Clinical trials start for stroke drug developed by Scripps Research, USC, and ZZ Biotech

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Clinical trials start this week for a stroke drug initially created by a team led by scientists at The Scripps Research Institute and the University of Southern California (USC), and further developed by biotech company ZZ Biotech.

The clinical trials will test the safety in humans of the experimental drug 3K3A-APC, which has been shown in animal models to reduce brain damage and improve motor skills after stroke when given in conjunction with a federally approved clot-busting therapy.

"I am incredibly excited about the potential for translating our science into a therapy that could have a significant impact on society," said Scripps Research Institute Professor John Griffin, who collaborated on the scientific work with Professor Berislav V. Zlokovic, director of the Zilkha Neurogenetic Institute at the Keck School of Medicine of USC. "Stroke and its aftereffects are a huge problem in this country."

Kent Pryor, chief operating officer of ZZ Biotech, said, "We are very pleased to have received approval from The Austrian Agency for Health and Food Safety (AGES) to initiate our first human study with 3K3A-APC. Our extensive preclinical studies into the neuroprotective effects of 3K3A-APC suggest that it is a promising candidate for the treatment of ischemic stroke."

Fourth-Leading Cause of Death

Stroke, which occurs when blood flow to a part of the brain stops, is the fourth-leading cause of death and the leading cause of adult disability in the United States. A stroke occurs when blood flow in the brain is interrupted, cutting off part of the brain from oxygen. Some brain damage happens immediately, but even when blood flow is restored, brain cells continue dying for hours or days.

According to the American Stroke Association, the Food and Drug Administration-approved tPA (tissue plasminogen activator) is the best treatment for stroke caused by a blocked artery, but to be effective, it must be administered within three hours after symptoms start. If given outside that three-hour window, tPA has shown serious side effects in animal and human brains, including bleeding and breakdown of the brain's protective barrier.

Generally, according to the American Stroke Association, only three to five percent of those who suffer a stroke reach the hospital and satisfy relevant criteria in time to be considered for tPA treatment.

A New Approach

When Griffin's hematology lab and Zlokovic's neuroscience lab began collaborating more than a dozen years ago, activated protein C (APC) was known to stop the growth of blood clots and reduce inflammation, and was being tested for the treatment of adult severe sepsis.

By 2003, their collaborative work pointed to a previously unsuspected ability of APC to directly prevent programmed cell death in brain, which had emerged as a key to reducing the effects of stroke. The team found that APC dramatically decreased the cellular signals that convince brain cells to kill themselves after a stroke and boosted the cellular signals that persuade the cells to survive.

However, APC's natural blood-thinning properties posed a potential problem to using APC as a treatment for stroke, possibly inducing bleeding in the brain. In response to this challenge, the Griffin lab (including Scripps Research scientists Laurent Mosnier and Andrew Gale) produced an engineered version of APC.

"The protein normally is an anticoagulant," Griffin explained. "We separated out the beneficial effects of the protein acting on cells from this anticoagulant activity. This was done by protein engineering of the 3K3-APC variant to lose most of its anticoagulant activity while retaining its direct actions on cell signaling."

Promising Data

Further work from the team on the engineered 3K3A-APC lent support to the decision to proceed with clinical trials. Large-scale production of this biologic drug, 3K3A-APC, was accomplished by ZZ Biotech with the guidance of Griffin and Thomas Davis, who is a distinguished professor of pharmacology at the University of Arizona.

The journal *Stroke* published a paper by Zlokovic, Griffin, and colleagues online ahead of print on July 17, 2012 (doi:10.1161/strokeaha.112.658997), showing the results of giving the federally approved stroke treatment tPA—alone and in combination with 3K3A-APC—to mice and rats four hours after onset of ischemic stroke. The team also gave 3K3A-APC for three consecutive days after stroke and measured the amount of brain damage, bleeding, and motor ability of the rodents up to seven days afterward.

The researchers found that, under those conditions, tPA therapy alone caused bleeding in the brain and did not reduce brain damage or improve motor ability when compared to the control. The combination of tPA and 3K3A-APC, however, reduced brain damage by more than half,

eliminated tPA-induced bleeding, and significantly improved motor ability.

"We have developed something that not only counteracts the bleeding, but also reduces brain damage and significantly improves behavior after stroke," said Zlokovic. "I feel very strongly that this approach will extend the therapeutic window for tPA."

The Next Step

The stage is now set for ZZ Biotech, founded by Zlokovic with USC benefactor Selim Zilkha, to launch the first clinical trials in humans for 3K3A-APC under the supervision of a leading stroke trialist, Professor Patrick Lyden, chair of the Department of Neurology at Cedars-Sinai Medical Center, Los Angeles.

The new Phase 1 study is a randomized, double-blind, placebo-controlled, single-center trial that will investigate the safety and pharmacokinetics of single and multiple ascending doses of 3K3A-APC in healthy adult volunteers. Approximately 62 eligible adult subjects will be assigned sequentially to 1 of 10 cohorts, at successively higher single doses, followed by successively higher multiple doses. Results of the study are anticipated in the first quarter of 2013.

"We are excited by the prospect of one day putting 3K3A-APC in doctors' hands to help reduce the tremendous suffering caused by stroke ," said Joseph Romano, chief executive officer of ZZ Biotech.

Provided by Scripps Research Institute