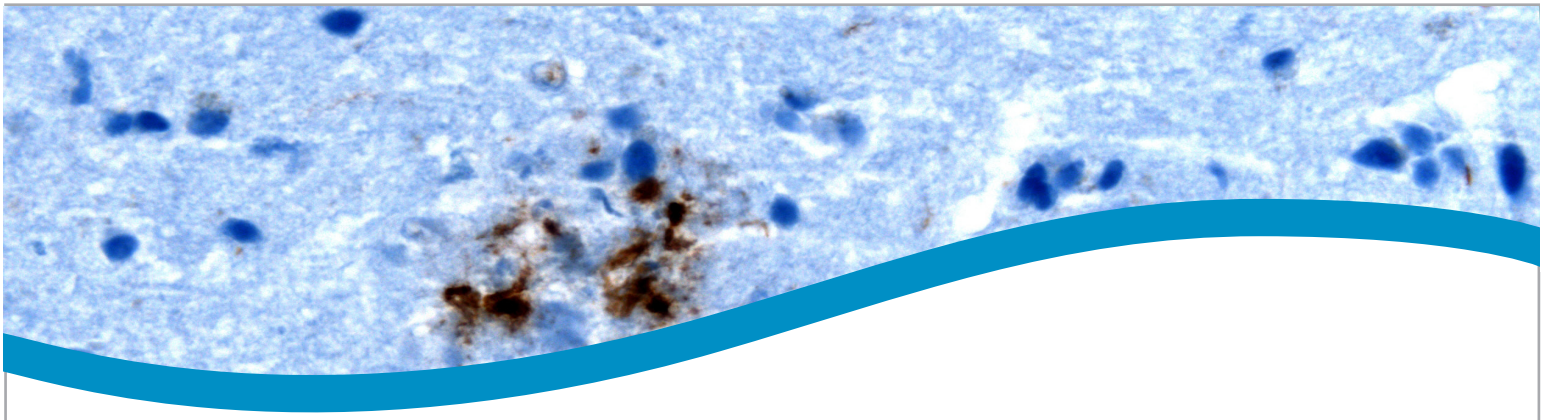

Examining Tau Phosphorylation as a Potential Alzheimer's Disease Biomarker

By: Jordan Jensen, PhD, Product Development Scientist, Antibody Products, Covance
Robert Martone, Neuroscience Therapeutic Area Lead, Biomarker Center of Excellence, Covance

Covance scientists are always on the lookout to apply the latest research to their work and contribute additional findings to the scientific community. They will present a poster studying the regulation of Tau phosphorylation at the upcoming 2013 Society for Neuroscience conference in San Diego.

The interest in this research was first sparked at last year's 2012 Alzheimer's Association International conference in Vancouver, Canada, where Covance scientists heard discussions on the effects of anesthesia on Alzheimer 's disease (AD) patients.

Anesthesia can induce hypothermia, and this has been shown to increase the phosphorylation of a protein called Tau. Researchers want to know more about why this change happens and understand the signaling pathways involved.

Tau proteins, mostly found in neurons of the central nervous system, have an important role in stabilizing microtubules, critical structures responsible for various movements in cells. If Tau is hyperphosphorylated, it loses effectiveness in stabilizing microtubules and starts to aggregate. Hyperphosphorylation and aggregation of Tau is observed in dementias like Alzheimer's. For this reason, Tau is considered to be a key marker in AD research.

The Covance team decided to explore the pathways involved in regulating Tau. They first looked at other researchers' observations from nature. Anesthesia-induced hypothermia is closely related to the changes that happen naturally in hibernating animals. For example, hibernating Arctic ground squirrels experience a lower metabolism and a decreased body temperature; additionally the Tau protein in their brains becomes hyperphosphorylated during hibernation.

This response to hypothermia has also been reported in an animal commonly used in research, the wild type mouse. A previous study demonstrated that an anesthetized wild type mouse with induced hypothermia had a decrease of activity in a protein called protein phosphatase 2A (PP2A).[1] PP2A is responsible for dephosphorylating the Tau protein, but only when the portion of the enzyme that has catalytic activity (PP2AC) is modified by methylation. It has been reported that hibernating Arctic ground squirrels have decreased PP2AC methylation and increased Tau phosphorylation.[2] Given this background, Covance researchers wanted to know if decreased PP2AC methylation during hypothermia resulted in Tau hyperphosphorylation in mice.

After performing the study, Covance researchers confirmed that phosphorylated Tau levels increased in wild type mouse brains after anesthesia. However, they determined that this effect was not caused by a decrease in PP2A expression or PP2AC methylation. They also did not observe decreased levels of PPM1, a protein that is responsible for methylating PP2AC.

Covance researchers had expected to find evidence for signal alteration, but these results suggest that the mechanisms of PP2A were not at play. They suspect that hypothermia-induced Tau hyperphosphorylation may alternatively function via increased Tau kinase activity, based on earlier research published by Bretteville *et al.*[3]

Ruling out this particular hypothesis will spur the research community to look at different potential pathways. At Covance, the informatics team will continue to model and build their networks to further evaluate known interactions between the different proteins. This may help determine which related pathways should be part of the next focus.

Covance participated in this important research as an opportunity to make an impact in basic science and to demonstrate some of its offerings, including a wild type mouse model of Tau hyperphosphorylation and antibodies to Tau phosphorylation pathway proteins. Going forward, Covance researchers will continue to explore novel topics to benefit the global research community and they hope to help elucidate the pathways involved in Tau regulation.

About the Authors:

Jordan Jensen, PhD *is a Product Development Scientist for the Covance Antibody Products group. He joined Covance in 2011 after four years of industry experience in drug discovery and five years of basic research experience at Ohio State University.*

Robert Martone *is the Neuroscience Therapeutic Area Lead for the Covance Biomarker Center of Excellence. He joined Covance in 2010 after 17 years of industry experience in drug discovery and eight years of basic research experience at Columbia University*

[1]Planel E, Richter KE, Nolan CE, Finley JE, Liu L, Wen Y, Krishnamurthy P, Herman M, Wang L, Schachter JB, Nelson RB, Lau LF, Duff KE (2007) Anesthesia leads to Tau hyperphosphorylation through inhibition of phosphatase activity by hypothermia. *J Neurosci* 27(12):3090-7.

[2]Su B, Wang X, Drew KL, Perry G, Smith MA, Zhu X (2008) Physiological regulation of Tau phosphorylation during hibernation. *J Neurochem* 105(6):2098-108.

[3]Bretteville A, Marcouiller F, Julien C, El Khoury NB, Petry FR, Poitras I, Mouginot D, Lévesque G, Hébert SS, Planel E (2012) Hypothermia-induced hyperphosphorylation: a new model to study Tau kinase inhibitors. *Sci Rep* 2:480.

THE AMERICAS +1.888.COVANCE (+1.888.268.2623) +1.609.452.4440
EUROPE/AFRICA +800.2682.2682 +44.1423.500888
ASIA PACIFIC +800.6568.3000 +65.6.5686588

 ARTBCOE002-1013

COVANCE®