionally, a group of participants that don't have the mutation will be included in the mix, and will receive the placebo -- a measure taken to ensure that the family

members in the study don't know whether or not they have the mutation. In total, 300 members of the family will be participating in the first phase of the study.

Kosik, who has been concentrating on the genetic and ethical side of the research, said he agonized over whether the family members should be told of their genetic status.

"It's very dangerous knowledge," said Kosik. "I saw a 23-year-old man who said that if he found out he had the mutation, he would commit suicide." On the other hand, there are people like the young female family member he encountered who wanted to have children but was terrified at the prospect of passing down the mutated gene.

In the end, he said, since there was no capability for genetic counseling at this early phase, the family members had to agree that they wouldn't know which ones had the mutation.

"As this program develops, hopefully what some of these funds will be used for is to begin to offer genetic testing and counseling for those who want it," said Kosik.

There will be several tests to assess whether Crenezumab is successful at delaying or even stopping the onset of dementia. The tests will involve cognitive thinking and memory skills. The researchers will also be assessing any changes in emotional state that could signal the emergence of the disease. Added to these evaluations will be physiological examinations and other measurements to determine the health of the brain. Results could come as soon as two years into the study, and there are breakpoints at which the investigators may deem efforts a success or a failure, at which point they may move on to test another drug.

In the larger picture, Kosik sees a shift in how Alzheimer's Disease may be diagnosed. Currently, clinical diagnosis is contingent upon the presence of cognitive impairment, which has been too late for treatment with today's medications. If the disease could be found early using genetic markers, a clinical diagnosis could be made sooner.

But, Kosik cautions against going to the other extreme -- for instance, the genetic bias of finding the mutation in a 10-year-old boy and diagnosing an otherwise healthy individual with a fatal disease.

"It's a shifting line right now," he said. "It's an extremely interesting area."

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† Middle image: The researchers presenting the clinical trial to the families in the Colombian municipality of Angostura. From left to right, they are Francisco Lopera, the Colombian neurologist who has been working with members of the family for decades; Kenneth Kosik; Argentinian neurologist Facundo Manes; and Pierre Tariot, director at Banner Alzheimer's Institute in Arizona. Credit: Grupo Neurociencias

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