ISN Symposium Report
Helen M. Bramlett, PhD
President, 2014-2015
National Neurotrauma Society

Title of the ISN Sponsored Symposium: Purines: Forgotten Mediators of CNS Injury
Main Meeting: National Neurotrauma Symposium
Locale: Santa Fe, New Mexico USA
Dates: June 28-July 1, 2015

The National Neurotrauma Symposium was one of our more successful meetings with the number of attendees (627) and abstracts (340) submitted for presentation close to the highest. The attendees were composed of 148 students/postdocs, 37 exhibitors and 442 faculty/speakers. A breakdown by country participation is as follows: 22 Canada, 3 China, 8 Finland, 1 France, 3 Germany, 1 India, 1 Israel, 2 Italy, 3 Japan, 1 South Korea, 1 Malaysia, 1 Mexico, 1 South Africa, 2 Sweden, 1 Switzerland, 4 United Kingdom, 565 USA.

Our ISN sponsored symposium was organized and chaired by Dr. Patrick Kochanek from the University of Pittsburgh School of Medicine. Our outstanding group of speakers presented novel and interesting data on purines from a variety of perspectives. Edwin Jackson, PhD from the University of Pittsburgh gave a talk on "Role of The 2',3'-Camp-Adenosine Pathway In Traumatic Brain Injury". Our second speaker, Detlev Boison, PhD from the Robert Stone Dow Neurobiology Laboratories, Legacy Research Institute presented a talk on the "Role of Adenosine in Posttraumatic Seizures and Epilepsy: A Potential New Target". Our final speaker for the session was Michael Schwarzschild, MD, PhD from Harvard Medical School and MassGeneral Institute for Neurodegenerative Disease presented on "Urate – A Novel Potential Therapy in CNS Injury and Neurodegeneration". All three speakers discussed purines as an emerging area of research in CNS injury. This topic had not been previously discussed in such detail at the National Neurotrauma Symposium. The session was well attended, approximately 120 people, and a lively discussion followed each presentation.

The ISN support of $4200 provided partial reimbursement for all three speakers. The breakdown of costs were as follows: Domestic Speaker Transportation (flights) = $700 x 3 = $2100, Domestic Speaker Transportation (ground transport) = $100 x 3 = $300, Speaker Hotel Accommodation (2 nights) = $500 x 3 = $1500, Registration for conference = $575 x 3 = $1725, Total = $5625.

Abstracts for the session:

ROLE OF THE 2',3'-CAMP-ADENOSINE PATHWAY IN TRAUMATIC BRAIN INJURY
Edwin Jackson[1], Patrick Kochanek[2]; [1]*University of Pittsburgh, Pharmacology and Chemical Biology, Pittsburgh, USA,* [2] *University of Pittsburgh, Critical Care Medicine, Pittsburgh, USA*

Using mass spectrometry, we recently dis-covered that some tissues generate a positional isomer of 3',5'-cAMP, namely 2',3'-cAMP. Ad-di-tionally, we established that: 1) the bio-synthesis of 2',3'-cAMP is stimulated by cellular injury; 2) 2',3'-cAMP derives from the breakdown of mRNA; 3) 2',3'-cAMP is exported to the extra-cellular com-partment; and 4) extra-cellular 2',3'-cAMP is metabolized to 2'-AMP and 3'-AMP, which are subsequently metabolized to extra-cellular ade-no-sine. We call this bio-chemical sequence (in-tra-cellular 2',3'-cAMP -⇒ extra-cellular 2',3'-cAMP ⇒ 2'-AMP/3'-AMP ⇒ ade-no-sine) the "2',3'-cAMP-ade-no-sine pathway." Emerging evidence sug-gests that in-tra-cellular 2',3'-cAMP pro-motes opening of brain mito-chondrial perme-ability trans-ition pores and that extra-cellular ade-no-sine is a key neuro-pro-tective autacoid. Thus we hypo-thesize that the 2',3'-cAMP-ade-no-sine pathway may be an important mecha-nism for pro-tection against neuro-trauma. In support of this concept, we find that neu-rons, oligo-dendro-cytes, astro-cytes, and micro-glia con-vert 2',3'-cAMP mostly to 2'-AMP (with oligo-dendro-cytes being most efficient) and 2'-AMP to ade-no-sine (with micro-glia being most efficient), and knock-out of 2',3'-cyclic nucleotide 3'-phos-phodiesterase (CNPase) attenuates the ability of oligo-dendro-cytes to metabolize 2',3'-cAMP to 2'-AMP. Micro-dialysis experiments in mice demon-strate that traumatic brain injury (TBI; controlled cortical impact) activates the brain 2',3'-cAMP-ade-no-sine pathway; similar experiments in CNPase knock-out mice sug-gest that CNPase is involved in the meta-bolism of endo-genous 2',3'-cAMP to 2'-AMP and to ade-no-sine and pro-vides neuro-pro-tection. In CSF from TBI patients, 2',3'-cAMP is in-creased in the initial 12 hours after injury and cor-rel-ates with CSF levels of 2'-AMP and ade-no-sine. We conclude that the 2',3'-cAMP-ade-no-sine pathway exists in the brain and is likely neuro-pro-tective.

ROLE OF ADENOSINE IN POSTTRAUMATIC SEIZURESAND EPILEPSY: A POTENTIAL NEW TARGET

Detlev Boison; *Legacy Research Institute, Robert Stone Dow Neurobiology Laboratories, Portland, USA*

Brain trauma and related injuries trigger a sequela of events that cause glial activation. Astroglio-sis is a major consequence of traumatic brain injury and as-so-ci-ated with in-creased ex-pression of the major ade-no-sine metabolizing enzyme ade-no-sine kinase (ADK); those changes result in ade-no-sine deficiency as char-acter-istic chronic re-sponse of affected brain areas to a prior injury. In rodent models of neu-ronal injury and epilepsy we have demon-strated that *(i)* overex-pression of ADK and resulting ade-no-sine deficiency can be a direct cause for epileptic seizures, and *(ii)* that ade-no-sine deficiency induces changes to the epigenome resulting in in-creased DNA methyl-ation status. Based on those mecha-nisms, ade-no-sine augmentation therapies hold pro-mise for the treat-ment, as well as pre-vention, of post-traumatic epilepsy. Data are pre-sented showing that therapies that recon-struct ade-no-sine homeo-stasis locally (e.g. by ade-no-sine releasing bio-engineered brain implants, or gene therapy) can effectively suppre-ss epileptic seizures in rodent models of epilepsy. Further-more, trans-ient thera-peutic ade-no-sine augmentation affects patho-genic changes of the epigenome (i.e. hyper-methyl-ation of DNA) long-term and thereby pre-vents the de-velop-ment and pro-gression of epilepsy.

URATE - A NOVEL POTENTIAL THERAPY IN CNS INJURY AND NEURODEGENERATION

Michael Schwarzschild; *MGH, Neurology, Boston, USA*

Urate elevation has recently emerged as a pro-mising and realistic neuro-pro-tective strategy for the treat-ment neuro-degenerative dis-eases and acute neu-ronal injury. Urate (a.k.a. uric acid) circulates at higher levels in humans and other hominoids due to mutations in the gene encoding the urate-catabolizing enzyme urate oxidase (UOx) during primate evolution. Although the in-creased levels now pre-dis-pose humans to urate crystal dis-orders like gout, they likely conferred an evolutionary advantage to our ancestors. The dis-covery that urate has po-tent anti-oxidant pro-perties equivalent to those of ascorbate and is the main source of anti-oxidant capacity in human plasma led to the theory that urate serves as an endo-genous pro-tectant against dis-eases char-acter-ized by oxi-dative damage, including Parkinson's dis-ease (PD). Higher urate has been iden-tified as a robust inverse risk factor for PD and as a favorable pro-gnostic bio-marker among people already diagnosed with PD. Similarly, lower urate levels have been linked to the de-velop-ment or more rapid pro-gression of other neuro-degenerative dis-eases including ALS. Laboratory studies in cellular and animal models of PD have further sub-stanti-ated the

neuro-pro-tective po-tential of urate, and in-ter-estingly have implicated an astro-cyte-de-pen-dent mecha-nism through the Nrf2 anti-oxidant re-sponse pathway. Of note, the urate pre-cursor inosine has been found to be impro-ve re-cov-ery in animal models of spinal cord and traumatic brain injury (TBI), and both inosine and urate are markedly in-creased locally after TBI. Based on con-vergent lines of evidence sug-gesting that urate may be a mediator as well as a marker for slower dis-ease pro-gression, a randomized double-blind placebo-controlled phase 2 clinical trial of the inosine in early PD was conducted, find-ing that urate levels in blood and CSF could be effectively, safely and chronically elevated in this population. In para-llel, urate itself has been shown to confer pro-tection against acute cerebral ische-mia in rodent models of stroke and led to a phase 2 randomized double-blind placebo-controlled phase 2 clinical trial of in-tra-venous urate in the setting of an acute ischemic stroke, with encouraging safety and efficacy results.

Symposium Chair and Speakers:

Left to right: Edwin Jackson, PhD, Detlev Boison, PhD, Michael Schwarzschild, MD, PhD and Patrick Kochanek, MD

I would like to thank ISN for sponsoring this exciting session and your support and presence truly enhanced the meeting.

Best regards,

Helen M. Bramlett, PhD