Sustainable research activities of ISEM against COVID-19 pandemic

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The COVID-19 caused by the novel coronavirus has become a worldwide pandemic which has persisted for nearly a year and a half. The academic conferences, where many researches attend, were canceled or postponed, and new measures such as remote communication methods were adopted in a number of conferences. Thus, the conference organizers were forced to give thought to a new style of communication in the future.

We are currently unable to attend international conferences due to strict travel restrictions. Amid such grim situation, there is a remarkable society which cross-sectionally connects basic and clinical medicine through microsurgery named the International Society for Experimental Microsurgery (ISEM). I would like to introduce the latest research outcomes of ISEM's Governance members.

ISEM was initially founded in 1992 by late Professor Sun Lee who introduced microsurgery into organ transplant research in 1960 and has established a solid

foundation to organ transplant treatment in the 20th Century by utilizing his experimental models. ISEM covers the fields of the basic medicine to clinical medicine, regardless of type of organ if the topic is related to microsurgery. Although a total number of members is not large, the members reside all over the world, follow the teachings of Professor Sun Lee, and are interacting like a big family. Every two years we hold international conference in a different country around the world, and as 10th president, I have organized an international conference in Brazil in 2010, supported by Professor **Edna Montero** and her colleagues. In 2020, ten years after a conference in Brazil, 15th conference was originally scheduled in Sweden by Congress president **Mihai Oltean** and Congress Chair **Yelena Akelina** and colleagues. Unfortunately, like many other international conferences, our 15th conference was postponed until the following year. And finally, it will be held online on September 10, 2021: **ISEM | International Society for Experimental Microsurgery** www.myisem.org

It is worthwhile saying that ISEM core members are continuously communicating and now seeking the future conference activities through online discussions.

President Professor **Mihai Oltean** (Sahlgrenska University Hospital, Sweden) is working strenuously in various types of organ transplantation such as small bowel

transplantation (ITx). He reviewed the recent publications pertaining to experimental ITx and highlighted the main current research topics as the follows (1). During the recent years, ischemia-reperfusion injury (IRI) and Graft-versus-host disease have gradually replaced acute rejection as the main research topic. New additives to established preservation solutions and relatively novel approaches such as luminal interventions during cold storage may prolong the storage time and alleviate IRI. The ischemic susceptibility seems to differ between species, which may impact the translatability of the experimental findings. A new experimental model of modified multivisceral transplantation including the donor spleen may offer a new tool with which to study GVHD, besides the classical Lewis–Brown Norway rat combination. Flushing the graft with fludarabine may mitigate GVHD in rats. T-cell activation inhibitor-mitochondrial was downregulated in the peripheral blood leukocytes before other signs of acute and severe chronic rejection could be observed.

Professor **Norbert Nemeth** (University of Debrecen, Hungary) with Professor **Rene H. Tolba** (RWTH Aachan University, Germany) also reviewed experimental IRI phenomenon which has been associated with adverse clinical outcomes (2). IRI related tissue damage is characterized by various chronological events depending on the

experimental model or clinical setting. He introduced that IRI research has been in the spotlight of scientific interest for over three decades with a significant and continuous increase in publication activity over the years and the large number of pharmacological and surgical therapeutic attempts introduced, not many of these strategies have made their way into everyday clinical practice. Furthermore, he addressed that hemorheological factors play an important role in determining tissue perfusion and orchestrating mechanical shear stress-dependent endothelial functions. Antioxidant and anti-inflammatory agents, ischemic conditioning protocols, dynamic organ preservation techniques may improve rheological properties of the post-reperfusion hepatic blood flow and target endothelial cells, exerting a potent protection against hepatic IRI.

Corresponding Secretary member, Professor **Hao Wang** (Tianjin Medical University, China) is the head of digestive surgery division, and has been coaching his junior colleagues in the basic research area while serving as a mentor of experimental microsurgery to his fellow colleagues. Professor Wang is also an outstanding researcher of regenerative medicine, especially in mesenchymal-like endometrial regenerative cells (ERCs). Using mouse system, they showed that CD73 expression was critical to ERC-induced attenuation of graft pathology (3). The blockage of CD73

expression on ERCs was related to the percentage decline of tolerogenic dendritic cells (Tol-DCs), macrophages type 2 (M2), and regulatory T cells (Tregs). As compared with anti-CD73 mAb pretreated ERCs group, CD73 expressing ERCs significantly increased the level of anti-inflammatory cytokine IL10 but decreased levels of pro-inflammatory cytokines including IFN-γ and TNF-α. In addition, CD73 expressing ERCs showed tissue protective function via the regulation of adenosine receptor expression which was related to the infiltration of CD4+ and CD8+ cells in the allografts. Furthermore, significant increase of A2B receptors in the cardiac allograft was also associated with CD73 expressing ERC-induced prolongation of cardiac allograft survival.

Treasury member, Professor **Zheng Jenny Zhang** (Northwestern University, U.S.A.) is an expert of organ transplant mouse and rat model, and is a dedicated researcher of immunology. Recently, they developed a novel devise of fully implantable and bioresorbable cardiac pacemakers without leads or batteries (4). Temporary cardiac pacemakers used in periods of need during surgical recovery involve percutaneous leads and externalized hardware that carry risks of infection, constrain patient mobility and may damage the heart during lead removal. Then, they developed a leadless, battery-free, fully implantable cardiac pacemaker for postoperative control

of cardiac rate and rhythm that undergoes complete dissolution and clearance by natural biological processes after a defined operating timeframe. They showed that these devices provide effective pacing of hearts of various sizes in mouse, rat, rabbit, canine and human cardiac models, with tailored geometries and operation timescales, powered by wireless energy transfer.

From Japan, Secretary General Professor **Shintaro Yagi** (Kanazawa University, Japan) and **I** advocated the micro- and macro-borderless surgery (MMBS) using a novel high-resolution (4K) three-dimensional (3D) video system. To confirm the applicability of this concept, we tested the following 3 preclinical experiments (5). Experiment 1 (non-inferiority test) consisted of dissection and anastomosis of carotid artery, portal vein, proper hepatic artery, and pancreatoduodenectomy with surgical loupe versus MMBS. Experiment 2 (feasibility test) consisted of intra-abdominal and intra-thoracic smaller arteries anastomosed by MMBS as a pre-clinical setting. Experiment 3 (challenge on new surgery) consisted of orthotopic liver transplantation of the graft from a donor after circulatory death maintained by machine perfusion. Circulation of the cardiac sheet with a vascular bed in experiment 2 and liver graft during preservation in experiment 3 was evaluated with indocyanine green

fluorescence imaging equipped with this system.

I also did my best to generate a functional small intestinalized colon (SIC) by replacing the native colonic epithelium with ileum-derived organoids using a rat model (6). Organoid technology enables an efficient expansion of intestinal epithelium tissue in vitro, but reconstruction of the whole small intestine, including the complex lymphovascular system, has remained challenging. We first found that xenotransplanted human ileum organoids maintain their regional identity and form nascent villus structures in the mouse colon. In vitro culture of an organoid monolayer further revealed an essential role for luminal mechanistic flow in the formation of villi. We then developed a rat SIC model by repositioning the SIC at the ileocaecal junction, where the epithelium is exposed to a constant luminal stream of intestinal juice. This anatomical relocation provides the SIC with organ structures of the small intestine, including intact vasculature and innervation, villous structures, and the lacteal (a fat-absorbing lymphatic structure specific to the small intestine). The SIC has absorptive functions and markedly ameliorates intestinal failure in a rat model of SBS, whereas transplantation of colon organoids instead of ileum organoids invariably leads to mortality. These data provide a proof of principle for the use of intestinal organoids for

regenerative purposes, and offer a feasible strategy for SBS treatment.

I have introduced the academic activities of several ISEM members. I hope it enabled readers to further understand that we the ISEM members, connected by microsurgery, are cross-sectionally active in many fields from basic research to clinical research. Furthermore, amid the pandemic, we are committed as academia to fulfill our duties to overcome COVID-19. Even though the COVID-19 pandemic is prolonged, our members around the world are actively working, at times encouraging each other, to challenge the current difficulties.

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