A stage for Translational Medicine

The 2013 Annual meeting of the International Chinese Academy of Anesthesiology at University of California San Francisco

Renyu Liu, MD, PhD (liur@uphs.upenn.edu)

With the great effort of the leaders and enthusiastic members of the International Chinese Academy of Anesthesiology (ICAA, www.icaahq.org) and many third parties, the second annual meeting of ICAA was successfully held on the famous and beautiful campus of the University of California San Francisco (UCSF), hosted by the department of Anesthesiology at the UCSF (local host: Dr. Lingzhong Meng). Dr. Zhiyi Zuo, the president of ICAA, Dr. Lee Fleisher (video), the president of the Association of University Anesthesiologists (AUA), Dr. Jin Liu (video), the president of the Chinese Society of Anesthesiology (CSA), Dr. Jane Fitch, the president-elect of the American Society of Anesthesiologists (ASA), and Dr. Maze, the Chairman of the department of Anesthesiology at UCSF, who delivered the congratulation and warming speech at the opening of the event. The leaders believe that ICAA is a great platform to foster international academic exchanges and collaborations especially for Chinese anesthesiologists. Dr. Jianguo Xu, the Editor in Chief of the Chinese Journal of Clinical Research, and Dr. Hong liu, the Director of Clinical Anesthesia Research at the Department of Anesthesiology at the University of California Davis Health system moderated the opening session. Dr. Ronald Miller from UCSF attended this event.

The major feature of the annual meeting of the ICAA is the special panel of translational anesthesiology. This panel is moderated by Dr. Adrian Gelb from the UCSF and Dr. Renyu Liu from the University of Pennsylvania. Dr. Maninder (Mini) Kahlon, the Executive Director of the Clinical & Translational Science Institute (CTSI) at

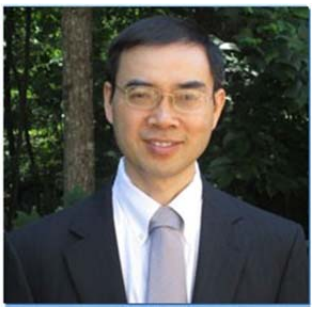
UCSF, delivered a keynote speech on Accelerating Research to Improve Health: infrastructure, services and networks to enable translational research. UCSF's CTSI is the largest renewed center of a 60-institution network funded by the National Institute of Health (NIH) to accelerate research to improve health. Dr. Kahlon described efforts to address pressing challenges in translational research such as the 'valley of death' between basic science and clinical research, barriers of conducting large-scale clinical trials, and the challenges of converting good science into improvements in community health. In each case, local, regional, national or international strategies are used, depending on the scale of the problem and the potential solution. Clinical research training is a major component leading the nation in developing distance learning approaches that go beyond delivering videos for didactic education to support the multi-faceted training necessary to nurture and develop clinical researchers. The training model has been implemented with national and international partners including in the UK and China and is briefly described.

Dr. Roderic G. Eckenhoff, the vice chair for Research, the Austin Lamont Professor of Anesthesiology & Critical

Care at the Perelman School of Medicine of the University of Pennsylvania, presented a novel approach to the discovery and development of new anesthetic chemotypes using a high-throughput screen. This screen used the fluorescent general anesthetic 1-aminoanthracene and apoferritin as a surrogate for the functional protein target of general anesthetics.[1-3] From a chemical library of over 350,000 compounds, they identified about 2,600 (~0.7%) as "top actives," and thereby having potential to be novel anesthetics. These compounds were narrowed further through structural criteria, secondary screens and in vivo testing. A final chemotype was varied using medicinal chemistry approaches to produce a novel anesthetic with potency approaching propofol. Dr. Eckenhoff also discussed the advantages and pitfalls of the HTS approach, when applied to a complex, poorly defined action like anesthesia.

Dr. Yan Xu, the vice Chair for research and Professor of Anesthesiology and Structural Biology at the University of Pittsburgh, presented engineered receptors as a new class of analgesic drugs for treating chronic pain. Chronic pain affects approximately 100 million Americans – more people than heart disease, cancer, and diabetes combined. What makes this debilitating condition even more devastating is that treatment options are limited. The current standard care for chronic pain involves continuous use of potent analgesics with undesirable risks of drug tolerance, dependence, or abuse. Very few new drugs have surpassed the traditional painkillers derived from empirical folk remedies. Dr. Xu's research team designed and engineered non-native, surveillance chloride (Cl–) ion channels that attenuate pain signal propagation by modulating nociceptors in the peripheral nerves. These channels are designed to either automatically respond to inflammation-induced pH changes, or be activated by nontoxic, non-psychoactive, exogenously administered small molecules that would otherwise have negligible or no pain-killing effects. Using the OpenEye Scientific software (www.eyesopen.com), Dr. Xu's group performed structure-based in silico screening of chemical databases to search for activator candidates as potential analgesics and successfully used this technology in vivo to treat inflammatory pain in animals and evaluated the efficacy of the engineered channels as antihyperalgesic responders based on behavioral pain testing. This innovative technology will lead to the development of a fundamentally different class of pain medication that will completely change chronic pain management for certain types of pain and at the same time reduce the problem of prescription drug dependence and abuse.

Dr. Zhiyi Zuo, the President of the ICAA and the vice Chair for Research and Robert M. Epstein Professor of



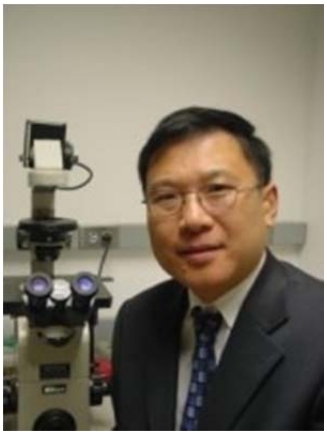
Anesthesiology, Professor of Neuroscience and Neurological Surgery at the University of Virginia, introduced that pyrrolidine dithiocarbamate could be novel medication for neuro-protectant for brain hypoxia and ischemia in the neonatal subject.[4,5] The World Health Organization estimates that 4 to 9 million neonates suffer from birth asphyxia each year in the world. This leads to about 1.2 million deaths and the same number of infants with severe disability. Most of these deaths and disabilities are due to hypoxic-ischemic (HI) brain injury. Currently, no effective therapy has been developed to reduce brain HI injury. Since intensive resuscitation to resume circulation and oxygen supply to organs is the top priority immediately after birth asphyxia, efforts to deliver potential neuroprotective drugs may be limited. In addition, intravenous line may be difficult to establish even in the best hands under this situation. Dr. Zuo's proposal of an intranasal application of pyrrolidine dithiocarbamate (PDTC) as a neuroprotective drug is very innovative. Preclinical data to support the intranasal PDTC use for neuroprotection in neonates and the advantages of this application are presented.

Dr. Renyu Liu, the secretary general of ICAA and an assistant professor at the Department of Anesthesiology and

Critical Care at the Perelman School of Medicine of the University of Pennsylvania introduced salvinorin A as a potent cerebral vascular dilator and potential neuroprotectant. Dr. Liu overviewed the findings related to salvinorin A (SA) in two animal species (piglet and mouse). Using the piglet model, Dr. Liu's group demonstrated that SA potently induces cerebral vascular dilatation, an important property necessary for protection against hypoxia/ischemia (HI) injury, via an endothelial nitric oxide synthase (eNOS) mediated mechanism in a dose dependent manner.[6] SA administration before HI upregulates the ERK/MAPK (extracellular signal-regulated kinase/mitogen-activated protein kinase) pathway and preserves cerebral vascular autoregulation, an important component for neurovascular integrity.[7]SA administration after HI prevents ERK upregulation induced by HI and preserves cerebral vascular

autoregulation.[8] Using a mouse hypoxia model, Dr. Liu's group found that SA administration before hypoxia insult reduces mortality significantly and prevents hypoxia- induced neurological outcomes. These findings indicate that SA could be a potential novel medication for preventing catastrophic lifelong neurological disabilities. SA is the only known naturally occurring non-opioid KOR agonist that has been consumed by humans for centuries with known safety profiles. Unlike opioid KOR agonists, SA is highly selective for KOR, and produces no frank dysphoric effects. Because of its rapid onset when delivered either via oral mucosa or inhalation. It could be a unique medication that can be delivered quickly in acute settings especially where IV access is unavailable for neurological events like cerebral ischemic stroke and sudden cardiac arrest in out-of-hospital settings.

Dr. Huafeng Wei, an associated professor at the Department of Anesthesiology and Critical Care at the Perelman School of Medicine of the University of Pennsylvania, discussed the potential to use dantrolene as a potential new treatment for Alzheimer's disease. Alzheimer's disease (AD) is a devastating neurodegenerative disease without effective treatment. Recent studies suggest that disruption of intracellular calcium homeostasis play important roles in neuropathology of AD. Particularly, the numbers of ryanodine receptors, a calcium channel located on endoplasmic reticulum (ER) membrane, were dramatically increased in both AD transgenic mice and patients. The overactivation of ryanodine receptors results in excessive calcium release from the ER, and subsequent neuropathology in AD. Dantrolene, a ryanodine receptor antagonist and a drug to reduce mortality of malignant hyperthermia dramatically (from 80% to 5%) in anesthesia practice, is a potent antagonist of ryanodine receptor and can be tolerated by patients relatively well. Recent study from Dr. Wei's lab demonstrated that early parental use of dantrolene nearly abolished the memory losss in triple transgenic mice (3xTG: APP, Presenilin-1 and Tau mutations), which was associated with significant inhibitioin of amyoid burden in hippocampus of brain.[9,10] Late treatment with oral dantrolene even long after initiation of amyloid aggregation still remarkably inhibit amyloid plaque formation in 3XTG AD mice. Dr. Wei concluded that dantrolene may be potential therapeutic agent for AD and need to be studied extensively further, especially in AD patients.



Another important feature of this special panel is the lecture from Dr. Lei Fang (Lei.Fang@sutherland.com), a patent attorney from Sutherland Asbill & Brennan LLP, Atlanta, GA, lectured on the Role of Intellectual Property Protection in Commercializing University Technologies. Dr. Fang's presentation provides an overview of the US Bayh-Dole Act and patent system, including the most recent US patent reform, the America Invents Act (AIA); how these Acts would impact university research and university-industry cooperation on the emergence of new technologies and products in the marketplace; and what every university professor and/or researcher needs to know in seeking protection and maximizing the commercial value of his/her invention(s) properly and diligently. In the fiscal year of 2011, more than 1.8-billion US dollars were earned by universities and their professor inventors from commercializing their academic research; 5,398 licenses were completed; 12,090 new patents were filed; and 617 start-up companies were created. All of these achievements would not have happened if the US Congress had not passed the "Bayh- Dole Act" in 1980. The Bayh-Dole Act promotes cooperation among academia, small business, and industry by providing patent rights to universities and research institutions on certain inventions arising out of government-sponsored research and development (R&D). The Bayh- Dole Act has been particularly successful in meeting its objectives of encouraging the commercialization of new technologies by controlling the ownership of patent and/or other Intellectual Property title.

Following the special panel, 20 outstanding abstracts were presented in clinical and basic science sessions with very enthusiastic discussion by anesthesiologists from US and China. The following principle investigators received Excellence in Translational Medicine Award: Dr. Roderic G Eckenhoff, Dr. Yan Xu, Dr. Zhiyi Zuo, Dr. Renyu Liu, and Dr. Huafeng Wei. Dr. Junfeng Zhang from Dr. Zhiyi Zuo's lab and Dr. Longqiu Yang from Dr. Zhongcong Xie's lab received Creative Science Awards for their creative and outstanding research. The following candidate received Outstanding Research Award: Dr. Feixiang Wu, Dr. Shanshan Wang, Dr. Yiying Zhang, and Dr. Zhongxing Wang. 7 candidates received the Fine Science Award. It is worth noting that Dr. Roderic G. Eckenhoff from the University of Pennsylvania received the Outstanding Mentorship Award. Dr. Adrian Gelb from the UCSF received the "Excellence in International Collaboration" award from ICAA. Dr. Lingzhong Meng (the local host of the meeting) and Dr. Lei Fang (the patent attorney Sutherland Asbill & Brennan LL) received Outstanding Contribution to ICAA award. Dr. Zhongcong Xie is elected to be the next president of ICAA starting from January 1, 2014 during the meeting. Dr. Chuanyao Tong, the chair of the scientific committee, spent huge effort on the rich scientific program and is projected to be the president elect of ICAA.

Corresponding author: Renyu Liu, M.D., Ph.D. Assistant Professor, Mailing address: Department of Anesthesiology and Critical Care, Perelman School of Medicine at the University of Pennsylvania, 336 John Morgan building, 3620 Hamilton Walk, Philadelphia PA, 19104 USA.
Phone : 2156623750, Fax: 2153495078
Email: liur@uphs.upenn.edu

Acknowledgement: Dr. Liu appreciates the support from the Penn China Anesthesia Partnership Program and the technical editing from Ms. Jingyuan Ma at the Department of Anesthesiology and Critical Care at the University of Pennsylvania.

References:

1. Rai G, Bu W, Lea WA, Liang D, Weiser B, et al. (2010) Discovery of Novel General Anesthetics Using Apoferritin as a Surrogate System. Probe Reports from the NIH Molecular Libraries Program. Bethesda (MD).
2. Oakley S, Vedula LS, Bu W, Meng QC, Xi J, et al. (2012) Recognition of anesthetic barbiturates by a protein binding site: a high resolution structural analysis. PloS one 7: e32070.
3. Liu R, Loll PJ, Eckenhoff RG (2005) Structural basis for high-affinity volatile anesthetic binding in a natural 4-helix bundle protein. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 19: 567-576.
4. Wang Z, Zhao H, Peng S, Zuo Z (2013) Intranasal pyrrolidine dithiocarbamate decreases brain inflammatory mediators and provides neuroprotection after brain hypoxia-ischemia in neonatal rats. Experimental neurology 249: 74-82.
5. Li J, Sheng W, Feng C, Zuo Z (2012) Pyrrolidine dithiocarbamate attenuates brain Abeta increase and improves long-term neurological outcome in rats after transient focal brain ischemia. Neurobiology of disease 45: 564-572.
6. Su D, Riley J, Kiessling WJ, Armstead WM, Liu R (2011) Salvinorin A produces cerebrovasodilation through activation of nitric oxide synthase, kappa receptor, and adenosine triphosphate-sensitive potassium channel. Anesthesiology 114: 374-379.
7. Su D, Riley J, Armstead WM, Liu R (2012) Salvinorin A pretreatment preserves cerebrovascular autoregulation after brain hypoxic/ischemic injury via extracellular signal-regulated kinase/mitogen-activated protein kinase in piglets. Anesthesia and analgesia 114: 200-204.
8. Wang Z, Ma N, Riley J, Armstead WM, Liu R (2012) Salvinorin A administration after global cerebral hypoxia/ischemia preserves cerebrovascular autoregulation via kappa opioid receptor in piglets. PloS one 7: e41724.

9. Peng J, Liang G, Inan S, Wu Z, Joseph DJ, et al. (2012) Dantrolene ameliorates cognitive decline and neuropathology in Alzheimer triple transgenic mice. Neuroscience letters 516: 274-279.

10. Inan S, Wei H (2010) The cytoprotective effects of dantrolene: a ryanodine receptor antagonist. Anesthesia and analgesia 111: 1400-1410.