SAGL FIRST ANNIVERSARY INTERNATIONAL SYMPOSIUM
"AGING RESEARCH AND MEDICAL INNOVATION"
SAGL-PUSAN NATIONAL UNIVERSITY JOINT SYMPOSIUM 2024

FEBRUARY 17, 2024 FUKUOKA

RICHMOND HOTEL TENJIN NISHIDORI

Organizers:

Isao Shimokawa (SAGL, LLC/ Nagasaki University School of Medicine)

Jaewon Lee/ Hae Young Chung (Pusan National University College of Pharmacy)

Supported by

SAGL, LLC/ Dept. Pathology 1, Nagasaki University School of Medicine

【 Opening Remark 】

Welcome, everyone. Thank you very much for joining us today for the symposium commemorating the first anniversary of the establishment of SAGL, Limited Liability Company.

SAGL was established here in Fukuoka on January 18th last year. With financial support from Dr. Hayashida, the president of Hayashida Financial Management, we will conduct joint research with universities and research institutes to apply knowledge of the biology of aging to extend the health span in older people.

We have already started research for seeking calorie restriction (CR) mimetics, which are compounds that mimic the effects of CR without limiting food intake. The Center for Medical Innovation at Nagasaki University (NU) has unique libraries of marine microbe extracts. We will conduct screening of those libraries with the CR mimetics screening system we have established. For this project, we collaborate with many NU members, including Professor Yoshimasa Tanaka of the Center for Medical Innovation and Dr. Ryoichi Mori of the Graduate School of Biomedical Sciences.

SAGL and Hayashida Financial Management hope to support aging research from various perspectives, aiming at regulating aging and related diseases. We have already started a collaboration with Dr. Takahiko Shimizu of the National Center for Geriatrics and Gerontology for anti-aging supplements, Dr. Takamasa Ishii of Tokai University for senescent cells and tissue repairs, and Professor Tomoshi Tsuchiya of Toyama University for tissue repair and cancer therapy, all of whom are joining here today.

In addition, we have now agreed to develop the academic exchange with the Division of BIT convergence-based innovative drug development targeting metainflammation at the College of Pharmacy, Pusan National University (PNU). The academic relationship with researchers at the College of Pharmacy of PNU was initiated during my tenure at NU. Now, we agree to continue these exchanges and facilitate research activities on molecular mechanisms of aging and its clinical applications. Today, Professor Jaewon Lee and professors from PNU are here for this first-anniversary symposium and the signing ceremony of the MOU for academic exchange.

I have retired from NU, but as CEO of SAGL, I would like to contribute to extending the health span of older people, which is a significant issue in modern society.

In conclusion, I would like your continued support in this endeavor. Thank you again for attending today's symposium commemorating the first anniversary of the establishment of SAGL and the MOU between SAGL and Pusan National University.

Isao Shimokawa, M.D., Ph.D.
CEO of SAGL, LLC.
Professor Emeritus, Nagasaki University School of Medicine

【 Program Overview 】

Opening remarks

14:00-14:10 Isao Shimokawa, CEO（SAGL）

Invited lecture

14:10-15:00 Cancer immunotherapy harnessing PD-1 immune checkpoint inhibitors and innate immune cells — Prof. Yoshimasa Tanaka (Nagasaki University Center for Medical Innovation)

(chaired by Dr. Isao Shimokawa)

Session 1 chaired by Dr. Ryoichi Mori(Nagasaki University Graduate School of Biomedical Sciences)

15:00-15:20 Organ Engineering for Disease Models — Prof. Tomoshi Tsuchiya (Toyama University Hospital Comprehensive Cancer Center/Chest Oncology Center)

15:20-15:40 Mitochondrial stress response in osteocytes regulates nuclear structure and bone metabolism via ATF4-lamins-sclerostin axis in aged bone — Dr. Takahiko Shimizu, Project leader (Geroscience Research Center・Aging Stress Response Research Project Team)

Break

15:40-15:50

Session 2 chaired by Dr Takamasa Ishii(Tokai University School of Medicine)

15:50-16:10 Systematic Omics Analysis of Large-scale Cancer Cell Lines Identifies CCR6 as a Potent Therapeutic Target to Combat Cancer Resistance to EGFR Inhibitors — Prof. Haeseung Lee (Pusan National Univeristy Colleage of Pharmacy)

16:10-16:30 Glucogenic role of renal FOXO1 during starvation and its implication in kidney disease — Assoc. Prof. Ki Wung Chung (Pusan National Univeristy Colleage of Pharmacy)

16:30-16:50 The Incidence of Thyroid-related Adverse Events in Cancer Patients on Immune Checkpoint Inhibitors: A Real-World and Retrospective Cohort Study — Prof. Nakyung Jeon (Pusan National Univeristy Colleage of Pharmacy)

Closing remarks

16:50-17:00 Prof. Jaewon Lee (Pusan National Univeristy Colleage of Pharmacy)

Signing ceremony

17:00-17:10 Signing ceremony of MOU between SAGL, LLC-Japan and Division of BIT convergence-based innovative drug development targeting metainflammation, Pusan National University - Korea

Free discussion

17:30-19:00 Free discussion for current topics of aging and future collaboration

Invited lecture

chaired by Dr. Isao Shimokawa
(SAGL, LLC)

Professor Yoshimasa Tanaka
(Nagasaki University Center for Medical Innovation)

CancerimmunotherapyharnessingPD-1 immune checkpoint inhibitors and innate immune cells

Curriculum Vitae

Yoshimasa Tanaka, Ph.D.

Affiliation
Center for Medical Innovation, Nagasaki University

Education
1992: Ph.D. from Hokkaido University, Japan

Professional experience
2019-present: Director and Distinguished Professor, Center for Medical Innovation, Nagasaki University, Nagasaki, Japan
2017-2019: Research Professor, Department of Cancer Immunotherapy, Hyogo College of Medicine, Nishinomiya, Japan (Cross-appointment)
2015-2019: Associate Professor, Center for Bioinformatics and Molecular Medicine, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan
2012-2015: Associate Professor, Center for Therapeutic Innovation, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan
2008-2012: Associate Professor, Center for Innovation in Immunoregulative Technology and Therapeutics and the Department of Immunology and Cell Biology, Kyoto University Graduate School of Medicine, Kyoto, Japan
2007-2008: Assistant Professor, Kyoto University Graduate School of Medicine, Kyoto, Japan
1999-2007: Assistant Professor, Kyoto University Graduate School of Biostudies, Kyoto, Japan with Professor Tasuku Honjo, Nobel Laureate in Physiology or Medicine in 2018
1998-1999: Assistant Professor, Kyoto University Graduate School of Medicine, Kyoto, Japan with Professor Nagahiro Minato, President of Kyoto University
1996-1998: Assistant Professor, Tokyo Women's Medical College, Tokyo, Japan
1995-1996: Research Scientist, Osaka Bioscience Institute, Osaka, Japan
1994-1995: Research Associate, Albert Einstein College of Medicine, Bronx, NY with Professor Barry R. Bloom (Later he became Dean of Harvard T.H. Chan School of Public Health, Harvard University, MA, U.S.A.)

1992-1994: Associate, Howard Hughes Medical Institute, Albert Einstein College of Medicine, Bronx, NY with Professor Barry R. Bloom

Achievements/Recent publications

1. Identification of isopentenyl pyrophosphate and its analogs as stimulators of γδ T cells expressing Vγ2Vδ2 TCRs

In 1990, I was an exchange student in the lab of Professor Barry R. Bloom at Albert Einstein College of Medicine, NY, U.S.A. I screened a chemical library consisting of a large number of natural and synthetic small molecules for their ability to stimulate human γδ T cells and identified monoethyl phosphate as one of the active compounds. Based on this result, I synthesized a series of phosphomonoesters and found that they were able to stimulate human γδ T cells, but not mouse γδ T cells. I further showed that active compounds from mycobacteria were similar to the synthetic compounds because they were <500 Daltons, contained critical phosphate residues, and were protease resistant. These findings were published in a PNAS article. In 1992, I started working as a post-doc in the same Bloom lab. In 1994, I isolated and identified isopentenyl pyrophosphate (IPP) as one of the active compounds from *Mycobacterium smegmatis*. IPP, an isoprenoid metabolite present in all living organisms, was a potent stimulator of human γδ T cells. I then synthesized nucleotide conjugates of IPP that were also active in stimulating human γδ T cells. These findings were published in Nature, which was the first report showing that nonpeptide isoprenoid metabolites stimulate human γδ T cells. Later, the more potent (*E*)-4-hydroxy-3- methylbut-2-enyl pyrophosphate (HMBPP) in the DOXP pathway was discovered. I showed that these compounds directly stimulated human γδ T cells without antigen processing and did not require MHC class I or II or CD1 antigen-presenting molecules in a paper published in Immunity. I also demonstrated that stimulation was mediated by the Vγ2Vδ2 TCR and dependent on CDR3 motifs.

(a) **Yoshimasa Tanaka**, Shigetoshi Sano, Edward Nieves, Gennaro DeLibero, Domenico Rosa, Robert L. Modlin, Michael B. Brenner, Barry R. Bloom, and Craig T. Morita. Nonpeptide ligands for human γδ T cells. ***Proc. Natl. Acad. Sci. U.S.A.*** 91: 8175-8179 (1994).

(b) **Yoshimasa Tanaka**, Craig T. Morita, Yoko Tanaka, Edward Nieves, Michael B. Brenner, and Barry R. Bloom. Natural and synthetic antigens recognized by human γδ T cells. ***Nature*** 375: 155-158 (1995).

(c) Craig T. Morita, Evan Beckman, Jack F. Bukowski, **Yoshimasa Tanaka**, Hamid Band, David E. Golan, Barry R. Bloom, and Michael B. Brenner. Direct presentation of nonpeptide prenyl pyrophosphate antigens to human γδ T cells. ***Immunity*** 3: 495-507 (1995).

(d) Fumi Miyagawa, **Yoshimasa Tanaka**, Seiji Yamashita, Bunzo Mikami, Kiichiro Danno, Masami Uyehara, and Nagahiro Minato. Essential contribution of germline-encoded lysine residues in Jγ1.2 segment to the recognition of nonpeptide antigens by human γδ T cells. ***J. Immunol.*** 167: 6773-6779 (2001).

2. Discovery that PD-1 immune checkpoint blockade unleashes natural tumor immunity

In 1999, two PD-1 ligands, PD-L1 and PD-L2 were identified as Ig superfamily proteins related to B7-1 and B7-2. While I was in Nagahiro Minato lab, I collaborated with Dr. Hiroyuki Nishimura in Honjo lab. We found that PD-1-deficient Balb/c mice developed cardiomyopathy and published this finding in a Science paper in 2001. We found that this was due to autoantibodies to cardiac troponin I and this was published in a Nature Medicine paper in 2003.

In 2000, I established monoclonal antibodies specific for murine PD-1, PD-L1, and PD-L2. Because I was working on cancer immunotherapy involving γδ T cells at the time, I assessed the effect of anti-PD-L1 mAb on cancer immunotherapy. Mr. Masayoshi Ishida, one of my students, and I found that treatment with anti-PD-L1 mAbs reduced tumor cell growth rates in mice in studies done in 2001. **This finding was published in PNAS in 2002 and was the first report that natural anti-tumor immunity was enhanced by PD-1/PD-L1 immune checkpoint blockade.** To further analyze the PD-1/PD-L1 interaction, I collaborated with Dr. David Garboczi at the NIH to solve the crystal structure of the PD-1/PD-L1 complex. We showed that this binding was similar to the pairing of the V regions of immunoglobulin heavy and light chains. This was published in PNAS in 2007. Mr. Masashi Iwasaki, one of my students, and I also analyzed the function of the PD-1 immune checkpoint in human γδ T cells and found that PD-1 delivered a negative signal to human γδ T cells similar to that observed for αβ T cells in mice.

(a) Hiyoyuki Nishimura, Taku Okazaki, **Yoshimasa Tanaka**, Kazuki Nakatani, Masatake Hara, Akira Matsumori, Shigetake Sasayama, Akira Mizoguchi, Hiroshi Hiai, Nagahiro Minato, and Tasuku Honjo. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. ***Science*** 291: 319-322 (2001).

(b) Yoshiko Iwai, Masayoshi Ishida, **Yoshimasa Tanaka**, Taku Okazaki, Tasuku Honjo, and Nagahiro Minato. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. ***Proc. Natl. Acad. Sci. U.S.A.*** 99: 12293-12297 (2002).

(c) David Yin-wei Lin, **Yoshimasa Tanaka**, Masashi Iwasaki, Apostolos G. Gittis, Hua-Poo Su, Bunzo Mikami, Taku Okazaki, Tasuku Honjo, Nagahiro Minato, and David N. Garboczi. The PD-1/PD-L1 complex resembles the antigen-binding Fv domains of antibodies and T cell receptors. ***Proc. Natl. Acad. Sci. U.S.A.*** 105: 3011-3016 (2008).

(d) Masashi Iwasaki, **Yoshimasa Tanaka**, Hirohito Kobayashi, Kaoru Murata-Hirai, Hideto Miyabe, Tomoharu Sugie, Masakazu Toi, and Nagahiro Minato. Expression and function of PD-1 in human γδ T cells that recognize phosphoantigens. ***Eur. J. Immunol.*** 41: 345-355 (2011).

Research Interest

Cancer immunotherapy; PD-1 immune checkpoint inhibitors; γδ T cells; NK cells

Cancer immunotherapy harnessing PD-1 immune checkpoint inhibitors and innate immune cells

Yoshimasa Tanaka, Ph.D.

Center for Medical Innovation, Nagasaki University, Japan

PD-1 immune checkpoint inhibitors have revolutionized cancer therapy and many immunologists and oncologists have paid much attention to cancer immunotherapy. In 1999 to 2001, we established monoclonal antibodies specific to PD-1, PD-L1, and PD-L2 and demonstrated that these PD-1 immune checkpoint inhibitors could be utilized for treatments of cancer in animal models. Whereas PD-1 immune checkpoint therapy is beneficial for some patients, the therapeutic effect is limited in other cancer patients. We have been developing combination therapies harnessing PD-1 immune checkpoint inhibitors and interleukins. When tumor cells exist, dendritic cells recognize the tumor cells and move into proximal lymph nodes, where they present tumor-derived antigenic peptides to naïve T cells. The tumor antigen-specific naïve T cells are differentiated into effector T cells, which exhibit potent cytotoxicity against tumor cells. Some tumor antigen-specific naïve T cells can be differentiated into stem cell memory T cells. The stem cell memory T cells are differentiated into central memory T cells, which are further differentiated into effector memory T cells. Finally, the effector memory T cells are differentiated into tumor antigen-specific effector T cells. We recently found that interleukins augment the induction of early memory T cells including stem cell memory T cells and central memory T cells and that the combination of PD-1 immune checkpoint inhibitors and interleukins exhibit potent cytotoxicity against tumor cells.

In addition, we have recently developed adoptive transfer therapy for cancer. We first established a protocol to efficiently expand human γδ T cells and NK cells. In case of γδ T cells, PBMC were stimulated with a nitrogen-containing bisphosphonate prodrug and IL-2. After 11 days of incubation, the proportion of γδ T cells increased up to 99% without any

purification steps. When NK cells are expanded from CD3-negative fractions of PBMC with interleukins, the proportion of NK cells reached up to 95% or greater. It is noteworthy that these human innate immune cells expressed a high level of CD86 and HLA-DQ, which are typically expressed on antigen-presenting cells. When tumor cells were challenged by γδ T cells, most cell lines were killed by γδ T cells in the presence of a nitrogen-containing bisphosphonate antigen or anti-tumor monoclonal antibodies. NK cells directly exhibit cytotoxicity against tumor cells and the tumoricidal activity was enhanced by the addition of antibodies.

In conclusion, cancer immunotherapy harnessing PD-1 immune checkpoint inhibitors and interleukins and/or innate immune cells would be more effective cancer treatments than currently available standard therapies.

Session 1

chaired by Dr. Ryoichi Mori

(Nagasaki University Graduate School of Biomedical Sciences)

Dr. Tomoshi Tsuchiya
(Toyama University Hospital Comprehensive Cancer Center/Chest Oncology Center)

Dr. Takahiko Shimizu
(Geroscience Research Center・Aging Stress Response Research Project Team)

Curriculum Vitae

Tomoshi Tsuchiya

Affiliation
Professor, Department of Thoracic Surgery,
Director, Thoracic Oncology Center

Education
Nagasaki University School of Medicine
Department of Pathology & Gerontology, Nagasaki University Graduate School of Biomedical Sciences

Professional experience
Thoracic Surgery, Tissue/Organ Engineering, Cell Therapy
Lung Transplantation, Pathology

Achievements/Recent publications
1. Timing of Mesenchymal Stromal Cell Therapy Defines its Immunosuppressive Effects in a Rat Lung Transplantation Model. Cell Transplant. 2023 Jan-Dec; 32:963689723120717 7. doi: 10.1177/09636897231207177. PMID: 37950374
2. A novel ex vivo lung cancer model based on bioengineered rat lungs. Front Bioeng Biotechnol. 2023 Jun 26;11:1179830. doi: 10.3389/fbioe.2023.1179830.
3. Adipose-Derived Mesenchymal Stem Cells Attenuate Immune Reactions Against Pig Decellularized Bronchi Engrafted into Rat Tracheal Defects. Organogenesis. 2023 Dec 31;19(1):2212582. doi: 10.1080/15476278.2023.2212582.
4. FOXA2 Cooperates with Mutant KRAS to Drive Invasive Mucinous Adenocarcinoma of the Lung. Cancer Res. 2023 May 2;83(9):1443-1458. doi: 10.1158/0008-5472.CAN-22-2805. PMID: 37067057
5. Prediction of visceral pleural invasion of clinical stage I lung adenocarcinoma using thoracoscopic images and deep learning. Surg Today. 2023 Oct 20. doi: 10.1007/s00595-023-02756-z. Online ahead of print. PMID: 37864054
6. Anticancer agent a-sulfoquinovosyl-acylpropanediol enhances the radiosensitivity of human malignant mesothelioma in nude mouse models. J Radiat Res. 2022 Jan 20;63(1):19-29. doi: 10.1093/jrr/rrab090. PMID: 34738103

Research Interest
Lung Organ Engineering, Lung Transplantation, Lung Cancer, COPD

Organ Engineering for Disease Models

Tomoshi Tsuchiya

Department of Thoracic Surgery, University of Toyama

Introduction: There are many disease models for drug development, including transwell culture, organoids, and patient-derived xenografts (PDX), each with its own strengths and weaknesses. In this presentation, a novel disease model based on ex vivo lung bioengineering will be presented. Materials and Methods: The bioengineered lung was developed using a decellularized rat lung scaffold. The scaffold was recellularized in a bioreactor by rat lung microvascular endothelial cells (RLMVECs) and whole rat lung cells. Lung cancer models were developed by injecting human cancer cell lines into bioengineered lungs. Results and Discussion: Each cell line exhibited different phenotypes in the lung cancer model, particularly A549 cells, which showed mucin-associated tube formation. Gefitinib treatment selectively affected epidermal growth factor-positive PC9 cells but not A549 cells. This ex vivo disease model has several advantages: normal and cancer cells coexist, it can be created in as little as 5 days, it does not require special growth factors, it is easy to use for histopathological studies, live imaging is possible, and mechanical stress (such as respiratory exercise) can be applied. This presentation will also include an overview of similar studies at other institutions.

Curriculum Vitae

Takahiko Shimizu, PhD

Affiliation

Aging Stress Response Research Project Team, National Center for Geriatrics and Gerontology (NCGG)

Education

Ph. D. Hiroshima University (1995)

Professional experience

ResearchScientist(1997–2011),Tokyo Metropolitan Institute of Gerontology, Japan

Associate Professor (2011–2019), Chiba University Graduate School of Medicine, Japan

Project Leader (2019-Present), NCGG, Japan

Visiting Professor (2020–Present), Sanyo-Onoda City University, Japan

Achievements/Recent publications

Izuo, N., Watanabe, N., Noda, Y., Saito, T., Saido, T.C., Yokote, K., Hotta, H., Shimizu, T. Insulin resistance induces earlier initiation of cognitive dysfunction mediated by cholinergic deregulation in a mouse model of Alzheimer's disease. *Aging Cell*, 22, e13994 (2023).

Shibuya, S., Watanabe, K., Sakuraba, D., Abe, T., and Shimizu, T. Natural compounds that enhance the motor function in a mouse model of muscle fatigue. *Biomedicines* 10, 3073 (2022).

Shibuya, S., Watanabe, K., Ozawa, Y., Shimizu, T. Xanthine oxidoreductase-mediated superoxide production is not involved in the age-related pathologies of *Sod1*-deficient mice. *Int J Mol Sci* 22, 3542 (2021).

Watanabe, K., Shibuya, S., Ozawa, Y., Toda, T., Shimizu, T. Pathological relationship between intracellular superoxide metabolism and p53 signaling in mice. *Int J Mol Sci* 22, 3548 (2021).

Sagi, H., Shibuya, S., Kato, T., Nakanishi, Y., Tsuboi, A., Moriya, S., Ohno, H., Miyamoto, H., Kodama, H., Shimizu, T. SOD1 deficiency alters gastrointestinal microbiota and metabolites in mice. *Exp Gerontol* 130, 110795 (2020).

Ozawa, Y., Watanabe, K., Toda, T., Shibuya, S., Okumura, N., Okamoto, N., Sato, Y., Kawashima, I., Kawamura, K., Shimizu, T. Heterosis extends the reproductive ability in aged female mice. *Biol Reprod* 100, 1082-1089 (2019).

Kim, J., Toda, T., Watanabe, K., Shibuya, S., Ozawa, Y., Izuo, N., Cho, S., Seo, D.B., Yokote, K., Shimizu, T. Syringaresinol reverses age-related skin atrophy by suppressing FoxO3a-mediated matrix metalloproteinase–2 activation in copper/zinc superoxide dismutase–deficient mice. *J Investig Dermatol,* 139, 648-655 (2019).

Research Interest

Aging, Stress response, Mitochondria, ROS

Mitochondrial stress response in osteocytes regulates nuclear structure and bone metabolism via ATF4-lamins-sclerostin axis in aged bone

Takahiko Shimizu, Kenji Watanabe, Shuichi Shibuya

Aging Stress Response Research Project Team, National Center for Geriatrics and Gerontology (NCGG)

Osteocytes embedded in bone matrix reach out bone canaliculi to communicate with surrounding cells and also secrete bone regulatory factors such as sclerostin (SOST). Interestingly, osteocytes have a much longer lifespan (1-50 years) than other bone-related cells, making them a target cell for aging stress. Morphological observation of cortical bone in aged mice show age-related bone changes, such as abnormal osteocyte orientation and reduced number of bone canaliculi, in addition to marked atrophy of the bone cortex. These changes closely resemble the pathology of bones in the elderly peoples, and are considered to be common aging changes. Here, we further found that abnormal nuclear structure of osteocytes in aged and mitochondrial SOD2-deficient bones. We have demonstrated that osteocyte-specific *Sod2*-deficient mice exhibit age-related bone loss associated with osteocyte mitochondrial dysfunction and increased sclerostin production. These nuclear abnormalities were accompanied by decreased expression of the major nuclear lamina proteins, lamin A/C and lamin B, *in vivo*. *In vitro* experiments revealed a mitochondrial uncoupler also downregulated *Lmna* and *Lmnb* expression and upregulated *Sost* expression associated with nuclear abnormalities, suggesting contribution of mitochondrial stress response. Furthermore, we found nuclear accumulation of mitochondrial stress response transcription factor, ATF4 under a mitochondrial dysfunction condition. In addition, ATF4 insufficiency improved lamins and sclerostin expression as well as nuclear morphology and bone phenotypes *in vitro* and *in vivo*. Finally, we found that dietary restriction also delayed molecular and nuclear abnormalities in bones of aged rats. These results strongly suggest that osteocytes with mitochondrial dysfunction alter the mitochondrial stress response axis and nuclear lamina structure, resulting in bone loss due to dysregulation of bone regulatory factors.

Session 2

chaired by Dr. Takamasa Ishii

(Tokai University School of Medicine)

Dr. Haeseung Lee
(Pusan National Univeristy Colleage of Pharmacy)

Dr. Ki Wung Chung
(Pusan National Univeristy Colleage of Pharmacy)

Dr. Nakyung Jeon
(Pusan National Univeristy Colleage of Pharmacy)

Curriculum Vitae

Haeseung Lee, Ph.D.

Affiliation
Assistant Professor, College of Pharmacy, Pusan National University, Republic of Korea
Email: haeseung@pusan.ac.kr

Education
2009 – 2015 Ph.D., Bioinformatics, Ewha Women's University
2005 - 2009 B.S., Life Science, Ewha Women's University

Professional experience
2021 – present Assistant Professor, Pusan National University College of Pharmacy
2020 – 2021 Researcher, Korea Institute for Oriental Medicine

Selected publications (‡corresponding authors, *first authors)
1. Kim JW*, Kim MJ*, …, Lee SC†, **Lee H‡**, Lee EW† (2023) FSP1 confers ferroptosis resistance in KEAP1 mutant non-small cell lung carcinoma in NRF2-dependent and -independent manner. ***Cell Death & Disease*** 14(8): 567
2. Kim A*†, Park SM, Kim NS, **Lee H‡** (2023) Ginsenoside Rc, an Active Component of Panax ginseng, Alleviates Oxidative Stress-Induced Muscle Atrophy via Improvement of Mitochondrial Biogenesis. ***Antioxidants*** 12(8): 1576
3. Kwon OS, …, **Lee H‡**, Cha HJ† (2020) Systematic identification of a nuclear receptor-enriched predictive signature for erastin-induced ferroptosis. ***Redox Biology*** 37:101719
4. Kwon OS*, **Lee H***, …, Kim W†, Cha HJ† (2020) Connectivity Map-based drug repositioning of bortezomib to reverse the metastatic effect of GALNT14 in lung cancer. ***Oncogene*** 39:4567-4580.
5. Hong SK*, **Lee H***, Kwon OS*, …, Kim W† Cha HJ†, (2018) Large-scale pharmacogenomics based drug discovery for ITGB3 dependent chemoresistance in mesenchymal lung cancer, ***Molecular Cancer*** 17(1):175.

Research Interest
1. Artificial Intelligence (AI)-based drug discovery
2. Omics-guided drug target discovery

Systematic Omics Analysis of Large-scale Cancer Cell Lines Identifies CCR6 as a Potent Therapeutic Target to Combat Cancer Resistance to EGFR Inhibitors

Eun-Ji Kwon[1], Hyuk-Jin Cha[1], **Haeseung Lee[2]**

[1] College of Pharmacy, Seoul National University, Republic of Korea

[2] College of Pharmacy, Pusan National University, Republic of Korea

Epidermal growth factor receptor inhibitors (EGFRi) have exhibited promising clinical outcomes in the treatment of various cancers; however, their widespread application has been limited by low patient eligibility and the emergence of resistance. To address these challenges, we conducted an integrative analysis of multi-omics and phenotypic data derived from more than 1000 cancer cell lines. We explored molecular signatures linked to EGFRi responsiveness and found that expression signatures involved in the estrogen response could recapitulate cancer cell dependency on EGFR, a phenomenon not solely attributable to EGFR-activating mutations. By correlating genome-wide loss-of-function screening data with EGFRi responses, we identified chemokine receptor 6 (CCR6) as a potential druggable target to mitigate EGFRi resistance. We employed two sets of isogenic cell models to verify this prediction and demonstrated that the pharmacological inhibition of CCR6 effectively reversed acquired EGFRi resistance. Our data-driven approach highlights the significance of integrative omics analysis in identifying novel drug-response biomarkers and therapeutic targets for resistance, thus expanding their applicability to a broader range of patients and enhancing the effectiveness of targeted therapies.

Curriculum Vitae

Ki Wung Chung, Ph.D.

Affiliation
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Education
2010-2017PusanNational University, Republic of Korea Ph.D. in Pharmacy
2006-2010 Pusan National University, Republic of Korea B.S. in Pharmacy

Professional experience
2020–present Assistant, Associate Professor College of Pharmacy, Pusan National University
2017–2019 Postdoctoral Res

Achievements/Recent publications
1. Kim J, Ha S, Son M, Kim D, Kim MJ, Kim B, Kim D, Chung HY, **Chung KW**. TLR7 activation by miR-21 promotes renal fibrosis by activating the pro-inflammatory signaling pathway in tubule epithelial cells. ***Cell Commun Signal.*** 2023 Aug 18;21(1):215.
2. Ha S, Yang Y, Kim JW, Son M, Kim D, Kim MJ, Im DS, Chung HY, **Chung KW**. Diminished tubule epithelial farnesoid X receptor expression exacerbates inflammation and fibrosis response in aged rat kidney. ***J Gerontol A Biol Sci Med Sci.*** 2023 Jan 26;78(1):60-68.
3. Ha S, Yang Y, Kim BM, Kim J, Son M, Kim D, Yu HS, Im DS, Chung HY, **Chung KW**. Activation of PAR2 promotes high-fat diet-induced renal injury by inducing oxidative stress and inflammation. ***Biochim Biophys Acta Mol Basis Dis.*** 2022 Oct 1;1868(10):166474.
4. **Chung KW**, Dhillon P, Huang S, Sheng X, Shrestha R, Qui C, Kaufman BA, Park J, Pei L, Baur J, Palmer M, Susztak K. Mitochondrial Damage and Activation of the STING Pathway Lead to Renal Inflammation and Fibrosis. ***Cell Metab.*** 2019 30(4):784-799.
5. **Chung KW**, Lee EK, Lee MK, Oh GT, Yu BP, Chung HY. Impairment of PPARa and the Fatty acid oxidation pathway aggravates renal fibrosis during aging. ***J Am Soc Nephrol.*** 2018 29(4):1223-1237.

Research Interest
1. Kidney and Liver Fibrosis
2. Lipid and Glucose Metabolism
3. Role of mitochondria in cellular senescence and aging

Glucogenic role of renal FOXO1 during starvation and its implication in kidney disease

Mi-jeong Kim, Haeseung Lee, **Ki Wung Chung**

College of Pharmacy, Pusan National University, Republic of Korea

Renal gluconeogenesis is important in maintaining glucose homeostasis particularly under the starved condition. However, the exact mechanism and its implication in kidney disease has not been fully discovered. Here, using starved mice and renal tubular epithelial cells, we aimed to elucidate the glucogenic role of renal FOXO1 during starvation, and its implication in kidney disease. In the starved kidney, FOXO1 activation was detected with increased gluconeogenic gene expression in the kidney tubule cells. Using NRK52E cells, we further found that starvation-induced FOXO1 activation is needed to produce glucose in the tubule epithelial cells. To find out FOXO1's role and implication in kidney disease, we analyzed mice model with kidney fibrosis. We found that fibrotic kidneys had reduced FOXO1 and gluconeogenic protein expression. However, serum glucose levels did not change implying reduced FOXO1 does not contribute to circulating glucose levels. We further found that under the diseased condition, starvation-induced FOXO1 activation and gluconeogenesis were impaired with decreased circulating glucose levels. Similar to diseased condition, aged mice exposed to starvation also showed impaired gluconeogenic response in the kidney, contributing to reduced circulating glucose levels. Finally, we found that profibrotic TGFβ1 reduces starvation-induced gluconeogenesis by directly reducing FOXO1 signaling pathway in the tubule cells. Collectively, we demonstrated glucogenic role of renal FOXO1 during starvation and its implication in the kidney disease state.

Curriculum Vitae

Nakyung Jeon, Ph.D.

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Education
2012 - 2017 Ph.D., Department of Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida
2009 – 2011 M.P.H., School of Public Health, Seoul National University
2005 - 2009 B.S., College of Pharmacy, Ewha Women's University

Professional experience
2022-present Assistant Professor, Pusan National University College of Pharmacy
2019-2022 Assistant Professor, Chonnam National University College of Pharmacy
2018-2019 Assistant Professor, University of Utah College of Pharmacy

Achievements/Recent publications
1. **Jeon N***, Jacqueline Kent-Marvick, Jessica N, Sanders, Heidi Hanson, Sara E. Simonsen**.** Comparing maternal factors associated with post partum depression among primiparous adolescents and adults: A lar ge retrospective cohort study. *Birth*. 2023; 00: 1-11.
2. Park C-K, **Jeon N(co-first),** Park H-K, Oh H-J, Kim Y-C, Jeon H-L, Kim Y-H, Ahn S-J, Oh I-J. A Propensity-Matched Retrospective Comparative Study with Historical Control to Determine the Real-World Effectivene ss of Durvalumab after Concurrent Chemoradiotherapy in Unresecta ble Stage III Non-Small Cell Lung Cancer. Cancers. 2023; 15(5):1606.
3. **Jeon N,** Park H, Segal R, Brumback B, Winterstein AG*. Non-steroidal anti-inflammatory drug-associated acute kidney injury: does short-ter m NSAID use pose a risk in hospitalized patients? *Eur J Clin Pharmaco l.* 2021;77(9):1409-17
4. **Jeon N,** Bortolato M*. What drugs modify the risk of iatrogenic impuls e-control disorders in Parkinson's disease? A preliminary pharmacoe pidemiologic study. *PloS ONE*. 2020;15(1):e0227128

Research Interest
1. Pharmacoepidemiology
2. Healthcare bigdata analysis

The Incidence of Thyroid-related Adverse Events in Cancer Patients on Immune Checkpoint Inhibitors: A Real-World and Retrospective Cohort Study

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Background:
This study aims to estimate the incidence of hyperthyroidism, hypothyroidism, and thyroiditis among cancer patients treated with an ICI at a university-affiliated tertiary hospital in Korea.
Methods:
We used electronic health record at Pusan National University Hospital transformed to Observational Medical Outcomes Partnership (OMOP) - Common Data Model (CDM). Patients received at least one dose of atezolizumab, avelumab, durvalumab, ipilimumab, nivolumab, or pembrolizumab between Jan 2011 and Jun 2022 were included. Excluded patients were who had a record of abnormal T3, Free T4 or thyroid stimulating hormone (TSH) level at or within 3 months before the first dose of an ICI (=index date). The primary outcome was thyroid-related adverse events (TRAE) ascertained by the presence of prescription records, abnormal thyroid function test (TFT) results, or diagnosis codes indicating hyper- or hypothyroidism. Patients were censored at 2-years after the index date or 2022.06.30 (data cut-off) whichever occurred first. The incidence was calculated by the number of new TRAE cases divided by the number of patients-at-risk. Incidence density was also estimated by the number of new cases per 1000 person-day. All statistical analysis was performed with SAS software. Data were summarized using descriptive statistics or contingency tables if appropriate.
Results: A total of 870 patients received at least one ICI during the study period. Atezolizumab (N=295, 34%) and pembrolizumab (N=276, 32%) were the most prevalent ICIs followed by nivolumab (N=245, 28%). Twenty-eight patients

received a dual ICI treatment, and the majority of them (N=25, 89.3%) was a nivolumab-ipilimumab combination. The mean number of days between treatment cycles were similar between different ICIs ranging from 16 days (standard deviation, SD=18.7) for nivolumab to 22 days (SD=10.9) for atezolizumab. About 20% (N=105) of patients developed TRAE; the incidence and incidence density of each type of TRAE are as follow: hypothyroidism (N=105, 12%, 0.274/1000 person-days) and hyperthyroidism (N=47, 5%, 0.113/1000 person-days).

Conclusions:

In line with the findings from the meta-analyses of clinical trials, we found that thyroid-related adverse event (AE) occurred frequently, with the higher incidence of hypothyroidism then hyperthyroidism. While experiencing adverse event is generally considered inevitable during cancer therapy, the detailed safety profile of individual ICI in real-world setting would provide clinical insight into better patient health outcomes. Further research to characterize and identify patients at increased risk for developing thyroid-related AE is warranted.

Curriculum Vitae

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Education

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Professional experience

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2007-2009 Research Associate Institute for Behavioral Genetics, Colorado University at Boulder, USA
2005-2007 Post Doctoral Research Fellow Department of Molecular Life Science, Tokai University School of Medicine

Achievements/Recent publications

1. Harada K., Yahata T., Onizuka M., Ishii T., Ibrahim A.A., Kikkawa E., Gondo Y., Ando K. (2023) Mitochondrial electron transport chain complex II dysfunction causes premature aging of hematopoietic stem cells. ***Stem Cells*** 41: 39-49.
2. Ishii T., Takanashi Y., Sugita K., Miyazawa M., Yanagihara R., Yasuda K., Onouchi H., Kawabe N., Nakata M., Yamamoto Y., Hartman P.S. and Ishii N. (2017) Endogenous reactive oxygen species cause astrocyte defects and neuronal dysfunctions in the hippocampus: a new model for aging brain. ***Aging Cell*** 16: 39-51.

3. Moro T., Nakao S., Sumiyoshi H., Ishii T., Miyazawa M., Ishii N., Sato T., Iida Y., Okada Y., Tanaka M., Hayashi H., Ueha S., Matsushima K., Inagaki Y. (2016) A Combination of Mitochondrial Oxidative Stress and Excess Fat/Calorie Intake Accelerates Steatohepatitis by Enhancing Hepatic CC Chemokine Production in Mice. ***PLoS One*** 11: e0146592.
4. Sukmawati D., Fujimura S., Jitsukawa S., Ito-Hirano R., Ishii T., Sato T., Hayashi A., Itoh S., Mizuno H., Daida H., Tanaka R. (2015) Oxidative stress tolerance of early stage diabetic endothelial progenitor cell. ***Regenerative Therapy*** 1: 38-44.
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6. Ishii T., Miyazawa M., Onouchi H., Yasuda K., Hartman P.S., Ishii N. (2013) Model animals for the study of oxidative stress from complex II. ***Biochim. Biophys. Acta.*** 1827: 588-597.
7. Uchino Y., Kawakita T., Miyazawa M., Ishii T., Onouchi H., Yasuda K., Ogawa Y., Shimmura S., Ishii N., Tsubota K. (2012) Oxidative stress induced inflammation initiates functional decline of tear production. ***PLoS One*** 7: e45805.
8. Onouchi H., Ishii T., Miyazawa M., Uchino Y., Yasuda K., Hartman P.S., Kawai K., Tsubota K., Ishii N. (2012) Mitochondrial superoxide anion overproduction in Tet-mev-1 transgenic mice accelerates age-dependent corneal cell dysfunctions. ***Invest. Ophthalmol. Vis. Sci.*** 53: 5780-5787.
9. Ishii T., Miyazawa M., Onodera A., Yasuda K., Kawabe N., Kirinashizawa M., Yoshimura S., Maruyama N., Hartman P.S. and Ishii N. (2011) Mitochondrial reactive oxygen species generation by the SDHC V69E mutation causes low birth weight and neonatal growth retardation. ***Mitochondrion*** 11: 155-165.
10. Yasuda K., Hartman P.S. Ishii T., Suda H., Akatsuka A., Shoyama T., Miyazawa M. and Ishii N. (2011) Interrelationships between mitochondrial fusion, energy metabolism and oxidative stress during development in *Caenorhabditis elegans*. ***Biochem. Biophys. Res. Commun.*** 404: 751-755.

Research Interest

1.Accelerated pathophysiological aging by mitochondrial oxidative stress

2.Innate immune and inflammatory responses with oxidative stress

3.Replication stress and DNA damage responses with by-product of energy metabolism

Curriculum Vitae

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Professional experience
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2016-present: Associate Professor, Department of Pathology, Nagasaki University School of Medicine, Japan

Achievements/Recent publications
1. Umehara T, et al. circRNAs bay be involved in dysfunction of neutrop hils of type 2 diabetic mice through regulation of specific miRNAs. ***Bi omedicines,*** 10, 3129, 2022.
2. Umehara T, et al. Identification of specific microRNAs in neutrophils o f type 2 diabetic mice: overexpression of microRNA-129-2-3p acceler ates diabetic wound healing. ***Diabetes,*** 68, 617-630, 2019.
3. de Kerckhove M, et al. Targeting miR-223 in neutrophils enhances th e clearance of *Staphylococcus aureus* in infected wounds. ***EMBO M ol Med****,* 10, e9024, 2018

Research Interest

Tissue repair is a complex biological process involving multiple cell lineages that must proliferate, migrate and contract the wound closed in a temporally coordinated fashion. Associated with the postnatal tissue repair process is an inflammatory response whose prime function is to kill invading microbes and prevent infection at the site of repair. However, inflammatory cells, largely neutrophils and macrophages, also release a barrage of growth factor and cytokine signals during the repair process and some of these have been shown to be detrimental to healing. For example, we have shown that macrophages express PDGF at the wound site that is responsible for induction of *osteopontin* in wound fibroblast which in turn leads them to become fibrotic and form a scar (Mori R et al, *J Exp Med,* 2008). Chronic, non- healing wounds, as suffered by diabetics and the elderly, are always associated with a persistent and aberrant inflammatory response, and it is considered that chronic inflammation is the root cause of many human pathologies from arthritis to psoriasis. For this reason, any mechanisms of inflammatory cell resolution that might be harnessed for therapeutic dampening of the inflammatory response, are of both fundamental interest and significant clinical relevance.

MicroRNAs (miRNAs) are an abundant class of short (approx. 22 nucleotides), non-protein-coding RNAs involved in posttranscriptional gene regulation by translational repression or degradation of target mRNAs. Recently, we identified inflammation-related miRNAs using PU.1 KO mice lacking inflammatory response and found that *miR-142* and *miR-223* are involved in *Staphylococcus aureus* clearance at skin wound sites (Tanaka K et al, *J Invest Dermatol,* 2017) (de Kerckhove M et al, *EMBO Mol Med,* 2018) (Mori R, *Dev Growth Differ,* 2018).

Exacerbation of scarring can originate from a minority fibroblast population that is morphologically normal but has undergone inflammatory-mediated genetic changes in the wound microenvironment. However, the fundamental relationship between the molecular-spatial organization of the wound site and repair of the tissue at the single-cell level is unclear. So now, we try to develop a novel, high-resolution spatial multiomics method that integrates the spatial transcriptome with single-cell RNA sequencing and can identify new characteristic features of cell–cell communication and signaling directions during the repair process. The novel methodology described here may reveal the molecular mechanisms underlying fibroblast–inflammatory cell interactions and cell differentiation lineages that represent the initiation of scarring. The ultimate goal is to elucidate the wound tissue architecture as regulated by inflammation.

Curriculum Vitae

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Education
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Professional experience
2004-Present. Assistant Professor/Associate Professor/Professor
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2020-2022 Dean, College of Pharmacy, Pusan National University, Busan, Korea
2019-2020 Vice Dean, PNU International, Pusan National University, Busan, Korea
2013-2014 Visiting Professor, Laboratory of Neurosciences Biomedical Research Center, NIA, Baltimore, MD, USA
2008-2011 Department Head/ Vice Dean, Pharmacy, Pusan National University
2002-2004 Postdoctoral research Fellow, MAMMAG Department of Biological Chemistry University of California Irvine, Irvine, CA, USA

Achievements/Recent publications
Over 170 publicatins
Citations (12357), h-index (55), i10-index (143)

1. Arch Pharm Res. 2023 May;46(5):423-437
2. Carbon. 2023 Sep;213:118275
3. Free Radic Biol Med. 2023 Nov 1;208:194-210.
4. Talanta. 2024 Jan 15;267:125252. doi: 10.1016/j.talanta.2023.125252. Epub 2023 Sep 27.
5. Int J Biol Macromol. 2023 Nov 6;254(Pt 2):127903. doi: 10.1016/j.ijbiomac.2023.127903.
6. Mol Neurobiol. 2023 Nov 18. doi: 10.1007/s12035-023-03785-y.

Research Interest
1. Aging and age-related neurodegenerative disease
2. Environmental neurotoxicity

【 Closing Remark 】

I want to express my sincere gratitude to all who joined us at the SAGL-Pusan National University Joint Seminar 2024 focused on "Aging Research and Medical Innovation." It has been a truly enriching and collaborative event, where experts from diverse fields came together to share their knowledge and insights on aging and age-related diseases.

Throughout this symposium, I had the privilege of witnessing remarkable presentations and engaging discussions that have truly expanded my understanding and set the stage for future advancements in this vital field. The exchange of ideas and the connections formed between our institutions have been invaluable in driving innovative research and enhancing the well-being of the elderly.

I would like to extend my warm gratitude to all the organizers, speakers, and attendees who have contributed to the success of this symposium. Your dedication and passion have been instrumental in creating a platform for intellectual exchange and promoting interdisciplinary collaboration.

Once again, thank you all for your participation and valuable contributions. We eagerly anticipate future collaborations and the growth of our research communities. Thank you again for all participants and committee and hope to success our collaboration research.

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