Translational Perioperative and Pain Medicine
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Editorial

A Stage for Translational Perioperative and Pain Medicine

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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 and third annual meeting of ICAA were successfully held on the campus of the University of California San Francisco (UCSF) in 2013, hosted by the department of Anesthesiology at the UCSF (local host: Dr. Lingzhong Meng) and on the campus of Tulane University School of Medicine, hosted by the department of Anesthesiology of Tulane University School of Medicine (local host, Dr. Henry Liu). The major feature of these two annual meetings of the ICAA is the special focus on translational anesthesiology, basic science in 2013 and clinical research in 2014. Here are some of the highlights from the invited speakers from both 2013 and 2014.

Dr. Maninder (Mini) Kahlon, the Executive Director of the Clinical & Translational Science Institute (CTSI) at UCSF, delivered a keynote speech in 2013 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. Daniel Sessler, the Michael Cudahy Professor and Chair of the Department of Outcome Research at Cleveland Clinic delivered an important educational talk on "Clinical Research Design" in 2014. Clinical research is potentially subject to five classes of error: chance, selection bias, confounding, measurement bias, and reverse causation. The extent to which each degrades results is a strong function of research design. The best protection is provided by randomization which prevents selection bias and confounding, and by blinding which reduces measurement bias. Appropriately randomized and blinded trials are thus considered to provide the highest level of evidence. Parallel-group trials are by far the most common type of clinical trial. Cross-over designs allow treatment effects to be reliably identified with far fewer subjects. However, cross-over designs are only reliable for stable disease states and for time-limited treatments. Those restrictions preclude using the design for "hard" outcomes such as stroke, infarction, cancer recurrence, and death. An attractive design that is becoming more common is a factorial approach that allows investigators to test two or more interventions simultaneously. Not only is the approach efficient, but it permits evaluation of interactions among interventions that would be impossible in sequential trials. Increasingly investigators recognize that the results of small trials are "fragile" (not necessary correct) and that small studies typically over-estimate treatment effect. There is thus a trend to power studies better' that is, not just for statistical significance, but to provide reliable estimates of treatment effect.

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 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.

Another important effort is to invite a patent attorney, Dr. Lei Fang (Lei.Fang@sutherland.com) from Sutherland Asbill & Brennan LLP (Atlanta, GA) to provide an educational lecture on the Role of Intellectual Property Protection in Commercializing University Technologies in 2013. 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.

I strongly believe such activities are important in promoting translational perioperative and pain medicine, and I am looking forward to more such great international activities.

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