The 54th Scientific Meeting of the Japanese Medical Society for Lung Surfactant and Biological Interface

日本肺サーファクタント・界面医学会（旧 日本界面医学会）

第54回学術研究会

肺サーファクタントおよび
界面現象に関する学術集会

会 期 2018年 10月27日（土）

会 場 九州大学医学部百年講堂
福岡県福岡市東区馬出3丁目1−1

会 長 橋本 修一
福岡歯科大学
生体構造学講座 病態構造学分野

テーマ

肺上皮研究の最前線

−幹細胞研究から再生医療へ−

第54回日本肺サーファクタント・界面医学会学術研究会
開催にあたって

日本肺サーファクタント・界面医学会 第54回学術研究会
会 長　**橋本 修一**　福岡歯科大学 生体構造学講座
病態構造学分野

この度、伝統ある日本肺サーファクタント・界面医学会第54回学術研究会を福岡で開催させていただくことになり大変光栄に存じます。また、福岡での開催は、私の恩師であります居石克夫先生（元 九州大学医学部病理学第一講座）が平成2年に第26回の学術研究会を担当されて以来、28年ぶりの開催になり、皆様を福岡の地に久しぶりにお招きすることができ大変喜ばしく存じます。

肺サーファクタントは肺胞Ⅱ型上皮細胞から産生分泌されるアポ・リポ蛋白で難治性の呼吸器疾患の発症に関わる重要な物質として本学会の主な研究テーマとなってきました。近年は、肺サーファクタントそのものに関する研究から、Ⅱ型・Ⅰ型肺胞上皮の機能・発達異常や傷害と、肺の発達異常、急性肺傷害、間質性肺炎、COPD および肺癌などの発生との関連、また、肺サーファクタントの肺炎などの炎症における免疫学的防御機構への関与など幅広い分野への研究発展がなされてまいりました。さらには、肺胞Ⅱ型上皮の発現に特異的な SFTPC や Club/Clara 細胞に特異的な CCSP などの遺伝子発現を利用した分化マーカーや、これらの遺伝子のプロモーター領域を利用してのそれぞれの肺上皮特異的遺伝子発現あるいは欠損を誘導するトランスジェニックマウスの開発、また、それらを利用した肺幹細胞の同定や肺上皮分化誘導の研究など肺上皮に関する分子細胞生物学的な基礎研究も飛躍的に進歩し、再生医療への応用研究でも進展がみられるようになってきました。

今回の学術研究会では、これまでの肺サーファクタントの研究テーマを基盤に、さらに、“肺上皮の幹細胞からの分化誘導と機能分化、再生医療への応用”にテーマをおいた学会にしたいと考えています。これに即し、この分野の研究の発展を期待して、今回は米国から肺の幹細胞研究の世界的権威であります Prof. Barry R. Stripp、および、Prof. Darrell N. Kotton をお呼びして、二人の招請講演に加え、国内の研究の第一線でご活躍中の先生方の教育講演、特別講演、若手特別講演を企画いたしました。本学術研究会の開催を通して、関連諸氏のみなさまに多くのご参加をいただき、意見交換の場の良い機会となって、少しでも医学全体の発展に貢献できれば幸甚に存じます。

開催概要

肺上皮研究の最前線
―幹細胞研究から再生医療へ―

Front-line of Lung Epithelial Research
―Stem Cell Research to Regenerative Medicine―

会　期	2018年10月27日（土） 8：50～17：40
会　場	九州大学医学部百年講堂（福岡県福岡市東区馬出3丁目1-1） 口演会場：中ホール1＋2 ポスター会場：中ホール3
会　長	橋本 修一（福岡歯科大学 生体構造学講座 病態構造学分野）

懇親会	2018年10月27日（土） 18：00～20：00
会　場	九州大学医学部百年講堂 カフェテリア（Century Cafe）
会　費	5,000円

役員会	2018年10月26日（金） 17：00～17：45
会　場	九州大学医学部百年講堂 会議室3

会長招宴 （役員のみ）	2018年10月26日（金） 18：30～20：30
会　場	博多 百年蔵 https://www.ishikura-shuzou.co.jp/
会　費	10,000円
備　考	会長招宴開始直前に記念撮影を会場内で執り行います。

演者へのお願い

(1) 今回の第54回学術研究会の一般発表は全てポスター発表で行うこととさせていただきます。

(2) 口演スライドの作成は英語表記で、ポスターの作製も可能な限り英語表記で行ってください。
また、口演発表は英語で、ポスター発表の質疑応答も可能な限り英語でお願いいたします。

(3) 口演発表

1) 演者の先生へ

- 発表は基本的に全て Windows 用 PowerPoint のデータで受け付け致します。USB にデータを保存し受付にお渡しください。
- 演者は発表の30分前までにデータの受付と試写を済ませてください。
- DLP プロジェクターと PC との接続は D-Sub 15ピン（アナログ）端子接続しか対応していません。
どうしてもご自分のコンピューターを使用されたい方は、あらかじめ事務局にご報告の上接続の変換ケーブルをご用意ください。
- 発表および質疑時間は以下のとおりとします。時間厳守で発表をお願いいたします。

教育講演	：発表40分＋質疑応答10分　計50分
特別講演1・2	：発表40分＋質疑応答10分　計50分
招請講演1・2	：発表50分＋質疑応答10分　計60分
若手特別講演1・2	：発表25分＋質疑応答 5 分　計30分

- 口演発表は英語でお願いいたします。次演者は、前演者の登壇後、直ちに次演者席にお着き下さい。
- 発表終了1分前に1回の呼鈴を、発表終了時間に2回の呼鈴を鳴らして合図を行います。
- ポインターは学会側で準備いたします。

2) 座長の先生へ

- 座長の先生は、ご担当のセッション・講演開始30分前までに次座長席にお着き下さい。質疑応答を含め、すべて英語での進行をお願いいたします。

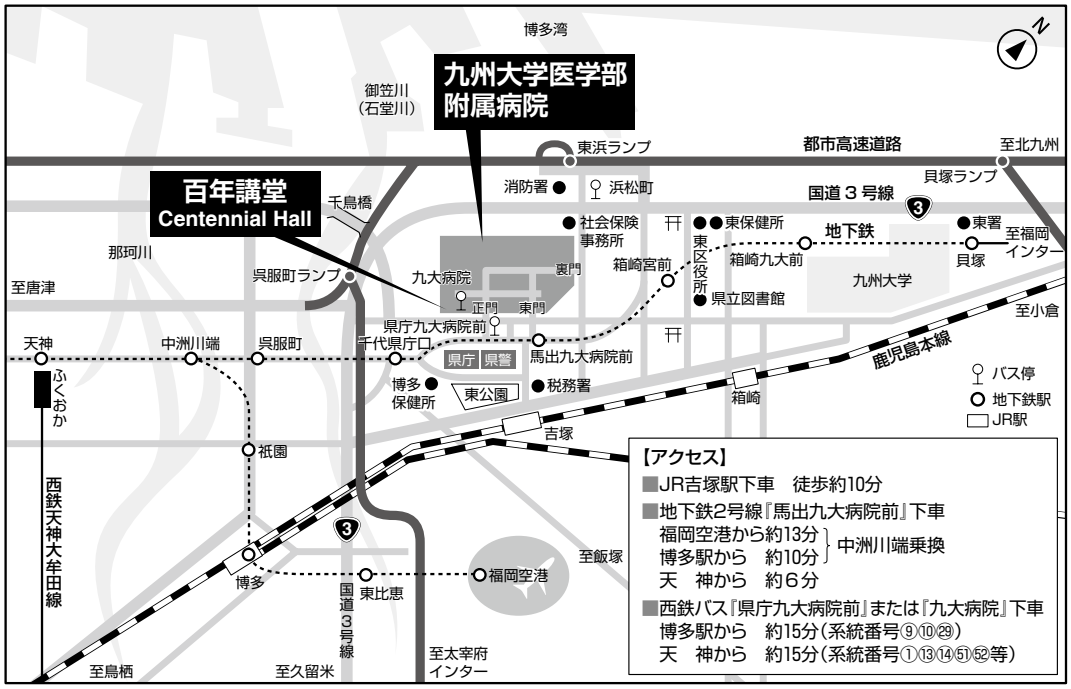
(4) ポスター発表

- ポスターの大きさは縦180㎝×横120㎝(パネル面積)以内とします。
- ポスター上部の発表タイトル左の縦20㎝×横20㎝の領域内に、学会から割り当てられた演題ナンバー(P-xx)を記載してください。
- 受付を発表当日の8:30までに済ませ、9:00までにはパネルへの掲示を終了してください。
- ポスター掲示はあらかじめ指定されているご自分のポスターナンバー(P-xx)の位置に掲示してください。
- ポスター発表者は、15:10～16:20のポスターディスカッションの時間帯は自分の発表ポスターの前に在席し、閲覧者からの質問にお答えください。座長は設けませんので英語でのご説明など各自でご対応をお願いします。
- ポスター発表終了後は16:30までにポスターを撤去してください。
- 最優秀ポスター賞を選出し、若手特別講演2の終了後に、筆頭演者に対し表彰を行います。
  選出は第54回学術研究会に出席された本学会役員の投票による最多得票数で決定させていただきます。

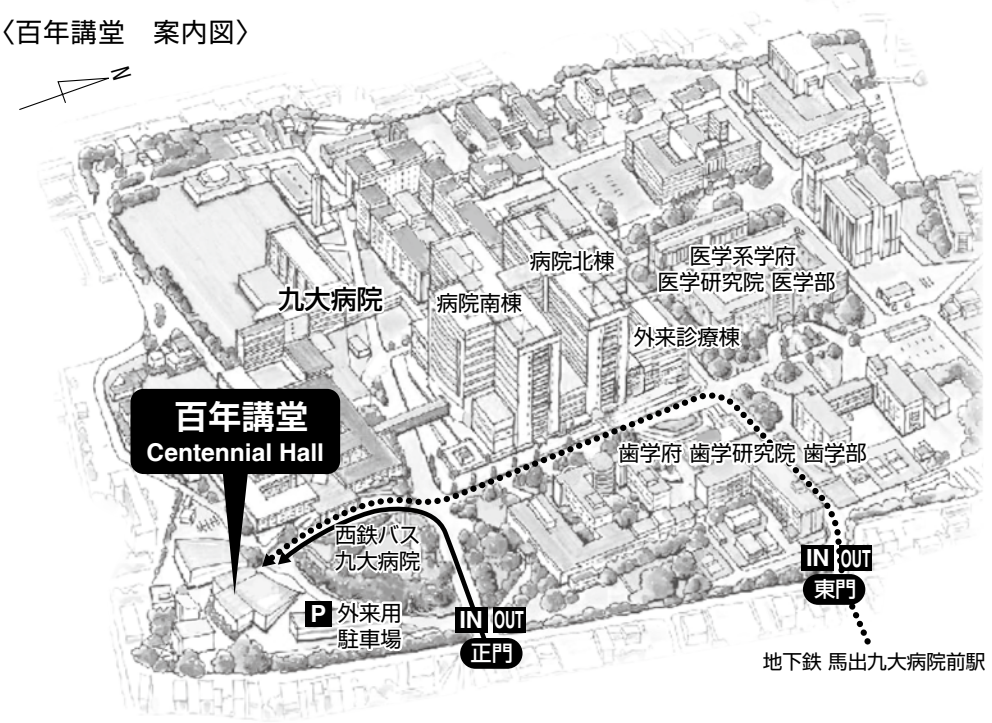
  ※本学会役員の皆様へ:
  学会当日の受付で最優秀ポスター賞を選ぶための投票用紙を配布いたします。投票用紙に最も優秀と考えられたポスターNo.(P-xx)と発表筆頭演者の氏名、ならびに投票者の氏名をご記入後、ポスターディスカッションの終了時(16:20)までに投票箱(学会受付に準備しておきます)にご投入下さい。尚、記名投票といたしますので、投票者の記名のないものは無効といたします。

会場周辺図

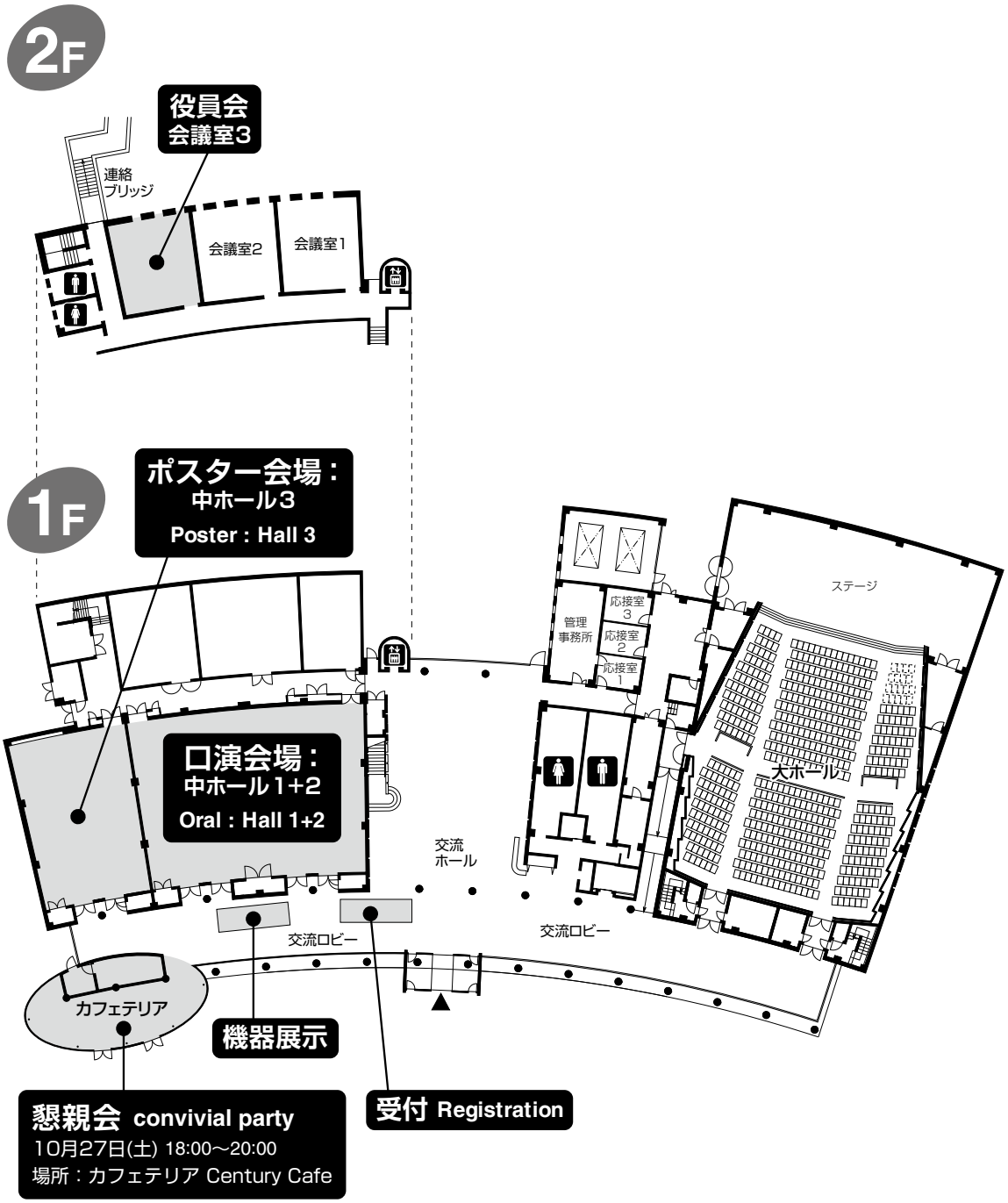
〈会場への交通〉



〈百年講堂　案内図〉



フロア図


2F
役員会
会議室3
連絡
ブリッジ
会議室2
会議室1
1F
ポスター会場：
中ホール3
Poster : Hall 3
口演会場：
中ホール1+2
Oral : Hall 1+2
管理
事務所
応接室
3
応接室
2
応接室
1
ステージ
大ホール
交流
ホール
交流ロビー
交流ロビー
カフェテリア
機器展示
懇親会 convivial party
10月27日(土) 18:00～20:00
場所：カフェテリア Century Cafe
受付 Registration

プログラム

Oral session：Hall1＋2（口演発表：中ホール 1＋2）

8：50～9：00

Opening address（開会の辞）

Shuichi Hashimoto, Pres.

9：00～9：50

Instructive Lecture（教育講演）

Chair：Prof. Hiroki Takahashi（Department of Respiratory Medicine and Allergology, Sapporo Medical University School of Medicine）

“Role of group 2 innate lymphoid cells in lung diseases”

Kazuyo Moro　Team Leader of Laboratory for Innate Immune Systems
RIKEN Center for Integrative Medical Sciences (IMS)

9：50～10：40

Special Lecture 1（特別講演1）

Chair：Prof. Jun Ohno（Research Center for Regenerative Medicine, Fukuoka Dental College）

“Application of human iPS cell technologies for lung research”

Shimpei Gotoh　Associate Professor of
1. Department of Drug Discovery for Lung Diseases, Graduate School of Medicine, Kyoto University
2. Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University

10：40～11：30

Special Lecture 2（特別講演2）

Chair：Prof. Akira Suwabe（Department of Laboratory Medicine, Iwate Medical University School of Medicine）

“Application of decellularized organ scaffolds for respiratory tissue engineering”

Tomoshi Tsuchiya　Associate Professor of Division of Surgical Oncology, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences

11:30～11:50

Plenary meeting（総会）

11:50～12:55

Lunch break・Poster viewing（昼休憩・ポスター閲覧）

12:55～13:00

President-Elect address（次期会長挨拶）

Masaki Fujita（Professor of Respiratory Medicine, Fukuoka University）

13:00～14:00

Invited Lecture 1（招聘講演1）

Chair：Prof. Shuichi Hashimoto（Section of Pathology, Department of Morphological Biology, Fukuoka Dental College）

“Epithelial progenitor cell dysfunction in chronic lung disease”

Barry R. Stripp
Professor of Medicine & Biomedical Sciences
Goldsmith Chair in Gene Therapeutics Research
Director, Lung Stem Cell Research
Lung & Regenerative Medicine Institutes
Director, Postdoctoral Program
Cedars-Sinai Medical Center

14:00～15:00

Invited Lecture 2（招聘講演2）

Chair：Prof. Shuichi Hashimoto（Section of Pathology, Department of Morphological Biology, Fukuoka Dental College）

“Modeling surfactant dysfunction with pluripotent stem cell-derived alveolar epithelium”

Darrell N. Kotton
David C. Seldin Professor of Medicine
Director, Center for Regenerative Medicine (CReM)
Boston University and Boston Medical Center

15:00～15:10

Conferment of certificate of appreciation（感謝状授与）　Shuichi Hashimoto, Pres.

15:10～16:20

Poster discussion・Vote for the Poster Award（ポスターディスカッション・採点）

16:30～17:00

Special Lecture by Young Researcher 1（若手特別講演1）

Chair：Associate Prof. Shinji Okano（Section of Pathology, Department of Morphological Biology, Fukuoka Dental College）

“MOB1 controls lung morphogenesis and tumor formation”

Kohei Otsubo　Assistant Professor of
1. Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu University
2. Cancer Center, Kyushu University Hospital

17:00～17:30

Special Lecture by Young Researcher 2（若手特別講演2）

Chair：Associate Prof. Shinji Okano（Section of Pathology, Department of Morphological Biology, Fukuoka Dental College）

“Gene signature driving invasive mucinous adenocarcinoma of the lung”

Koichi Tomoshige　Senior Pneumoconiosis Examination Physician
Industrial Health Division, Occupational Safety and Health Department, Labour Standards Bureau, Ministry of Health, Labor and Welfare

17:30～17:35

Poster Award ceremony（最優秀ポスター賞授賞式）　Shuichi Hashimoto, Pres.

17:35～17:40

Closing address（閉会の辞）　Shuichi Hashimoto, Pres.

Poster session：Hall 3（ポスター発表：中ホール3）

8：00～9：00

Poster display（ポスター掲示）

9：00～16：20

Poster viewing（ポスター展示）

15：10～16：20

Poster discussion・Vote for the Poster Award（ポスターディスカッション・採点）

P-01 Carboxypeptidase M (CPM) expression analysis in the developing and mature mouse lung

○Shohei Yoshimoto[1)], Shinpei Gotoh[2)3)], Shuichi Hashimoto[1)]

1）Section of Pathology, Department of Morphological Biology, Division of Biomedical Sciences, Fukuoka Dental College

2）Department of Drug Discovery for Lung Diseases, Graduate School of Medicine, Kyoto University

3）Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University

P-02 Recapitulating Alveolar Epithelial Type 2 Cell Dysfunction in Hermansky-Pudlak Syndrome Type 2 Patient-derived Induced Pluripotent Stem Cells

○Yohei Korogi[1)], Shimpei Gotoh[1)2)], Satoshi Ikeo[1)], Yuki Yamamoto[1)], Naoyuki Sone[1)], Koji Tamai[1)], Isao Asaka[3)], Akitsu Hotta[4)], Toyohiro Hirai[1)]

1）Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University

2）Department of Drug Discovery for Lung Diseases, Graduate School of Medicine, Kyoto University

3）Department of Fundamental Cell Technology, Center for iPS Cell Research and Application, Kyoto University

4）Department of Clinical Application, Center for iPS Cell Research and Application, Kyoto University

P-03 An electron microscopic study of the pathogenesis for the pulmonary surfactant lamellar structural bodies

○Hidekatsu Matsumura[1)2)], Tsunetomo Takei[3)], Shoichi Chida[3)], Takashi Takagi[4)], Motoaki Kobayashi[5)], Hibiki Takahashi[5)], Seiou Nakamura[6)]

1）Kouaikai Kounosu Kyousei Hospital

2）Kounosu Kyousei Clinic

3）Iwate Medical College

4）Syouwa University Electron Microscopic Room

5）Seputosapie (Inc)

6）Seiseigen (Inc)

P-04 Double stranded RNA induces vulnerability of airway epithelial barrier integrity by influencing airway basal cells

○Shinichi Okamoto, Shuichiro Maruoka, Kota Tsuya, Asami Fukuda, Shiho Yamada, Yusuke Kurosawa, Kaori Soda, Yasuhiro Gon

Division of Respiratory Medicine, Department of Internal Medicine, Nihon University School of Medicine

P-05 SF-10 adjuvant derived from pulmonary surfactant enhances incorporation of antigens into intestinal antigen presenting cells and induces antigen specific immunities

○Takashi Kimoto, Sakai Satoko, Keiko Kameda, Etsuhisa Takahashi, Hiroshi Kido

Div. of Enz Chem., Inst. for Enz Res., Tokushima Univ

P-06 Induced Expression of Mutant Surfactant Protein C in Mice Results in an Idiopathic Pulmonary Fibrosis Phenotype

○Shinichi Nureki[1)2)], Yaniv Tomer[2)], Alessandro Venosa[2)], Scott J. Russo[2)], Jeremy Katzen[2)], Surafel Mulugeta[2)], Junichi Kadota[1)], Michael F. Beers[2)]

1) Department of Respiratory Medicine and Infectious Diseases, Oita University Faculty of Medicine

2) Pulmonary, Allergy, and Critical Care Division, Department of Medicine, Perelman School of Medicine, University of Pennsylvania

P-07 Role of pulmonary surfactant protein in mouse lung injury model with dioxins

○Kunihiro Suzuki, Toyoshi Yanagihara, Naoki Hamada, Eiji Harada, Koichiro Matsumoto, Yoichi Nakanishi

Research Institute for Diseases of the Chest Graduate School of Medical Sciences Kyushu University

P-08 Serum KL-6 and SP-D Levels in Patients with Pleuroparenchymal Fibroelastosis

○Hisako Kushima[1)2)], Hiroshi Ishii[1)2)], Kentaro Watanabe[1)2)], Masaki Fujita[1)], Takashi Ogura[2)3)]

1) Department of Respiratory Medicine, Fukuoka University Hospital

2) Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center

3) The Tokyo Diffuse Lung Disease Study Group

P-09 Development of treatment for chronic obstructive pulmonary disease based on inducing differentiation by 1, 25-dihydroxyvitamin D3

○Tomomi Akita[1)2)], Chikamasa Yamashita[1)2)]

1) Department of Pharmaceutics and Drug Delivery, Faculty of Pharmaceutical Sciences, Tokyo University of Science

2) Fusion of Regenerative Medicine with DDS, Research Institute for Science and Technology, Tokyo University of Science

P-10 Nicotine induces resistance to erlotinib therapy in non-small cell lung cancer cells treated with serum from human patients

○Tatsuya Imabayashi, Nobuyo Tamiya, Yoshiko Kaneko, Tadaaki Yamada, Junji Uchino, Koichi Takayama

Department of Pulmonary Medicine, Kyoto Prefectural University of Medicine Graduate School of Medical Science

P-11 A possibility of B cell activating factor as a therapeutic target for Autoimmune Pulmonary Alveolar Proteinosis

○Masaki Hirose, Toru Arai, Chikatoshi Sugimoto, Yoshikazu Inoue

National Hospital Organization Kinki-Chuo Chest Medical Center

P-12 Genetic diversity of Alveolar capillary dysplasia with misalignment of pulmonary veins in Japanese infants

○Masahiko Ikeda, Kazutoshi Cho, Yuta Furuse, Tetsuo Onda, Akiko Ando, Hidemichi Watari

Maternity and Perinatal Care Center, Hokkaido University hospital

P-13 Two cases of autoimmune pulmonary alveolar proteinosis: Exploring the pathogenesis through case studies

○Kimiyuki Ikeda[1)], Hirofumi Chiba[1)], Takafumi Yorozuya[1)], Takeyuki Sawai[1)], Atsushi Saito[1)2)], Koji Kuronuma[1)], Hirotaka Nishikiori[1)], Mitsuo Otsuka[1)], Hiroki Takahashi[1)]

1) Department of Respiratory Medicine and Allergology, Sapporo Medical University School of Medicine

2) Department of Biochemistry, Sapporo Medical University School of Medicine

P-14 Surface properties of Gemini type perfluorinated surfactants with DPPC at the air-water interface

○Osamu Shibata[1)], Riku Kato[1)], Hiromichi Nakahara[2)]

1) Department of Biophysical Chemistry, Faculty of Pharmaceutical Sciences, Nagasaki International University

2) Laboratory of Industrial Pharmacy, Daiichi University of Pha

P-15 Langmuir film properties of partially perfluorinated alcohol with F-DPPC at the air-water interface

○Osamu Shibata[1)], Ryosuke Kawata[1)], Hiromichi Nakahara[2)]

1) Department of Biophysical Chemistry, Faculty of Pharmaceutical Sciences, Nagasaki International University

2) Laboratory of Industrial Pharmacy, Daiichi University of Pharmacy

P-16 Langmuir film of a tetrazine-containing gemini amphiphile: Interaction with biomembrane lipids

○Osamu Shibata[1)], Hiromichi Nakahara[2)], Masayori Hagimori[3)], Takahiro Mukai [4)]

1) Department of Biophysical Chemistry, Faculty of Pharmaceutical Sciences, Nagasaki International University
2) Laboratory of Industrial Pharmacy, Daiichi University of Pharmacy
3) Department of Pharmaceutical Informatics, Graduate School of Biomedical Sciences, Nagasaki University
4) Department of Biophysical Chemistry, Kobe Pharmaceutical University

P-17 Toward the Prediction of Translocation Studies of Nanoparticles Using in Vitro Alveolar Epithelial Models

○Kikuo Komori[1)], Kodai Harano[1)], Xinying Xu[1)], Ayaka Uemura[1)], Rie Ogasawara[2)], Akira Suwabe[2)], Yasuyuki Sakai[1)]

1) The University of Tokyo
2) Iwate Medical University

16：20～16：30

Poster removal（ポスター撤去）

Abstract

Instructive Lecture

Special Lecture

Invited Lecture

Special Lecture by Young Researcher

Poster session

Role of group 2 innate lymphoid cells in lung diseases

Kazuyo Moro

Team Leader of Laboratory for Innate Immune Systems
RIKEN Center for Integrative Medical Sciences (IMS)

Recent studies have revealed new types of lymphocytes functioning in innate immune responses that are collectively called innate lymphoid cells (ILCs). Unlike T and B lymphocytes, ILCs lack Rag-dependent antigen-specific receptors and are activated by cytokines produced by other innate immune cells or epithelial cells. ILCs have been divided into 3 groups based on their cytokine production profiles; group 1 ILC including NK cells and ILC1 produce IFN γ, group 2 ILC (ILC2) including natural helper cells, nuocytes and innate helper type 2 cells produce type 2 cytokines such as IL-5, IL-6 and IL-13, and group 3 ILC including lymphoid tissue inducer (LTi) cells and ILC3s produce IL-17 and IL-22.

ILCs play important roles in protection against various invading microbes including multicellular parasites, and in the maintenance of homeostasis and repair of epithelial layers. ILC2 produce a large amount of IL-5 and IL-13 in response to IL-25 or IL-33, and induce eosinophilia and goblet cell, both of which act to protect against helminth infection and exacerbation of allergy. Since we discovered ILC2 in 2010, many other research groups have joined this research field and identified new immune responses that are regulated by ILC2. In particular, the importance of ILC2 in allergic diseases has received a fair amount of attention and new evidence indicates that allergic disorders occur not only from allergen-specific pathways but are also induced by allergen non-specific pathways due to ILC2 activation.

Curriculum Vitae

EDUCATION:

2003 D.D.S.	Nihon University School of Dentistry
2010 Ph.D.	Keio University School of Medicine

Main Research Field:

Immunology (Allergology, Parasitology)

RESEACH FELLOWSHIPS:

2007-2008	Postdoctoral fellow; The 21st Century COE, Keio University School of Medicine
2008-2011	Postdoctoral fellow; Global COE, Keio University School of Medicine
2011-2016	Investigator; PRESTO, JST
2012-2013	Senior research scientist; Laboratory for Immune Cell System, RCAI, RIKEN
2013-2015	Senior research scientist; Laboratory for Immune Cell System, IMS, RIKEN
2013-2016	Visiting associate Professor; Division of Immunobiology, Department of Medical Life Science, Graduate School of Medical Life Science, Yokohama City University
2015-	Team leader; Laboratory for Innate Immune System, IMS, RIKEN (present)
2016-	Visiting professor; Division of Immunobiology, Department of Medical Life Science, Graduate School of Medical Life Science, Yokohama City University (present)
2016-	Programing officer; Japan Agency for Medical Research and Development (present)
2018-	Visiting professor; Graduate School of Medicine, Osaka University (present)

Application of human iPS cell technologies for lung research

Shimpei Gotoh

Associate Professor of

1. Department of Drug Discovery for Lung Diseases, Graduate School of Medicine, Kyoto University

2. Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University

Lung epithelial cells are directly exposed to air and often affected by foreign matter or pathogen resulting in various lung diseases. Although animal disease models have been used for finding novel mechanisms of the diseases and developing novel therapeutic approaches, it has been sometimes difficult to apply the results of mouse models to human diseases. In order to diminish the discrepancy of mouse models and human diseases, human organoid models are expected to be another approach toward first-in-human study. Organoid technologies have been originally developed from the study of tissue stem cells. They were also reported to be beneficial for inducing functional ectoderm such as cerebral cortex from embryonic stem cells. We applied these analogous techniques to lung cell differentiation in organoids from human induced pluripotent stem cells (iPSCs).

Human iPSCs were stepwise differentiated into definitive endoderm, anterior foregut endoderm and NKX2.1+ lung bud cells, recapitulating lung development in a dish. After Carboxypeptidase M (CPM)-based cell sorting, lung bud cells were further differentiated into airway or alveolar cells in organoids, respectively. The induced airway cells involved various lung cells and proved to have muco-ciliary function, whereas the induced alveolar cells demonstrated well organized lamellar bodies and functions of restoration and secretion of phospholipids. In the era of genome editing, disease modeling by using human iPSCs is drastically advancing. If we could obtain patients' blood or fibroblasts, patient-specific iPSCs can be generated and we are able to obtain airway and alveolar cells of the patients. If the iPSCs are genetically corrected, we can characterize the mechanism of the disease by comparing patient-specific iPSCs with the isogenic counterparts. Disease modeling is also achievable by genetic modification of normal human iPSCs.

Although there is an increasing demand for human lung cells, it is still difficult to obtain and expand the primary lung cells such as type II alveolar cells unlimitedly. Human iPSCs provide not only normally differentiated lung cells but also disease specific cells for studying human lung diseases. Applications of hiPSC-derived lung cells to disease modeling and regenerative medicine are still at the beginning but we are hopeful about the future.

Curriculum Vitae

Research Interests and Experience

Cell biology and translational research

Application of human iPS cells for respiratory medicine

Education

2004:	M.D. (Kyoto University)
1998-2004:	Mentored by Dr. Shoichiro Tsukita for cell biology
2015:	Ph.D. (Kyoto University)
2009-2014:	Mentored by Dr. Kenji Osafune for stem cell biology and Dr. Michiaki Mishima for respiratory medicine

Positions Held

Apr. 2017:	Associate Professor, Graduate School of Medicine, Kyoto University
Mar. 2015:	Assistant Professor, Kyoto University Hospital
Sep. 2014:	Clinical Fellow, Kyoto University Hospital
Oct. 2008:	Clinical Fellow, National Hospital Organization Minami-Kyoto Hospital
Apr. 2004:	Resident Doctor, St. Luke's International Hospital (Tokyo)

Awards and Memberships

- Kyoto University Medical Student Support-Fund Young Investigator Award (KMYIA) (2015)
- Health-promoting Association for Respiratory Medicine of Nishi-Nippon, Medical Prize (2014)
- ISSCR Travel Award (2014)
- Fellow of the Japanese Society of Internal Medicine
- Board Certified Member of Japanese Society of Respiratory Medicine

Publications (*Corresponding author)

- Yamamoto Y, Gotoh S*, et al. ***Nat Methods.*** 2017; 14:1097-1106.
- Konishi S, Gotoh S*, et al. ***Stem Cell Rep.*** 2016; 6: 18-25.
- Gotoh S*, Ito I*, et al. ***Stem Cell Rep.*** 2014; 3: 394-403.
- Gotoh S* and Chohnabayashi N. ***N Engl J Med.*** 2009; 360: e29. (Image In Clinical Medicine)
- Gotoh S*, et al. ***Eur Respir J.*** 2008; 31: 1268-1273.
- Nitta T, Hata M, Gotoh S, et al. ***J Cell Biol.*** 2003; 161: 653-660.
- Kiuchi-Saishin Y, Gotoh S, et al. ***J Am Soc Nephrol.*** 2002; 13: 875-886.

Application of decellularized organ scaffolds for respiratory tissue engineering

Tomoshi Tsuchiya

Associate Professor of Division of Surgical Oncology,
Department of Translational Medical Sciences,
Nagasaki University Graduate School of Biomedical Sciences

Although biomaterials had been used for a long time in the field of medicine, the expression "tissue engineering" first arose in the lexicon in 1993 with the remarkable achievement of the transplantation of human auricle-shaped regenerated cartilage into the back of a mouse. Since this success, tissue engineering studies have been advancing from simple tissue generation to a stage of whole organ generation with three-dimensional reconstruction. Decellularized scaffolds have been widely used in the field of cardiovascular surgery, plastic surgery and orthopedics because they can be easily harvested from animals or humans. When a patient's own cells can be seeded onto decellularized biomaterials, theoretically this will create immunocompatible organs generated from allo- or xeno-organs. The most important characteristic of this technique is that the delicate three-dimensional structure of the organ can be maintained during the tissue engineering process. The other major feature of using decellularized organ scaffolds correlates with immunogenicity; reseeding by the patient's own cells can generate organs with minimized immunogenicity. The creation of non-immunogenic organs provides the ideal transplant organ without the necessity of using immunosuppressive drugs which can have deleterious side effects.

Since the 2008 report of Ott and colleagues on the decellerization and reseeding of rat heart scaffolding, the potential of this technique for organ generation has been demonstrated in heart, liver and kidney. For the lung, many studies have been performed since the reports of Petersen and Ott in 2010. In 2011, we introduced the technique in Japan using rat lung and trachea models. In our research on preserving the pulmonary extracellular matrix (ECM), we showed that the pH of the CHAPS solution affected the decellularization process and that high alkaline NaOH itself could decellularize rat lungs. In our research on pulmonary vasculature reconstruction, we showed that adipose-derived stem cells (ASCs) express the pericyte markers NG2 and PDGFR β when co-cultured with rat lung microvascular endothelial cells (RLMVECs). This indicates that seeded ASCs wrap the outer lumen of the vasculature and can reconstruct mature vascular networks in the decellularized lung scaffold.

In this presentation, we will discuss our approaches using this technique, current trends, and future issues for medical application.

Curriculum Vitae

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE or POSITION	YEAR(s)	FIELD OF STUDY
Nagasaki University School of Medicine, Nagasaki, Japan	M.D.	1988-1993	Medicine
Department of Pathology & Gerontology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan	PhD.	1998-2002	Pathology and Molecular Biology
Department of Biochemistry, University of California, Riverside, USA	Postdoctoral Researcher	2002-2004	Biochemistry and Molecular Biology
Biomedical Engineering Vascular Biology and Therapeutics, Yale University, USA	Visiting Scientist	2011-2012	Biomedical Engineering
Division of Surgical Oncology, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan	Assistant Professor	2008-2010	Thoracic Surgery
	Senior Assistant Professor	2010-2015	
	Associate Professor	2015-	

Professional Experience:

1993-1995	Junior Resident - Toranomon Hospital, Tokyo, Japan
1995-1998	Senior Resident - Department of Surgery, Nagasaki University School of Medicine, Nagasaki, Japan
1998-2002	Research Assistant - Department of Pathology & Gerontology, Nagasaki University Graduate School of Biomedical Science, Nagasaki University School of Medicine, Nagasaki, Japan
2002-2004	Postdoctoral Researcher - Department of Biochemistry, University of California, Riverside, USA
2004-2008	Surgical staff - Oita Prefectural Hospital and Nagasaki University Graduate School of Biomedical Sciences
2008-2010	Assistant Professor - Department of Surgical Oncology, Nagasaki University Graduate School of Biomedical Sciences
2010-2015	Senior Assistant Professor
2011-2012	Visiting Scientist, Biomedical Engineering Vascular Biology and Therapeutics, Yale University, USA
2015-	Associate Professor - Department of Surgical Oncology, Nagasaki University Graduate School of Biomedical Sciences
2017-	Subdirector - Nagasaki Clinical Oncology Center

Epithelial progenitor cell dysfunction in chronic lung disease

Barry R. Stripp

Professor of Medicine & Biomedical Sciences
Goldsmith Chair in Gene Therapeutics Research
Director, Lung Stem Cell Research
Lung & Regenerative Medicine Institutes
Director, Postdoctoral Program
Cedars-Sinai Medical Center

Chronic diseases of small airways and the gas-exchange region have an enormous societal impact both within the US and worldwide. Of the estimated 225,000 deaths attributed to lung disease in the US in 2007, greater than 50% were due to chronic obstructive pulmonary disease (COPD). Less prevalent but with more limited treatment options is idiopathic pulmonary fibrosis (IPF), the most common type of interstitial pneumonia, which has a mean survival time of 3 years after initial diagnosis and afflicts upwards of 0.2% of the population in North America and Europe. Changes in lung function and cellular composition are pathognomonic of chronic lung disease. We used single cell RNA-sequencing to define changes in the molecular phenotype of lung cell types isolated from normal tissue donors and from explant tissue of patients undergoing transplantation for either end-stage IPF or COPD. We found significant depletion of normal alveolar type 2 (AT2) cells in both IPF and COPD, in addition to evidence for p53 activation and induction of epithelial senescence. We employed animal models of p53 gain- or loss-of function, in addition to a novel mouse model of conditional senescence, to show that p53 regulates both quiescence and differentiation of epithelial progenitor cells in the healthy and diseased lung and that senescence rather than loss of AT2 cells is the principal driver of progressive pulmonary fibrosis. Taken together, our data suggested an important role of pathways regulating progenitor cell renewal, differentiation and senescence in pathological tissue remodeling seen in patients with chronic lung disease.

Funded by the California Institute for Regenerative Medicine, NASA, NIH and the Bram and Elaine Goldsmith Chair in Gene Therapeutics Research (Stripp).

Curriculum Vitae

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of the West of England, Bristol, UK	B.S	05/1984	Applied Biological Sci.
East Carolina University School of Medicine, Greenville, NC.	Ph.D.	08/1989	Microbiology and Immunology
University of Cincinnati, Cincinnati, OH.	Postdoctoral	06/1991	Lung Molecular Biology

Positions and Honors

1991-1993	Research Scholar in Pulmonary Biology, Department of Pediatrics, CHRF, Cincinnati, OH.
1993-1994	Research Instructor in Pulmonary Biology, Department of Pediatrics, CHRF, Cincinnati, OH.
1994-1998	Assistant Professor of Environmental Med. and Peds., University of Rochester, Rochester, NY.
1995-1998	Assistant Professor of Oncology, University of Rochester, Rochester, NY
1995-1996	Director, U. of R. Transgenic Mouse Facility, University of Rochester, Rochester, NY.
1997-2000	Executive Director, U. of R. Transgenic Mouse Facility, University of Rochester, Rochester, NY.
1999-2001	Associate Professor of Env. Med., Peds. and Oncol., University of Rochester, Rochester, NY
2001-2003	Adj. Assoc. Professor of Environmental Medicine, University of Rochester, Rochester, NY.
2001-2006	Associate Professor of Environmental and Occupational Health, and of Cell Biology and Physiology, University of Pittsburgh, Pittsburgh, PA.
2001-2007	Director, Molecular Toxicology Training Program, University of Pittsburgh, Pittsburgh, PA.
2003-2007	Faculty of the University of Pittsburgh Cancer Institute, Pittsburgh, PA.
2006-2007	Director, Center for Lung Regeneration, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA.
2007	Professor of Environmental and Occupational Health, University of Pittsburgh, Pittsburgh, PA.
2007-2008	Instructor (Temporary) of Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, Duke University Medical Center, Durham, NC.
2008-2012	Professor of Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, Duke University Medical Center, Durham, NC.
2008-2012	Professor of Cell Biology, Duke University Medical Center, Durham, NC.
2008-2012	Full Member, Duke Comprehensive Cancer Center, Stem Cell and Signal Transduction Research Cores, Duke University Medical Center, Durham, NC.
2013-Pres.	Professor and Director of Lung Stem Cell Research and Research Scientist IV, Dept of Medicine, Lung and Regenerative Medicine Institutes, Cedars-Sinai Medical Center, Los Angeles, CA.
2013-Pres.	Professor, Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA.
2013-Pres.	Adjunct Professor of Medicine and Cell Biology, Duke University Medical Center, Durham, NC.
2013-Pres.	Bram and Elaine Goldsmith Chair in Gene Therapeutics Research, Cedars-Sinai Medical Center, Los Angeles, CA.
2014-Pres.	Professor of Medicine in Residence stage III, David Geffen School of Medicine, University of California at Los Angeles.
2015-Pres.	Full Member, Samuel Orshin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA.
2015-Pres.	Director, Cedars-Sinai Postdoctoral Training Program, CSMC, Los Angeles, CA.

Modeling surfactant dysfunction with pluripotent stem cell-derived alveolar epithelium

Darrell N. Kotton

David C. Seldin Professor of Medicine
Director, Center for Regenerative Medicine (CReM)
Boston University and Boston Medical Center

Lung alveoli, which are unique to air breathing organisms, have been challenging to generate from pluripotent stem cells (PSCs), in part because there are limited model systems available to provide the necessary developmental roadmaps for in vitro differentiation. Several groups have now optimized the generation of alveolar epithelial type 2 cells (AEC2s), the facultative progenitors of lung alveoli, from human PSCs. Our approach involves multicolored fluorescent reporter lines allowing investigators to track and purify human SFTPC+ alveolar progenitors as they emerge from endodermal precursors in response to stimulation of Wnt and FGF signaling. Purified PSC-derived SFTPC+ cells form monolayered epithelial "alveolospheres" in 3D cultures without the need for mesenchymal support, exhibit self-renewal capacity, and display additional AEC2 functional capacities. Footprint-free CRISPR-based gene correction of PSCs derived from patients carrying a homozygous surfactant mutation ($SFTPB^{121ins2}$) restores surfactant processing in the AEC2s. To model AEC2 dysfunction that might arise from more complex toxic gain-of-function mechanisms, we have generated iPSCs from children with I73T SFTPC mutations. Using AEC2s generated from these iPSCs or syngeneic lines corrected by gene editing, we find a variety of downstream toxicities present in iPSC-derived AEC2s that may be relevant to the in vivo dysfunction that leads to clinical disease in patients affected by these mutations. This presentation will review these new findings, and will illustrate approaches for employing PSC-derived AEC2s to provide a platform for modeling diseases resulting from surfactant dysfunction.

Curriculum Vitae

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Pennsylvania, Philadelphia, PA	B.A	05/1989	Psychology
Berklee College of Music, Boston, MA		05/1990	Music/Guitar Performance
Washington University, St. Louis, MO	M.D.	05/1994	Medicine

Positions

1994-95	Intern; Hospital of the University of Pennsylvania, Philadelphia, MA
1995-97	Resident; Internal Medicine, Hospital of the University of Pennsylvania.
1998-2002	Clinical Fellow; Pulmonary and Critical Care Medicine; Boston Medical Center/ Boston University, Boston, MA.
1999-2002	Research Fellow; Pulmonary and Critical Care Medicine, Laboratory of Alan Fine, MD, Boston University School of Medicine.
2002-2004	Post-Doctoral Research Fellow; Department of Genetics, Laboratory of Richard C. Mulligan, PhD, Harvard Medical School.
2002-2004	Instructor of Medicine, Department of Medicine, Boston University School of Medicine.
2004-2009	Assistant Professor, Department of Medicine, Boston University School of Medicine.
2006-2009	Assistant Professor, Department of Pathology and Laboratory Medicine, Boston University School of Medicine.
2009-2013	Associate Professor, Department of Medicine, Boston University School of Medicine
2009-2013	Associate Professor, Department of Pathology and Laboratory Medicine, Boston University School of Medicine.
2013-current	Professor, Departments of Medicine and Pathology, Boston University School of Medicine
2016-current	David C. Seldin Professor of Medicine
2002-current	Attending Physician, Division of Pulmonary and Critical Care Medicine, Boston Medical Center

Honors and awards

1985	Benjamin Franklin Scholar, University of Pennsylvania
1989	Phi Beta Kappa, University of Pennsylvania
1990	Distinguished Student Scholarship Award, Washington University School of Medicine
1990-94	Washington University School of Medicine Class President
1997	Penn Pearls Teaching Award, University of Pennsylvania School of Medicine
1997-2001	Director, Internal Medicine Overseas, Malawi, Health Volunteers Overseas, Washington DC
1999	Fellow of the Year Award, Boston University Department of Medicine
2001	Massachusetts Thoracic Society, 1st Place, Science Research Award
2001	Evans Days Research Award, 1st Runner Up, Boston University School of Medicine
2001	American Lung Association Research Fellowship Training Award
2001	Individual National Research Service Award, NIH/NHLBI
2007	L. Jack Faling Award for Excellence in Teaching, Boston University Pulmonary Center
2009	Co-Director, Boston Medical Center/Boston University Center for Regenerative Medicine (CReM)
2011	Elected to the American Society for Clinical Investigation
2013	Alpha-1 Foundation “Researcher of the Year” Award
2014	Robert Dawes Evans Senior Research Mentor Award, Boston Univ. Dept. of Medicine
2016	David C. Seldin (Inaugural) Endowed Professor of Medicine
2017	AAMC Inaugural Research Resources Sharing Award
2018	American Thoracic Society Research Achievement Award

MOB1 controls lung morphogenesis and tumor formation

Kohei Otsubo

Assistant Professor of

1. Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu University

2. Cancer Center, Kyushu University Hospital

Hippo signaling pathway was first identified as controlling organ size in Drosophila and is also thought to be an important signal pathway for controlling organ size and tumor progression even in mammals. MOB1, one of four core components of Hippo pathway, is reported to be mutated or downregulated in various human cancers. It has been reported that MOB1-knockout mice are embryonic lethal and tumors such as skin cancer, osteosarcoma, liver cancer are developed in mice with partially deficiency of MOB1. However, function of MOB1 in lung is unclear. To investigate MOB1's roles in lung development and tumorigenesis, we generated doxycycline (Dox)-inducible, bronchioalveolar epithelium-specific, null mutations of MOB1 in mice.

Most mutants receiving Dox in utero (E6.5-18.5) died of hypoxia within 1 h post-birth.

These mutants had immature alveolar epithelial cells with few lamellar bodies and showed decreased surfactant protein production, and these features are characteristic of human infant respiratory distress syndrome (IRDS).

Intriguingly, mutant mice that received Dox postnatally(P21-41) mice did not develop spontaneous lung tumors, and urethane treatment-induced lung tumor formation was decreased (rather than increased). Lungs of these mice exhibited increased detachment of bronchiolar epithelial cells and decreased numbers of the bronchioalveolar stem cells (BASCs) thought to be cancer initiating cells. As a cause of bronchial epithelial cell detachment, we clarified that the decrease in the expression of type 17 collagen (COL17A1), which is a constituent molecule of hemidesmosome, important for adhesion of epithelial cells and basement membrane, is decreased. In addition, we confirmed that detachment of bronchial epithelial cells and decrease of BASCs were observed in COL17A1-deficient mice. Furthermore, we found that YAP1 downstream of MOB1 form a complex with NKX2.1 (TTF-1) and controls transcription of COL17A1.

Our study revealed that MOB1 plays an important role in pulmonary morphogenesis and maintenance of stem cells and tumor initiation. Based on these data, we are now analyzing the function of MOB1 in human non-small cell lung cancer. In this symposium, we introduce research data obtained so far and future prospects of MOB1.

Curriculum Vitae

2006/3	Master of Science in Medicine, Kyushu University, Fukuoka, Japan
2006/4 - 2008/3	Junior Resident, Iizuka Hospital
2008/4 - 2008/6	Division of Respiratory Medicine, Iizuka Hospital
2008/7 - 2009/3	Division of Respiratory Medicine, Omuta Hospital
2009/4 - 2010/3	Division of Respiratory Medicine, Kyushu Central Hospital
2010/4 - 2011/3	Division of Respiratory Medicine, Kyushu University Hospital
2011/4 - 2014/3	Division of Cancer Genetics, Medical Institute of Bioregulation, Kyushu University
2014/4 - 2016/7	Division of Respiratory Medicine, Kyushu University Hospital
2016/8 -	Cancer Center, Kyushu University Hospital

Affiliation

The Japanese Society of Internal Medicine
The Japanese Respiratory Society
The Japanese Society of Medical Oncology
The Japan Society for Respiratory Endoscopy
T he Japanese Cancer Association

Publication (First Author)

1. Otsubo K, Goto H, Nishio M, et al. MOB1-YAP1/TAZ-NKX2.1 axis controls bronchioalveolar cell differentiation, adhesion and tumour formation. ***Oncogene*** 2017; 36: 4201-4211.
2. Otsubo K, Nakatomi K, Furukawa R, et al. Two cases of late-onset secondary adrenal insufficiency after discontinuation of nivolumab. ***Ann Oncol*** 2017; 28: 3106-3107.
3. Otsubo K, Nosaki K, Imamura CK, et al. Phase I study of salazosulfapyridine in combination with cisplatin and pemetrexed for advanced non-small-cell lung cancer. ***Cancer Sci*** 2017; 108: 1843-1849.
4. Otsubo K, Kishimoto J, Kenmotsu H, et al. Treatment Rationale and Design for J-SONIC: A Randomized Study of Carboplatin Plus Nab-paclitaxel With or Without Nintedanib for Advanced Non-Small-cell Lung Cancer With Idiopathic Pulmonary Fibrosis. ***Clin Lung Cancer*** 2018; 19: e5-e9.
5. Otsubo K, Seki N, Nakanishi Y, et al. Development of leptomeningeal carcinomatosis during a marked response of brain metastases to pembrolizumab in a patient with non-small-cell lung cancer. ***Ann Oncol*** 2018; 29: 780-781.
6. Otsubo K, Okamoto I, Hamada N, Nakanishi Y. Anticancer drug treatment for advanced lung cancer with interstitial lung disease. ***Respir Investig*** 2018; 56: 307-311.

Gene signature driving invasive mucinous adenocarcinoma of the lung

Koichi Tomoshige

Senior Pneumoconiosis Examination Physician
Industrial Health Division, Occupational Safety and Health Department,
Labour Standards Bureau, Ministry of Health, Labor and Welfare

Invasive mucinous adenocarcinoma of the lung (IMA) is pathologically well defined as a lung tumor with goblet cell morphology containing excessive intracytoplasmic mucins. Molecularly, a mutation of *KRAS* and the absence of NKX2-1 (TTF-1; a transcription factor) are frequently seen in human IMA (Travis et al., 2011). Whitsett, Jacks and colleagues previously reported that *Kras*-mutant lung cancer model mice with reduced expression of *Nkx2-1* developed mucinous lung tumors mimicking human IMA (mouse IMA; Maeda et al., 2012; Snyder et al., 2013), suggesting that molecular alterations, including *KRAS* mutation and the expression of transcription factors, impact lung cancer pathogenesis. Here, in order to understand the molecular pathogenesis of IMA comprehensively, we analyzed gene expression profiles of human IMA (n=6) using RNA-seq and compared them with gene expression profiles of mouse IMA. We identified 143 genes that are expressed in both human and mouse IMAs and determined that the genes comprise a gene signature for IMA. This gene signature was highly enriched in human IMA cases (n=9) retrieved from TCGA datasets, validating our analysis. The signature was also enriched in genes that are highly expressed in cancer cell lines from GI, lung adenocarcinoma, pancreatic and breast cancers, suggesting that IMA harbors a unique gene expression profile representing mucin-producing cancers while it maintains a lung lineage. Notably, the gene signature for IMA includes the pro-mucous transcription factors *FOXA3* and *SPDEF*, which were previously shown to induce airway goblet cells by Whitsett and colleagues (Park et al, 2007; Chen et al, 2014). In order to understand the role of FOXA3 and SPDEF in IMA, we created conditional transgenic mice, in which *Foxa3* or *Spdef* along with $Kras^{G12D}$ was induced in lung epithelium. Importantly, the transgenic mice developed mucinous lung tumors mimicking IMA, suggesting that the mucus-producing goblet cells are the origin of IMA. Of note, our analysis indicated that an immune checkpoint PD-L1 (B7-H1) was not highly expressed in IMA probably due to the absence of NKX2-1, suggesting immune checkpoint inhibitors such as nivolumab and pembrolizumab may not be effective for IMA. However, the gene signature for IMA included VTCN1 (B7-H4), a member of immune checkpoints, suggesting that a therapy targeting VTCN1 may be effective in the treatment of IMA. An anti-VTCN1 antibody-drug conjugate has been recently developed by Genentech (Leong et al., 2015). Collectively, our present study indicates that IMA is a molecularly distinct type of lung adenocarcinoma and may be therapeutically targetable with small molecule compounds or antibodies other than chemotherapy. This study was published in EMBO Mol Med (Guo*, Tomoshige* et al., 2017; *, contributed equally).

Curriculum Vitae

Education

Nagasaki University School of Medicine	April 1999- March 2005
Nagasaki University Graduate school of Biochemical Sciences	April 2011- March 2015

Post Graduate Training

2005.4-2007.3	Junior resident	Sasebo City General Hospital
2007.4-2008.3	Senior resident	Division of surgical oncology, Nagasaki University Graduate school of Biochemical Sciences
2008.4-2009.3	Senior resident	Syunan Memorial Hospital
2009.4-2010.3	Senior resident	The Japanese Red Cross Nagasaki Genbaku Hospital
2010.4-2011.3	Surgical staff	St.Fransisco Hospital
2011.4-2015.3	Research assistant	Division of surgical oncology, Nagasaki University Graduate school of Biochemical Sciences
2015.5-2017.8	Research Scientist	Division of Pulmonary Biology, Cincinnati Children's Hospital Medical Center
2017.9-2018.6	Assistant Professsor	Division of surgical oncology, Nagasaki University Graduate school of Biochemical Sciences
2018.7-	Senior Pneumoconiosis Examination Physician	The Ministry of Health, Labor and Welfare of Japan

Professional Qualification

Japanese Board of Surgery (No.1002068)

Japanese Board of Respiratory Surgeon (No.2000761)

P-01 Carboxypeptidase M (CPM) expression analysis in the developing and mature mouse lung

○Shohei Yoshimoto[1)], Shinpei Gotoh[2)3)], Shuichi Hashimoto[1)]

[1)] Section of Pathology, Department of Morphological Biology, Division of Biomedical Sciences, Fukuoka Dental College

[2)] Department of Drug Discovery for Lung Diseases, Graduate School of Medicine, Kyoto University

[3)] Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University

Carboxypeptidase M (CPM) is an extracellular peptidase attached to the outer membrane by a glycosyl-phosphatidylinositol (GPI) anchor and cleaves C-terminal lysines and arginines from peptides and proteins. CPM interacts with the seven-transmembrane domain kinin B1 receptor (B1R), which couples to both Gαq and Gαi, and enhances the B1R signaling, resulting in a new mode of G protein-coupled receptor (GPCR) activation. CPM is widely distributed in such lung, placental microvilli, kidney, blood vessels, intestine, brain and peripheral nerves. In the mature lung, CPM was reported to be expressed in Type I and/or Type II alveolar epithelial cells (AECs). Gotoh et al. identified CPM as a surface marker of NKX2-1+ "ventralized" anterior foregut endoderm cells (VAFECs) in fetal human and murine lungs, then they efficiently used CPM for generating type II AECs. However, CPM temporal and spatial expression in the developing lung are not fully understood.

In our immunohistochemical study, CPM was expressed in Type II AECs, bronchial/bronchiolar epithelial cells (BECs), and partly expressed in Type I AECs in post-natal 6w and 40w mouse lungs. In the developing mouse lung, CPM was expressed in primitive BECs. These finding suggest that CPM contributes to an important role in the BECs and AECs specification and maturation.

P-02 Recapitulating Alveolar Epithelial Type 2 Cell Dysfunction in Hermansky-Pudlak Syndrome Type 2 Patient-derived Induced Pluripotent Stem Cells

○Yohei Korogi[1)], Shimpei Gotoh[1)2)], Satoshi Ikeo[1)], Yuki Yamamoto[1)], Naoyuki Sone[1)], Koji Tamai[1)], Isao Asaka[3)], Akitsu Hotta[4)], Toyohiro Hirai[1)]

[1)] Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University

[2)] Department of Drug Discovery for Lung Diseases, Graduate School of Medicine, Kyoto University

[3)] Department of Fundamental Cell Technology, Center for iPS Cell Research and Application, Kyoto University

[4)] Department of Clinical Application, Center for iPS Cell Research and Application, Kyoto University

Hermansky-Pudlak syndrome (HPS) is an autosomal recessive disorder characterized by oculocutaneous albinism and bleeding diathesis, and one of the life-limiting complications of HPS is pulmonary fibrosis. Among 10 subtypes, HPS type2 (HPS2) is caused by the mutation of AP3B1 gene, encoding the beta-3A subunit of adaptor protein 3A (AP-3A) complex which is involved in formation and maturation of lysosome related organelles, such as lamellar bodies (LBs) in alveolar epithelial type 2 (AT2) cells. Although giant lamellar body degeneration in AT2 cells was documented in HPS patients with pulmonary fibrosis, the detailed characteristics of AT2 cells of HPS2 patients have not been reported, because of difficulties in obtaining and culturing patient-derived primary AT2 cells. Recently, we have developed a method of inducing and culturing AT2-like cells in alveolar organoids derived from human induced pluripotent stem cells (iPSCs). In this study, we established patient-derived iPSCs (HPS-iPSCs) and their gene-corrected counterparts (cHPS-iPSCs) from HPS2 patient fibroblasts. By comparing the alveolar organoids derived from these iPSCs, impaired secretion of LBs as well as their altered distribution and enlargement was demonstrated in the HPS2-iPSC-derived AT2 cells. These findings provide insights into the AT2 cell dysfunction in HPS2 patients and support the potential use of human iPSC-derived AT2 cells for future research on alveolar lung diseases.

P-03 An electron microscopic study of the pathogenesis for the pulmonary surfactant lamellar structural bodies

○Hidekatsu Matsumura[1)2)], Tsunetomo Takei[3)], Shoichi Chida[3)], Takashi Takagi[4)], Motoaki Kobayashi[5)], Hibiki Takahashi[5)], Seiou Nakamura[6)]

[1)]Kouaikai Kounosu Kyousei Hospital, [2)]Kounosu Kyousei Clinic
[3)]Iwate Medical College, [4)]Syouwa University Electron Microscopic Room
[5)]Seputosapie (Inc), [6)]Seiseigen (Inc)

Materials & Methods: We used 5 African lungfishes (Protopterus aethiopics including giant one). Two lungfishes used as a control.

We made an artificial summer sleep in the water boxes. After lungfishes were put in these water boxes, gradually the waters were decreased, on the other hand, the grounds were increased. One month later, these water disappeared macro-scopically, the lungfishes made round and calm conditions during 2 months.

Results: According to the electron microscopic prints we found that Golgi apparatus and multi-vesicular bodies(MVB) connected directly to the lamellar structural bodies within the cytoplasm of the second type of the alveolar epithelium. We discovered the pulmonary surfactant lamellar structural bodies continued directly each other. And we found that the previous degree of the lattice tubular myelin(LTM) was existed.

Conclusion: Golgi apparatus and MVB connected to the lamellar structural bodies. Lamellar structural bodies continued each other. The previous degree of LTM was discovered.

Discussion: Typical LTM was found on the internal sides of the Salamander's pulmonary lamellar structure. These continuing bodies were considered the same thing such as many Membranous Cytoplasmic Bodies(MCB) noticing within the cytoplasm of the cultured fiblocytes for the patient of GM1 gangliocytosis (infantile type), clinically. These MCB are continuing each other. These findings are correspond to the continuing pulmonary surfactant lamellar structural bodies. Our findings suggested that the pathogenesis for the pulmonary surfactant's figures(quoted in the Setoguti's paper, J.Jpn.Med.Soc.Lung Surfactant Biol.Interface 2009) were partially true.

P-04 Double stranded RNA induces vulnerability of airway epithelial barrier integrity by influencing airway basal cells

○Shinichi Okamoto, Shuichiro Maruoka, Kota Tsuya, Asami Fukuda, Shiho Yamada, Yusuke Kurosawa, Kaori Soda, Yasuhiro Gon

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Background: Virus infection is a major cause of exacerbation of asthma. Virus-derived dsRNA induces disruption of the epithelial barrier functions via TLR3/TRIF pathway. Airway basal cells, the epithelial progenitor cells, play an important role in conducting airway epithelium. However, little is known about the mechanism by which how dsRNA induces the vulnerability of airway epithelial barrier by influencing basal cells. Here we stimulated proliferating normal human bronchial epithelial cells (NHBEC) and airway basal cell line, VA10 with dsRNA and then measured airway epithelial barrier integrity in air liquid interface (ALI).

Methods: NHBEC and VA10 were cultured submerged in medium onto a transwell for 3 days with or without dsRNA (10μg/mL of poly (I:C)). Cells were then exposed to ALI without dsRNA for 7days to measure the epithelial barrier integrity using transepithelial electrical resistance (TER) and paracellular permeability. To confirm that proliferating NHBECs were basal cells, we stained the cells with CK5 and CK14, basal cell markers. To determine whether dsRNA induced barrier disruption via the TLR3/TRIF pathway, we transfected with TLR3/TRIF specific siRNAs respectively and measured TER and paracellular permeability.

Results: Proliferating NHBECs were all CK5 and CK14 positive cells. These cells stimulated by dsRNA decreased TER. Transfecting basal cells with TLR3/TRIF-specific siRNAs improved the dsRNA-induced disruption of airway epithelial barrier integrity.

Conclusions: These data show that stimulating dsRNA to proliferating airway basal cells induces vulnerability of airway epithelial barrier integrity via TLR3/TRIF pathway. Virus infection to airway basal cells might have potential influence on the determination of vulnerability of airway epithelial barrier in patients with asthma.

P-05 SF-10 adjuvant derived from pulmonary surfactant enhances incorporation of antigens into intestinal antigen presenting cells and induces antigen specific immunities

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Synthetic mucosal adjuvant SF-10 derived from pulmonary surfactant is an effective adjuvant for intranasal influenza vaccine (HAv). Recently, we found that orally administration of SF-10 combined with HAv (HAv-SF-10) strongly induces protective immunities compared with intranasal HAv-SF-10 administration. In this presentation, we reported the mechanism of SF-10 in the enhancement of antigen incorporation into intestinal antigen presenting cells (APC) and induction of antigen specific antibody secreting cells (ASC).

To investigate antigen incorporation, mice were orally administrated of 0.1 mg Alexa647-labeled ovalbumin (fOVA) with or without 1 mg SF-10. After administration of fVA-SF-10 for 12 hr, small intestinal cells were isolated, stained with anti-mouse I-A/I-E (MHC II), CD11b, CD11c and CD103 and analyzed by flow cytometry. SF-10 significantly enhanced fOVA incorporation into not only MHC II+CD11c+ cells (APC), but CD11b+CD103+ APC and CD11b+CD103- APC (major subsets of dendritic cells in intestine), compared with vaccination of fOVA alone. To detect HAv specific ASC, mice were orally administrated 1 μg HAv with or without 10 μg SF-10 at day 0, 3, 14 and 17. Two weeks after the last immunization, the lymphocytes in spleen, cervical lymph node (CLN), mesenteric lymph node (MLN), Peyer's patch (PP), stomach lymph nodes (SLN), and lung were isolated and HAv specific ASC were detected by enzyme-linked immunospot assay. ASC of anti-HAv IgA and IgG in mice immunized with HAv-SF-10 were detected in lung, spleen, CLN, MLN, PP and SLN, and showed significantly higher frequency than that in mice immunized with HAv.

These results indicate that SF-10 enhances antigen specific immunities via gastrointestinal mucosal APC. SF-10 is expected to use oral vaccine for gastrointestinal infection and food allergy.

P-06 Induced Expression of Mutant Surfactant Protein C in Mice Results in an Idiopathic Pulmonary Fibrosis Phenotype

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Rationale: Epithelial dysfunction is implicated in the pathogenesis of idiopathic pulmonary fibrosis (IPF). A missense isoleucine to threonine substitution at position 73 (I73T) is the most common SP-C gene [*sftpc*] mutation linked to sporadic and familial forms of IPF.

Approach: Inducible expression of a mutant SP-C^{I73T} sequence in mice (***I***^{ER}***-SP-C***^{I73T} line) was achieved by crossing a hypomorphic SP-C^{I73T} founder line (wherein *sftpc*^{I73T} knock-in alleles retained an intronic PGK-neomycin cassette) to a R26^{FlpOER} deleter line for tamoxifen-mediated removal of PGK-neomycin cassette.

Results: Expression of *sftpc*^{I73T} in alveolar epithelial type 2 (AT2) cells *in vivo* resulted in aberrant posttranslational processing, block in macroautopagy, and mistrafficking of mutant SP-C^{I73T} protein. Intraperitoneal tamoxifen (iTAM) treatment of ***I***^{ER}***-SP-C***^{I73T} mice rapidly up-regulated *sftpc*^{I73T} mRNA and SP-C^{I73T} proprotein accompanied by increased weight loss and mortality, progressive diffuse alveolar damage, and a substantial macrophage/neutrophilic/eosinophilic alveolitis. Six weeks post-iTAM, surviving ***I***^{ER}***-SP-C***^{I73T} mice exhibited lung pathology consistent with usual interstitial pneumonia, increased collagen content, and restrictive lung physiology. iTAM treated ***I***^{ER}***-SP-C***^{I73T} mice elaborated multiple biomarkers observed in human IPF.

Conclusions: Inducible expression of SP-C^{I73T} in mice offers proof of concept that dysfunctional AT2 epithelia are important upstream drivers of IPF-like fibrotic remodeling.

P-07 Role of pulmonary surfactant protein in mouse lung injury model with dioxins

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Introduction: Club cell is one of the rare cells expressing aryl hydrocarbon receptor (AhR) in the lung. Since dioxins cause cytotoxic action through AhR via the CYP1A1 pathway, injury of Club cells is the main reason for lung injury due to contamination by dioxins. Surfactant proteins are known to have not only surface tension-lowering effects but also defense effects against microorganisms. However, little is known whether pulmonary surfactant proteins have direct protective effects against cytotoxic molecules on lung cells, especially on Club cells. To investigate the cytoprotective effects of surfactant proteins, we developed in vitro experiments and a mouse model of dioxin-induced lung injury by administering AhR agonistic substance Benzo [a] pyren (BaP).

Method: Human Club cells (NCI-H441 cells) were treated with BaP to induce cell death. Recombinant human surfactant protein D (SP-D) was added, and cell death of NCI-H441 cells was assessed with Annexin V and propidium iodide by flow cytometry. C57BL/6J mice were administered BaP intratracheally and assessed for bronchoalveolar lavage fluid and lung tissues on day 7.

Result: SP-D treatment decreased BaP-induced apoptosis of Club cell line (NCI-H441 cells) in vitro. Thickening of bronchiolar epithelium and sequence change in the bronchiolar region were observed on day 7 after BaP instillation in vivo. PAS positive cells were observed in the terminal bronchiolar region. Expression of pulmonary surfactant protein (SP-A) was suppressed in the bronchial epithelium on the terminal bronchiolar side. Deficiency of SP-D exacerbated lung injury due to BaP.

Conclusion: These results indicate that surfactant protein A/D have protective effects on dioxins induced lung injury.

P-08 Serum KL-6 and SP-D Levels in Patients with Pleuroparenchymal Fibroelastosis

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Pleuroparenchymal fibroelastosis (PPFE) is a rare subset of idiopathic interstitial pneumonias. In 2015, a nationwide multicenter study was conducted by the Tokyo Diffuse Lung Disease Study Group in Japan to examine the clinical, imaging, and pathophysiological characteristics of PPFE. The serum levels of Krebs von Lungen-6 (KL-6) and surfactant proteins D (SP-D) measured by enzyme immunoassay at the time of diagnosis were obtained from 52 cases with PPFE diagnosed at 21 institutions from 2002 to 2015. After excluding three patients who had received lung transplantation, the remaining 49 cases comprised 21 survivors and 28 non-survivors. In the non-survivors, KL-6 levels were significantly higher ($p=0.001$) despite relatively-low levels (median 546 U/ml in all cases) and lower lung lesions on CT images were more frequently observed ($p=0.008$) than in the survivors. The SP-D levels in patients with PPFE tended to show a high value (median 208 ng/ml) but were equivalent between the survivors and the non-survivors. The prognosis of PPFE may be related to the serum levels of KL-6, which might reflect the development of fibrosing interstitial pneumonia in the lower lobes.

P-09 Development of treatment for chronic obstructive pulmonary disease based on inducing differentiation by 1, 25-dihydroxyvitamin D3

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Background: Chronic obstructive pulmonary disease (COPD) is major causes of death worldwide. COPD had been classified as emphysema or chronic bronchitis, and the presence of systemic comorbidities is also considered problematic. However, no drugs can regenerate lung tissue in COPD. A differentiation-inducing drug that can effectively treat distracted alveoli is needed. We have focused on active form of vitamin D3 1, 25-dihydroxyvitamin D3 (VD3) as a differentiation inducer. The aim of this study was to determine the usefulness of VD3 in differentiation-inducing therapy for COPD.

Methods: We examined the effects of VD3 on alveolar regeneration using 2 kinds of mouse COPD models, those of elastase-induced emphysema and adiponectin deficiency. The effects of VD3 on alveolar repair by pulmonary administration were evaluated Lm (distance between alveolar walls) values or lung function. Bone density was evaluated by calculating computed tomography (CT).

Results: Lm value and lung function were significantly improved in the VD3-treated group in elastase-induced emphysema COPD model. Lm value at 80 weeks old were significantly improved by VD3 in the adiponectin deficient-mice. In addition, the CT value of bone mass at 80 weeks old in the VD3-treated group was higher than that of Control-treated group.

Conclusion: VD3 administered to the lungs induced lung regeneration and inhibition of bone density reduction. The results suggested that VD3 may be useful as a differentiation inducer in COPD.

P-10 Nicotine induces resistance to erlotinib therapy in non-small cell lung cancer cells treated with serum from human patients

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We previously proved that nicotine reduced erlotinib sensitivity in a xenograft model of PC9, an epidermal growth factor receptor-tyrosine kinase inhibitor-sensitive non-small cell lung cancer cell line. Therefore, the present study aimed to prove that smoking induces erlotinib resistance in vitro. We assessed resistance to erlotinib by treating PC9 and HCC827 cell lines with erlotinib and one of two types of serum: serum collected from smokers within 30 minutes after smoking and serum collected from a non-smoker, as a control. We also assessed erlotinib resistance by treating PC9 cell lines exposed to serum from a smoker or non-smoker with serum from erlotinib users. Treatment of the PC9 and HCC827 cell lines with serum from smokers induced significant erlotinib resistance compared to the control ($p<0.05$). Comparing serum from the smokers, samples with a high concentration of cotinine (a nicotine exposure indicator) demonstrated stronger erlotinib resistance than that with low concentrations. Similar to the observations with erlotinib treatment of cell lines, the analysis of serum from erlotinib users revealed that smokers demonstrated significantly reduced sensitivity to erlotinib ($p<0.001$). In conclusions, our present results support the hypothesis that smoking contributes to resistance to erlotinib therapy in non-small cell lung cancer.

P-11 A possibility of B cell activating factor as a therapeutic target for Autoimmune Pulmonary Alveolar Proteinosis

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Background: The elevation of B cell activating factor belonging to the tumor necrosis factor family (BAFF) and a proliferation-inducing ligand (APRIL) in serum is reported in some autoimmune diseases. We confirmed the increased the concentration of BAFF and APRIL in the patients with autoimmune pulmonary alveolar proteinosis (APAP). We hypothesized that BAFF and APRIL in BALF also increase and reflects pathological condition of APAP. And we also evaluated the possibility of B cell activating factors as a therapeutic target of APAP.

Methods: Fifty patients with APAP, 30 healthy controls, and 13 lung disease controls were enrolled in this study. B cell activating factors (BAFF and APRIL) level in serum and BALF were measured by ELISA using commercially available kit (R&D systems and eBioscience). We compared the data with clinical measures and disease severity score (DSS).

Results: We found significant elevation of BAFF and APRIL levels in the patients with APAP compared to healthy control ($p<0.05$, respectively) in serum. And we also found significant elevation BAFF and APRIL levels in BALF ($p<0.0001$, respectively) compared to disease controls. BAFF level showed correlations with KL-6, surfactant protein (SP)-D, and SP-A ($p<0.05$, respectively) in serum and BALF. However, APRIL level in serum and BAFF did not show correlations with these serum biomarkers for APAP. BAFF level in BALF significantly correlated with DSS, however, APRIL level in BALF did not correlate with DSS.

Conclusion: APAP is a disease that many factors complicated in a pathogenesis and a disease progression. It is suggested that APAP requires the multidisciplinary treatments of GM-CSF inhalation, whole lung lavage, and inhibition of B cell activating factors.

P-12 Genetic diversity of Alveolar capillary dysplasia with misalignment of pulmonary veins in Japanese infants

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Introduction: Alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV) is a rare and lethal lung disorder that presents in the early neonatal period and diagnosed by unique pathological findings. Almost all individuals with ACDMPV show genetic variations in *FOXF1* of heterozygous point mutation, deletion in exon, intron and also upstream enhancer region. Genetic diversity of ACDMPV was not extensively studied in Japanese infants.

Methods: Fifteen Japanese infants with pathologically proven ACDMPV were enrolled in this study with written informed consent from parents. Genetic analyses were performed on DNA extracted from peripheral blood of 12 individuals, 3 had no compatible DNA specimens. Sequencing of exon region was performed for all cases by Sanger's method or next generation sequencing. We tried multiplex ligation-dependent probe amplification (MLPA) analysis to evaluate copy-number variation (CNV) in the area including *FOXF1* for the individuals without causative variations in exon.

Results: Of the 12 infants, we identified causative variations of *FOXF1* in 9, missense 2, nonsense 1 and frameshift 2 mutations and CNV 4. Two cases are under MLPA analysis and we could not detect the cause in remaining one case. Two infants with the same deletion in upstream region of FOXF1 were siblings. They had one additional sibling died of neonatal pulmonary hypertension without autopsy. We identified the same deletion with the affected siblings in DNA from stored umbilical cord and also DNA from their father.

Conclusion: This is the first report of ACDMPV case due to deletion CNV in *FOXF1* inherited from father.

P-13 Two cases of autoimmune pulmonary alveolar proteinosis: Exploring the pathogenesis through case studies

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Case 1: We report a case of autoimmune pulmonary alveolar proteinosis (PAP) discovered after one-time exposure to silica powder. A 76-year-old woman misused a silica-containing fire extinguisher and inhaled large amounts of its powder. She experienced prolonged cough and visited our hospital. Findings of chest computed tomography and surgical lung biopsy specimens led to the diagnosis of PAP. Elemental analysis revealed deposits of silicon in substances filling alveolar spaces. Interestingly, the anti-GM-CSF antibody were detected, therefore, both autoimmune characteristic and exposure to large amounts of silica may have caused the emergence of PAP in this patient.

Case 2: We report a case of autoimmune PAP in which low dose steroid had been associated with disease progression. A 63-year-old man diagnosed with PAP was introduced to our hospital because of rapid disease progression in short term. High serum level of anti-GM-CSF antibody led to the diagnosis of autoimmune PAP. Whole lung lavages were performed 3 times every 2 months; nevertheless, the disease progressed in the following month after a temporary improvement. However, discontinuation of corticosteroid (predonisolone 3 mg/day) for coexisting SAPHO syndrome resulted in dramatic improvement of PAP. There has been no report so far that very low dose steroid had been associated with disease progression.

In conclusion, these 2 cases provide important insights into the mechanisms leading to the emergence and progression of PAP.

P-14 Surface properties of Gemini type perfluorinated surfactants with DPPC at the air-water interface

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Fluorinated surfactants are more efficient than hydrogenated surfactants because of the surface tension can be reduced by small amounts of fluorinated surfactants. Moreover, the feature of hydrophobicity and lipophobicity provides phase separation and self-assembly. These properties are useful for applications in various fields such as biomedical and industry fields [1]. The perfluorinated double long-chain salts with divalent counterions which have various hydrocarbon spacer lengths have been synthesized [2, 3]. Herein, in this study, the binary monolayer properties of the fluorinated compounds and dipalmitoylphosphatidylcholine (DPPC) were investigated to understand the spacer length effect and an aspect of biomembrane interaction on their interfacial behaviour.

Discussion: We have investigated that the binary Langmuir monolayers of DPPC and CnBP(FC14)2 behaviour. Two-dimensional phase diagrams were constructed on the basis of the disordered/ordered phase transition pressure and the monolayer collapse pressure versus the molar fraction of CnBP(FC14)2 (XCnBP(FC14)2). The transition pressures and collapse pressures changed against XCnBP(FC14)2. In the morphology (BAM and FM), the dispersion degree of two regions (ordered and disordered) were depending on the spacer length of Gemini type perfluorinated surfactants. The miscibility is also confirmed by AFM at nanometer scales.

References

[1] M. P. Krafft, Soft Matter. 30 (2015): 5982-5994.

[2] Y. Matsumoto, H. Nakahara, Y. Moroi, O. Shibata, Langmuir 23 (2007) 9629-9640.

[3] J. Masuda, H. Nakahara, S. Karasawa, Y. Moroi, O. Shibata, Langmuir 23 (2007) 8778-8783.

[4] R. Kato, H. Nakahara, O. Shibata, J. Oleo Sci., 66 (2017) 479-489.

P-15 Langmuir film properties of partially perfluorinated alcohol with F-DPPC at the air-water interface

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A fluorocarbon chain is lower cohesiveness and higher rigidity than hydrocarbon chains. In addition, a fluorocarbon has hydrophobicity and lipophobicity simultaneously. These properties are useful for applications in various fields such as biomedical and industry fields [1]. We had already investigated the binary monolayer properties of the fluorinated compounds and DPPC system [2]. Herein, in this study, the binary monolayer properties of the fluorinated compound (F6H9OH) and 1-palmitoyl-2-[16-fluoropalmitoyl]-phosphatidylcholine (F-DPPC) were investigated to understand the interaction and an aspect of biomembrane interaction on their interfacial behaviour.

The data for the binary system were analysed using an additivity rule. The excess Gibbs free energy of mixing for the present system were calculated from the $\pi - A$ isotherms. Two-dimensional phase diagrams were constructed on the basis of the disordered/ordered phase transition pressure and the monolayer collapse pressure versus the molar fraction of F6H9OH. The transition pressures and which allows description of the collapse pressure of a monolayer made of two miscible components, was used to establish the miscibility within the monolayer. An interaction parameter and an interaction energy were calculated. These analyses suggested that the binary F-DPPC/F6H9OH monolayers were miscible with each other. The phase diagrams of the two systems were classified into the positive azeotropic type. Furthermore, morphological observations with Brewster angle microscopy (BAM) and fluorescence microscopy (FM) were carried out to support the binary miscibility. These results suggest that F6H9OH fluidizes F-DPPC monolayers.

References

[1] M. P. Krafft, Soft Matter. 30 (2015): 5982-5994.

[2] H. Nakahara, O. Shibata, et al., ACS Symposium Series, Vol. 1215, C. 2015, pp1-24

P-16 Langmuir film of a tetrazine-containing gemini amphiphile: Interaction with biomembrane lipids

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The property of a newly synthesized tetrazine derivative comprised of double C18-saturated hydrocarbon chain (C18-rTz-C18) has been studied in situ at the air－water interface. C18-rTz-C18 or a gemini amphiphile contributes to restriction of its tetrazine moiety on the interface, which is expected to be used for bioimaging and analytical reagents. Herein, to understand lateral interactions between Tz and biomembrane constituents, we investigated the interfacial behavior of Langmuir monolayers composed of C18-rTz-C18 and biomembrane lipids such as DPPC, DPPG, DPPE, PSM, and Cholesterol (Ch). The lateral interaction of the binary monolayers was analyzed with the surface pressure (π)－molecular area (A) and surface potential (ΔV)－A isotherms. These thermodynamic data indicate that all of the two-components are miscible with each other. In particular, as opposed to the others, the monolayer stability of DPPE, which is a major constituent of the inner surface of cell membranes, is attenuated by the small-amount addition of C18-rTz-C18. This specific interaction implies the membrane destruction from the inside. The phase behavior during monolayer compression was visualized with Brewster angle microscopy (BAM), fluorescence microscopy (FM), and atomic force microscopy (AFM). The obtained morphologies exhibit a coexistence state of two different liquid-condensed domains derived from extra phospholipids and phospholipids－C18-rTz-C18 monolayers.

References

[1] H. Nakahara, M. Hagimori, T. Mukai, O. Shibata, Langmuir, 32 (2016) 6591-6599

[2] H. Nakahara, M. Hagimori, T. Mukai, O. Shibata, Colloids and Surfaces B: Biointerfaces 164 (2018) 1–10.

P-17 Toward the Prediction of Translocation Studies of Nanoparticles Using in Vitro Alveolar Epithelial Models

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To predict translocation of nanoparticles (NPs) into secondary organs through lung, there has recently been an increasing interest in in vitro lung models, which allow control of experimental parameters and quantitative analyses. However, the present in vitro alveolar epithelial model is still far from completely mimicking the in vivo alveolar tissue due to lack of macrophages and other phagocytic cells. In the present study, we developed two types of in vitro alveolar models using transwell inserts consisting of a semipermeable membrane, which separates across to apical and basolateral compartments. One is a human cell-derived co-culture system consisting of human monocytic cell line THP-1, human alveolar epithelial type II cell line A549, and human umbilical vein endothelial cell HUVEC (THP-1/A549/HUVEC) and another is an isolated primary rat cell-based co-culture system consisting of rat macrophages and type I cell (macrophage/type I). We also examined the permeability of SiO2 NPs 30 nm in diameter from the apical to the basolateral sides through the in vitro alveolar models. The amount of SiO2 NPs translocated from the apical to the basolateral side was apparently suppressed in comparison with A549/HVEC and type I systems without THP-1 and macrophages. In addition, SiO2 NPs were accumulated in the cell layers and/or adsorbed at the surface of the semipermeable membrane, indicating that macrophages including differentiated macrophage-like cells phagocytosed the NPs. Thus, co-culture with macrophages enabled to improve physiological performance of the in vitro alveolar epithelial models in translocation study of NPs.

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