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Anniversary gift of Teikyo Univ. Hanoi Branch, Vietnam

Asia International Institute of Infectious Disease Control, Teikyo University
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EDITORIAL

6巻1号をお届けします。

【ADC研設立5周年記念国際シンポジウム】

前号（5巻2号）に引き続き、ADC研設立5周年記念国際シンポジウム後半として、Dr. Harry Malech（米国NIAID-NIH）と小澤敬也先生（自治医科大学名誉教授・客員教授、前東京大学医科学研究所附属病院長）による講演を行い掲載しました。これに続き、血管炎関連でProf. Ulrich Speck（米国メイヨー・クリニック）、Prof. Luis Felipe Flores-Suárez（メキシコFaculty of Medicine, Universidad Nacional Autónoma de México and the Instituto Nacional de Ciencias Médicas y Nutrición）およびDavid Jayne（英国ケンブリッジ大学Addenbrookes病院）とのディスカッションがありました。

【トピックス】

1）帝京大学ハノイ支所、医学部5年生のベトナム感染症実習、ベトナムからの訪問

ブランチ設置に向けた冲永佳史理事長・学長とLe Than Hai国立小児病院長間での覚書の調印式を掲載しました。

さらに3年目になる帝京大学医学部5年生のハノイの医療機関訪問、3回目になる「さくらサイエンスプラン（科学技術振興機構のプログラム）」で8名のベトナム医師・研究者の帝京大学ADC研での研修の様子を掲載しました。

2）Stem Cell Transplantation Consortium形成

また、2005年から鈴木和男所長と共同研究してきたベトナムVinmec国際病院附属研究所長（元国立小児病院長）が2018年6月13日に第23回日経アジア賞を受賞された記念に帝京大学ADC研の5周年記念シンポジウムにて講演されました（5巻2号参照）。その後、Vinmec国際病院附属研究所を訪問した冲永佳史理事長・学長とNguyen Liem所長との間でStem Cell Transplantation Consortium形成の内諾を受けて、2018年12月11日に開催された第1回Stem Cell Transplantation Consortium会議の様子を掲載しました。

【Nguyen Thu Thuyさんが医学博士を取得】

特筆すべきは、4年にわたりベトナムから文科省の国費留学生として帝京大学大学院医学研究科およびADC研で研究したNguyen Thu Thuyさんが医学博士を取得したことです。

帝京大学ADC研は、5年間の実績をふまえて、今後も感染症制御に関する研究および教育を推進し、その成果を社会に還元して参ります。

We are pleased to issue Vol. 6 No. 1.

【The international symposium continued of the 5th anniversary of the ADC】

As the international symposium continued of the 5th anniversary of the ADC establishment described in the previous issue (Vol. 5 No. 2), two lectures by Dr. Harry Malech (NIAID-NIH, USA) and Prof. Keiya Ozawa (Jichi Medical University, the previous director of the Institute of Medical Sciences, The University of Tokyo) are documented. Sequentially, there was discussion with Prof. Ulrich Speck (Mayo Clinic, USA), Prof. Luis Felipe Flores-Suárez (Mexican Faculty of Medicine, Universidad Nacional Autónoma de México and the Instituto Nacional de Ciencias Médicas y Nutrición, Mexico) and David Jayne (British Cambridge University Addenbrookes Hospital) in the satellite meeting.

【Hanoi Branch of Teikyo University】

The attentional topics were visit of 11 Teikyo University medical students in fifth grade in hospitals and medical institute in Hanoi, and also the setting of the Teikyo University Hanoi branch with the signing ceremony of the memorandum between Teikyo Univeristy Charman/President Yoshihito Okinaga and the National Children's Hospital Director/Prof. Le Than Hai. Also eight Vietnamese doctors and researchers visited Teikyo University ADC for training course supported by "SAKURA SCIECNCE PLAN" (program of Japan Science and Technology Agency) and it was their third times.

【The Stem Cell Transplantation Consortium】

Prof. Nguyen Liem received the 23rd Nikkei Asia Prize on June 13, 2018. Prof. Liem is the director of Research Institute, Vinmec International Hospital, Vietnam (the former director of the National Children's Hospital, Vietnam) collaborating with Prof. Kazuo Suzuki from 2005. He gave a lecture at Teikyo University ADC 5th anniversary memory international symposium (Vol. 5 No. 2). Afterwards, when Teikyo Univeristy Chairman/President Yoshihito Okinaga visited the research institute of Vinmec International Hospital, he communicated a tentative appointment with Prof. Nguyen Liem for joining with the Stem Cell Transplantation Consortium. Accordingly, the first meeting of Stem Cell Transplantation Consortium was held in Teikyo University on December 11, 2018.

【Ph.D. degree for Ms. Nguyen Thu Thuy】

A Ph.D. student Ms. Nguyen Thu Thuy from Vietnam has been studying in Teikyo University Graduate School of Medicine, and ADC supported him four years by a scholarship of the Ministry of Education, Culture, Sports, Science and Technology in Japan to take degree of Medical Doctor Ph.D.

Teikyo University ADC will continue to promote a study on infectious disease control and education in future, and will return the results to the society on the basis of the 5-year results.

ADC 5th ANNIVERSARY INTERNATIONAL SYMPOSIUM

アジア国際感染症制御研究所 創設５周年

メインシンポジウム

Global HIV Control and Challenging to Antimicrobial Resistance
グローバルHIVコントロール研究と多剤耐性克服への挑戦

2018年6月22日(金)15:00 - 18:00 臨床大講堂　　Organizer:鈴木和男　ADC研 所長

Session I　座長:斧　康雄教授(帝京大学)
「グローバルHIVコントロールに向けた最新の研究展開」
俣野哲朗センター長、教授
(国立感染研エイズ研究センター、東大医科研)

Session II　座長:Dr. Phung Thi Bich Thuy
(National Children's Hospital, Hanoi, Vietnam)
「ベトナムのHIV感染症事情」
Associate Professor Dung Thi Khanh Khu
(National Children's Hospital, Hanoi, Vietnam)

Session III　座長:山本友子(帝京大学)
「多剤耐性(AMR)問題と克服のための挑戦」
荒川 宜親教授(名古屋大院医分子病原細菌学)

サテライトシンポジウム－Ⅰ

Stem Cells: Ageing and Clinical Trials
幹細胞:ベンチからベッドサイドへ

2018年6月15日(金)15:30 - 18:00 大学棟2F 会議室　　Organizer:鈴木和男　ADC研 所長

Session I　座長:原田浩徳教授(東京薬科大学)
「造血幹細胞のエイジングと加齢関連腫瘍」
岩間厚志教授 (東京大学医科研・千葉大学院医)

Session II　座長:吉岡　昇講師 (帝京大学)
「Creating human cardiomyocyte model using "footprint-free" genome editing to understanding cardiovascular diseases」
Dr. Minh Duc Hoang, Vinmec Research Institute of Stem cell and Gene Technology

Session III　座長:中木敏夫教授(帝京大学)
「Memorial Lecture: Stem Cells Transplantation
(脳性麻痺の克服例、他)」
Prof. Nguyen Liem, Director, Vinmec Research Institute of Stem cell and Gene Technology

帝京大学アジア国際感染症制御研究所(ADC研)は2018年６月１日に創設５周年を迎えました。これを記念して、2018年度は種々のイベントを開催致しました。６月22日に、「ADC研創設５周年記念国際シンポジウム」を帝京大学板橋キャンパス臨床大講堂で開催し、学内外から多くの方々にご参加いただきました(写真左下)。またその前週には、サテライトシンポジウム－Ⅰ(写真右下)を開催、第23回日経アジア賞を受賞したNguyen Thanh Liem教授にご講演いただきました。今号では、７月以降に開催されましたシンポジウム－Ⅱおよび関連会議について紹介させて頂きます。

2013年６月１日に世界的視野に立った感染症制御に関わる研究・教育を推進するために創設されたADC研。今後もこの理念を推進するとともに、アジアにおける感染症制御のための国際交流を通じて、グローバルヘルスに一層貢献して参ります。

June 1st, 2018: Our Laboratory ADC celebrated the 5th anniversary of its founding. There were a variety of symposiums on the 5th anniversary in 2018.

On June 22nd 2018, an international symposium for 5th anniversary of ADC establishment was held at the clinical auditorium of Teikyo University Itabashi campus.

And on June 15th 2018, Satellite Symposium-I was held at the meeting room of Teikyo University Itabashi campus. They were topical theme and many people participated in these symposiums.

ADC was established on 1st June 2013 to promote research and education on infectious disease from a global perspective. We had many questions from participants even at the social gathering after closing and the event was ended successfully. ADC will continue to promote research and will contribute to society by publishing the research.

メインシンポジウム
懇親会

サテライトシンポジウム
会場

サテライトシンポジウム－Ⅱ

遺伝子治療の最前線
Gene Therapy and Gene Managements

日時：2018年7月25日（水）15：45－17：20
会場：大学棟 104講義室
Organizer：鈴木和男　ADC研 所長

「ADC研創設５周年記念国際シンポジウム」最後の１つ「サテライトシンポジウム－Ⅱ」が、2018年７月25日（水）帝京大学板橋キャンパス大学棟 104講義室にて開催されました。

海外からは、Dr. Harry Malech（米国NIAID-NIH）、国内からは、小澤敬也先生（自治医科大学名誉教授・客員教授、前東京大学医科学研究所附属病院長）にお越しいただき、ご講演いただきました。著名な先生方のご講演であり、大変多くの方にご参加いただきました。

On 25 July 2018, An International Symposium (satellite symposium-2) of 5th anniversary of ADC establishment “Gene Therapy and Gene Managements” was held at Teikyo University Itabashi Campus. The topic was about recent top researches and many people participated.

参加者の集合写真

Program

開会　Opening Remark　鈴木和男　ADC研 所長（帝京大学）	
Session Ⅰ	座長：白藤尚毅教授（帝京大学 医学部 内科） **「実用化が進み始めた遺伝子治療・細胞治療」** 小澤敬也教授（自治医科大学免疫遺伝子細胞治療学）
Session Ⅱ	座長：布井博幸病院長（宮崎：愛泉会日南病院） **「Lentivector X-CGD Gene Therapy Clinical Trial and Progress Toward Gene Editing Correction of CGD」** Dr. Harry Malech (NIAID-NIH, USA, Laboratory Chief)

Opening

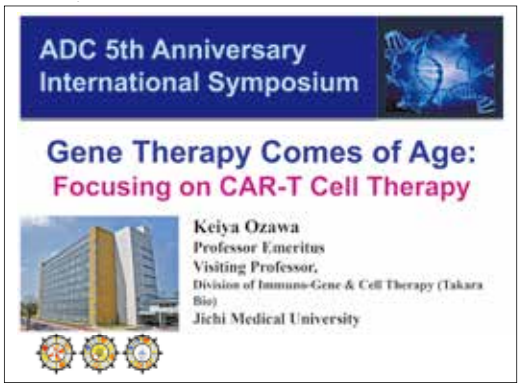
鈴木和男所長

Session I

Prof. Keiya Ozawa, M.D., Ph.D.

Professor Emeritus, Jichi Medical University, Visiting Professor
Division of Immuno-Gene & Cell Therapy (Takara Bio), Jichi Medical University

講演される小澤敬也先生



座長を務める白藤尚毅先生

Session Ⅱ

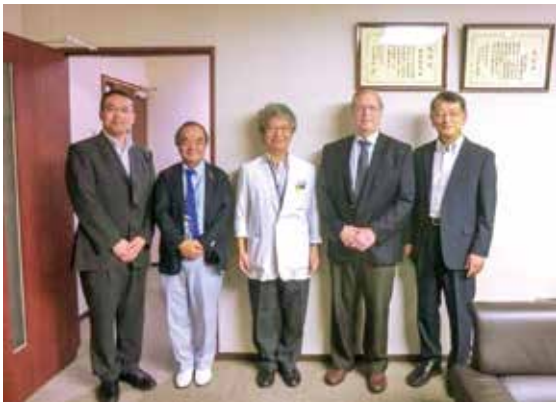
Dr. Harry L. Malech, M.D.

Chief of the Genetic Immunotherapy Section, and
Deputy Chief, Laboratory of Clinical Immunology and Microbiology
in the National Institute of Allergy and Infectious Diseases
(NIAID), National Institutes of Health.

講演されるDr. Harry Malech

座長を務める布井博幸先生

全体風景



医学部附属病院長室訪問 坂本哲也病院長と

ADC 5th ANNIVERSARY INTERNATIONAL SYMPOSIUM

5周年記念 シンポジウム関連会議 -1
Vasculitis Related Symposium-1 with Prof. Ulrich Speck and Prof. Luis Felipe Flores-Suarez
August 10, 2018

5周年記念シンポジウムの関連会議として血管炎の国際会議を2回開催致しました。

第1回目は、2018年8月10日（金）に呼吸器内科の専門であるProf. Ulrich Speck（Mayo Clinic, Rochester, USA）と Prof. Luis Felipe Flores-Suárez（Faculty of Medicine, Universidad Nacional Autónoma de México and the Instituto Nacional de Ciencias Médicas y Nutrición）お2人をお招きし、ADC研メンバー、帝京大学医学部内科学講座リウマチ・膠原病グループ河野肇教授、腎臓グループ山崎修講師、呼吸器・アレルギーグループ小林このみ助手から日本でのいくつかの症例について報告頂き、ディスカッションを行いました。短い時間でしたが、活発な討議を行い、大変有意義な時間となりました。

左から：小林このみ助手（内科）、河野 肇教授、Prof. Luis Felipe Flores-Suárez、冲永佳史理事長・学長、Prof. Ulrich Speck、鈴木和男所長、山崎 修講師（内科）、鈴木章一准教授（ADC研）、伊藤吹夕博士（ADC研）

前日、東邦大学病院（本間栄教授主催）にて開催された血管炎会議での集合写真

5周年記念 シンポジウム関連会議 -2
Vasculitis Related Symposium-2 with Prof. David Jayne and Associate Professor Toshiko Ihara
September 5, 2018

ひきつづき2018年9月5日（水）に2回目の血管炎会議を開催し、英国ケンブリッジ大学Addenbrookes病院のProf. David Jayneと猪原登志子講師（京都府立医科大学、京都大学）とディスカッションを行いました。

左から：伊藤吹夕博士（ADC研）、鈴木章一准教授、猪原登志子先生、冲永佳史理事長・学長、Prof. David Jayne、鈴木和男所長、柴田 茂教授（内科）

NEWS　Teikyo University HANOI Branch Opening Ceremony

帝京大学ハノイ支所　締結・開所式
MEMORANDUM OF UNDERSTANDING SIGNING AND TEIKYO UNIVERSITY HANOI BRANCH OPENING CEREMONY

August 21, 2018

帝京大学ADC研所長（鈴木和男）が、2005年からベトナム国立小児病院（VNCH）とインフルエンザに関する共同研究をスタートし、その後、2011年にPhung Thuy研究員の学位取得に協力した背景から、日本・ベトナム・フィリピン政府によるe-ASIA JRPでVNCH（Dr. Thuyをリーダー）と帝京大学ADC研は共同研究を進めました。

この背景から、2016年７月帝京大学はVNCHと単位互換協定を締結し、この３年医学部５年生の「ベトナム感染症」実習を実施してきました。

実習や共同研究を進めるためには、【帝京大学ハノイ支所】の設置が必要であることが検討され、今回2018年８月21日に冲永佳史理事長・学長とLe Thanh Hai病院長間で締結式が施行され、鈴木和男が初代ハノイ支所長になりました。【帝京大学ハノイ支所】は、Sウイング２階に２室設置されました。

締結式および支所の開所式には、日本大使館、JICAの方々にご臨席賜り、また国立小児病院、実習に参加していた11人の帝京大学医学部５年生と付添教員を含む帝京大学の関係者も列席しました。

From the background that Prof. Kazuo Suzuki, Director of Teikyo University ADC started collaborative investigation about influenza in the Vietnam National Children's Hospital (VNCH) since 2005, and cooperated with graduation of a researcher Ms. Phung Thuy in 2011, she works as a project leader in Vietnam side of the e-ASIA JRP program which was performed among Japan, Vietnam, Philippines. VNCH and the Teikyo University ADC will consider to continue collaborative investigation.

Furthermore, based on an agreement of Teikyo University with VNCH in July, 2016 for collaboration, the medical students of Teikyo Univeristy have been carried out in Vietnam infectious disease training for these three years.

It was considered that setting of [Teikyo University Hanoi branch] was necessary to achieve forward training and collaborative investigation. Therefore, a conclusion type was enforced between Dr. Yoshihito Okinaga, the President and Chariman Teikyo University, and the Director/Professor in Le Thanh Hai, VNCH on August 21, 2018. Director of Hanoi Branch is Prof. Kazuo Suzuki. Thus, the [Teikyo University Hanoi Branch] was established with two rooms in the S wing second floor.

In the ceremony, persons in relation to Teikyo University including 11 Teikyo University medical students and 7 staff who participated in the training, and persons in relation to the VNCH, Embassy of Japan, and JICA, attended the opening of a conclusion type and the branch.

冲永佳史帝京大学理事長・学長の挨拶
President Yoshihito Okinaga

帝京大学ハノイ支所設置締結書署名式

鈴木和男 帝京大学ハノイ支所長
Director of Hanoi Branch
Prof. Kazuo Suzuki

TEIKYO UNIVERSITY HANOI BRANCH

ハノイ支所　A室

ハノイ支所　B室

Stem Cell Transplantation治療のConsortium会議（キックオフ）-1st Meeting

December 11, 2018

1. 開会 Opening：鈴木和男 Kazuo Suzuki

2. 挨拶：冲永佳史理事長・学長 Message by Yoshihito Okinaga, President and Chairman Teikyo University

ステムセル移植コンソーシアム第一回会議によせて

2018年12月11日
帝京大学 理事長・学長 冲永佳史

ステムセル移植コンソーシアムが、基礎研究から臨床研究にわたり国際的に活躍される研究者の方々のサポートにより、第一回目を迎えることができましたことに先ずは感謝申し上げます。

本コンソーシアム発足のきっかけは、本学アジア国際感染症制御研究所所長である鈴木和男教授が親交を持たれている、Vinmec Research Institute of Cell and Gene Technologyのダイレクターである Nguyen Thanh Liem先生が、小児麻痺の治療において患者自身の骨髄由来のステムセルを用いて臨床レベルにおける有効性を見出され、その実績を重ねてこられたことにあります。

ステムセルに関する話題は、発生学的な基礎領域に限らず、昨今の創薬やガン治療或いは難治疾患治療において、盛んに取り上げられるようになりました。しかしながら、各領域におけるステムセルの活用において、それらが有効性を示す際の条件や機序については、未だ十分に解明されているとはいえず、ミクロ領域からマクロ領域に至るまでより客観的かつ科学的な検証を深めてゆく必要があります。

今般、Nguyen先生が示された臨床研究成果について、引き続き症例を積み重ねることに実証を深めるとともに、より科学的な分析方法を導入し、臨床レベルのみならず、科学的領域においても国際的評価に耐えうる知見を見出すこと、そしてこの治療方法が進化し、より多くの患者に対し適用され、ベネフィットを受ける人々を増やすことが、このコンソーシアムが目指すものであると認識しております。

つきましては、参加いただいております皆様のお力添えを心よりお願い申し上げますとともに、より早く当初の目的が達成されますことを祈念申し上げ、ご挨拶に代えさせていただきます。

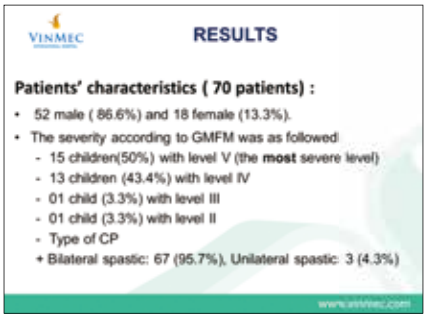
3. 出席メンバー Attendee

後列左から：岩間厚志先生、岡崎富男先生、布井博幸先生、
白藤尚毅先生、吉岡 昇先生
前列左から：小澤敬也先生、鈴木和男所長、三牧正和先生

構成員 Membership

メインオーガナイザー：鈴木和男（帝京大学 ADC研 所長）
リーダー：三牧正和（帝京大学医学部小児科教授）
帝京大学　白藤尚毅：医学部内科学講座血液内科教授＋治療スタッフ
吉岡　昇：医学部生理学講師
寺本民生：TARC 教授（アドバイザー）
東京大学医科研　岩間厚志：幹細胞治療研究センター幹細胞分子医学教授
東京薬大生命研　原田浩徳　教授（元広大・原医研）
自治医科大学　小澤敬也名誉教授・客員教授（東大医科研・前病院長）
重症心身重症施設
ときわ呉　岡崎富男　施設管理者
愛泉会日南病院　布井博幸　院長
ベトナム：Nguyen Thanh Liem, Directo（Vinmec Research Institute of Stem Cell and Gene Technology）
米国：Harry Malech（Chief, Genetic Immunotherapy Section, NIAID-NIH, Deputy Chief, Lab. of Clinical Immunology and Microbiology）

4. Nguyen Thanh Liem 先生の「日経アジア賞」受賞講演およびADC研5周年記念国際シンポジウムでの講演内容の説明



5. 次回2019年1月29日にVinmec Research Institute, Hanoiでの会議　日本から3名参加予定

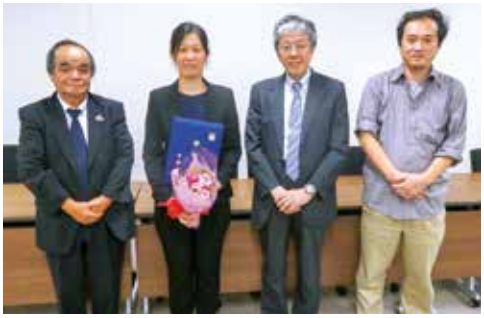
The Graduation Ceremony of Medical Doctor Ph.D.

September 19, 2018

4年にわたりベトナムから文科省の国費留学生として帝京大学大学院医学研究科およびADC研で研究したNguyen Thu Thuyさんが2018年9月に医学博士を取得し、修了式が行われました。Thuyさんは、9月末にベトナムに帰国し、現在国立ハノイ医科大学で助手として働いています。今後の活躍が期待されます。

Ph.D. student Ms. Nguyen Thu Thuy from Vietnam has been studying in Teikyo University Graduate School of Medicine and ADC supported for four years by a scholarship of the Ministry of Education, Culture, Sports, Science and Technology in Japan and took degree of Medical Doctor Ph.D. Now she works as researcher at Hanoi Medical University. We are hopeful for her success.

園生雅弘医学研究科長より修了証を授与



（左から）鈴木和男教授、Dr. Nguyen Thu Thuy、園生雅弘教授、鈴木章一准教授

Dr. Thuyからのコメント　Message by Dr. Nguyen Thu Thuy

It was lucky for me to get the Japanese Goverment (Monbukagakusho) schoolarship in 2014. Professor Kazuo Suzuki supported me to get the Ph.D. schoolarship. And I am very proud of becoming a Ph.D. student in Teikyo University. Professor Kazuo Suzuki and Associate Professor Shoichi Suzuki directly taught and guided me to perform my research project at ADC department. We worked hard and overcame failures to get the good data. As results of our efforts, our data was published in Tohoku journal of experimental medicine and I finished my Ph.D. course in Sep, 2018. I also attended many useful lectures of Professors in Teikyo university.

Furthermore, I and my family got much support and help from all members of ADC lab. That made our study and living in Japan easily and comfortably. We had many happy memories in Japan that we never forget.

I would like to thank to Prof. Suzuki, Asc. Prof. Suzuki and all members of ADC Lab. I also thank to Professors and Staffs in Teikyo university.

第一回帝京大学研究交流会シンポジウム

December 25, 2018

2018年12月25日（火）帝京大学板橋キャンパスにて、第一回帝京大学研究交流会シンポジウムが開催されました。帝京大学が有する貴重な研究シーズとニーズの価値を高め、その知見をさまざまな社会問題の解決に役立たせることを目的に、初の全キャンパス合同研究交流シンポジウムが開催されました。ポスター発表は260件にのぼり、ADC研からも5件の発表を行いました。

【発表ポスター】

- 鈴木和男
  アジア国際感染症制御研究所（ADC研）
  帝京大学研究ブランディング事業 -グローバルな視点からの危機管理3カテゴリー（事故、災害、テロ）の学際的エビデンス構築-【感染症部門】
- 鈴木章一
  ラクトペルオキシダーゼの産物「HOSCN」の役割の解明
- 菅又龍一
  16員環マクロライドによる抗インフルエンザAウイルス活性
- 伊藤吹夕
  Ⅰ. 抗インフルエンザ薬不良な小児のノイラミニダーゼ（NA）解析
  Ⅱ. カンジダ菌体抽出物誘導血管炎モデルマウスへの抗体投与

TAVP PLAN　Records of TAVP Training for 11 Students

帝京大学とベトナム国立小児病院および国立ハノイ医科大学との単位互換協定による
TAVP-TASP:さくらサイエンス・帝京大連携プログラム

医学部５年生
公衆衛生学実習【ベトナムでの感染症】

August 19-26, 2018

帝京大学医学部５年生のベトナム実習　　**コーディネーター：鈴木和男**

2015年の「さくらサイエンスプラン」を発展させるべく、一昨年７月に「帝京大学とベトナム国立小児病院および国立ハノイ医科大学との単位互換協定」を締結しました。同時に、医学部５年生「公衆衛生学実習」の中に「ベトナムでの感染症」を組み入れて頂きました。

主目的は、世界やアジアで発生している感染症の実状を視察し、国際的視野に立った医療人をめざすこととし、臨床実習、国際保健・予防医学、医療システム・アクセスの観点を含めて学習します。

2016年に第１期生７人、第２期生９人が参加し、大きな成果がありました（ADC Letter Vol.4 No.1、Vol.5 No.1）。今年は、それを上回る医学部５年生11名の参加となりました。

Training of the Medical Students in Vietnam　　**Coordinator: Kazuo Suzuki**

In order to develop the Sakura Science Plan of 2015, in July 2016 we signed a “unit compatibility agreement between Teikyo University and the National Children’s Hospital of Vietnam and the National Hanoi Medical University.” At the same time, it was incorporated into the fifth grade medicine “public health practice”.

The main objective is to observe the actual condition of infectious diseases occurring in the world and Asia, aim for a medical person from an international perspective, including clinical practice, international health and preventive medicine, medical system, access point of view learn.

Seven students participated in 2016 and 2017, and there were great results (ADC Letter Vol. 4 and Vol. 5 No. 1). This year, more than that, participation of eleven fifth graders participated.

参加者：上垣 怜央（全体リーダー）、笠井 健司（連絡係）、田中 悠太郎（会計・社会文化交流係）、安井 知樹（記録係）、長田 真季（サブリーダー）、永島 瑠乃（写真係）、長久 大介（連絡係）、桒原 佑実（会計・社会文化交流係）、柿原 杏那（サブリーダー）、小坂 晃輝（記録係）、宮川 公兵（写真係）

Coordinary：
鈴木 和男（アジア国際感染症制御研究所　所長）Kazuo Suzuki
河内 正治（アジア国際感染症制御研究所　副所長）Shoji Kawachi
中原 慎二（救急科　准教授）Shinji Nakahara
高橋 和浩（ADC研、小児科　講師）Kazuhiro Takahashi
玉井 大地（救命センター　医師）Daichi Tamai
鈴木 章一（ADC研　准教授）Shoichi Suzuki
Tran Huu Dat（帝京大学　大学院生、修練医）

Local Staff in Hanoi：
NCH：Hai 病院長、Dien 副院長、Thuy ラボチーフ、国際部長、病棟スタッフ
HMU：Thu 准教授（感染症科）

研修した部署：
ベトナム国立小児病院（ハノイ）：
ICU、呼吸器、循環器、感染症、救急、臨床疫学、他
国立ハノイ医科大学：感染症疫学
Vinmec 国際病院および附属 Stem Cell 研究所
日本大使館（ハノイ）、JICA（ハノイ）

Acknowledgements：
冲永 佳史　学長 President Yoshihito Okinaga
冲永 寛子　副学長 Executive Vice-President Hiroko Okinaga
中木 敏夫　教務部長 Prof. Toshio Nakaki
塚本 和久　教務部長 Prof. Kazuhisa Tsukamoto
大久保 孝義 衛生学公衆衛生学 教授 Prof. Takayoshi Ohkubo

実習スケジュール

	20Mon	21Tue	22Wed	23Thu	24Fri
AM	9:00-9:30 Opening Ceremony	9:00-10:00 Branch Opening Ceremony	9:00-11:30 Infectious Dept	9:00-11:00 Respiratory Dept	9:00-9:30 Closing Ceremony
	9:45-10:15 Laboratory visit	10:15-11:45 Cardiac intervention, Cardiology Dept			10:45-12:00 Embassy
	10:30-11:45 NICU visit				
Lunch					
PM	13:30-16:30 Emergency Dept	14:00-17:00 Vinmec Hospital	13:30-16:30 ICU	13:00-14:00 HUM Lecture Infectious Dis	
				15:00-17:00 SICU	15:00-16:30 JICA

受講証　2018年　Certificates for the Students

国立小児病院
National Children's Hospital（NCH）および研究所（RICH）

国立ハノイ医科大学
Hanoi Medical University（HMU）

Vinmec国際病院
Vinmec International Hospital

Topics

JICA Vietnam

JICA 訪問 高島 恭子企画調査員と
with Ms. Kyoko Takashima

Embassy of Jaoan, Hanoi

日本大使館にて、
常岡 豊先生、中馬書記官と
with Dr. Yutaka Tsuneoka
and Ms. Ai Chuman

報告 衛生学公衆衛生学実習「ベトナムにおける感染症」

帝京大学医学部５年
上垣怜央, 長田真季, 柿原杏那, 笠井健司, 桒原佑実, 小坂晃輝,
田中悠太郎, 長久大介, 永島瑠乃, 宮川公兵, 安井知樹

今年度も衛生学公衆衛生学実習の一環でベトナムを訪れる機会を得た。

ベトナムでの実習は今年は３年目で，規模も増して11人での実習となった。

実習で学んだ全てを紹介することは難しいので，そのいくつかを取り上げる。

(1) ベトナムの環境

ベトナムでの公衆衛生学実習を通じて、我々は新たな知識と体験を得ることができた。

日本から５時間ほどのフライトを経て降り立ったベトナムは、日本では味わうことがない蒸し暑さで包まれていた。この地で毎日、実習先の国立小児病院までのビルとビルの狭い道を歩いて通っていたが、大量のバイクで渋滞している道路の光景が、我々にとっては新鮮だった。さらにバイクに子供３人と大人２人の合計５人で乗っていたり、排気ガスの吸引防止で布のマスクをしてバイクを運転していたりしたのを見て、日本との交通ルールの違いを感じた。

歩いてみると、コンクリートで作られた立派なアパートの横に、木造で壊れそうな家が立っているのが当たり前で、ハノイ市全体に貧富の差が大きいことを実感した。また、酷い臭いの生ゴミが道に散らばっており、我々はゴミの分別と収集のシステムの未熟さを痛感した。

(2) 研究室

NCHの研究室には最新のPCR等最先端の研究設備が完備されていた。NCHは我々の眼から見ても非常に大きな病院であり、ベトナムの中でも最先端の機械が取り入れられているため、他の病院からも検体がたくさん送られてくるそうだ。我々の帝京大学病院のおよそ10倍の処理能力にあたる450検体を１日で処理できると聞いて非常に驚いた。

(3) NICU

NICUには２つのユニットと母子同室の部屋があった。１つのユニットは容態が安定している患者のため、もう１つのユニットは先天性心疾患や人口呼吸器を必要とする重症患者用であり、医師から許可が出ると母子同室が認められる。驚くべきことに、医師、看護師等NICUで働くスタッフ120人全員が女性であった。基本的な設備は日本とあまり変わらないが、このNICUは多くの親がかかりつけ医を信用していないため患児が多く患者隔離が不十分であり、医療従事者の質向上と患者教育の必要性を感じた。

(4) 感染症科

感染症科では、日本ではあまり出会うことのない麻疹や日本脳炎や寄生虫感染を見ることができた。ベトナム小児国立病院では2014年に麻疹のアウトブレイクが発生し、約100人の患者がなくなってしまった。原因として１つのベッドに２人以上患者を寝かせていたりと患者の隔離ができていなかったことが挙げられた。これを受けて昨年度から麻疹の患者は１人１部屋に隔離するという取り組みを行ったところ、それ以降300人の麻疹患者が入院したが１人も死者が出ていないとのことだった。このことから、院内感染防止のための改善が進められていることを知り、空気感染を引き起こす感染症の患者の部屋を隔離させることはとても大きな効果があるということを身をもっ

て学ぶことができた。ベトナムでは自分が麻疹のワクチンを打ったかどうかわからないという人が少なくなく、今後はそれについての対策も必要なのではないかと感じた。

(5) ICU

ICUは挿管を必要とするような重症患者と主に肺炎である軽症患者で分けられていた。アシネトバクター・E.coli等の耐性菌に対しては隔離が行われていた。主に肺炎と敗血症性ショックの患者がいた。印象に残った症例はパラコート中毒の子どもの患者で、母親の自殺に巻き込まれたとのことであった。パラコートは除草剤であるが、有害であることから日本では使用が中止されている。ベトナムでは現在も使われているが来年から使用が中止されるということで、今後こういった事故は減ると予想されるという。また、ICUの医師はこういった虐待ともいえる事故が減るような仕組みを周りが作らなければいけないと言っていた。ベトナムでは現在環境規制や子どもの権利に対する取り組みが行われている一方で、こういった現実があることを知った。

(6) 呼吸器科

呼吸器科には約50名の患者がおり、重症度によって3つのユニットに分けられていた。疾患の内訳としては、肺炎と気管支炎が患者の多くを占めていた。最も印象的だったことは、筵で作られたベッドが使用されていたということだ。病棟内は冷房が完備されておらずとても暑いため、暑さ対策として筵のベッドが使用されているとのことだった。また、アデノウイルス感染症患者に対して隔離部屋を用意するといった院内感染対策が行われていた一方で、患者のお見舞いに来た家族の方々はマスクをつけておらず、感染対策に関して改善できる面もあるのではないかと感じた。

(7) SICU

SICUは術後の患者が経過観察されている場所である。ベトナム国立小児病院ではSICUで管理している4、5人に1人は小腸閉鎖の術後の患者だった。これはダウン症で小腸閉鎖を合併している子供も含んでおり、ベトナムでは小腸閉鎖の子供は多い。またこの病院はベトナムで一番の小児病院であるため、地方からの縫合不全を起こした患者が運ばれるケースも少なくないという。ベトナムの地域の病院は医師の技術が少し劣っており、機材が不十分なために縫合不全が起きることで患者が死亡することも多い。

(8) ER

ERはEmergency & Poison control Departmentと呼ばれ、Reception & triage area、short stay area、consulting area、Short stay areaの4つのエリアに分かれている。

はじめに、Reception & triage areaでバイタルサインの測定と、患者の振り分けを行う。緊急性の高い患者はERで治療を受け、その他はconsulting areaにて問診後、各専門科に回される。

また、short stay areaは全28床で、4つ（新生児、呼吸器、重症患者、その他）に分類されている。看護師は各エリアに5人ずつ、医師は全15人いて、特に研修医は毎日朝7時～夜10時まで勤務している。重症患者の部屋には、10日前に発熱と痙攣を主訴に運ばれてきた患児がいた。瞳孔反射がなく蘇生は難しいが、DNARは行われていないようで、呼吸器はご両親が停止を希望するまで続けるようだ。

Short stay areaは、隔離部屋がいくつかあり、麻疹、結核などの空気感染と重症感染症患者の部屋、下痢と発熱、痙攣の患者をまとめた部屋があり、同じ部屋になった他の疾患の患者が二次感染する可能性が懸念された。

ERには1日70～100人の患者さんが来院する。115に電話すると、およそ50万ドン（約2,500円）で救急車を呼ぶことはできるが、到着に時間がかかるため、大抵は自家用車やバイクで来院する。

(9) 在ベトナム大使館

大使館では医務官である常岡豊先生の講義があった。講義の内容は発展途上国の感染症についてであり、ベトナムのみに関わらず先生がかつて赴任していた発展途上国での経験を踏まえての話を聞くことができた。先生は感染症には4つのファクターがあると考えており、その4つのファクターは環境、文化、教育、協力であり、この4つのファクターについて講義をしていただいた。まだまだ発展途上国には感染症の対策が必要であり各国間の協力が必要であることがわかった。

（10）JICA

JICAは日本の政府開発援助（ODA）を行う機関として、開発途上国への国際協力を行っている。JICAでは高島さんにお話を聞くことができた。近年ベトナムでは医療水準が向上しているとはいえ、まだまだ地域によって格差が大きい。JICAは地域医療が定着しないことを懸念しており積極的にこの問題に介入している。JICAは他にも母国語を話すことのできない54の少数民族の所へ直接出向き、治療やワクチン接種だけでなく医療知識なども提供している。このように様々なことをJICAは、日本の産業界、教育機関、自治体、市民社会等とも連携し、公正な社会・国づくりを包括的に支援している。

ベトナムでの公衆衛生学実習は今回で３年目となり、軌道に乗ってきたように思う。一生でもう二度とないかもしれないこの大変貴重な機会に私たちはとても多くのことを体験し、学習した。帝京大学医学部のカリキュラムにおいて唯一他国で実習ができるこの機会に我々総勢11名の学生を受け入れてくださった鈴木和男先生をはじめとする引率の先生方ならびにADC研のみなさま、国立小児病院などのベトナムの現地スタッフのみなさま、そして帝京大学に心より感謝を申し上げる。ありがとうございました。来年度以降の後輩たちの実習が更に良いものになるよう、祈念している。

5th year medical students in Teikyo university
Reo Uegaki, Maki Osada, Anna Kakihara, Kenji Kasai, Yumi Kuwahara, Kouki Kosaka, Yutarou Tanaka, Daisuke Chokyu, Runo Nagashima, Kohei Miyagawa, Tomoki Yasui

We got an opportunity to visit Vietnam this year as part of public health practical training.

This practical training in Vietnam is the third year, and we, students, are 11 people.

It is difficult to introduce everything studied in this practical training, so we will take up some of them.

(1) Environment of Vietnam

Through public health practice in Vietnam, we were able to gain new knowledge and experience.

After 5 hours flight from Japan I landed in Vietnam, and we were wrapped in sultry heat I have never experienced. Everyday we walked down the narrow roads of buildings and buildings up to the National Children's Hospital, and the sight of the road which is congested with a lot of motorcycles was fresh for us. In addition, I felt the difference in traffic rules with Japan, seeing that there are a total of 5 people including three children and two adults on a motorcycle and they're wearing masking cloth and driving a motorcycle by preventing suction of exhaust gas.

When walking, it was natural that a house that could be broken by wood was standing beside a fine apartment made of concrete, and I realized that the gap between rich and poor in Hanoi City is big. Also, raw garbage with a bad smell was scattered on the street, and we were keenly aware of the immaturity of the garbage separation and collection system.

(2) Laboratory

In the laboratory, there were the latest research facilities, such as the latest model of PCR. NCH was a huge hospital where the latest instruments were equipped, so many samples were sent from other hospitals to them. We were very surprised to hear that they could deal with 450 samples in a day which were ten times as many as that in Teikyo University Hospital.

(3) NICU

NICU was divided into 2 units and there were rooms for mothers and their babies. One unit was for stable condition patients and the other unit was for the patients with severe conditions who had congenital heart disease or need ventilator. With doctor's permission, mothers would be with their babies. To our surprise, there were only women staff (120 doctors and nurses). We thought that the quality of facilities in their NICU were the same level for that in Japanese hospitals, but patient isolation was not enough because parents who don't trust primary care doctors sent their babies for them, so there were huge number of patients in NICU. We felt the necessity for improvement of medical staff quality in Vietnam and education for patients.

(4) Infectious department

In the infectious disease department, we could see patients with measles, Japanese encephalitis and parasitic infections that we would rarely see in Japan. A measles outbreak occurred in 2014 at the hospital and about 100 patients passed away. They thought that they should have put patients with measles in quarantine. After that, when the patients with measles were isolated from last year, 300 measles patients were hospitalized, but no one had died yet. From this fact, I was able to learn about the

importance of taking measures against nosocomial infection and isolating patients with airborne infection. Many people in Vietnam do not know whether they had a measles vaccine, I thought that the countermeasure should be take for this.

(5) ICU

The ICU was divided between severe patients who need intubation and the patients with mainly minor injuries like pneumonia. Isolation was performed against resistant bacteria such as Acinetobacter and E.coli. There were mainly patients with pneumonia and septic shock. The patient who was most impressed for me was a child who was paraquat poisoned. He was involved in his mother's suicide. Although paraquat is a herbicide, its use is prohibited in Japan. Although it is still in use in Vietnam, it is expected that such accidents will decrease in the future as usage will be stopped next year. In addition, ICU doctor said that they should create the system to decrease these accidents that is more like abuse. Vietnam is currently engaged in environmental regulations and establishing rights to children, but in the other side Vietnam still has these reality we've never known till we visit.

(6) Respiratory department

The respiratory department has 50 hospitalized patients and it is divided into 3 units based on severity level of patients. Most of the hospitalized patients have pneumonia or bronchitis. And we were surprised that they lay on woven mats to prepare for the heat because hospital rooms had no air conditioners. Also we knew that some nosocomial infection measures were taken there, for example patients with adenovirus were treated in isolated rooms. However we realized that patients' families who came there didn't put masks. So we felt there was still room for improvement in infectious controls.

(7) SICU

SICU is a place where postoperative patients are being followed. In Vietnam National Children's Hospital, one out of 4 or 5 people managed by SICU was a postoperative patient with small intestinal obstruction. This includes children who have Down Syndrome with small intestinal obstruction and in Vietnam there are many children with small intestine obstruction.

In addition, because this hospital is the first children's hospital in Vietnam, there are many cases where patients who have caused anastimotic from rural areas are carried. Hospitals in the rural areas of Vietnam have a slightly inferior doctor's skills and patients often die of anastimotic due to insufficient equipment.

(8) ER

In VNCH, ER is called "Emergency & Poison control Department" and there were 4 areas of it, Reception & triage area, short stay area, consulting area, and Short stay area. First of all, patients who came to ER were checked their vital signs and were sorted by emergency at Reception & Triage area.

Patients in imperious needs would be treated in ER and the others were sent to each department after history taking at consulting area.

In short stay area, there were 28 beds divided into 4 parts (neonates, respiratory disease, severe patients, and others). Each part held 5 nurses. There were 15 doctors working at ER and especially residents were working from 5 am to 10 pm. At severe patients' part, we saw a boy with a fever and convulsions who has been hospitalized for 10 days. Although his pupil reflection was negative and his recovery was hopeless, because DNAR wasn't applied in Vietnam hospitals, respiratory apparatus would be continued until they want to stop it.

Short stay area had some isolation rooms. One for measles and tuberculosis, another room was for diarrhea, fever and convulsions. All the different patients were put together, which could cause second infection. The number of patients visit ER is 70-100 per a day. You can call an ambulance by dialing 115 for 500 thousand Don (approximately 2,500 yen), but it takes too long time, so most patients tend to come by cars or motorcycles.

(9) Embassy of Vietnam

At the embassy there was a lecture by Dr. Tsuneoka, a medical officer. The content of the lecture was about infectious diseases in developing countries and it was stories based on experience in the developing countries where Dr. Tsuneoka used to work. Dr. Tsuneoka considers that there are four factors for infectious diseases, and the four factors are environment, culture, education, cooperation and lectured on these four factors. We still need to take measures against infectious diseases in developing countries and it is necessary to cooperate between countries.

(10) JICA

JICA is engaged in Japan's Official Development Assistance (ODA) and is engaged in international cooperation with developing countries. Although medical standards have improved in Vietnam in recent years, the disparity is still largely depending on the region. JICA is concerned that regional medical care has not become established and actively intervenes in this problem. JICA also visits directly to the 54 ethnic minorities who cannot speak their mother tongue, offering medical knowledge as well as treatment and vaccination. JICA cooperates with Japanese industries, educational institutions, local governments, civil society, etc. in various ways, and supports comprehensively the creation of a fair society / country.

日本・アジア青少年サイエンス交流事業「さくらサイエンスプラン」
Japan-Asia Youth Exchange Program in Science
ベトナムから帝京大学へ

October 29 - November 7, 2018

研修参加者　Visitors for TASP Training Supported by SAKURA Science Plan of JST

ベトナム８名（国立小児病院：ハノイ４名、国立大学第一小児病院：ホーチミン４名）

Hanoi Vietnam National Children's Hospital
1. Dr. Sinh Thi Tran, (Ms), Molecular lab
2. Dr. Huong Thi Thu Tran, (Ms), Infectious Dis Dept
3. Dr. Xoay Dang Tran, (Mr), ICU
4. Dr. Tam Thi Thanh Pham, (Ms), Emergency Dept

Ho Chi Minh Children's Hospital 1
1. Dr. Vo Thanh Vu, (Mr), Pediatric ICU
2. Dr. Ma Phuong Hanh, (Ms), DHFever Dept
3. Dr. Nguyen Thi Hong Thien, (Ms), Surgical ICU
4. Dr. Nguyen Thanh Trang, (Ms), Infectious Dept

帝京大学アジア国際感染症研究所（ADC研）では、2018年10月29日～11月７日までJST（日本科学技術振興機構）の事業である日本・アジア青少年サイエンス交流事業「さくらサイエンスプラン」を実施し、ベトナムから８名の研修生（医師７名、研究員１名）を受け入れました。今回は、ベトナムで活躍する医師、研究者に、「感染症」、「安全管理」、「バイオセキュリティ」をテーマに研修を行いました。医学部附属病院安全管理部での医療安全、感染制御の研修、看護部の病院内ラウンド、中央検査部や薬剤部での研修、そして、本学医学部、薬学部、研究施設の見学を実施しました。また最新のウイルスや細菌検出技術の実習体験や授業への参加など、本学の教員や学生とも交流を深めました。さらに、ADC研と連携している結核研究所（東京都清瀬市）および聖路加国際大学（東京都中央区）も訪問しました。

We organized SAKURA Science Plan supported by JST from Oct. 29 to Nov. 7 in 2018 in ADC Teikyo University.

Contents of the Training

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   Introduction of Professors in ADC and ADC Staff
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3. 実験室研修：ADC感染症研究室、シミュレーション実技
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4. 講義：感染症、公衆衛生学、シミュレーション、薬学部
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   Certificate Celebration and Farewell Party

謝辞 Acknowledgements

冲永佳史学長、ADC研教授会メンバー（斧 康雄、古川泰司、槇村浩一、唐澤 健、山下 純、松永直久、井上まり子、高橋和浩の各先生方）、医学部、薬学部の教員のみなさま、病院スタッフ（坂本哲也院長、高田眞二講師、土谷明子看護師長）、安全管理部、感染制御部、中央検査部、看護部、薬剤部および臨床工学センターのみなさま。

研修スケジュール　Schedule of TASP

	AM	PM
October 29th（Mon）	Arrival at Narita / Tokyo Airport Check-in Toyoko inn 帝京大学着	大学棟ツアー 17：00 レセプション
October 30th（Tue）	ADC研 11：00 小児科（三牧、高橋）	13：30 病院薬剤部 15：00 病院看護部（土谷）
October 31th（Wed）	ADC研 11：00 病院安全管理部（河内）	13：05 鈴木（和）：１年生授業「世界に羽ばたく医療人」自己紹介 15：00 講義「バイオセーフティー」棚林室長（国立感染研）
November 1st（Thu）	10：00 病院感染制御部（松永）	13：30 病院中検 15：30 臨床工学センター（川崎）　滅菌室
November 2nd（Fri）	09：30 医学部微生物（斧）	結核研究所訪問
November 3rd（Sat）		
November 4th（Sun）	JST未来館	
November 5th（Mon）	10：00 シミュレーション研修（金子、竹内）	13：00 公衆衛生（井上） 14：00 薬学部（唐沢） 14：45 薬学部（山下）
November 6th（Tue）	10：30 聖路加訪問（瓜生田）	ADC研 17：30 修了証授与、送別会
November 7th（Wed）	Check-out Hotel	

帝京大学 医学部附属病院
Teikyo University Hospital


小児科 Pediatrics


NICU


看護部 Nurse Department

安全管理部 Safety Control Department


感染制御部 Infection Control Department


病院薬剤部 Parmacy Department


臨床工学センター、滅菌室
Medical Engeneering Department


中央検査部 Central Laboratories

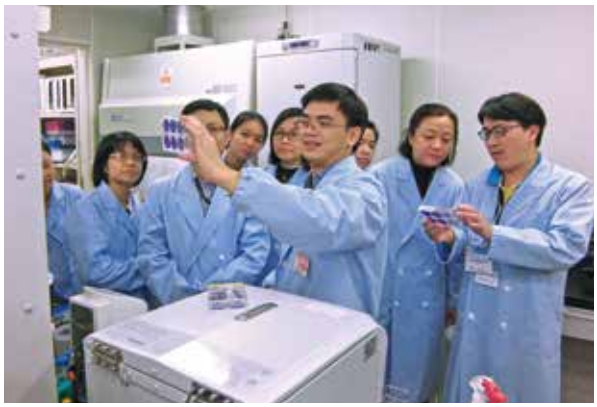
医学部
School of Medicine


微生物学教室 Microbiology Department


シミュレーションセンター
Simulation Center


衛生学公衆衛生学教室 Public Health Department

ADC研究所
ADC Laboratory


研究室 Laboratory


バイオセキュリティ講習会 Lecture of Biosecurity


1 年生授業「世界に羽ばたく医療人」Class “Worldwide Researchers and Medical Staffs”

学外：連携施設訪問
Visiting RIT and St. Luke’s International University

【連携施設】結核研究所 RIT

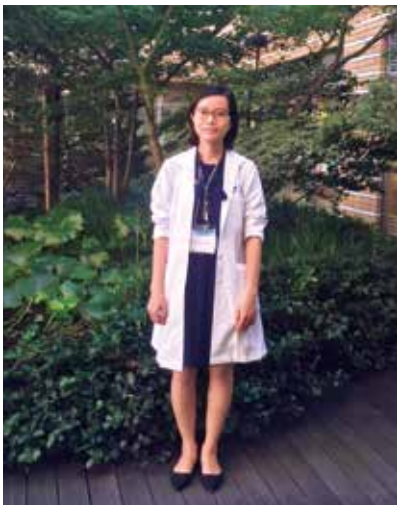

聖路加国際大学病院 St. Luke’s International University

鈴木所長からの研修終了証授与および歓送会
Certificate Celibrate and Farewell Party

Reports of Visitors

SAKURA Science Plan

Name: Tran Thi Thu Huong M.D.
Country: Vietnam
Department: Infectious diseases department, National Children's Hospital, Hanoi
Position: Pediatrician



My job

I have been working in the Infectious diseases department since 2008, and my daily job is to treat patient with infectious diseases in Vietnam such as encephalitis, meningitis, septicemia, influenza, dengue hemorrhagic fever. I have participated in some researches with other countries in the world such as study of encephalitis, hand foot mouth disease, influenza…I always want to find out many causes of encephalitis to find the best treatment to reduce mortality and sequelae of patients.

Summary of my training course

I felt really lucky to be taking this course. Although the course was only for 10 days but I learned a lot of things from Japan. The first was my impression of Tokyo, the city was crowded, interspersed with modern and traditional but clean and neat. The weather was very pleasant with beautiful scenery. Japanese are always on time but friendly and kind to help foreigners like us. We visited many places in Tokyo like Teikyo University and Hospital, St. Luke International University, Research Institute of Tuberculosis and I was really impressed the way they work and their warm welcome. As an doctor majoring in infectious diseases I really admired how they monitor and prevent hospital infections, take care and treat patients, and distribute drugs to patients, as well as the teamwork system in Japan. In Japan, modern medicine was developed, but don't forget the infectious diseases that are still very little in your country such as tuberculosis.

Potential Collaboration

I hope that in the future we will have more opportunity to collaborate with you to investigate infectious diseases, as well as to find better diagnosis and treatment for patients.

Name: Tran Thi Sinh Ph.D.
Country: Vietnam
Department: National Children's Hospital
Position: Researcher at Biomolecular research of Infectious Disease

My job
I have been working in National Children's Hospital since 2006. Now, I am working as a researcher at Biomolecular research for Infectious Diseases. My routine task is performing different types of molecular tests for detecting various pathogens. Besides, I am responsible for laboratory quality management in accordance to ISO 15189 standards.

Benefits from Sakura's Science Program
The training schedule gave us an opportunity to visit clinical settings, laboratories in Teikyo university and different research institutions such as ADC and Research Institution of TB. I was impressed with the safe control and infectious disease control activities at Teikyo hospital. The interesting presentation on current research topic at Microbiology and Immunology Department of Teikyo University not only updated my knowledge in molecular research area but also open the potential opportunity to collaborate between our institution and Japanese researchers. The tour to Miraikan museum opened my eyes on the innovative achievement of current technology. Lastly, I had excellent experience on enjoying delicious traditional Japanese food, seeing beautiful Mt. Fuji and meeting kind Japanese people.

Future collaboration
I believe that the future exchange programs would strengthen the collaboration between National Children's Hospital and Teikyo University in both medical research and medical training.

Name: Pham Thi Thanh Tam M.D.
Country: Vietnam
Department: Emergency and Poison control department, National Children's Hospital, Hanoi
Position: Pediatrician

My job:
I have been working at VN National children's hospital since 2010, in taking care of basic life support for ill children. I'm also part of poisoning control term in my department.

Summary of ten-day training course
This program was based mainly on Teikyo University and Teikyo University Hospital Session topics which covered emergency medical engineering, pharmacy, biosafety, safety division, infection control and medical examination. I also visited the Research Institute of tuberculosis in Japan to understand how to control tuberculosis in developing countries. When I went to St. Luke's International University, I was very impressed on how they managed safety for patients and prevented infection.
In addition, I've learnt a lot about Japanese culture and high techniques from National museum of Emerging Science and Innovation. Also, Japanese people are very kind, polite and hardworking.

In contribution:
- Improving my knowledge on infection fields especially in biosafety and how to control nosocomial infection.
- Benefiting to coordinating clinical department laboratory.

Future collaboration:
- In the future, I hope we'll have more opportunities to exchange students between NCH and Teikyo University.

Name: Tran Dang Xoay M.D.
Country: Vietnam
Department: Pediatric Intensive Care Unit, Vietnam National Children's Hospital, Hanoi, Vietnam
Position: Pediatrician

My job:
I have been working as pediatrician in PICU since 2014. I have 3 missions: treatment for critically ill childrens such as ARDS, septic shock, fulminant myocarditis, etc…; training for local hospital Basic Pediatric Life Support, Advanced Pediatric Life Support, etc…; and research about critical care medicine such as severe Bordetella pertussis, Influenza, and Enterovirus.

Summary of Sakura Exchange Science Program:
During 10 days in Japan I visited Teikyo University – Hospital, Research Insitute of Tuberculosis and St. Luke's International University, I have more expericences and knowledges about your health care system. I see some similar system in Vietnam and I learned from your modern system of digital medical record, risk management and hard working. It was the first time I have visited hybrid operation room, and I also was really impressed with pharmacology department preparing medicines for patients. When I come back home, I hope to change something to make my department can do better.
We also have some social events to visit wonderful Mt. Fuji by shinkansen, visit Miraikan and I like AI techniquies which will change life in near future. I enjoyed Japanese foods, Japanese cultures and made more friends as well.
I would like to say many thanks to Japan Science and Technology Agency, Prof. Kazuo Suzuki, A/Prof Shoichi Suzuki, Ph.D. Fuyu Ito, Ph.D. Ryuichi Sugamata and others in ADC helped us during this training course.

Future collaboration:
I will support for Japanese students who will become Sakura Exchange Science participants in Hanoi, Vietnam.
Furthermore, I would like to take part in the Ph.D. of Public health in Japan and promote research cooporation between Vietnam National Children's Hospital and Teikyo University.

Name: MA PHUONG HANH, M.D.
Country: Vietnam
Department: Dengue Hemorrhagic Fever Children's Hospital No. 1 Ho Chi Minh City
Position: Pediatrician

Job Description
I have worked as a pediatrician since 2008 and my working schedule is from Monday to Friday. I do the physical checkup, analyze many medical test results and provide appropriate treatment to my patients every day. In addition, I also receive new patients for hospitalization, and constantly provide consultation to those from other departments whenever their test results showing some abnormal signs. Generally, my department diagnoses and treats various diseases such as: Dengue Hemorrhagic Fever, Anemia, Hemolysis Anemia, Thalassemia, Hemophilia and so on.

Benefits from Sakura Science Program
This was my honor to be able to participate in this wonderful training program which was organized by Asia International Institute of Infectious Disease Control (ADC), Teikyo University. All of the people were so kind, enthusiastic, and friendly. Everything was so wonderful to me.
I was guided to visit so many places, such as: Pediatric Department, Pharmacy Department, Nursing Department, Operation Department, Clinical Laboratory Science, Microbiology Department, JATA (Tuberculosis) Department… and I also had

precious time to visit the St. Luke's International University. Overall, the medical equipment and the facility were so modern, clean, and in order. The patient receiving process and the treatment stage were so standardized and strictly followed-up by the Standard Treatment Guidelines, this kind of operation was really helpful to avoid human errors and easily to be traced back in case any errors may happen.

One of my most excitements was the Pediatric Department; there was room for children to eat and to play with smart designs for education purposes. In addition, each department had some caregivers to play with the children, so that their parents could have more free time and able to concentrate on their daily works. Furthermore, I was so impressed by the network of infectious disease control in the hospital which appeared in all clinical departments. This arrangement was really helpful for patients in term of early detection, rapidly isolation and timely handling for each contagious case in order to prevent cross infection. Last but not least, I also received a lot of guidance and valuable advices by many dedicated Professors and the kind-hearted staff of ADC during my stay there.

Beside the intensive training lessons, I was so lucky to be able to enjoy the Halloween Event in Shibuya district where young Japanese and foreigner alike dress up with elaborate costumes. I also visited the Mount Fuji, the highest mountain and the well-known symbol of Japan.

Then, I was strongly recommended to visit the National Museum of Emerging Science and Innovation, known as the Miraikan in Odaiba District of Tokyo. Over there, I could experience the advanced technologies which have become part of our everyday life, and learnt about Japanese technological innovation. Having said that, I also had wonderful opportunity to visit some big shopping centers in Ginza, Tokyo and enjoyed Japanese delicious foods such as: Sushi, Sashimi, and Yakiniku.

Once again, I would like to say thank you for providing us such an excellent training program. The content was really informative and useful. I strongly believe that I can apply a lot of things for my daily work in Children's Hospital 1 Ho Chi Minh City.

Potential Collaboration

I sincerely hope that ADC will continue and develop this exchange program to have more short-term and long-term training courses for young doctors in Children's Hospital 1 Ho Chi Minh City, especially in the field of Infectious Disease Control.

Name: NGUYEN THI HONG THIEN, M.D.
Country: Vietnam
Department: Surgical Intensive Care Unit & Cardiac Intensive Care Unit (SICU&CICU), Children's Hospital 1, Ho Chi Minh City
Position: Pediatrician and Intensivist

Job description:

I have been working as pediatrician and intensivist in Children's Hospital 1, Ho Chi Minh City for 14 years. My work is to deal with very severe patients. I have worked in Emergency Deparment and Pediatric Intensive Care Unit (PICU) for several years; then, I was assigned to take part in the team for the implement and development of the Open Heart Surgery program in my hospital, and have been working in Surgical Intensive Care Unit & Cardiac Intensive Care Unit since then.

Summary of the 10 days training course in Sakura program:

We have had a very busy schedule in our course to visit many departments and places such as: Pediatric department, NICU department, ADC laboratory, Pharmacology department, Safety Control department, Infectious Disease Control and Prevention department, Clinical laboratory department, Medical Engineering sterilization centre, Microbiology department, Simulation center laboratory, Public health department, Faculty of pharmaceutical, JATA (tuberculosis), and St. Luke's international university hospital.

Everything in each place was very modern and was operated very well and logically. We found many new things, and above all, we admired the moderness and especially the way of working everywhere we visit. Devices and equipments may be almost the best ones. Japan's way of working is very precise, detailed, and professional. Especially, the cooporation between departments and other parts and throughout the whole mediacal system was great.

We also had time in weekend to visit Mount Fuji - considered the symbol of Japan, and enjoyed very beatiful lanscape there, with yellow and red leaves at beginning of autumn, which was so great. We visited Miraikan museum with impressive developed technology exhibition. We experienced Japanese culture, with very nice people that ready to help us from heart; dilicious food; cool and cold weather that we never get in South Vietnam... All are unforgetable events and memories.

Benefits from Sakura Science Program:

The work of taking care of critically ill patients was relevant to many fields including clinical and laboratory ones. Every day, I also contacted the laboratory department, the pharmacists, microbiology department… to solve some problem in treating my

patients. Knowing the way other departments work and what devices and equipments be operated in those departments helped me a lot in solving problem when treating patients.
Especially, gradually in my working, I have realized more and more important role of the controlling for plenty of risks in the department when treating and giving care for severe patients. Without controlling the risks, everything we try all our best to do to cure and treat our patient will be gone away at all. For examples: a very difficult surgery of transpositon of great arteries (TGA) that all the team rush into the hospital at midnight to do and sucessfully operated, but after 7 days patients collapsed and could not recover because of CLABSI (central line - associated blood stream infection), how regretful and grieved for it that everyone feel! We have now tried to elevate the quality of taking care of patients and do the programs in controlling infection, safety…
Besides, I also take part in some training couses for my staff in the hospital and other hospitals, and the way of training I have seen and have had chance to participate in Japan's hospital and university such as at Simulation center in Teikyo university impressed me much. It is a promissing way for training and improving the effectiveness of training.

Potential collaboration:
The visit at Japan thanks to Sakura Science program opens a new promissing up-and-coming collaboration with Japan and our hospital, especially with the place I have visited as Teikyo University and Teikyo Hospital, St. Luke's Hospital…in many fields: laboratory work, microbiology, training doctors and nurses and all the hospital staff about basic and advanced life support with more modern equipments and devices, and especially: the fields in controlling risks as Safety Control and Infection Control.
I would like to say many thanks to Prof. Kazuo Suzuki, all the staff members in ADC laboratory, Teikyo Hospital and University as thanks to every place and unit I visit in Japan, and Sakura science progam.
I hope that the program will continue in the future to give chance for more persons in the staff of our hospital to visit Japan, to be able to approach a modern and proffesional medical system, to help improve the quality of health care and uphold the relationship between Japan and Vietnam.

Name: Vo Thanh Vu, M.D.
Country: Vietnam
Department: Pediatric Intersive Care Unit of Children's Hospital 1, Ho Chi Minh City
Position: Vice Head of Pediatrics Intersive Care Unit

Job Description:
Children Hospital Number 1 is one of the leading pediatric care, research and teaching centers in the southern Vietnam. The hospital has 1,600 beds, 1,649 staffs, the last line of treatment for pediatric patients in Ho Chi Minh City and the southern provinces, where medical and nursing students from medical universities and doctors from the southern provinces practise. Besides our hospital cooperates with many international hospitals, universities such as: England, Australia, Taiwan, CDC.
Pediatric Intersive Care Unit has 25 beds with 16 doctors and 45 nurses. My deparment is one of the most important departments in my hospital for taking care of pediatric patients, supporting medical students, nurses, and provincial physicians in practising pediatric field and cooperating with international universities and hospitals.
I have worked in the department for 11 years. My everyday task includes;
- Treating children with serious illness, especially those with serious infections such as sepsis shock, severe hemorrhage Dengue fever shock, hand foot mouth disease and hospital pneumonia and sepsis requiring mechanical ventilation, supporting shock and dialysis.
- Guiding new doctors and nurses to pediatric rehabilitation techniques, updating new treatments and techniques in hemodialysis.
- Participating in the hospital researches and collaboration researches with other domestic hospitals and abroad ones.

Benefits from SSP
After a 10-day tour through the SSP, I learned more about Japan, Japanese people and learned many things from the faculties at Teikyo University Hospital. The weather in Japan was cool and fresh, the university campus was very large, and canteen food was very delicious. Through communication with Japanese, I realized that the Japanese people were kind, friendly, close and had professional working style. I was deeply impressed with safety control department, how infectious control department worked to find and control the infection, how pediatric department and NCIU

cared to children. The infectious control department worked quickly, timely to find and control the infection, through which I have more knowledge to apply in my department. I was very interested in practising in the simulation center, outside activities such as visiting JATA (tubelocrosis), Miraikan Museum, St. Luke's International University Hospital and Mt. Fuji. I sincerely thank the SSP, Professor Suzuki and his colleagues for giving me the opportunity to explore Japan and practise in the Teikyo University Hospital.

Potential Collaboration

I hope in the future the SSP and Teikyo University Hospital will support our hospital and our faculty in training and developing infection control system like Teikyo University Hospital. We look forward to farther cooperation between the two hospitals.

Name: NGUYEN THANH TRANG, M.D.
Country: Vietnam
Department: Infectious Disease Department, Children's Hospital 1, Ho Chi Minh City
Position: Pediatrician

Job description:

- Treat children with infectious diseases such as: HIV, hepatitis, typhoid fever, malaria, hand foot mouth disease, encephalitis, meningitis, chicken pox, measle, etc.
- Oversee and collect data for the database of patients with meningitis, hand foot mouth disease
- Participant in TREAT Asia Researches
- Manage HIV children in Outpatient clinic

About 10 days of SAKURA Science Plan:

It was a great pleasure for me to attend this program. It was one of the best memories I've ever had. I not only spent interesting time in sharing the experience from the advanced scientific technology and in conducting exchange with Teikyo university and research institutions but also explored beautiful Japan, kind people and fascinating culture.

This exchange program gave me an opportunity to visit many places in your universities and your hospitals. Both of them has the modern infrastructure and equipment needed for treatment and training. I was very impressed with your safety control system, especially biosafety control system. You even have a private manual of annual safety management which is really useful for all staffs in protecting patients and in preventing occupational accidents and diseases. Risk managers presenting in all departments help to control the safety in the hospital. These things will be a good reference for us in setting up our safety control system.

The quality of infectious disease control is the most important thing that I would like to learn from your country. I really love the way infectious disease control department managing and isolating all new cases of infectious diseases every day in each clinical department. It helps to diminish the spreading of the contamination effectively.

The medical students and staffs here have a lot of chances of practicing and training the skills in Simulation Center Laboratory. Assessment list, recorded video, simulator dolls, high technology equipment and creating real clinical situations are really excellent for diagnostics training and clinical training. The environment of Itabashi Campus is very fresh and comfortable, the lovely cafeteria is the good place for taking a rest, discussing or studying.

Research Institue of Tuberculosis and St. Luke's International University Hospital were truly two wonderful places to visit. We experienced pleasure in understanding how to control tuberculosis in your country and how the hospital practice safety control and prevent infection.

Besides spending time in your hospital and university, we also had the great time to visit some beautiful places in your country (Tokyo station, Shibuya station, Sensoji temple, Tokyo Skytree, Fuji moutain, ect.). Spending time to visit Miraikan- the National Museum of Emerging Science and Innovation was one of the most wonderful time I will never forget. We enjoyed learning advanced science, including earth environment, robots, space and life science. I absolutely appreciate your perfect preparation for this exchange program. I'm definitely satisfied.

Potential Collaboration:

I hope that the relationship between your hospital, your university and ours can strongly develop through learning, research exchange and training, especially SAKURA exchange program can be expanded in Ho Chi Minh City in the future also as in Ha Noi City. We hope that not only short term program but also Ph.D. program and master program will be opened for us to conduct some researches and expand the knowledge.

川崎病update　病理学的解析を中心に

東邦大学医療センター大橋病院病理診断科 教授　日本川崎病学会 会長　髙橋　啓

Update on pathogenesis of Kawasaki disease vasculitis

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Kawasaki disease (KD) is a systemic vasculitis that affects mainly children under 5 years of age. Although over 50 years have passed since Dr. Tomisaku Kawasaki first reported KD, its cause remains unclear. We have been performing a histopathological study on vasculitis of KD. In addition, we established a murine model of systemic arteritis by injecting a *Candida albicans* cell wall polysaccharide. The arteritis that develops in the model shows a predilection for manifesting in the coronary artery and aortic root. Careful observations of human and experimental model provide principal information for the pathogenesis of KD.

川崎病の現況

川崎病は、1967年に川崎富作博士により報告された乳幼児の急性熱性発疹性疾患である[1]。当初は予後良好と考えられていたが全身の血管炎が惹起され、なかでも冠動脈炎に基づく動脈瘤の血栓性内腔閉塞による虚血性心疾患で死亡する症例の存在が明らかになり社会的注目を集めた。現在、新規川崎病患者数は年間15,000人に達し、累積患者数は35万人を超える。小児人口の減少も相まって罹患率はさらに上昇を続けている[2]（図1）。

川崎病の病因はいまだに不明であるが、過去に3度の全国的流行が存在したこと、現在でも小規模地域内流行があり流行は隣接地域へと移動すること、季節変動が毎年同じように繰り返されること、6か月未満児の罹患率は低く0歳後期にピークを有する一峰性の罹患率を示すことなどの疫学的特徴は何らかの感染因子が発症に関与していることを物語る[3]。これまでにリケッチア、ウイルス、各種の細菌やスーパー抗原などが病因として提唱されてきたが再現性ある結果が得られていない。一方、人種間で発生率に違いがある点、親子例、同胞例が存在しこれらの発症リスクが高い点などは川崎病の発症に遺伝的要因が関与することを示す。これまでに*FCGR2A, CASP3, BLK, ITPKC, CD40*などが罹患感受性遺伝子候補として報告されている[4]。

治療には免疫グロブリンの経静脈的大量投与（IVIG）とアスピリンとの併用療法が広く施行されている。全国調査[2]によれば急性期川崎病患者の93.5%にIVIG治療が行われ、13%にIVIGとsteroidの併用療法がなされている。しかし、IVIGが投与された患者の18%はIVIG単回投与のみでは効果が不十分であり、この群から心血管合併症が高率に発生している。追加・補充療法としてIVIG再投与、抗TNF-α製剤、免疫抑制薬、血漿交換療法などが試みられている。現在の急性期心血管合併症発生率は8％弱、後遺症は2.3%であり、死亡率は0.01%に著減している。

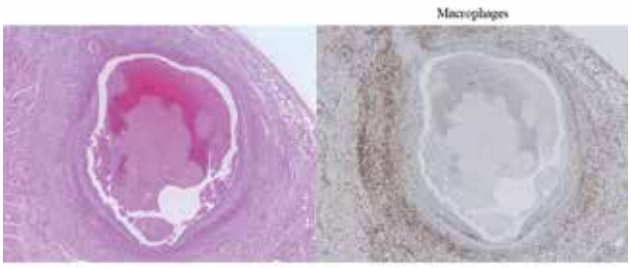
（図1）第24回全国川崎病調査成績

川崎病の病理学的検索

私は1985年に東邦大学医学部大橋病院病理学研究室に入局し直江史郎教授の基で川崎病の病理学的検索を始めた。当時急性期川崎病冠動脈炎の基本的病理組織像は、増田ら[5]、Naoeら[6]、Amanoら[7][8]、Hamashimaら[9]により報告されていた。これらに共通する川崎病動脈炎の組織学的特徴を要約すると以下のようになる。1）血管炎は冠動脈はじめ筋型中型動脈優位に生じるが、大動脈から小型動脈まで全身の動脈に病変は分布する。2）臓器外動脈が主として侵襲され、臓器内動脈に血管炎が生じることはまれである。3）全身各所の血管炎はほぼ同時期に始まり速やかにピークに達した後、徐々に消退し治癒する。4）病変は単球/マクロファージの集簇からなり、フィブリノイド壊死はまれである。5）腎糸球体や肺などの毛細血管病変はなく、免疫複合体の沈着も証明されない。

急性期川崎病の冠動脈炎はおよそ6週間の急性炎症性経過を呈する[5]。冠動脈炎の最も早期の組織学的変化は発症後6～8日死亡例で観察される動脈中膜の水腫性疎開性変性と呼ばれる変化で、平滑筋細胞の変性と共に中膜が水腫のために離開する。この時、炎症細胞浸潤は内膜と外膜に少数観察されるのみであるが、第8～10病日に中膜に達し動脈壁全層の炎症に至る。病変部の単球/マクロファージ、内皮細胞、平滑筋細胞などにはTNF-α、IL-6などの炎症性サイトカイン/ケモカイン、接着因子などが発現しており、活性化された諸細胞が血管壁内に侵入し蛋白融解酵素や活性酸素などを放出し、組織を傷害して炎症が生じると考えられる[10]。我々は最近、炎症、血管新生、組織修復、線維化を制御する細胞外マトリックス蛋白であるテネイシンCが急性期血管炎局所で発現していることを明らかにした[11]。汎動脈炎は速やかに動脈全周に波及し、炎症はピークに達する。内弾性板や中膜などの成分が著しく傷害される結果、発症後10～12病日頃に動脈は風船が膨らむように拡張を始める（図2）。炎症細胞浸潤は約2週間継続した後、徐々に消退していき40病日頃には瘢痕を残し治癒する。

炎症細胞の消失後も炎症瘢痕は長期にわたって残存する。動脈瘤を形成した場合様々な動脈炎後遺病変が生じ、内腔閉塞の危険がある。特に、巨大動脈瘤が残存した場合、瘤壁には広範な石灰化が生じ瘤の流入・流出部では内腔狭窄がもたらされる。瘤内には新旧混在する血栓による内腔閉塞像が認められる。さらに、成人期に達した川崎病既往例では瘤部に一致して高度の粥状動脈硬化症を認めることがあり、瘤が残存した場合には川崎病後遺症は粥状動脈硬化症の危険因子になり得る[12]。一方、動脈瘤の血栓性閉塞後に再疎通が生じた場合、その割面は蓮根の様な肉眼像を呈する。そして再疎通血管も新生内膜肥厚により狭窄する場合がある。動脈瘤の退縮や一過性拡張を示したと推測される動脈の多くにも遠隔期には血管炎瘢痕が残存することが確認されている[13]。

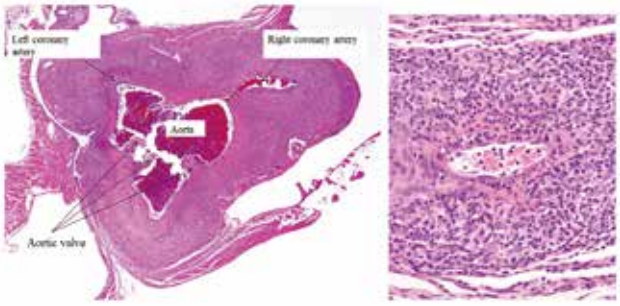


（図2）川崎病冠動脈炎

川崎病血管炎動物モデルを用いた病態解析

当教室では、川崎病剖検例を用いた病理組織学的検索を進める一方で、村田ら[14]が確立したカンジダ菌体アルカリ抽出物（*Candida albicans*-derived substance, CADS）による川崎病類似マウス系統的血管炎誘発モデルについて検討を進めてきた。そんな中、鈴木和男先生、大野尚仁先生と巡り合い、カンジダ菌体培養上清から抽出した*Candida albicans* Water Soluble Fraction（CAWS）が強力な血管炎誘発活性を有することを知った[15]。CAWSはα-マンナン、β-グルカンを含む糖タンパク複合体であり、マウス系統により血管炎発生率に大きな差がある。すなわち、DBA/2、C57BL/6N、C3H/HeNの血管炎感受性は高いが、CBA/Jにおける感受性は低い[16]。一方、CADS誘発動脈炎モデルにおいて、血管炎好発系であるC3H/HeNと嫌発系であるCBA/JNとを交配して得られたF1に戻し交配をしてN1を作製し、実験を実施する一方で冠動脈炎関連遺伝子の染色体マッピングを行った結果、第1染色体と第4染色体上にそれぞれ血管炎感受性領域と血管炎抵抗性領域が存在することが明らかになった[17]。本モデルの血管炎は複数の遺伝子の影響を受けている可能性がある。

本モデルで最も高頻度に侵襲されるのは冠動脈と大動脈起始部で、冠動脈の炎症は大動脈分岐直後の心筋層外動脈に限局し心筋層内動脈は侵されない（図3）。心以外には腎動脈や肋間動脈、腸骨動脈などが侵される[18]。動脈病変に出現する細胞の大多数はCD11b陽性で、CD68や抗マウス好中球抗体に陽性を示す。また、CD5あるいはCD45RB陽性細胞がごく少数混在する。動脈内膜は細胞線維性肥厚を来たし、中膜平滑筋層の消失や内・外弾性板の断裂を伴う。外膜にも広い範囲で大単核細胞をはじめとする諸細胞の集積が認められる。フィブリノイド壊死をみることは稀である。

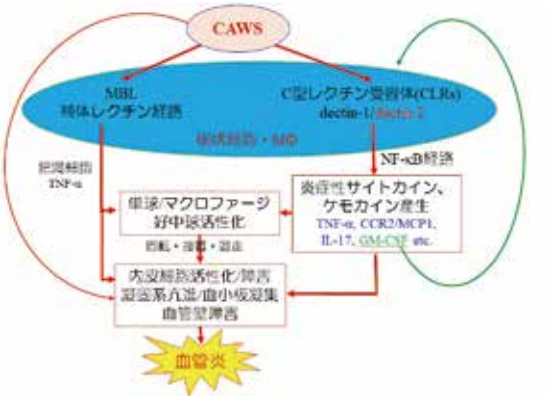


（図3）*Candida albicans*菌体成分誘発冠動脈炎

本血管炎モデルにおいてヒト免疫グロブリンを投与すると血管炎の発生は抑制される。さらに、抗TNF-α製剤を投与すると血管炎は著しく抑制されることから、TNF-αは本モデル血管炎発生のKey cytokineの一つと考えられる[19]。

近年、川崎病の発症には自然免疫が関与するとの仮説が注目されている。本血管モデルでもヌードマウスやSCIDマウスで血管炎が誘導されることから、血管炎発生には自然免疫系が関与していると推測される。また、カンジダ菌体由来物質は培養条件によってマンナン構造が変化し血管炎誘発活性が変化する[20]。さらに、TLR2、4両欠損マウスでは血管炎は抑制されないが、自然免疫受容体の1つであるデクチン2（αマンナン受容体）欠損マウスでは血管炎は発生しない（投稿中）。このように起炎物質中のαマンナンがPAMPs（pathogen-associated molecular patterns）として血管炎発症に関与する可能性があり、本モデルの血管炎発症機構が少しずつ明らかに

なっている（図4）。血管炎発生に至るシグナル伝達機構が明らかになれば、新規血管炎治療薬開発にも寄与できるものと期待される。



（図4）*Candida albicans* 菌体成分誘発冠動脈炎 発症仮説

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PEER-REVIEWED ORIGINAL ARTICLE

The gut microbiota positively regulates anti-tumor immune responses through the activation of CD8$^+$ T cells

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Abstract

Inhibitors of the immune checkpoint molecules PD1 and CTLA4 have been used to enhance the T cell anti-tumor immune response, leading to successful treatment for some tumor types. However, not all patients benefit from treatment with these inhibitors. Recently, it was reported that the gut microbiota boosts the anti-tumor immune response to immune checkpoint therapy. However, the mechanism(s) by which the gut microbiota enhance tumor immunity are not fully understood. Here, by depletion of the gut microbiota, we asked how the microbiota influences the anti-tumor immune response, in particular examining the activation of tumor-specific CD8$^+$ T cells. We found that the number of tumor antigen-specific CD8$^+$ T cells in spleen, and the number of activated CD8$^+$ T cells in draining lymph node and tumor tissue in the absence of the gut microbiota were reduced. Furthermore, tumor-infiltrating CD8$^+$ T cells were impaired in their ability to produce IFNγ. These findings suggest that the gut microbiota contributes to the prevention of exhaustion of tumor-infiltrating CD8$^+$ T cells and to the activation of systemic CD8$^+$ T cells.

Introduction

The gut microbiota plays a crucial role in homeostasis of the normal intestinal environment[1]. On the other hand, certain gut microorganisms are associated with the pathogenesis of inflammatory bowel diseases and colon tumorigenesis[2,3]. These observations suggest that the composition of the gut microbiota must be tightly controlled to maintain a healthy intestine. Recently, it was reported that gut microbiota dysbiosis influences the pathogenesis of not only intestinal diseases but also several systemic diseases such as autoimmune diseases, metabolic syndrome, cancer and allergy[4,5]. It has been known for decades that oral administration of antigens tends to induce immune tolerance rather than activation, leading to suppression of allergic and experimental autoimmune diseases[6,7]. It has also been reported that short chain fatty acids such as butyrate, which are produced by certain members of the gut microbiota as metabolites of a high-fiber diet, ameliorated autoimmune and allergic diseases[8,9,10]. These reports indicate that gut microbiota-induced immune responses and/or the gut microbiota itself are strongly associated with immune homeostasis, not only in the intestines but also throughout the body.

Developing tumor cells are eliminated by the immune surveillance system before showing clinical presentation[11]. However, once tumor cells make the transition to the progression phase, they establish a tumor microenvironment that is immunosuppressive, leading to escape from immune surveillance. Several mechanisms for this escape have been identified. Tumor cells can express immune inhibitory molecules such as PD-L1, which upon binding to PD-1 on tumor-specific CD8$^+$ T cells inhibits their proliferation and may induce apoptosis. Tumor-specific CD8 T cells in the lymph nodes draining the tumor are chronically antigen stimulated, leading to a state of "exhaustion" characterized by upregulation of the CD80/86 inhibitory receptor CTLA4[12]. Recently, neutralizing antibodies to the immune checkpoint molecules PD1, PD-L1 and CTLA4 have been developed and used therapeutically to break the exhausted status of tumor-specific CD8$^+$ T cells, and have shown good efficacy in some patients and with several different tumors[13]. However, this immunotherapy has been successful in some patients but not others, even for treatment of the same tumor type, therefore many researchers have explored ways enhance the efficacy of immune checkpoint therapy. Gajewski's group found that the particular member of the gut microbiota, *Bifidobacterium*, enhances immune response to anti-PD1 therapy in a murine tumor model[14]. It has also been reported that *Akkermansia muciniphilia, Faecalidacterum* and *Bacteroidales* are abundant in the gut microbiota of patients who responded well to PD1 immunotherapy[15,16], suggesting that the gut microbiota has the potential to promote the immune response to tumors and enhance the effectiveness of immune checkpoint inhibitors. However, the mechanism by which the gut microbiota enhances tumor immunity is not fully understood.

In this study, we asked a simple question of whether the global gut microbiota, but not a particular genus, influences the anti-tumor immune response, especially the activation of tumor-specific CD8$^+$ T cells, and find that the gut microbiota is required to suppress the exhaustion of tumor-infiltrating CD8$^+$ T cells. We also find that depletion of the gut microbiota reduces the number of tumor antigen-specific CD8$^+$ T cells in the spleen. These findings suggest that the global gut microbiota contributes to the escape from exhaustion by tumor-infiltrating CD8$^+$ T cells and the activation of systemic CD8$^+$ T cells.

Materials and Methods

Mice

C57BL/6 (B6) mice were obtained from Sankyo Labo Services. All animals were maintained under specific pathogen-free conditions in our facility. All experiments were performed in accordance with protocols approved by the Animal Care and Use Committee of Tokyo University of Science.

Cell lines

The Lewis lung carcinoma cell line expressing LCMV gp33 from a minigene (LLC-gp33) was established previously[17] and maintained in high glucose DMEM supplemented with 10% FBS, 2mM l-glutamine, 100U/ml penicillin, streptomycin and 1mg/ml G418.

Antibodies

PE-anti-KLRG1 and efluor780-anti-CD44 monoclonal antibodies (mAbs) were purchased from eBioscience (San Diego, CA, USA). The LCMV gp33 tetramer was purchased from MBL (Nagoya, Japan). FITC-anti-CD8a, biotin-anti-

TCRβ, PE-anti-CD3ε and APC-anti-IFNγ mAbs were prepared in-house.

Flow cytometry analysis

Cells were treated with FcgRII/III mAb (laboratory prepared) to block nonspecific binding. 7AAD (BD) was used to exclude nonviable cells. A Canto II (BD) and Gallios (Beckman Coulter, Brea, California, United States) were used for analysis. Data were analyzed using FlowJo software (Tree Star, Ashland, Oregon, United States).

Intracellular staining of IFNγ

Isolated tumor-infiltrating cells were stimulated with LLC-gp33 cells which were stimulated by IFNγ to induce the expression of MHC class I or PMA and Ionomycin for 12 h *in vitro* in the presence of monensin (Sigma-Aldrich Inc.). After staining for surface antigens, the cells were fixed 4 % PFA, then permeabilized with 0.5% Triton X-100 and stained with anti-mouse IFNγ mAbs.

Inoculation of tumor cells into mice receiving antibiotics water

Mice were provided water containing ampicillin (1 mg/ml), metronidazole (1 mg/ml), neomycin (1 mg/ml) and vancomycin (0.5 mg/ml) *ad libitum*. At 1 month after treatment with antibiotics, LLC-gp33 cells ($1x10^5$ cells/ mouse) were intradermally inoculated into mice, and then tumor size was measured every 3 days.

Isolation of lymphocytes from tumor tissue

The tumor tissue was minced into small pieces. To isolate lymphocytes, the tissue was treated twice with 0.5 mg/ml type I collagenase (Roche, Basel, Switzerland), 0.02 mg/ml hyaluronidase and 0.01 mg/ml DNAse I (Sigma Aldrich, St. Louis, Missouri, United States) for 30 min at 37°C. After filtration, cells were suspended in RPMI with 10 % FBS.

Statistical analysis

Statistical analysis was performed by a two-tailed unpaired Student t-test and a Kaplan-Meier method in Prism6 (GraphPad Software, San Diego, California, United States). The *p*-values < 0.05 were considered significant.

Results

The depletion of gut flora increases tumor growth in mice

To investigate whether gut microbiota influenced the anti-tumor immune response, we intradermally inoculated LLC-gp33 cells into mice that had received antibiotic water (ampicillin, vancomycin, metronidazole and neomycin) for four weeks previously and continued to receive it for the course of the experiment (Fig. 1A). At first, to confirmed whether the depletion of the gut flora influenced T cells, we analyzed the frequency of $CD8^+$, $CD4^+$ T cells and $CD8^+$ $CD44^{high}$ population in the peripherally blood lymphocytes (PBLs). The frequencies of total $CD8^+$, total $CD4^+$ T cells and $CD8^+$ $CD44^{high}$ population in PBLs were not differences between control and antibiotics-treated mice (Fig. 1B-1D). Compared with controls, there was significantly increased tumor growth in mice that had received antibiotic water (Fig. 1E), and also a decreased survival rate (Fig. 1F). These data imply that the depletion of the gut flora attenuates anti-tumor immune response, resulting in increased tumor growth.

Activated $CD8^+$ T cells are decreased in lymphoid organs and the tumor of antibiotic-treated mice.

To dissect the influence of the gut microbiota on the anti-tumor immune response, we analyzed the activation status of $CD8^+$ T cells in spleen, draining lymph node (dLN) and tumor tissues using antibodies to CD44 and KLRG1 as activation markers and the tetramer of gp33 to detect tumor-specific $CD8^+$ T cells. Compared with control mice, the numbers of gp33-reactive T cells but not total $CD8^+$ T cells, $CD8^+$ $CD44^{high}$ cells, $KLRG1^+$ $CD8^+$ T cells and total $CD4^+$ T cells were decreased in the spleen of antibiotic-treated mice (Fig. 2A-2F), suggesting the possibility that the gut microbiota can influence systemic activation of tumor-specific $CD8^+$ T cells. Different from spleen, the number of total lymphocytes, total $CD8^+$ T cells and total $CD4^+$ T cells were reduced in the dLN of antibiotic-treated mice (Fig.2G, 2H, 2L). Also, $CD44^{high}$ and $KLRG1^+$ $CD8^+$ T cells in dLN were significantly decreased by the depletion of the gut microbiota (Fig. 2I and 2J), but the number of gp33-reactive cells was not difference between control and antibiotic-treated mice (Fig. 2K). Different from dLN, the frequency of total $CD8^+$ T cells in tumor-infiltrating lymphocytes was not difference between control and antibiotic-treated mice, and most of tumor-infiltrating $CD8^+$ cells express CD44 in both groups (Fig. 2M, 2N). Meanwhile, the frequency of $KLRG1^+$ $CD8^+$ T cells and gp33-reactive cells tended to decrease in antibiotic-treated mice (Fig. 2O, 2P). These data suggest the possibility that the gut microbiota also activate tumor-specific $CD8^+$ T cells in the local lesion.

Gut flora increases IFNγ-producing $CD8^+$ T cells in tumor tissue

In Figure 2, the frequency of $CD44^{high}$ $CD8^+$ T cells was similar between the control and antibiotics groups. It is reported that CD44 is highly expressed on exhausted $CD8^+$ T cells, which are hypo-responsive to antigen stimulation and have impaired production of cytokines such as IFNγ[18]. Therefore, we considered the possibility that $CD44^{high}$ cells in tumor tissues of antibiotics-treated mice were of the exhausted phenotype. To address this, we analyzed the ability of the in tumor-

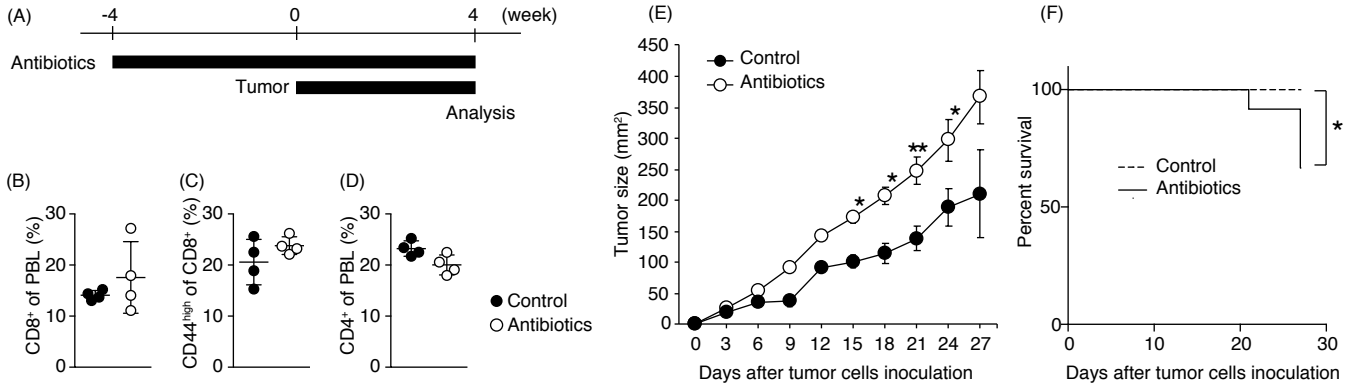

Figure 1. Depletion of the gut microbiota promotes the growth of tumor cells *in vivo*.
(A) Experimental design to analyze the influence of the gut microbiota on tumor growth and survival. Mice were given untreated water as control or water containing antibiotics (ampicillin, metronidazole, neomycin and vancomycin) for 1 month. LLC-gp33 cells were inoculated intradermally and antibiotic treatment was continued until the experiment was concluded 1 month later. (B-D) The peripheral blood lymphocytes (PBLs) at 4 weeks after the orally administration of antibiotics were analyzed by flow cytometry. The frequency of total $CD8^+$ T cells (A), $CD44^{high}$ in $CD8^+$ T cells (B) and total $CD4^+$ T cells (C) in PBLs. (E) Graph indicates mean ± SE of tumor size (mm^2). Mean ± SE was calculated every 3 days from 11 control mice and 7 antibiotic-treated mice, which survived until the endpoint. P-values from student's t-test: **p*<0.05, ***p*<0.01. (F) Survival rate shown by the Kaplan-Meier method from 11 control mice and 12 antibiotic-treated mice. **p*<0.05.

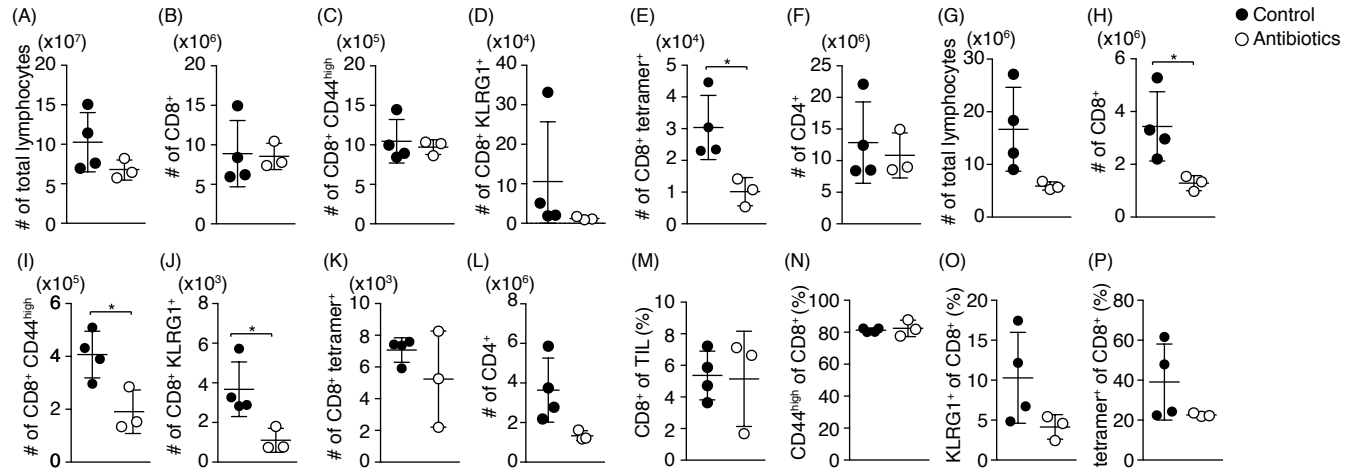

Figure 2. The gut microbiota influences local and systemic activation of CD8⁺ T cells.
CD44- and KLRG1-expressing CD8⁺ T cells and gp33 MHC tetramer-reactive CD8⁺ T cells in spleen, inguinal lymph node (ILN) and tumor tissues of tumor-bearing mice at 4 weeks after cell inoculation were analyzed flow cytometry. (A-F) The number of total lymphocytes (A), total CD8⁺ T cells (B), CD44^{high} (C), KLRG1⁺ (D), tetramer⁺ CD8⁺ T cells (E) and total CD4⁺ T cells in spleen. (G-L) The number of total lymphocytes (G), total CD8⁺ T cells (H), CD44^{high} (I), KLRG1⁺ (J), tetramer⁺ CD8⁺ T cells (K) and total CD4⁺ T cells (L) in ILN. (M-P) The frequency of total CD8⁺ T cells in tumor-infiltrating lymphocytes (M), CD44^{high} (N), KLRG1⁺ (O) and tetramer⁺ CD8⁺ T cells (P) in tumor tissues (n=4 for control, n=3 for antibiotics). P-values from student's t-test: *p<0.05.

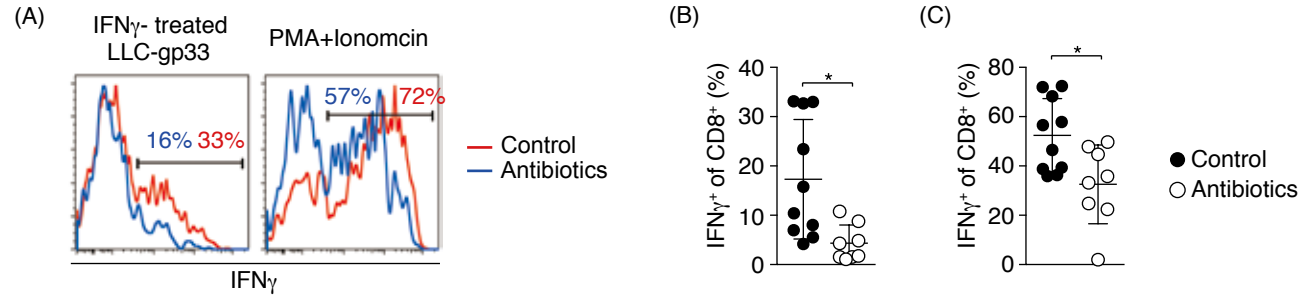

Figure 3. Depletion of the gut microbiota impairs IFNγ production by tumor-infiltrating CD8⁺ T cells.
Isolated tumor-infiltrating CD8⁺ T cells were stimulated with IFNγ-treated LLC-gp33 cells, or PMA and Ionomycin for 12h. The ability to produce IFNγ was analyzed by intracellular staining. (A) Representative histogram showing IFNγ⁺ CD8⁺ T cells. (B, C) Summary data for the frequency of IFNγ-producing CD8⁺ T cells stimulated with IFNγ-treated LLC-gp33 cells (B) and PMA+ Ionomycin (C). Data were pooled from three experiments (n=10 for control, n=8 for antibiotics). P-values from student's t-test: **p<0.01.

infiltrating CD8⁺ T cells to produce IFNγ. Consistent with the frequency of gp33-reactive cells, the tumor-infiltrating cells from mice receiving antibiotic water rarely had a significantly reduced IFNγ response when incubated with IFNγ-treated LLC-gp33 cells (Fig. 3A and 3B). The IFNγ response was similarly reduced in T cells from antibiotic-treated mice upon stimulation with PMA and ionomycin (Fig. 3A and 3C). These data indicate that the depletion of the gut flora induces CD8⁺ T cell hypo-responsiveness as well as a reduction in the number of tumor-reactive cells, consisted with the enhanced tumor growth and diminished survival of antibiotic-treated mice.

Discussion

Recently, it was reported that gut microbiota enhances the anti-tumor immune response induced by the blockade of immune checkpoint molecules[14,15,16]. But, how the gut microbiota enhances anti-tumor immune response, especially CTL activity, remains unclear. Here, we showed that depletion of the gut microbiota led to increased tumor growth and a reduction in the number of tumor-antigen specific CD8⁺ T cells in the spleen. In addition, tumor-infiltrating CD8⁺ T cells were impaired in their ability to produce IFNγ in the absence of the gut microbiota. Together, the gut microbiota might influence CD8⁺ T cell activation both systemically and locally, leading to the enhancement of anti-tumor immune response.

In this study, we demonstrated that depletion of the gut microbiota decreased the anti-tumor immune response. But the question remains, do most members of the gut microbiota enhance anti-tumor immune responses or only a few? Sivan et al. demonstrated that the anti-tumor immune response depended on the source of the mice, and thus was different between mice derived from Jackson Laboratory and Taconic Farms, and this difference was due to differences in the gut microbiota[14]. Also, recently, the transplantation of human feces to germ free mice showed that mice receiving a fecal transplant from a human responder to anti-PD1 immunotherapy had a significantly enhanced anti-tumor immune response, compared with mice receiving feces from a non-responder[15]. On the other hand, it is well-known that bacteria from the genus *Clostridium* strongly induce the development of regulatory T cells (Tregs) in the intestine, and it is thought that such Tregs influence immune tolerance systemically[19]. These reports indicate that there are several constituents of the gut microbiota that can contribute to either the activation or the suppression of systemic immune response. However, in our studies, the depletion of the gut microbiota reduced immune responses to a tumor. Therefore, it is possible that the majority of the gut microbiota might activate systemic immune response rather than promote immune tolerance.

CD8⁺ T cells infiltrate into tumor tissues to eliminate tumor cells. However, tumor cells and the tumor microenvironment gradually cause CTLs to become exhausted T cells, for example via PD1-PDL1 interaction. These exhausted T cells are hypo-responsive to TCR stimulation and impaired in cytokine production, and lose the capacity to kill tumor cells[12]. To break the exhausted state of CD8⁺ T cells, antibodies to PD1 and PDL1 are administrated into the patients with several types of tumors as immune checkpoint therapy. Recent reports showed a relationship between the therapeutic efficacy of antibodies to PD1/PDL1 and the gut microbiota, and suggested that particular members of the gut microbiota enhance anti-tumor immune responses via blockade of the PD1-PDL1 interaction[14,15,16]. However, the mechanism by which the gut microbiota enhances immune responses mediated by PD1 blockade is poorly understood. In this study, we observed that the ability of tumor infiltrating CD8⁺ T cells to produce IFNγ

was impaired in the absence of gut microbiota, suggesting the possibility that the gut microbiota suppresses the exhaustion of tumor infiltrating $CD8^+$ T cells. It is reported that $PD1^+$ $LAG3^+$ exhausted $CD8^+$ T cells are more dysfunctional than $PD1^+$ exhausted $CD8^+$ T cells[20]. Based on these observations, it is thought that the above identified species might suppress the terminal differentiation of PD1- and LAG3-coexpressing exhausted T cells, leading to good efficacy of immune checkpoint therapy. But, to properly address this issue, further experiments are required.

In this study, we have described that the depletion of the gut microbiota by orally administration of antibiotics reduces anti-tumor immune response. But, we have to consider the direct effect of antibiotics on immune cells, because it is reported that antibiotics broadly influence immune response such as the number of immune cell and cytokine production[21]. Here, we confirmed that the frequency of $CD8^+$ and $CD4^+$ in PBLs was not difference between control and antibiotics-treated group. However, we cannot exclude the possibility that antibiotics influence on cytokine production from these T cells, and the homeostasis and the function of other immune cells. Therefore, to clarify whether antibiotics directly influence on immune cells and suppress anti-tumor immune response, further experiments are required.

In conclusion, we demonstrated that gut flora activates local and systemic immune responses to tumor, leading to the inhibition of tumor growth. We believe that our observations will increase the understanding of anti-tumor immune response and immune evasion by tumor cells.

Acknowledgements

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ADC LABORATORIES-2

The 25th Japanese Society of Novel Action of Macrolides

July 6-7, 2018

2018年7月6-7日に第25回マクロライド新作用研究会が家の光会館コンベンションホールで開催されました。ADC研からは、菅又龍一講師と留学生のTran Huu Datさんが発表を行い、貴重な意見交換をしてきました。

■16員環マクロライドLeucomycin A3による抗インフルエンザウイルス活性機序の解析
菅又龍一

■Anti-influenza 2009 pandemic virus activity of azithromycin derivatives
Tran Huu Dat

Tran Huu Datさん

The 24th MPO Meeting

September 1-2, 2018

2018年9月1-2日に第24回MPO研究会が北海道大学保健科学研究院で開催されました。ADC研のメンバーは、ほぼ全員が発表し、例年通り活発な討議がなされ、充実した2日間となりました。次回のMPO研究会は、2019年11月29-30日、順天堂大学で濱野慶朋先生が世話人として開催されることが決まりました。

We held the 24th MPO meeting in Hokkaido University from Sep. 1st to 2nd. We had lively discussions. Next MPO meeting will be held in Tokyo on Nov. 29th-30th, 2019 with the chair Dr. Yoshitomo Hamano (Juntendo Univ.).

Attendee of the 24th MPO Meeting

【ADC Staff's Research Presentations】

- The study for anti-influenza A virus mechanism by LM-A_3 macrolide
  Sugamata R, *et al.*
- Anti-influenza 2009 pandemic virus activity of azithromycin derivatives
  Tran Huu Dat, *et al.*
- Hypothiocyanous Acid Suppresses PolyI:C-Induced Antiviral Responses by Modulating IRF3 Phospholation in Human Airway Epithelial Cells
  Thuy Thu Nguyen and Shoichi Suzuki, *et al.*
- Tuberculous pneumonia-induced severe ARDS complicated with DIC in a female child: A case of successful treatment
  Shoji Kawachi, *et al.*
- Administration of Anti-GAP2 Antibody on the *Candida Albicans* Water-Soluble Fraction (CAWS)
  Fuyu Ito, *et al.*

INTERNATIONAL MEETING AND SYMPOSIUM

開催したイベント（2018.7.1～2018.12.31）

日程	イベント名	演者など	
2018年12月11日(火)	第1回 Stem Cell Transplantation Consortium会議		本部棟 会議室
2018年10月31日(水)	第1回 バイオセキュリティ講習会(英語)	棚林清 感染研バイオセーフティ管理室 室長	大学棟 セミナー室
2018年10月29日(月)～11月7日(水)	SAKURA Science Plan 2018	Vietnamから研究生 8名	
2018年9月5日(水)	Prof. David Jayne (UK) ADC研訪問		ADC研
2018年9月1日(土)～9月2日(日)	第24回 MPO研究会	ADC研	北海道大学
2018年8月31日(金)	TAVP 報告会	医学部5年生 11名	本部棟
2018年8月19日(日)～8月26日(日)	TAVP Training for 11 Students (5-year)	国立小児病院、ハノイ医科大学ほか	Hanoi, Vietnam
2018年8月10日(金)	Prof. Ulrich Speck (U.S.) and Prof. Luis Felipe Flores-Suárez (Mexico) ADC研訪問		ADC研
2018年7月25日(水)	ADC研創立5周年 サテライトシンポジウム2	Dr. Harry Malech, 小澤敬也教授	大学棟 講義室

今後のイベント情報（2019.1.1～2019.6.30）

日程	イベント名	演者など	
2019年6月7日(金)	防災「震災後のブラックアウト」	札幌医大救命救急 成松英智教授、前東京消防庁 高野甲子雄氏	
2019年5月14日(火)	危機管理と防災	板橋キャンパス危機管理委員会、ADC研	臨床大講堂
2019年5月13日(月)～6月7日(金)	医学部6年生(3名)海外BSC	Univ. Pennsylvania, Philadelphia, Cambridge Univ., UK, Joslin Diabetes Center, Boston	
2019年4月7日(日)～10日(水)	The 19th International Vasculitis and ANCA Workshop		Philadelphia PA, United States of America
2019年2月23日(土)	第2回 Stem Cell Transplantation Consortium会議		東大 医科研
2019年1月29日(火)	第1回 Stem Cell Transplantation Consortium国際会議	鈴木和男、岡崎富男、布井博幸	Vinmec, Hanoi, Vietnam
2019年1月11日(金)	第2回 バイオセキュリティ講習会(日本語)	棚林清 感染研バイオセーフティ管理室 室長	大学棟 講義室

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