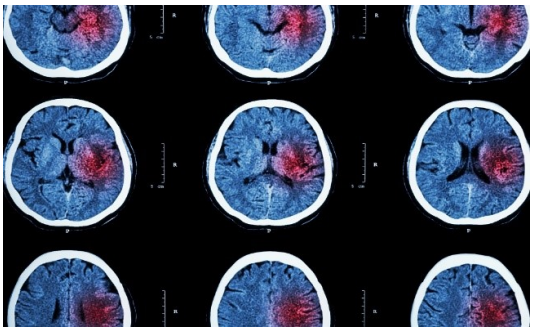
INNOVATIVE STROKE TREATMENT LEADS TO PATENT APPLICATIONS



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BY GISELE GALOUSTIAN | 11/29/2018

Stroke is the third leading cause of death and disability in the United States, with one person dying every four minutes. Nearly 800,000 people have a stroke each year and about 87 percent are ischemic strokes, where blood flow to the brain is constrained or clogged. While there have been significant strides made in stroke research as well as major advances in stroke care, effective treatments are still insufficient and require a continued quest for new remedies. Current drugs designed for stroke intervention and treatment are based on their anti-oxidative properties or blockers of calcium channels or glutamate receptors. However, no clinically effective therapeutic intervention for stroke has yet been developed.

Jang-Yen (John) Wu, Ph.D., distinguished professor of biomedical science and neuroscientist in the Schmidt College of Medicine at Florida Atlantic University, has filed a patent application with the U.S. Patent and Trademark Office (USPTO) for a novel agent that is showing real promise for the treatment of stroke. Researchers at FAU conducted *in vitro* and *in vivo* studies to test the agent, Carbamathione, S-(N, N-diethylcarbamoyl) glutathiones, an active metabolite of Disulfiram, which has been used for decades to treat alcohol-use disorder. They discovered that Carbamathione could be used to treat conditions associated with hypoxia – a lack of oxygen to tissues – such as stroke. It has been demonstrated that more than 60 percent of patients acquire hypoxia within the first 60 hours after a stroke.

Jang-Yen (John) Wu, Ph.D., distinguished professor of biomedical science and neuroscientist in FAU's Schmidt College of Medicine.

In addition, Wu has filed a patent application with the USPTO for Granulocyte colony-stimulating factor (GCSF), a novel gene therapy for stroke and Alzheimer's disease. This unique therapy could provide a long-term and sustainable supply of GCSF for the treatment of these diseases.

"The most central mechanisms of tissue damage in stroke are scarcity of oxygen or hypoxia, glucose, excitotoxicity, the excess release of glutamate from affected cells, and production of injurious free radicals. Stroke causes a flow of events that can provoke the glutamate release and increase free radical production via numerous different pathways," said Wu. "Our research provides neuroprotective evidence that Carbamathione could protect against excitotoxicity damage by preserving mitochondrial and endoplasmic reticulum function in the brain of ischemia."

Stroke or ischemia leads to a rise in the extracellular concentrations of excitatory amino acids, largely in glutamate. Glutamate is the key excitatory neurotransmitter. In small amounts it is crucial for normal function, however, in extreme amounts it is a neuronal poison or toxin called excitotoxin. It is thought that brain ischemia followed by glutamate excitotoxicty leads to intracellular calcium overload and initiates a series of intracellular events, such as the release of apoptotic proteins leading to apoptotic cell death.

Many neurological disorders such as Alzheimer's disease, Parkinson's disease as well as stroke have been related to the over-activation of glutamatergic transmission and excitotoxicty as a known pathway of neuronal injury.

Carbamathione has an antagonistic effect on brain glutamate receptors and Disulfiram has been demonstrated that it exerts its anti-alcohol effect only after bio-activation to the active metabolite DETC-MeSO.

In prior studies, Wu and collaborator Howard Prentice, Ph.D., a professor of biological sciences in FAU's College of Medicine, identified an important neuroprotective role for DETC-MeSO and two other FDA-approved drugs, Sulindac and G-CSF,used to enhance blood cellular development and neuronal regeneration.

Wu and Prentice discovered that each agent individually produced potent pro-survival responses. Furthermore, the combination of these three drugs also resulted in strong neuroprotection even when the agents were employed at low doses compared to the respective standard drug doses. They patented this novel approach earlier this year. The researchers studied Carbamathione to test their hypothesis that it provides neuroprotection like DETC-MeSO by inhibiting apoptosis and endoplasmic reticulum stress in the brain in a rodent model of stroke.

"Results from our study show that Carbamathione is a very effective agent for protecting cells from hypoxia/re-oxygenation induced cell damage, which we think may be due to the inhibition of Carbamathione on glutamate receptors," said Wu. "Carbamathione may play a dual role in preventing hypoxia-induced cell death, in which it could suppress the glutamate release from the presynaptic sites of neurons and the activation of glutamate receptors post-synaptically on neurons."

The stroke discoveries by Wu and Prentice are being developed by CHS Pharma, Inc., a South Florida-based biotechnology development company that has an intellectual property portfolio for potential treatments related to ischemic stroke, dry macular degeneration and other age-related disorders such as Alzheimer's disease.

"Every 40 seconds, someone in America has a stroke. The impacts of stroke have devastating and lasting effects on the individual and their family as well as enormous costs associated with health care services and other related care," said Stephen Chakoff, director and founder of CHS Pharma, Inc., who has been working with scientists from FAU for almost a decade. "If successful, this latest discovery by Dr. Wu has the potential to be a game changer in the way we treat stroke."

Wu and Prentice also serve as scientific advisors for CHS Pharma, Inc. working in collaboration Chakoff.

The potential promise of Wu's discovery has enticed experts in the fields of neurology and pharmacology to make this stroke treatment a reality.

"We are excited about the preclinical data and I am very encouraged to help develop this important therapy and move it forward, " said Daniel Laskowitz, M.D., vice chair of neurology at Duke University School of Medicine and a scientific and medical advisor at CHS, who is working closely with Morris Faiman, Ph.D., professor emeritus of pharmacology and toxicology at the University of Kansas School of Pharmacy, and a member of CHS Pharma, Inc.'s team of scientific and medical advisors.

Wu and Prentice have developed several mechanism-based treatments for neurodegenerative diseases including Parkinson's disease, ischemic stroke, Alzheimer's disease and epilepsy. Wu has several patents to his credit. Prentice's research is focused on tissue hypoxia and ischemia and in molecular pathways of neuroprotection in stroke therapy.

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