

World Summit on

# STRESS, MINDFULNESS AND PHILOSOPHY &

5<sup>th</sup> International Conference on

# STRESS, MENTAL HEALTH AND DEMENTIA

August 27-28, 2018 | Boston, USA

## **Restoration of Iron Homeostasis by small molecules directed to the Iron Response Element (IRE) of the Amyloid Precursor Protein (APP) and Ferritin (FtH) 5'UTRs protect against toxic Pb exposure to neurons**

Catherine M Cahill<sup>1</sup>, Vivek Venkataramani<sup>2</sup>, Kevin Hodgetts<sup>1</sup> and Jack T Rogers<sup>1</sup>

<sup>1</sup>Harvard Medical School, USA

<sup>2</sup>University Medical Center, Germany

Prenatal and postnatal exposure to lead (Pb) is associated with neurodevelopmental delay, autism, and neurodegeneration later in life. Lead IV oxide is used in the production of batteries and paints, and Pb toxicity has historically been associated with the use of Pb(II) acetate as a sweetener. Pb contamination of water due to corrosion of Pb pipes has resulted in elevated blood Pb levels in the population as occurred in Flint Michigan in 2014. Pb in the body is notoriously hard to get rid of and is stored in bone. It can traverse the blood-brain barrier, via the divalent metal transporter (DMT1) which is the major iron transporter in neurons. As we age, and bone breaks down Pb seeps into the bloodstream and compounds the aging process with added inflammatory and oxidative stress pathways. Treatment of acute Pb poisoning by use of metal chelators is associated with a myriad of side effects and chronic low-level exposure often goes untreated. We have shown that exposure of neuronal SHSY5 cells to Pb 11 or Pb (1V) compromises iron homeostasis and neuronal cell viability by inhibiting translation (targeting the Iron Response Element/Iron Response Element Binding Protein interaction) of 2 iron homeostatic proteins, Ferritin (FtH) the iron storage protein, and Amyloid Precursor Protein (APP) involved in iron export. The consequent build-up of intracellular redox reactive Fe<sup>2+</sup> was detected by calcein assay. Overexpression of APP 695 isoform protected SHSY5 cells from Pb toxicity. A High Throughput Screen (HTS) of the Broad Institute Molecular Library, for modulators of the cellular Prion protein (PrPc) 5'UTR, screened BL-1, a small molecule which increases FtH and APP expression and protected neurons from Pb toxicity. Small molecules that modulate iron homeostasis have the potential to protect neurons from Pb toxicity and could potentially be developed for the clinical treatment of Pb poisoning.

### **Biography**

Catherine M Cahill is an Assistant Professor of Psychiatry at Harvard Medical School and co-directs the Neurochemistry Lab at Massachusetts General Hospital. She has worked in the area of iron homeostasis and neurodegeneration for the past decade. At MGH, she and her colleagues were the first to discover an iron response element in the 5'UTR of the, Amyloid precursor protein mRNA and in several other neurodegenerative disease-associated genes. High throughput screens using the 5'UTRs of these mRNAs have landed several small molecules that modulate Iron Homeostasis. Catherine's other interests are in the inflammation associated transcription factors, Activator Protein 1 and Nuclear Factor Kappa B. Her discovery of a novel cross-talk pathway between these factors together with her work on the developmental expression of AP-1 in the intestine has potential to develop into therapies for intestinal inflammation and cancer.

ccahill@helix.mgh.harvard.edu

### **Notes:**