2019

ISCHEMIC/HYPOXIC DISEASE INSTITUTE INTERNATIONAL SYMPOSIUM

From Bench to Space

December 6 (Fri), 2019

Education Building #401 (교육관 401호), SNU College of Medicine

Time	Title	Speaker/Chair	
13:00~13:10	Welcoming Address	Chan Soo Shin	(Dean, SNU College of Medicine)
13:10~13:20	Opening Remark	Yang-Sook Chun	(Director, IHDI)
Session I		Chair : Sung Wan Kim (SNU, Korea)	
13:20~13:50	Engineering 3D tissues in vitro	Junji Fukuda	(YNU, Japan)
13:50~14:20	Cardiac myocytes in normal and pulmonary hypertensive right heart failure	Sung Joon Kim	(SNU, Korea)
14:20~14:50	Epithelial Remodeling: A Therapeutic Target in Chronic Rhinosinusitis	Hyun-Woo Shin	(SNU, Korea)
14:50~15:20	HIF-1 regulates lipid metabolic reprogramming in cancer	Yang-Sook Chun	(SNU, Korea)
15:20~15:40	Coffee Break		
Plenary Lecture			
15:40~16:30	Artificial Gravity Exercise for Deep-Space Missions	Alan R. Hargens	(UCSD, USA)
Session II		Chair : Sung Joon Kim (SNU, Korea)	
16:30~17:00	Applying Aerospace Technology to Medicine	Sung Wan Kim	(SNU, Korea)
17:00~17:30	Lower body positive pressure treadmill exercise for rehabilitation after Achilles tendon repair	Jong Moon Kim	(Joen Hospital, Korea)
17:30~18:00	Feasibility of Ultrasound-Guided Trigger Point Injection in Patients with Myofascial Pain Syndrome	Dong Kyu Kim	(KKU, Korea)
18:00	Closing		

서울대학교 의과대학

Program

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Plenary Lecture

Dr. Alan Hargens, PhD
Professor of Orthopaedic Surgery
University of California, San Diego

Dr. Hargens is Professor and Director of the Orthopaedic Clinical Physiology Lab at t he University of California, San Diego. He previously served as Chief of the Space P hysiology Branch and Space Station Project Scientist at NASA Ames Research Center and as Consulting Professor of Human Biology at Stanford University. He teaches ort hopaedic residents, medical students and graduate and undergraduate students at UC-S an Diego. His recent research concerns gravity effects on the cardiovascular and musc uloskeletal systems of humans and animals. He has edited ten books, published more than 300 peer-reviewed articles and 60 chapters and holds eight patents. Two of his student s were astronauts. One flew on the Space Shuttle five times and was the first astron aut to climb to the top of Mt Everest. The other spent 6 months on the International Space Station, grew and ate vegetables in space and returned to Earth in 2015. Dr H argens is the PI of two current space flight projects on the International Space Statio n: "Risk of Intervertebral Disc Damage after Prolonged Space Flight" and "Fluid Distribution before,
during and after Prolonged Space Flight", the most complicated and crew-intensive investigation on the International Space Station to date. He also investigates e xercise devices to maintain astronaut health and performance in space. This research i s translated to help post-surgical treatment and rehabilitation of orthopaedic patients an d to improve performance of athletes. His recent awards include a Citation Award fr om the American College of Sports Medicine and the Distinguished Public Service M etal, NASA's highest award.

Artificial Gravity Exercise for Deep-Space Missions

Alan R Hargens, PhD
Professor of Orthopaedic Surgery
University of California, San Diego

In general terms, mechanisms responsible for physiologic adaptations to the microgravity of space include: 1) loss of hydrostatic (gravitational) pressures within fluid columns of the body such as arterial and venous blood, cerebrospinal fluid and lymph, 2) loss of body weight and greatly-reduced mechanical loads, 3) decreased sensory inputs, and 4) altered transcapillary and lymphatic pressures as well as fluid transport. Normal daily activity on Earth involves about 16 hours of upright posture with activity. The remaining part of the day consists of about eight hours of sleep without axial loading. In actual microgravity, daily weight-bearing activities (sitting, walking, running and stair climbing) are minimal. The greater compression of tissues on Earth due to body weight increases interstitial fluid pressures and probably dehydrates tissues due to greater interstitial flow into the microcirculation. The recently-defined Space Flight Associated Neuro-Ocular syndrome, or SANS, is evidenced by visual changes in astronauts during prolonged space flight. SANS is an example of a maladaptive outcome of microgravity such as bone loss and muscle atrophy that may persist long after return to Earth, perhaps permanently. Countermeasures for prolonged space travel should include integrated cardiovascular and musculoskeletal exercises to reproduce normal, daily Earth-like stresses. Until a validated human centrifuge is available, lower body negative pressure (LBNP) is a physiologic and integrated countermeasure for deep-space travel. Our long-term objectives are to: 1) promote crew health and well-being inflight, 2) optimize post-flight rehabilitation and translate our findings for Earth benefit. Supported by grants from NASA and NIH.

Session 1

Prof. JUNJI FUKUDA

Graduate School of Engineering, Yokohama National University (YNU), JAPAN

Prof. Junji Fukuda is a full professor at the Faculty of Engineering, Yokohama National University, Japan. He obtained Ph.D in 2003 at Chemical Engineering Department, Kyushu University, Japan. His research area has been in the synthesis, processing, and evaluation of new biomaterials for Tissue Engineering and Regenerative Medicine. His lab is currently developing technologies to transfer cells from a culture surface based on electrochemical reactions and fabricate vascularized tissues with appropriate microarchitectures. His lab is also working on a research project to generate hair organoids in vitro for hair regenerative medicine. He has published 93 peer reviewed papers, 38 book chapters, more than 50 proceedings for international meetings, and 35 patent/disclosure applications. His work has been published in journals such as Biomaterials, Lab on a chip, Analytical Chemistry, and Scientific Reports. He is currently a member of the BioMEMS Technical Activities Committee for the IEEE-Engineering in Medicine and Biology Society.

Engineering 3D tissues in vitro.

Junji Fukuda
Graduate School of Engineering, Yokohama National University (YNU), JAPAN

Oxygen is a fundamental factor in engineering three-dimensional tissues and organs. We have developed a spheroid microarray device with oxygen permeable silicone rubber where cells form a large number of spheroids with uniform diameter in spatially-aligned microwells under improved oxygen supply. In the culture device, hepatic, pancreatic, and cardiac spheroids showed better functions compared to that made with non-oxygen permeable plastic. Self-organization of two types of hair follicle stem cells was also observed in the device, resulting in spontaneous formation of hair follicle germs with efficient hair regeneration activity after transplantation. These aggregates can be used as small tissues for transplantation, but also useful as building blocks for engineering larger tissues. In engineering larger tissues, the lack of fabrication strategy of perfusable vascular networks is a fundamental barrier. Such approaches should be designed by considering not only oxygen supply to entire tissues, but also minimizing oxygen shortage during the fabrication processes at the beginning. We have proposed a rapid vasculature fabrication approach. In this approach, an electrochemically cleavable oligopeptide was used for cell transfer from a gold-coated culture surface to a hydrogel. By transferring vascular endothelial cell layer from gold-coated needles with this electroactive oligopeptide, we fabricated vascular-like structures whose internal surface was covered with endothelial cells in a hydrogel within 7 min. The endothelial cells transferred were then migrated and formed luminal structures in the hydrogel, leading to formation of perfusable macro- and micro-vascular networks. Furthermore, we prepared spheroids with iPS-derived hepatic endoderm and encapsulated them between the vasculatures, resulting in functional liver tissues with vascular networks. This simple and versatile approach is potentially applicable for engineering three-dimensional thick tissues and organs *in vitro*.

Sung Joon Kim
Seoul National University College of Medicine (SNU), Korea

Professor Sung Joon Kim is the Chair-Professor of Department of Physiology and Department of Biomedical Sciences at Seoul National University College of Medicine (SNUCM). Dr. Kim received M.D. in 1991 and Ph.D. in Physiology (smooth muscle and ion channel) in 1997 from SNUCM. He is leading Cardio-Vascular and Ion Channel physiology (CIVIC) Laboratory at SNUCM. He is serving as the vice-Chief Editor of Korean Journal of Physiology & Pharmacology, and also as an editorial board of Pflugers Archiv-European Journal of Physiology. Since 1997, he has published more than 150 papers in the peer-reviewed international journals.

His current research interests are, 1) pulmonary arterial pathophysiology, 2) right heart failure-associated changes in cardiomyocytes, and 3) electrophysiological properties of ion channels (KCNK family, TMEM16 family, and CALHM channels) and their molecular mechanisms. He has published several papers for integrative understanding of hypoxic pulmonary vasoconstriction mechanisms and also novel roles of eNOS unconventionally expressed in the vascular smooth muscle. Also, a series of papers revealing the molecular mechanisms of phospholipid- and pH-dependent regulations of KCNK10 (TREK-2) K+ channels are drawing attention.

Cardiac myocytes in normal and pulmonary hypertensive right heart failure

Sung Joon Kim
Department of Physiology, Department of Biomedical Sciences, Ischemic/Hypoxic Disease Institute, Seoul National University College of Medicine, Seoul 03080, Korea

Introduciton In comparison with cardiomyocytes of left ventricle (LVCM), the physiological and pathophysiological properties of right ventricular cardiac myocytes (RVCM) are far less known. Here we compared the electrophysiological properties, Ca^{2+} transients, and contractile properties of RVCM with those of LVCM. Left ventricular failure (LVF) shows dysregulated Ca^{2+} signaling with increased risk of arrhythmia, especially in β-adrenergic stimulation (β-AS). One of the arrhythmia mechanisms is sarcoplasmic reticulum (SR) Ca^{2+}-leak through RyR, a target of cardiac NO synthase (NOS) signaling. Compared with LVF, the mechanism of arrhythmia and altered excitation-contraction coupling (E-C coupling) in right ventricular failure (RVF) and hypertrophy (RVH) under pulmonary arterial hypertension (PAH) is largely unknown. **Materials and methods** (1) Isolation of single cardiac myocytes using Langendorff perfusion and enzyme treatment. (2) Patch clamp technique for action potential (AP) and ionic current recording. (3) Ionoptix and fura-2 ratiometry for single myocyte contraction and Ca2+-sensitivity, (4) Laser scanning confocal microscopy for detecting abnormal Ca2+ wave generation underling arrhtymic depolarization **Results & Discussion** (1) RVCM showed shorter AP duration (APD) than LVCM, which owes to higher density of transient outward K+ current in RVCM. Despite the shorter APD, the peak amplitudes of $[Ca^{2+}]_c$ transient were not significantly different between RVCM and LVCM. Interestingly, the shortening-relaxation of RVCM were slower and smaller than LVCM. The expression of myofilaments was not different while the Ca^{2+}-binding troponins were lower in RVCM. (2) In monocrotaline-injection induced PAH rats, RVCM showed prolonged APD with less significant changes in sarcomere shortening and calcium transient, implying less efficient E-C coupling in RVF. Interestingly, inhibition of NOS (L-NAME, 1 mM, 30 min) combined with β-adernergic stimulation induced arrhythmic contractions of RVH and RVF myocytes, e.g. spontaneous contractions, delayed afterdepolarization (DAD). Confocal microscopic imaging of Ca^{2+} signals revealed abnormal Ca^{2+} leaks from SR in RVH and RVF myocytes when treated by both isoprenaline and L-NAME or by SMCT (nNOS-inhibitor). The pro-arrhythmic effects of NOS inhibitors in RVH under β-stimulation suggest a critical role of NOS in RV myocytes.

Keywords: Right ventricle, E-C coupling, NO synthase, Pulmonary hypertension, Arrhythmia

Hyun-Woo Shin

Seoul National University College of Medicine (SNU), Korea

Professor Hyun-Woo Shin is a physician-scientist who working in the Department of Pharmacology at Seoul National University College of Medicine and the Department of Otorhinolaryngology and Head-and-Neck Surgery at Seoul National University Hospital. He received his M.D. degree in medicine in 2004 and his M.S. degree in otorhinolaryngology in 2009 from Seoul National University College of Medicine, and his Ph.D. degree in respiratory pharmacology in 2012 from Seoul National University. He is the director of Obstructive Upper airway Research Laboratory (OUaR Lab) at Seoul National University College of Medicine, Seoul, Korea. He has served as an Associate Editor of the "Allergy, Asthma & Immunology Research (AAIR)" journal since 2016.

His research interests focus on the pathophysiology of obstructive upper airway diseases including chronic rhinosinusitis, nasal polyps and obstructive sleep apnea. He endeavors to discover novel diagnostic biomarkers reflecting the hypoxic exposure, to clarify the immunological and biochemical mechanisms of upper airway remodeling and to identify the underlying key environments related to it through the diverse collaborations. He has published numerous outstanding articles in top-ranked journals including as a leading author and has intellectual properties on the innovative diagnostic and therapeutic technologies in obstructive airway diseases.

Epithelial Remodeling: A Therapeutic Target in Chronic Rhinosinusitis

Hyun-Woo Shin
Department of Pharmacology, Department of Biomedical Sciences, Seoul National University College of Medicine, Department of Otorhinolaryngology, Seoul National University Hospital, Seoul, 03080, Korea

The respiratory epithelium constitutes the barrier between external and internal environments and is crucial for the protection of the sinonasal mucosal interior milieu. The most basic function of the epithelium relies on its ability to form tight junctions between cells, creating a physical barrier between the airway lumen and subepithelial tissue. Tight junction-associated proteins, such as zona occludens-1, junctional adhesion molecule-A, cingulin, occludin, and claudins, are central to epithelial cytoprotection at the cellular level. Decreased epithelial cohesion and integrity can allow entrance of pathogens and environmental antigens into the sinonasal mucosa.
Chronic rhinosinusitis (CRS) is one of the most common presentations of upper airway illness and severely affects patient quality of life. Its frequency is not surprising given levels of environmental exposure to microbes, pollutants, and allergens. Inflammatory cells, inflammatory cytokine and chemokine production, and airway remodeling have been detected in the sinonasal mucosae of CRS patients, although the precise pathophysiological mechanisms causing such persistent inflammation remain unclear. Given its high prevalence and considerable associated morbidity, continued research into CRS is necessary to increase our understanding of factors likely to contribute to its pathogenesis, and facilitate the development of novel therapeutic strategies to improve treatment.
Recently my colleagues and I presented the novel mechanisms for epithelial remodeling related to hypoxia and inflammatory cytokines in CRS and nasal polyps (NP), and proposed the therapeutic targets based on them. I propose that these novel targets could provide more effective and selective treatment modality for the patients of CRS with NP in the future.

Keywords: Chronic rhinosinusitis, Nasal polyps, Epithelial remodeling, Therapeutic target, Inflammation

Yang-sook Chun
Seoul National University College of Medicine (SNU), Korea

Dr. Yang-Sook Chun is a professor at Seoul National University College of Medicine. Dr. Chun received a doctoral degree from Seoul National University in 1991 and was a visiting scientist at National Cancer Institute in Japan (1992~1994). She did Post. Dr. at Harvard Medical School in Boston (1996~1998). Dr. Chun received many awards from SNU Hospital and SNU medical school. She has served for the IUPS as a council and Chair of Genomics and Biodiversity. She has worked in the field of Hypoxia signaling and epigenetic regulation. She published papers in the outstanding journals such as Oncogene, JNCI, Cancer research and Cell Research. She will talk about **HIF-1 regulates lipid metabolic reprogramming in Cancer**.

HIF-1 regulates lipid metabolic reprogramming in Cancer

Yang-sook Chun
Seoul National University College of Medicine

Glucose metabolism by HIF-1 is a well-characterized strategy for advanced cancer cells to cope with hypoxia. HIF-1 stimulates anaerobic glycolysis to produce energy under hypoxic condition. However, reprogrammed lipid metabolism in cancer is currently rising. Cancer cells enhance fatty acid uptake and lipid storage and decrease beta-oxidation to use lipid as membrane structures or signaling molecules. However, the specific mechanism and its following key transcription factor are yet to be elucidated. Since HIF-1 is a metabolic switch by modulating genes that encode metabolic enzymes, we hypothesized that HIF-1 functions as a key regulator of lipid-related metabolic carcinogenesis. Here, we analyzed HIF-1-interacting protein and identified fatty acid binding protein, an intracellular fatty acid binding protein with high affinity for long-chain fatty acid. Using GEO datasets, we found that FABP is increased in HCC patients and a gene set enrichment analysis showed that FABP up regulation is associated with expression of HIF-1 downstream genes. Thus, we propose hypoxic signaling coupled by HIF-1 and FABP regulates lipid metabolic reprogramming in liver cancer.

Session 2

Dr. Sungwan Kim

Professor, Dept. of Biomedical Engineering

Director, Institute of Bioengineering

Chairman, Interdisciplinary Program in Bioengineering

Seoul National University

Professor Sungwan Kim received the B.S. degree in Electronics Engineering and the M.S. degree in Control and Instrumentation Engineering from Seoul National University (SNU), Seoul, Korea, in 1985 and 1987, and the Ph.D. degree in Electrical Engineering from University of California at Los Angeles, Los Angeles (UCLA), in 1993. He is a Professor with the Department of Biomedical Engineering, College of Medicine, SNU since March 2010. Prior to joining to the SNU, he worked with the Dynamic Systems and Control Branch at National Aeronautics and Space Administration (NASA) Langley Research Center, Hampton, Virginia, USA, as a Senior Researcher and his two primary research areas include - 1) guidance, navigation, and control (GN&C) systems design and analysis and 2) system identification and mathematical modeling. He has led research teams since 1994 as a Principal Engineer with The Boeing Company and a Senior Project Manager at Lear Astronics Corporation. During 2001~2013, Dr. Kim had served as an Associate Editor for the IEEE Journals (Transactions on BioMedical Engineering & Transactions on Control Systems Technology). He is an Associate Fellow of the AIAA, a Senior Member of the IEEE, and a Technical Committee Member of IEEE & IFAC.

Applying Aerospace Technology to Medicine

Sungwan Kim

Professor, Dept. of Biomedical Engineering
Director, Institute of Bioengineering
Chairman, Interdisciplinary Program in Bioengineering
Seoul National University

The state-of-the-art aerospace technology has been applied to diverse fields. In this presentation, recent research and development efforts in Biomedical Engineering at Seoul National University (SNU) are presented. For surgical robot, two innovative ideas of fly-by-wire (FBW) and multi-purpose pilot stick motivated from aerospace engineering are applied. Those concepts have been US patented recently and the proto-types have been developed to demonstrate feasibilities and those are getting surgeon's attention now. Then, a gimbal-based ducted-fan idea is applied to develop capsule endoscope, which could change a paradigm of diagnosis and treatment of internal organs in the future. Finally, SNU's research activity on human physiology under micro-gravity is described for the preparation of trip to space.

Jong Moon Kim

Department of Physical Medicine and Rehabilitation, School of Medicine, Konkuk University

Professor Jong Moon Kim is a physician who has been working in the Department of Physical Medicine and Rehabilitation at KonKuk Medical School and Konkuk University ChungJu Hospital from 2000 to 2018, and currently he is working as a medical director of The-Joen Hospital. He received his M.D. degree in medicine in 1993, his Ph.D. degree in Anatomy in 1999 from Korea University, and granted a Board Certified in Sports Medicine in 1999. He has researched as a post doctoral fellowship in Clinical Physiology Laboratory of Department of Orthopaedic Surgery, University of California, San Diego from 2006 to 2008. He has been a Board member of “Legislation Committee in Korean Academy of Rehabilitation Medicine”, Secretary of “Korean Society of Thermology”, Secretary of “Korean Academy of Independent Medical Examiners”, academic board member of “Korean Society of Sport Biomechanics” and the Medical Consultant for many Korean government agencies. His research interests focus on sports medicine and disability evaluation. He has published numerous original articles and wrote chapters of six books. He received “Academic Award for the Best Research” by Korean Association of Rehabilitation in 2009 and by Korean Society of Thermology in 2001, 2002, 2003 and 2009. Nowadays, his main concern is rehabilitation for the aged related to the sports activities.

Lower body positive pressure treadmill exercise for rehabilitation after Achilles tendon repair

Jong Moon Kim[1], Brandon R. Macias[2], Alan R. Hargens[2]
Department of Physical Medicine and Rehabilitation, School of Medicine, Konkuk University, Chungju 27376, South Korea[1]
Department of Orthopaedic Surgery, University of California, San Diego, CA 92103-8894. U.S.A.[2]

The purpose of this case report is to present a rehabilitation program using upright lower body positive pressure (LBPP) exercise which may minimize pain and risks of re-fracture as well as restore gait imbalance and improve functional recovery. A 35-year-old female pole vaulter who had an Achilles tendon repaired had been provided five sessions of LBPP treadmill exercise after pre-exercise evaluation. Weight balance was calculated by Symmetry Index (SI). The injured foot was loaded about 30% less than the uninjured foot before LBPP treadmill exercise, but was loaded only 14% and 9% less than the normal foot after 5 sessions of LBPP treadmill exercise. SI changed from 34.30 to 15.32 at 3.2 km/h with full body weight, and from 42.98 to 9.66 at 9.7 km/h with 65% of body weight after training. LBPP exercise is a viable method to decrease overall recovery time and help athletes return to their competition.

KEY WORDS: Achilles tendon injury, early athlete rehabilitation, reduced weight bearing, symmetry index

Dong-Kyu Kim

Department of Rehabilitation Medicine, Konkuk University Chungju Hospital, Konkuk University School of Medicine

Professor Dong-Kyu Kim is a Rehabilitation Doctor who working in the Department of Rehabilitation and Physical Medicine at KonKuk University College of Medicine at ChungJu Hospital. He received his M.D. degree in medicine in 2004 and his M.S. degree in 2015 from Kosin University College of Medicine, and his Ph.D. degree in Bioengineering in 2019 from PuKyung University. He has researched in Department of Orthopaedic Surgery University of California, San Diego in 2017. He is the chief of the Department of Rehabilitation and Physical Medicine at KonKuk University College of Medicine at ChungJu Hospital. His research interests focus on musculoskeletal pain. He has published numerous outstanding papers as a leading author and has intellectual properties on the innovative diagnostic and therapeutic technologies in mwusculoskeletal disorders.

Feasibility of Ultrasound-Guided Trigger Point Injection in Patients with Myofascial Pain Syndrome

Jung Joong Kang , Jungin Kim, Seunghun Park , Sungwoo Paek, Tae Hee Kim and Dong Kyu Kim
*Department of Rehabilitation Medicine, Konkuk University Chungju Hospital, Konkuk University School of Medicine, Chungju 27376, Korea

We compared the feasibility of ultrasound (US)-guided myofascial trigger point (MTrP) injection with that of a blind injection technique following the use of shear wave elastography (SWE) for the measurement of sti_ness at the MTrPs in patients with trapezius myofascial pain syndrome (MPS). A total of 41 patients (n = 41) were randomized to either the trial group (n = 21, SWE combined with US-guided injection) or the control group (n = 20, SWE combined with blind injection). At baseline and four weeks, they were evaluated for the manual muscle test (MMT), the range of motion (ROM), pain visual analogue scale (VAS) scores, Shoulder Pain and Disability Index (SPADI) scores and Neck Disability Index (NDI) scores during the abduction, adduction, flexion, extension, external rotation and internal rotation of the shoulder joint. Di_erences in changes in pain VAS scores, NDI scores and SPADI scores at four weeks from baseline between the two groups reached statistical significance ($p = 0.003$, 0.012, and 0.018, respectively). US-guided MTrP injection is a more useful modality as compared with a blind injection in patients with MPS.

Keywords: shoulder; superficial back muscles; myofascial pain syndromes; trigger points; ultrasonography