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# ADC Letter
## for Infectious Disease Control

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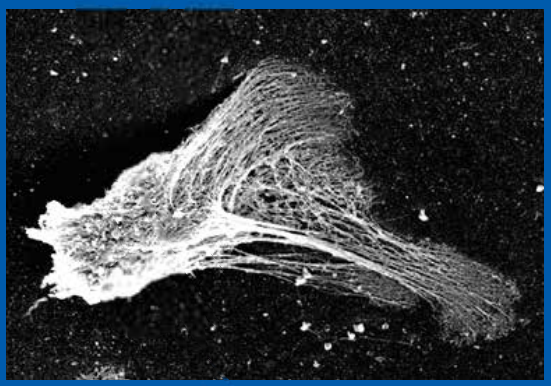

Human Neutrophil Chemotaxis to fMet-Leu-Phe: SEM



Asia International Institute of Infectious Disease Control, Teikyo University
〒173-8605 東京都板橋区加賀2-11-1 Kaga 2-11-1, Itabashi-ku, Tokyo 173-8605, Japan
Tel : +81-3-3964-1211 Fax : +81-3-3964-2580 E-mail : office-adc@med.teikyo-u.ac.jp
http://www.teikyo-u.ac.jp/affiliate/laboratory/adc_labo/
J-STAGE: https://www.jstage.jst.go.jp/browse/adc

# EDITORIAL

第５巻１号をお届けします。今号より表紙のデザインを一新しました。

帝京大学アジア国際感染症制御研究所は2013年６月１日に設立し今年は５周年を迎えます。今回は、記念すべき発刊となります。

国費留学大学院生 Nguyen Thu Thuyさんは、本号に１報目の論文を発表し、主論文が投稿間際で、今秋、学位取得をめざしています。

昨年の7月からADC研のメンバーによる多数の感染症の研究発表会やイベントがありました。なかでも鈴木和男所長が千葉大大学院医からADC研までの長期にわたって共同研究してきた大村智先生と7月21-22日の第24回マクロライド新作用研究会でお会いし、Dat君と菅又講師が中心となって発表した新規マクロライドの感染症制御の研究の結果に関心を寄せていただきました〈Ⅰ〉。今後もこの研究は重要であり北里大学・大村先生、砂塚先生とともに推進していきます。

また、11月4日には、友人のPennsylvania大学Peter Merkel教授が主催する米国血管炎コンソーシアム研究者会議がSanDiegoで開かれ、日本発の研究や国際臨床試験として鈴木和男所長と猪原登志子先生（京大病院・臨床総合研究センター）や厚労省難治性血管炎班・国際協力分科会で協力体制を組み、「ARAMIS＝川上民祐先生（聖マリアンナ医大・皮膚科）」、「P-PREG＝河野肇先生（帝京大学・内科）」、「肺限局型血管炎＝本間栄先生（東邦大学・呼吸器内科）」への参加も提案しました〈Ⅱ〉。

続いて11月29-30日には傳染病研究所創立125周年・医科学研究所改組（東京大学）50周年記念に招待されました〈Ⅲ〉。思い出してみると50年前ごろに私が予研で梅澤濱夫先生と新田和男先生のもとで学生のバイトをしていた時に、２週間毎に傳研で作製されたマウスを受け取りに行き、また、毎週水曜日に新田和男先生に連れられてセミナーを聞きに行った頃が蘇ってきました。

そして、留学生のDat君は、昨年秋JST主催のScience Agoraで発表し（本号27ページ）、また、厚労省から承認された修練医として頑張っています。

次号（第５巻２号）には、設立５周年記念特集号を発行する予定です。６年目からの新たな出発にご期待ください。

We are pleased to issue ADC Letter Vol. 5 No. 1.

Asia International Institute of Infectious Disease Control, Teikyo University established in June 1, 2013, and this year is the 5th anniversary year.

Graduate student Nguyen Thu Thuy in ADC published her paper in this issue as the first paper for her, and she continues her work on for her Ph.D. thesis by this autumn.

There were a lot of meetings for giving papers of an infection and related events by members in ADC since last July. In meeting of Society of Novel Action of Macrolide on July 21-22, we met Prof. Satoshi Omura who has been collaborating with us for long time from Chiba Graduate School of Medicine to ADC Institute for macrolide study, and he also showed interest in results of Mr. Tran H, Dat and Dr. Sugamata〈Ⅰ〉. This study will also important, and I would like to continue the study with Prof. Omura and Prof. Sunazuka in Kitasato University.

The VCRCI Meeting (Vasculitins Consortium Researcher Investigators) was held in SanDiego on November 4th organized by my friend Prof. Peter Merkel in University of Pennsylvania. In the meething, Japan-originated project were proposed by Prof. Kazuo Suzuki and Dr. Toshiko Ihara in Kyoto University and Office for Clinical Trial and the project members of Ministry of Health, Labour and Welfare Vasculitis, the International cooperation subcommittee, and ARAMIS = Prof. Tamihiro Kawakami (St. Marianna Medical University, Dermatology), V-PREG = Prof. Hajime Kono (Teikyo University, Internal Medicine) and Pulmonary-limited vasculitis = Prof. Sakae Homma (Toho University, Respiratory Medicine) were also proposed〈Ⅱ〉.

Next it was invited to 125th anniversary of Denken (research center for infectious diseases) establishment and reorganization to Institute of Medical Science, University of Tokyo 50th anniversary commemoration on November 29 and 30〈Ⅲ〉. When I had student's part-time work under Drs. Hamao Umezawa and Kazuo Nitta in National Institute of Health around 50 years ago when it is remembered, I went to receive mice breaded in Denken every 2 weeks also he was taken by Dr. Nitta on every Wednesday for seminar.

Further, graduate student Tran H, Dat presented in the Science Agora sponsored by JST last autumn (current issue 27 page), and he has been approved as a trainer doctor by the Ministry of Health, Labour and Welfare.

We will issue an 5th anniversary commemoration special edition in a next issue (Vol.5 No.2). Please expect our activity after 5th anniversary.

〈Ⅰ〉第24回マクロライド新作用研究会

With Prof. Akagawa, Dr. Kudo, Prof. Omura, Dr. Suzuki, Dr. Sugamata and Tran H Dat

〈Ⅱ〉November 4, 2017 VCRCI Meeting, San Diego, USA 100人近い参加者：欧米から

Prof. Merkel & Japanese investigators

Prof. Hajime Kono and V-PREG members

〈Ⅲ〉東京大学医科学研究所 創立125周年 改組50周年記念


Prof. Peter Merkel (University of Pennsylvania) & Kazuo Suzuki

Prof. Pagnoux Christian (Sinai Health, Canada)

Prof. Ulrich Specks (Mayo Clinic)

Dr. Toshiko Ihara (Kyoto Univ.)

**編集長：鈴木和男** Editor-in-Chief : Kazuo Suzuki, Director　　**事務局：伊藤吹夕** Editorial Office : Fuyu Ito, Ph.D.

# TAVP PLAN　Records of TAVP Training for 9 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 20 - 27, 2017

**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」の中に組み入れていただきました。

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、国際的視野にた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・アクセスの観点も含めて学習します。

2016年に第１期生７人が参加し、大きな成果がありました（ADC Letter Vol. 4 No. 1）。今回は、それを上回る医学部５年生９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, last July we signed a “Unit Compatibility Agreement between Teikyo University and the National Children’s Hospital of Vietnam (NCH) and the National Hanoi Medical University (HMU).” 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. Participants will study from the viewpoint of clinical practice, international health and preventive medicine, medical system, medical access.

Seven students participated in 2016, and there were great experience for them (ADC Letter Vol. 4 No. 1). In 2017, more than that, nine fifth graders participated.

Coordinators：
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（ADC 研　副所長、麻酔科　教授）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　講師）Shoichi Suzuki


**Acknowledgements**

Local Staff in Hanoi：
NCH：Hai 病院長、Dien 副院長、Thuy ラボチーフ、
Phuc 国際部長、病棟スタッフ
HMU：Van 副学長、Vu Quoc Dat 医師、他
VINMEC：Liem 所長

Teikyo University：
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
大久保 孝義 衛生学公衆衛生学 教授 Prof. Takayoshi Ohkubo


**Training Program at VNCH for Teikyo University Medical Students**
**August 20 - 27, 2017**

Group 1

| | Mon | Tue | Wed | Thu | Fri |
|---|---|---|---|---|---|
| AM | Meeting | ICU | Respiratory | ER | Closing |
| PM | Laboratory | ID | Cardiovascular | NICU | Lecture at HMU |

Group 2

| | Mon | Tue | Wed | Thu | Fri |
|---|---|---|---|---|---|
| AM | Meeting | Respiratory | ER | ICU | Closing |
| PM | Laboratory | Cardiovascular | NICU | ID | Lecture at HMU |

ER: Emergency dept, ID: Infectious Diseases Dept, NICU: Neonatal ICU

*Responsible persons*

| Department | Person in charge | Position |
|---|---|---|
| Clinical Laboratories | Dr Phung Bich Thuy | Head of Laboratories |
| ICU | Dr Phan Huu Phuc | Vice head of dept |
| Infectious Diseases | Dr Nguyen Van Lam | Head of dept |
| Respiratory | Dr Dao Minh Tuan | Head of dept |
| Cardiovascular | Dr Nguyen Ly Thinh Truong/ Dr Cao Viet Tung | Vice head of dept |
| ER | Dr Le Ngoc Duy | Vice head of dept |
| NICU | Dr Le Thu Ha | Head of dept |
| Coordinator | Ms Vu Thi Mai Anh<br>Ms Nguyen Hai Ha | International Cooperation dept<br>Training dept |
| Hanoi Medical University | Dr Ta Thi Dieu Ngan | Infectious Diseases<br>Vice Director of Training<br>Center-National Hospital of Tropical Diseases |

## 単位授与　Certificate for 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）

## Topics

### JICA Vietnam

牛尾光宏専門官（右端）
定本ゆとり様　（左端）

### 国立産婦人科病院


### VINMEC International Hospital Research Institute




Liem 所長

報 告

# 公衆衛生学実習「ベトナムでの感染症」

帝京大学医学部５年
朝野紗稀子, 市川尚寛, 閏井智郷, 曽根雅之, 高村日菜子, 長坂彩, 成川智彩, 秦美能理, 堀江恭子

## （1）ベトナムの環境

１週間の公衆衛生学･衛生学を通じて、ベトナムの医療･生活環境･文化などから多くのことを学ぶことが出来た。

ハノイ市内の環境は私たちの日本での日常生活とは大きく異なり、その多くが印象深いものであった。滞在期間中は雨期であった為湿度が非常に高く、体感温度は40度近い日が続いた。フランス風の街並みが非常に美しい都市であるが、到着してすぐに街にバイクが溢れているのに驚かされた。大量の荷物を運搬するバイクや子供を含めた４人乗りなども時折見受けられ、交通量が多く初日は道を渡るのもためらうほどであった。排気ガスを避けるため人々は皆布製のマスクを着けて運転していた。

路肩に目を向けるとホテルの周りにも屋台が建ち並び、低く張り巡らされた電線には洗濯物が干されているなど食文化や独特な生活の様子を垣間見ることが出来た。その一方でゴミの分別収集のシステムは確立されていない様子で、街中だけでなく病院でも感染性廃棄物など特別なもの以外は特に決められた分別がないことは印象的であった。

様々な生活の仕組みが作られている途中であり公衆衛生の状況は日本と大きく異なる印象は受けるものの、街全体が活気に満ちていて新興国として今まさに国が大きくなっているところであるというエネルギーを感じた。

## （2）JICA

実習期間中にJICAを訪問し、ベトナムでのJICAの活動や今後の取り組みなどについてお話を伺うことが出来た。医療の分野では日本人医師による技術の指導などがあることや、JICAのプロジェクトとして円借款で病院建設が動いていることなど、ベトナムと日本の医療分野での協力関係について教えていただいた他、ベトナムでも近年は先進国の食文化が多く入ってきている影響で、生活習慣病が問題になるなど、新興国というよりは中進国のような状況に変わりつつあるなど、感染症以外の医療事情についても多くを学ぶことができた。

また、JICAが進めているインターンシップのプロジェクトでは、今後臨床で活動する医師や看護師もJICAの支援が学びやすくなるように、現地で臨床が出来るように進めようという動きがあるなど、行政に携わる方から国際医療について様々なお話をしていただく貴重な機会となった。

## （3）NCHの研究室

検査部では、最新のPCRなど最先端の研究設備が取り入れられていた。NCHは巨大な病院であり、最先端の機械があるため、他病院からの検体も多く送られてくるということであった。また、私たちがベトナム滞在時に流行していた感染症、特にデング熱の患者数についてなどもお話を伺うことが出来、NCHに来院する感染症の患者やベトナムでの感染症の発生状況について、普段検査をしている先生方や技師の方からの全体的な印象を教えていただくことが出来た。

## （4）呼吸器

呼吸器内科の病棟では、主に肺炎の患者さんが多く入院していた。しかしNCHでは、どの診療科も患者数が非常に多く常に満床に近いため、呼吸器科を含め多くの病棟でベッド間距離が非常に近く、麻疹などの一部の疾患の患者を除いて感染症患者の隔離は満足にできていない状況だった。呼吸器科病棟の見学中に、先生方から何人かの患者さんのカルテを見せていただき、病状を説明していただいた。その際非常に驚いたことは、日本の院内肺炎と比較して、多剤耐性菌による肺炎が非常に多いということだ。カルバペネム系の抗菌薬にも耐性を持つなど、原因菌に対する治療が困難な患者さんも度々見かけられ、そのような患者さんには、コリスチンなど日本で

は未承認の薬剤が用いられていた。このような耐性菌が増加した背景には、一部の抗菌薬がOTCの薬剤として薬局で処方箋なしで販売されていることや、処方箋が必要な抗菌薬であっても、一部の医師が処方箋なしで患者に販売してしまう状況など、日本と異なった抗菌薬の使用状況であることが挙げられる。

また、肺炎以外で呼吸器科に入院している患者として増加傾向であるのは、殺虫剤を飲んで自殺を図った患者であるとのお話を伺った。ベトナムでは、自殺の方法として入手が簡便であることから、殺虫剤を飲む人が増えているとのことで、私たちが呼吸器科病棟で会った患者さんも若年の女性であり、感染症以外にベトナムが抱える問題も垣間見ることが出来た。

### (5) 循環器

NCHのCICUを見学させていただき、非常に複雑な症例の患者さんに対しても日常的に手術が行われていることに驚いた。大動脈縮窄症と左室低形成に心室中隔欠損と動脈管開存を合併しているなど、日本ではごく一部の限られた医療機関でしか対処することの出来ない症例の患者さんが、何人も入院していた。中には手術を受けて回復し、間もなく退院という患者さんもいて、循環器病棟、特にCICUでは、重症例に対する高度な医療が毎日のように提供されていると分かった。

### (6) 救急科 ER

救急科の患者数は1日100～200人で、ベッドが足りなくなってしまう時には1つのベッドを2人の患者が使っているとのことだった。私たちが実習をしに行った日も、ベッド不足のため1つのベッドに2人横になっており、実際に見てみると衝撃的な光景だった。救急科は、1日程度で他科に送られる、比較的軽症の患者がいるショートステイの部門と、痙攣、昏睡がある患者や、診察で酸素投与が必要と判断された重症な患者がいるERの2つに分かれていた。来院する患者の疾患には季節性があり、夏はデング熱、日本脳炎、髄膜炎が多い。ここでは日本ではあまり見られないレプトスピラ症の症例を見ることができた。レプトスピラ症の症状である黄疸、腎障害は、木の皮などから作られる少数民族の伝統的な薬を服用することによっても起きると聞き、問診の重要性を感じた。人体に害を及ぼす危険性のあるものが一部では薬だと信じられていることに驚き、病気に関する知識を浸透させる難しさを感じた。

### (7) 新生児集中治療室 NICU

NICUは2つに分かれており、80床の先天性心疾患や人工呼吸器を必要とする重症患者のフロアと、100床の容体が安定している患者のフロアがあった。とても驚いたことに、医師、看護師などNICUで働くスタッフ120人全員が女性で、ベトナムの女性の社会進出度の高さを実感した。ここでは、血液培養でカンジダと多剤耐性緑膿菌が検出された症例を学んだ。緑膿菌は薬剤感受性試験で全てに耐性があるとわかり、コリスチンを使用していた。耐性菌が多いのは、ベトナムでは医師の処方がなくても市販薬として抗菌薬を入手できるため、抗菌薬が適切に使用されていないからだと聞き、薬剤耐性対策は世界的な問題だと思った。RSウイルス感染症の患者が多く隔離室に空きがなかったため、多剤耐性緑膿菌が検出されているにもかかわらず、隔離されていなかった。早産児などRSウイルス感染後の危険性が高い患者にも、予防に用いられるパリビズマブは高価なため使用していないとのことだった。

### (8) 集中治療室 ICU

ICUの病床数は70で、45床は重症患者、25床は軽症患者が入っていた。ICUに入院する原因疾患として最多なのは肺炎で、次いで脳炎、髄膜炎、敗血症性ショックが多いとのことだった。ICUで印象に残った症例は、日本脳炎である。日本ではワクチン接種により予防されており、ほとんど見られない疾患であるが、ベトナムではワクチン接種が普及していないため、未だに多くの日本脳炎患者がいる。ベトナムでも日本脳炎ワクチンの接種は推奨されているが、無料でないこと、山間部に住んでいるとワクチン代の他に交通費も高額になってしまうこと、そもそも両親がワクチンの存在を知らないことなど様々な要因があり、必要とする回数全てを接種し終える人はとても少ないとICUの医師は言っていた。

### (9) 感染症科 Infection Department

感染症科でとても驚いたのは、ベッド間の距離がとても近いこと、X線やCT画像を親が管理していることである。日本であれば2ベッドしか入れられないような部屋に4ベッド入っていて、医師がX線写真などを確認する時は親がベッドの下から引っ張り出したり、棚の上から持ってきたりと、適切とは言えない管理だった。感染症科の医師は17人いるとのことだったが、実習で行った時は3人しかおらず、説明していただくのが申し訳なくなるほどとても忙しそうだった。日本脳炎の慢性期で、肺炎を起こしている人工呼吸器装着患者がいたが、痰がつまり、$SpO_2$が61%に低下してしまうまで気付かれないという、スタッフ不足を顕著に感じる出来事に遭遇した。

### （10）ハノイ医科大学での講義

国立小児病院での実習が全て終わった後、ハノイ医科大学でベトナムにおける感染症についての講義を受けることができた。ベトナムは熱帯に属しているため、熱帯病はもちろん問題になる。また、人間と動物の接触が多いため、人獣共通感染症が問題になっている。街中でも生きた鶏などを見る機会があり、人間と動物の距離の近さを実感した。実習中、デング熱が大流行しており、国立小児病院でも多くの患者を見たが、本来デング熱はベトナムの南部に多く、ハノイのある北部には少ないはずの病気である。実際、ハノイ以外の北部の地域ではそれほど流行していない。ハノイで流行しているのは、デング熱のウイルスを媒介するネッタイシマカが、人やものの移動とともに南部から移動してきたからだと考えられるとのことだった。人やものの流れが活発になり便利に感じることも多いが、その一方で、このように新しい問題が発生してしまい、課題は増えるばかりだと感じた。この講義で一番印象に残ったのは*Streptococcus suis*と呼ばれる病原菌の感染症である。これは髄膜炎、敗血症性ショックの原因となる。ベトナムには豚の血や内臓を調理せず食べる習慣を持つ人がおり、未調理の豚を食べる、傷口から豚の血が入ることで感染する。日本でもレバーの生食が規制されても食べる人がいるように、危険性を訴えても、食習慣を変えることは難しいことだと感じた。

この度の実習では、ベトナムの感染症状況だけでなく、その背景にあるベトナムの社会システムや経済面での問題、そして文化的違いなど、様々なことを学んだ。日本とは全く異なる問題点を、その土地の雰囲気ともども感じ取ることができ、また様々な方々からお話を伺うことができ、非常に貴重な経験となった。

また、英語、特に医療英単語や表現というのは、どの世界においても医療従事者間のコミュニケーションの潤滑剤となり、必須となることを実感し、これからの更なるモチベーションにもつながった。

この１週間で学び経験したことを、学生中はもちろんのこと医師になっても忘れずに、国際的な視野を持ち続けていきたい。

今回の実習を企画してくださった先生方、１週間に渡りご指導してくださったベトナム・日本の先生方、スタッフの皆様、実習に快く協力してくださった患者様に、心から感謝申し上げます。準備期間から、大変お世話になりました。このような貴重な機会を設けてくださり、本当にありがとうございました。

**Sakiko Asano, Naohiro Ichikawa, Chisato Urui, Masayuki Sone, Hinako Takamura, Aya Nagasaka, Chisa Narikawa, Minori Hata, and Yasuko Horie**

### (1) Environment of Hanoi, Vietnam

Hanoi is a capital of Vietnam. It recovered from the ravages of war. Its streets surge with scooters constantly blaring horns, and all around layers of history reveal periods of French and Chinese occupation.

The climate is tropical, with wet and hot weathers much of the year. When we visited, it was monsoon season so felt like about 40 degrees Celsius.

Vietnam is known for its astonishing variety of inexpensive and delicious street food from quick snacks to entire meals, and that's a local way of life. For me, this is not the first time to visit Vietnam and I love the street food culture and have never had food poisoning so far, so I could enjoy that culture but the other students had a problem of eating them… The most common illnesses related to consuming and producing street food are gastrointestinal diseases causing diarrhea. The key cause is not respecting hygiene standards and this causes contamination and leads to disease. These days food administration in Vietnam and WHO undertake some efforts to make street food safer for both vendors and consumers. For street food vendors, Vietnam food administration organizes training on hygiene and food safety. Consumers are educated through various communications channels to recognize clean and safe street food stalls. Armed with that knowledge, consumers will stay away from any remaining unsafe food stalls and this will create pressure for potentially unsafe vendors to either improve the hygiene of their

stall or withdraw from the market.

Street food is one of the greatest cultures in Vietnam so I hope they can find good balance and reserve it with taking care of hygiene.

**(2) JICA**

We visited JICA in Vietnam during this practice and asked how they support Vietnam. In Vietnam, the social and economic development so called "10-year strategy (2011-2020)" positions institution improvement, human resource development, infrastructure development as priority fields. Based on that, JICA works in collaboration with Japanese industry, educational institutions, local governments, and NGOs to strengthen Vietnam's growth and international competitiveness towards modernized industrialization in 2020, and respond to vulnerability and they support comprehensively the creation of a fair society and country through strengthening of governance.

As one of Asian newly industrialized countries, the number of patients suffering from life style related diseases are increasing in Vietnam. Its given considerable weight as same as hygiene management for them.

**(3) Laboratory in National Children Hospital (NCH)**

In the laboratory, the latest research facilities for example simple PCR, multiplex PCR and Cap/CTM48 are in place. We had a great chance to talk to Dr. Thu Thi Bich Phung who got Ph.D. in Chiba University supervised by Prof. Suzuki, majors in molecular biology research using Reverse Transcription Polymerase Chain Reaction (RT-PCR). Many samples are sent from other hospitals to NCH because it is one of the biggest hospitals in Hanoi and have such a state-of-art facility. Even it's few in Japan to find such a favorable environment. We were also able to hear the story about the infectious diseases, which were prevalent for example Dengue fever when we stayed.

**(4) Respiratory department**

In respiratory division, most hospitalized patients had pneumonia. However, some patients were not isolated despite they had high risk to infect other patients. We were also surprised that space between beds was small, so we thought this environment is not good to prevent in hospital infection. The doctors explained some patients' symptoms and medical histories. We were surprised that there were many patients with pneumonia caused by drug-resistant bacteria. Some cases were difficult to treat because the patients were resistant to strong antibiotics such as Carbapenem, therefore the patients were used colistin which has not been approved in Japan.

In Vietnam, people can buy antibiotics at drug stores without doctors' prescriptions. This system caused a serious problem of drug-resistant bacteria in Vietnam. In Japan we need doctors' prescription to buy antibiotics, so it was a shocking story for us. We heard that the number of people who drink insecticide to commit suicide is increasing. In Vietnam, many people use insecticide to commit suicide because it is easy to buy. We could learn not only medical care but also social problems in Vietnam.

**(5) Cardiology department**

In cardiovascular division, one hundred patients with complicated heart diseases are performed high level operations per a month. After operations, patients move to PICU (Post Intensive Care Unit), CICU (Cardiac Intensive Care Unit), and a cardiovascular ward in this order. We could see many rare cases such as hypoplastic left heart syndrome (HLHS) complicated by aortic stenosis (AS), ventricular septal defect (VSD) and patent ductus arteriosus (PDA). We also saw a patient with transposition of the great arteries (TGA). The patient was performed a switching operation only two weeks after Blalock-Taussig operation. We were surprised that patients were discharged soon after operations. For example, the patient with AS and VSD was discharged ten days after the operation. We could see the level of cardiovascular division is very high in Vietnam.

**(6) ER**

There are 100 to 200 patients in emergency department; therefore bed control is very difficult so that we saw a situation that two patients were lying on one bed. Emergency department is mainly divided into two areas: short stay and emergency room (ER). In short stay area, there are 20 beds and patients are sent to different department one or two days later. Severe patients stay in ER and most patients need oxygen masks or ventilators. In summer patients who visit the emergency department commonly have pneumonia, Dengue fever, Japanese encephalitis, and meningitis. We saw a case of Leptospirosis infection that we couldn't see in Japan. The main symptoms of Leptospirosis are jaundice and renal dysfunction. A doctor in the ER told us that some Vietnamese take traditional drugs that were made from trees, then the drugs caused jaundice or renal dysfunction. We learned how important history taking is, and how difficult to make people understand correct medical information.

**(7) NICU**

NICU is divided into 2 floors, for sever condition patients who have congenital heart disease or need ventilator and for about 100 beds of stable condition patients. To our surprise, there are only women staffs (120 doctors and nurse etc.). We impressed that the high social advancement rate. At this department, we learned cases of candida and multidrug-resistant Pseudomonas aeruginosa infection. The Pseudomonas was found to be resistant for all the anti-bacterial drugs by DST, then doctors used colistin. In Vietnam, because people can get anti-bacterial drugs easily without any prescriptions, drug-resistant strains have grown. We thought some measure should be taken for it.

Dispite multidrug-resistant Pseudomonas aeruginosa has detected, there are not enough isolated room to ward off RS virus. We also learned that Plivizumab which is used for prevention for RS virus is too expensive to be used for premature infant.

**(8) ICU**

ICU have 70 beds, 45 for the patients with sever condition and 25 for mild one. The most common disease in ICU is pneumonia, and the others are encephalitis, meningitis and septic shock. The most impressed case for us was Japanese encephalitis. In Japan, as everyone knows, it is very common to receive a vaccine, so we seldom see this disease. But in Vietnam, there are still many patients of Japanese encephalitis because receiving vaccines is very rare. Actually a vaccine is recommended in Vietnam, but children who completely receive antibodies are very few for some reasons. Doctor in ICU said that because it is not free, it is expensive especially for people living in mountain area and the parents doesn't ever have any knowledge about vaccines.

**(9) Infection department**

The most surprising experience in the infection Department was that too many beds in the room and parents own Xp and CT images. We heard that there are 17 doctors in the Department, but we went to there, only 3 doctors worked. They looks so busy that we felt very sorry for asking any questions there. At that time, we accidentally encountered one happening, because of shortage of doctors, doctors missed the children who has pneumonia at the chronic stage of Japanese encephalitis had sputum stuck at the throat and his $SpO_2$ declined to 61%.

**(10) Lecture at Hanoi Medical University (HMU)**

After finishing all practices in NCH, we had a chance to have a lecture about tropical diseases in Vietnam from M.D. Vu Quoc Dat at Department of Infectious diseases in HMU. We learned Vietnam is a hotspot for emerging and infectious diseases, in particular, zoonotic and vector-borne diseases, as a result of many factors. As a result of emerging and re-emerging diseases in last 10 years, what they have learned is that they must be better prepared to respond to new threats. The key is to be alert, be prepared and be able to respond rapidly in a coordinated manner.

Through the lecture I thought we cannot be so indifferent to that problems because Japan is an island country, we can have vector-born diseases like Dengue fever at any time. We also need to be alert to prepare so that immediate action can be taken when we faced any kind of problems. And I believe if we faced on that kind of problems in the future, we would learn and get tips from the country like Vietnam.

# 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

October 16 - 25, 2017

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

ベトナム 6 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2名）

**Ngo Tien Dong (Pediatrician)　Dao Huu Hung (Nurse)　Do Minh Thuy (Nurse)**
**Do Thu Huong (Researcher)　Nguyen Ngoc Tu Anh (Pediatrician)　Le Thi Thanh Thuy (Pediatrician)**

帝京大学アジア国際感染症研究所（ADC研）では、2017年10月16日から10月25日（10日間）、ベトナムから6名を招いて、JST（科学技術振興機構）「さくらサイエンスプラン」を実施しました。

本事業の目的に沿い、科学技術の分野でアジアと日本の青少年が交流を深めるため、大学院生、研究員・教員、医師看護師を帝京大学アジア国際感染症制御研究所（ADC）に招聘しました。

今回は、医師や看護師としてベトナムで活躍する 6 名が来学し、「感染症」と「安全管理」をテーマとした研修を行いました。

We organized SAKURA Science Plan supported by JST from Oct. 16 to 25 in 2017 in ADC, Teikyo University.

## Contents of the Training

**1．ADC研教授会での紹介**
Introduction of Professors in ADC and ADC Staff
鈴木和男所長、槇村浩一教授（医療共通教育研究センター）、松永直久准教授（医学部附属病院感染制御部）、ADC研スタッフ、医学研究科大学院生（ADC研、他）、医学部学生

**2．講習会：バイオセーフティ (感染研　棚林先生)、医療安全**
Trainings and Lectures: Biosafety and Safety Control in Hospital
**講義：感染症、公衆衛生学、シミュレーション、薬学部**
Lectures: Infectious Diseases, Public Health, Healthcare Simulation and Faculty of Pharmacy

**3．実験室研修：ADC感染症研究室、シミュレーション実技**
Trainings in ADC Laboratories and Healthcare Simulation

**4．医学部附属病院ラウンド：病院長、看護部、感染制御部、中央検査部、薬剤部、患者相談室の視察**
Tour of Teikyo University Hospital

**5．医学部4年生への来年度公衆衛生学実習ガイダンス：ベトナムでの感染実習**
Joining with Medical Students in Teikyo University 4-year's guidance

**6．学外：ADC研と連携している結核研究所および聖路加国際大学訪問**
Visiting RIT and St. Luke's International University

**7．研修修了証授与および歓送会**
Certificate Celebration and Farewell Party

## 謝辞 Acknowledgements

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## 研修スケジュール　Schedule of TASP

| | AM | PM |
|---|---|---|
| 16-Oct　Mon | Arrival at Narita Airport | Orientation<br>13：00 救急<br>16：00 ME 部（川崎部長）<br>18：00 Welcome party |
| 17-Oct　Tue | 10：00 薬学部（高橋教授） | 14：00 看護部院内ラウンド（土谷部長）<br>16：00 病院薬剤部（渡邊部長代理：安野副部長） |
| 18-Oct　Wed | 09：30 小児科（高橋先生）<br>11：00 安全管理部（髙田先生） | 13：05 鈴木所長講義（訪問者自己紹介、質疑応答）<br>15：00 バイオセーフティー（国立感染研・棚林室長） |
| 19-Oct　Thu | 09：45 感染制御部（松永部長） | 14：00 微生物（斧教授）<br>16：30 公衆衛生大学院（井上先生） |
| 20-Oct　Fri | レポート作成 | 13：30 中央検査部（古川教授、小松技師長）<br>16：00 シミュレーション（竹内先生） |
| 21-Oct　Sat | 未来科学館訪問 | |
| 22-Oct　Sun | | |
| 23-Oct　Mon | 10：20 シミュレーション（金子先生） | 14：00 結核研究所訪問（加藤所長） |
| 24-Oct　Tue | 聖路加国際大学訪問（瓜生田様） | Discussion<br>17：00 Farewell party |
| 25-Oct　Wed | Departure from Narita Airport | |

## 1. ADC研教授会での紹介
### Introduction of Professors in ADC and ADC Staff


With ADC Lab Members


Prof. Makimura and Dr. Matsunaga

## 2. 講習会および講義
### Trainings and Lectures

1）医療安全（Trainings: Safety Control in Hospital）
安全管理部「WHOの医療安全ガイドライン」のレクチャーと討論


With Director of Teikyo University Hospital Prof. Sakamoto, Prof. Kawachi, Dr. Takada and Staff of Safety Control Department

2）薬学部（Faculty of Pharmacy）


With Prof. Takahashi, Dr. Makino and Dr. Tabata

3）バイオセーフティ（Biosafety）


Biosafety Lecture by Dr. Tanabayashi, NIID

4）微生物学講座 斧研究室（Prof. Ono's Lab.）


Lecture by Associate Prof. Ubagai and Dr. Kamoshida

5）シミュレーション実習（Simulation Training）


Lecture by Dr. Kaneko

## 3. 実験室研修
### Trainings in ADC Laboratories and Healthcare Simulation

1）ADC感染症研究室（ADC Lab）

2）シミュレーション室（Simulation Education Research Center）

## 4. 医学部附属病院ラウンド
Tour of Teikyo University Hospital

看護部（Nurses Units）

Medical Heliport with Head of Nurse Ms. Tsuchiya

## 5. 医学部４年生への公衆衛生学実習ガイダンス
Joining with Medical Students in Teikyo Univ 4-year's Guidance

## 6. 学外：ADC研と連携している結核研究所，聖路加国際大学訪問
Visiting RIT and St. Luke's International University

### The Research Institute of Tuberculosis, Japan（RIT）

With Dr. Kato, Director of RIT

Dr. Yamada in Electron Microscope Lab

Library

### St. Luke's International University

## 7. 鈴木所長からの研修修了証授与および歓送会
Certificate Celebration and Farewell Party

# Reports of Visitors

# SAKURA Science Plan

**Name:** Ngo Tien Dong M.D.
**Country:** Vietnam
**Department:** Pediatric intensive care unit, National children's hospital, Hanoi
**Position:** Pediatrician

**About my job**

I am working as pediatrician in ICU since 2009, for taking care of critical illness children (septic shock, ARDS, encephalitis). Also I am collaborating with colleagues from other country and I am part of pediatrics advance life support term in my hospital. I am interested in Echocardiography in critically ill patients.

**Summary of the 10 days training course**

- Tours of Teikyo university and Teikyo hospital to observe how actually gets done
- Visited to Research institute of tuberculosis in Japan for understanding how to control tuberculosis in developing countries
- Visited to St.Luke's International University to understand international version of nursing training program and the structure of the healthcare-associated infection prevention and control system
- Very interesting and useful lectures on infection fields, that was taught by experts, who are not only with very good knowledge but also with enthusiasm and responsivility
- What do I think of Japan? Japanese people are very hardworking, diligent, honest, extremely polite, especially really professional in work. The technology is very advanced, Japanese technology is often being looked up by many people. And Japanese food is often healthy and fresh, which can explain why the Japanese have the longest life expectancy

**Contribution of this training**

- Improving my knowledge on infection fields, especially in how to control nosocomial infection, biosafety
- Benefits of coordinating clinical department and laboratory

**Potential Collaboration**

- Study on mechanism of drug resistant bacterial (Acinerbacter baumannii, klebsiella pneumonia)
- Collaboration with Teikyo Simulation Education Center to improving quality of APLS training course

**Name:** Dao Huu Hung
**Country:** Vietnam
**Department:** National Children's Hospital, Hanoi
**Position:** Nursing Unit Manager


**My job:**
I have been working at Vietnam National Children's Hospital for 10 years. Most of the time, I worked in the Surgical ICU as a Nursing Team Leader and Clinical Nurse Educator. However, I am now a Nursing Unit Manager at the General Paediatric Department S, which is a private unit. I am responsible for training and managing all nursing activities in the department in order to provide the best possible care for children and their families.

**About this training course:**
I was extremely happy having the opportunity to study in Tokyo, Japan. For the ten days, I took part in a structured training program. This program was based mainly on at Teikyo University. Session topics covered emergency, medical engineering, pharmacy, biosafety, safety division, infection control, and medical examination. In addition, I was with my colleagues observing clinical, para clinical and educational activities throughout Teikyo University and Teikyo University Hospital. I have observed that in Japan, doctors and nurses work effectively in a wide range of clinical and non-clinical settings. There are many differences compared with healthcare systems in Vietnam, especially a lot of modern medical equipments and good working culture in Teikyo University Hospital. Therefore, I have enhanced my knowledge and experience while studying here, particularly in infection control and delivering safety care to patients.

**At the weekend:**
We spent time discovering Tokyo – one of the most spectacular cities in the world. Although we have only 10 days, we didn't miss the opportunity to visit National Museum of Emerging Science & Inovation, St. Luke's International University, many beautiful places and shopping centres, and enjoy a variety of traditional food in Tokyo.

**Future collaboration:**
After the training course, I got contacts with many key persons with different disciplines. This will definitely help me in the future because I can ask for help if I need any information regarding to patient care and so on. Furthermore, I would like to enhance the collaboration between Vietnam National Children's Hospital and ADC, SSP, Teikyo University and Teikyo University Hospital.

Finally, I want to say a heartfelt thank to all members of ADC, SSP, Teikyo University and Teikyo University Hospital for giving me this excellent opportunity!

**Name:** Do Minh Thuy
**Country:** Vietnam
**Department:** Education-Training Department-RICH-National Children's Hospital, Hanoi
**Position:** Specialist in Education-Training Department, Teacher

**Job Description:**
Every day, I admit and consult for new participants including nurses and doctors who have been graduated from University and want to become a pediatric health provider. In addition, we are cooperating with some Medical Universities such as Hanoi Medical University, Hai Phong University of Medicine and Pharmacy, Military Medical University, Thang Long University, etc. So that, we have a lot of students studying at hospital and my responsibility is taking care of them, especially nursing students. Sometimes I have a lecture about pediatric procedures and guide them how they can communicate in Emergency environment. In my lecture for nursing students, I usually emphasize the importance of preventing infection by hand hygiene, particularly in nurses often do all of simple procedures such as I.V cannula, urinary catheter, take blood samples. Beside the work in my office, I have on duty at night at Respiratory Intensive Care unit as the nurse. It supported for me about clinical skills.

**Benefits from SSP:**

I was very glad to participate in the Sakura Science Program. I recognized that, SSP was very useful for me in terms of both knowledges and clinical skills. I have gained more new knowledge about biosafety, patient safety, infection control, etc. It was very excited for me when I worked in RICU and taught for students. I can tell with my colleagues and students how they could protect themself and others from risks. Moreover, I could learn about the way Professors in Teikyo University teach for student and researcher.

Althought we had only 10 days with SSP, we've seen most of department in Teikyo University and some places such as: Tuberculosis Laboratory, St. Luke's International University. We were very impressed on how the way St. Luke's International University managed safety patient and prevention infection. We had an active discussion with expert about hand hygiene, infection control and visited at Pediatric Dpt, ICU, CSSD…

In addition with SSP, I've known more about Japanese culture and country especially in Teikyo University. They are very kind, careful, enthusiastic and intelligent. I would like to say many thanks to Prof. Kazuo Suzuki, Ms. Kaoru Tosaka, Ms. Aihara Hatsuyo, Mr. Kishinami and others in ADC helped us during this training course.

**Potential Collaboration:**

I hope in the future, we will have more opportunities to join the student exchange course beetwen NCH and Teikyo University. It is a great chance for NCH's students learn and research in Teikyo University– one of the biggest medical universities in Tokyo.

**Name:** Huong Do Thu
**Country:** Vietnam
**Department:** Research Biomolecular for Infectious Disease Department, National children's Hospital, Hanoi
**Position:** Researcher

**Summary of my training course in ADC Teikyo University**

It is an interesting experience when I participate in the training course in ADC Teikyo University. This is a good chance for me to get more knowledge not only my major but also other fields that will support me very much. I have a wide field of vision when touring around the Teikyo Hospital. All things here are perfect. Each department also has private arrangement but it is very scientific.

I also visit St. Luke's International University which is the long history of training nurse. The Healthcare-associated Infection Prevention and Control System at St. Luke's International Hospital is really worth to learn.

Especially, I am deeply impressed by people's kindness here. All people are enthusiastic, hard-working and warm-hearted.

**Job Description**

My main job is using Realtime PCR and Multiplex Realtime PCR techniques for detecting microorganisms like as viruses, bacteria and fungi. Some of main groups microorganisms are viruses and bacteria that cause respiratory infections; viral encephalitis, meningitis; viral hepatitis; group of opportunity viruses; intestinal viruses and bacteria. I also do some Multiplex Realtime PCR techniques: Multiplex Realtime PCR for diagnose sepsis – Septifast (Roche) for detecting 25 bacteria Gram negative, Gram poistive and fungi; xTAG® Respiratory Viral Panel (RVP) detecting for 18 respiratory viruses; xTAG® Gastrointestinal Pathogen Panel (GPP) for the simultaneous qualitative detection and identification of multiple viral, parasitic, and bacterial nucleic acids in human stool specimens; Fast track diagnostics: FTD33, FTD N9…

Besides, I also participate in some oversea Projects like as: Influenza projects (South EastAsia Network); South EastAsia Encephalitis Project; ARDS Study, rTM Study, Flu Study with NIID, Japan.

**Contribution of this training to my job**

Firstly, I learn how the way Japanese people do. Secondly, I take more knowlegde about safety division, infectious disease control and update new protocols in the laboratory etc... Thirdly, I realise I need study more to improve my skills.

**Collaboration plan with ADC Teikyo University**
I hope in the future, the relationship between My hospital and ADC Teikyo University are more stronger. I also can have opportunity to take part in these cooperative programs.

**Name:** Nguyen Ngoc Tu Anh, M.D.
**Country:** Vietnam
**Department:** Clinical Microbiology Department of Children Hospital #1, Ho Chi Minh City
**Position:** Vice Head of Clinical Microbiology Department

**Job in the CH1:**
My main work every day is to do the test and answer to the requests in identification and antibiotics susceptibility. In addition, I answer questions about treatments, antibiotics which were used in patients to clinicians, and I do tests for the environment to provide data to Infectious Disease Control Dept., take part in surveillance, do the research, and teach students...
My hospital is a first rate one of southern pediatrics branch, so there are a lot of children come to check health and get treatments. We have average 5,000 to 6,000 outpatients per day, and have 1,550 beds for inpatients, divided into 13 clinical departments.
We have traditional, standard microbiology to isolate and do the test, which has received helping to established from Denmark. After that, we have cooperated with OUCRU (Oxford University Clinical Research Unit) in many surveillances, we have studied and learned more about modern techniques such as PCR, real time PCR, and gained much knowledge in molecular diagnostic techniques. We have also done research with Taiwan to set up the culture virus lab. And now, the first time to have chance to visit Japan, Teikyo hospital, Teikyo university, ADC lab, I feel so happy and get much interested information.
In Sakura Science Plan, I got a very good arrangement to visit Teikyo hospital, Teikyo university, ADC lab…a very modern system to get academic education for healthcare field. Tuberculosis Bacteria Institute visit and listening informations made me feel very impressed about data in prevention and control of this disease. In addition, I have also visited St. Luke's International University, a very nice place, and I think your patients will be very happy when they come, and get a good take care activities.
Besides, I have known a group of staff, strictly working, working hard, and very friendly.

**Summary of the course in the Sakura Science Plan**
The course mentioned helpful topics, about Biosafety and Infectious Disease Control, which is very necessary to prevent the transmission, and it is going to help us to set up a good infectious control system.
In general, the system and organisation of the healthcare activities and education work in the hospital and the university made me surprised and impressed. I have recognised the insufficient procedure in my hospital. I have received much experiences to improve infectious disease control system.
I have been introduced about many modern techniques, equipments in labs.
This course brings me so many things to learn, to think. It is realy helpful.
I have been get well impressed in the culture, foods, silent city inspite of capital of a country.

**Potential Collaboration:**
Setting a good relationship in science goal, in healthcare mission.
Do research cooperation to exchange new technology, helpful techniques with my department and treatment method with other fields.

**Name:** LÊ THỊ THANH THỦY, M.D.
**Country:** Vietnam
**Department:** Children's Hospital 1, Ho Chi Minh City
**Position:** Infection Prevention and Control Department (IPC)

**Job description:**
— Manage the Central Sterile Supply Department (CSSD) to provide all sterilizable devices for all departments in my hospital
— Do healthcare-associated infection surveillance such as bloodstream infections (BSI) and central line-associated bloodstream infections (CLABSI), urinary tract infections (UTI) and catheter-associated urinary tract infections (CAUTI), hospital-associated

pneumonia (HAP) and ventilator-associated pneumonia (VAP), surgical site infection (SSI).
— Training and education about hand hygiene compliance, personal protective equipments and new guidelines or procedures in infection prevention and control from the Ministry of Health.

**Benefits from Sakura Science Programme:**
SSP gave me a chance to explore country, people, Japanese culture and spirit. I felt extremely warm because of your kindness, ethusiasm and friendliness in the 11°C cold. Your work load was always huge while you still kept calm. That was the Japanese spirit I admired most. Dishes were very delicious especially Janpanese style BBQ beef and hot spot.
Visiting Luke's International Hospital that founded at the beginning of 19th century was my pleasure. The old Luke's International Hospital where received JCI in 2012 and accredited in 2014, had excellent Quality Improvement Center. It was a precious experience for our hospital to look forward JCI certification.
All your up-to-date lectures showed me many interesting and useful information. The model combined the university for teaching and the hospital for practicing was excellent. Teikyo University and Teikyo University Hospital had the modern and high technique equipments for examine and do research. Biosafety understanding was very practical to apply for my CSSD. Most of lectures were remarkable. My most excitement is visiting the Infection Control and Prevention Deprartment with Doctor Naohisa Matsunaga. He told me how to recognize nosocomial infection cases to feedback to local hospital and report to the clinical departments to isolate those patients; distinguish between Carbapenem-resistant *Enterobacteriaceae* (CRE) and Carbapenem-producing *Enterobacteriaceae* (CPE), practice hand hygiene and personal protective equipment and so on. He also quickly responded my questions with the evidence-based information. Most of all, Teikyo University Hospital had maximum 70 MRSA cases during 3 years. This amazing data reflected how well your infection prevention and control system worked. It brought me more motivation to work for my hospital after coming back.

**Potential Collaboration:**
At first, I hope that SSP will continue to support for Children Hospital 1's medical doctor to approach the Japan modern medical foundation. Not only short-term but also Ph.D. course would be a good chance for our staffs to widen our knowledge and do serious researches.
Furthermore, I would like to take part in the research projects that related to healthcare-associated infection and support your visiting students and research projects with all my best at my hospital.


# 川崎病の治療の変遷

社会福祉法人　広島県リハビリテーション協会
重症心身障害児･者医療福祉センター施設責任者　岡崎　富男

# History of Treatment in Kawasaki Disease

Tomio Okazaki
Tokiwa-Kure Facilities for Persons with Severe
Motor and Intellectual Disabilities, Kure, Hiroshima

私が広島市民病院の小児科に在職していた時、川崎病が大流行していた1982－83年ごろからの数年間、当時、放射線影響研究所（広島）におられた鈴木和男先生と研究室のみなさんと「好中球機能不全」について研究を行った。血小板上昇前のリスク期（動脈瘤形成期）に好中球からのMPO放出能が亢進し、動脈瘤形成との関係が示唆され、この成果を第２回 国際川崎病シンポジウム［1986年11月30 ～ 12月3日、開催場所 Kauai Hilton Hotel, Kauai, Hawaii, USA、会長 Prof. Stanford T. Shulman（Children's Memorial Hospital, Northwestern University, Chicago, USA）］で発表した[1]。今回、川崎病の治療の変遷について概説する。

川崎病が発見された当初は、感染症やアレルギー疾患と考えられ、抗生物質や副腎皮質ステロイド剤、免疫抑制剤がその治療に多く用いられていた。1970年代前半から副腎皮質ステロイド剤が主として使用され、プレドニン2~4mg/kg/日の経口投与が行われ、さらにメチルプレドニゾロンによるパルス療法が行われた。しかし、ステロイド剤により冠動脈瘤の形成が助長されると云う疑いが指摘された。

## アスピリン治療

1977年に東京女子医科大学小児科の草川三治らが解熱作用や抗炎症作用だけでなく抗凝固作用を有するアスピリン30~50mg/kg/日が川崎病の治療に有効である事を提唱し、その後、厚生労働省の研究班によるコントロールスタディでアスピリンが最も良い治療成績を示したため、標準的な治療法として広く使用された。

## 免疫グロブリン療法

アスピリンだけでは冠動脈瘤の発生を抑える効果が十分でなく、25％程度の患者に冠動脈病変が認められ、さらに強力な抗炎症作用のある治療法が必要であった。1983年に小倉記念病院小児科の古庄巻史らが、1981年にLancetに報告されたImbachらの特発性血小板減少性紫斑病患児へのガンマグロブリン大量療法（400mg/kg/日5日間点滴静注投与）にヒントを得て、川崎病患児に同様のガンマグロブリン大量療法を始め翌年、静脈用ガンマグロブリン（IVIG）の大量投与が冠動脈病変の発生を抑制することを報告した。更に他施設の治験研究を実施し、その有効性を証明した。しかし、その後100mg/kg/日や200mg/kg/日5日間投与でも冠動脈病変の抑制が可能ではないかとの意見もあり比較研究が行われ、冠動脈病変の合併率減少効果は100mg/kg/日では劣るものの、200mg/kg/日とでは顕著な差が認められなかったため、1990年に200mg/kg/日を5日間投与する方法が保険承認された。しかし、Morikawaらによる多施設の治療研究では200mg/kg/日5日間より400mg/kg/日5日間の方が冠動脈病変の発生を抑制する効果が大きいことが報告された。

一方、アメリカでは1991年にNeuburgerらが他施設の治療研究で、400mg/kg/日4日間投与より2g/kgを10時間以上かけて１回で投与した方が良い治療成績を示すことを報告し、American Heart Association（AHA）もこの用法・用量を推奨している。また、Durongpisitkulらは文献的にIVIG療法の報告例を集計し、冠動脈病変の頻度は投与量が多いほど低く、しかも単回大量投与法が有用であることを報告している。その後、わが国においても、2g/kg１回投与法が優れているという治療研究が相次いで報告された。

## ステロイドパルス療法

IVIG大量療法を行っても、その治療効果が十分得られない症例が全体の10~20%に存在する。その場合、ガンマグロブリンの再投与に続いて、ステロイドパルス療法と血漿交換療法が行われた。

ステロイドパルス療法は、メチルプレドニゾロンをゆっくりとした速度で点滴静注する。ステロイドは、体内で

作られるホルモンの一種で、免疫や炎症を抑える強力な作用があり、アレルギーなどの多くの難治性疾患で効果を挙げている。以前の治療研究で川崎病に対しては一時、禁忌とされていたが、近年再評価されている。

**血漿交換療法**

血液は血漿と血球で構成されているが、患児の血漿が川崎病の血管炎に関与していることが分かっている。そのため、患児の血漿を輸血由来の正常な血漿に置き換えるのが血漿交換療法である。血液から血漿と血球を分離させるフィルターを持つ装置を通して、少しずつ時間をかけて交換する。ガンマグロブリンと同様に、輸血血液を使用するため未知のウイルスなどの病原体感染のリスクは排除できない。

**川崎病の新たな治療法**

ガンマグロブリン療法の普及により、冠動脈病変の発生率は減少したが、残存した動脈瘤の大きさ別でみると、中等度の冠動脈流と巨大瘤の発生頻度は殆ど変わらず今後の課題であり、原因究明とガンマグロブリン大量療法に不応例に対する治療法の開発が待たれる。

**・RAIS　Study**

血液検査結果や年齢などから、ガンマグロブリンが統計的に効きにくいと予想できる患者にステロイドとガンマグロブリンを併用する研究で、治療研究で有意な結果を残している。

**・好中球エラスターゼ阻害剤（ウリナスタチン）**

白血球がつくる炎症を惹起する酵素を阻害する薬を併用することで、防衛医科大学などの研究グループが有意な結果を出している。

**・抗サイトカイン製剤**

川崎病の急性期に炎症性サイトカインが血中に増加していることに注目し、これを阻害するインフリキシマブを投与する。ガンマグロブリン不応性の川崎病患者において効果が認められ、国内でも使用が検討されるようになっている。その他、シクロスポリンも投与され、有用であったとの報告もある。

**心臓血管外科的冠動脈バイパス手術**

川崎病の冠動脈病変の後遺症として、虚血性心疾患を起こす子どもたちも少なくはなって来ているが、1975年に大阪大学の川島康生と北村惣一郎らが日本で初めて冠動脈バイパス手術に成功している。その後も大伏在静脈や内胸動脈を用いてのバイパス手術が行われている。

**参考文献**


1. Okazaki, T, Suzuki, K. et al. Enzyme release and O2- production of neutrophils and vascular lesions in gamma globulin therapy of Kawasaki disease. *Prog Clin Biol Res.* **250**: 557-558, 1987.
2. 草川三治・他：川崎病の急性期治療研究：aspirin, flurbiprofen, prednisolone＋dipyridamoleの3治療群による prospective study. 日本小児科学会雑誌, **87**(12): 2486-2491, 1983.
3. 古庄巻史・他：川崎病における γ―グロブリンの大量点滴療法.基礎と臨床, **17**(2): 672-695, 1983.
4. 岡崎富男・他：川崎病に対する免疫グロブリン療法：その治療効果と投与量について. 小児科診療, **51**(5): 1094-1100, 1988.
5. Morikawa, Y. et al.: A multicenter, randomized controlled trial of intravenous gamma globulin therapy in the children with acute Kawasaki disease. *Acta Paediatr. Jpn.* **36**(4): 347-354, 1994.
6. Newburger, J.W. et al.: A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki disease. *N. Engl. J. Med.* **324**(23): 1633-1639, 1991.
7. Durongpisitkul, K. et al.: The prevention of coronary artery aneurism in Kawasaki disease:a metaanalysis on the efficacy of aspirin and immunoglobulin treatment. *Pediatrics,* **96**(6): 1057-1061, 1995.
8. Sato, N. et al.: Selective high dose gamma-globulin treatment in Kawasaki disease: assessment of clinical aspects and cost effectiveness.
   *Pediatr. Int.,* **41**(1): 1-7, 1999.
9. Wright, D.A. et al.: Treatment of immune globulin-resistant Kawasaki disease with pulsed dose of corticoids. *J. Pediatr.* **128**(1): 1159-1164, 2001.
10. 石井正浩・他：川崎病―免疫グロブリン療法の全て.小児科療, **64**(8): 1159-1164, 2001.
11. 竹下誠一郎・他：川崎病の治療戦略―古くて新しい視点から. ウリナスタチン療法は有効か？第22回日本川崎病研究会抄録集, 2002, p26.
12. 今川智之・他：川崎病における血漿交換療法. 小児科臨床, **50**(10): 2217-2221, 1997.

PEER-REVIEWED MINI REVIEW

# GM-CSF-PPARγ Axis Plays Critical Roles in the Development, Surfactant Homeostasis and Anti-inflammatory Activity of Alveolar Macrophages

Kiyoko Akagawa

Kitasato Institute for Life Sciences, Kitasato University 5-9-1, Shirokane, Minato-ku, Tokyo 108-8641, Japan

Kiyoko Akagawa
E-mail: akagawak@zb3.so-net.ne.jp

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**Abstract**

**AMΦs have an organ-specific function to maintain surfactant homeostasis that is critical to alveolar stability and lung function. AMΦs poses unique features such as aerobic respiration, high anti-oxidant capacity, and AMΦs alone among the all tissue MΦs are adapted to aerobic environment. Inflammation of the lungs causes respiratory failure and interferes with life sustaining. Therefore, treatment of foreign antigens with AMΦs should be done without inflammatory response as much as possible. AMΦs originate from fetal monocytes, are long-lived cells and their maintenance depend on self-renewing. GM-CSF is essential for the development of AMΦs but not other tissue MΦs. Characteristics of GM-CSF-induced human monocyte-derived MΦs (GM-MΦs) is the same as that of human AMΦs, indicating that the GM-MΦs become a model of human AMΦs. Expression of PPARγ in nucleus of AMΦs depends on GM-CSF, and is essential for the development of AMΦs. In this article, recent findings on the origin and the essential role of GM-CSF-PPARγ axis in the development, surfactant homeostasis and anti-inflammatory activity of AMΦs are reviewed.**

## Introduction

Macrophages (MΦs) exist various tissues in the body, and have roles in development, tissue homeostasis, inflammation, tissue regeneration, lipid metabolism and host defense against microorganisms and tumors. Tissue-resident MΦs constitute heterogeneous populations with unique functions and distinct gene-expression signatures, and are known by different names (e.g., alveolar MΦs (AMΦs) in the lung, peritoneal MΦs (PMΦs) in the peritoneum, Kupffer cells in the liver, microglias in the brain and osteoclasts in the bone).

AMΦs comprise up to 90-95% of the leukocytes present in mouse or human bronchoalveolar lavage (BAL) under steady state. AMΦs have an organ-specific function to maintain surfactant homeostasis in the lung which is critical to alveolar stability and lung function. AMΦs are known to possess high anti-oxidant capacity and the energy metabolism of AMΦs relies primarily on aerobic respiration, whereas that of other tissue MΦs depends primarily on glycolysis. These unique features of AMΦs may result from their location in the lung in which AMΦs are exposed to high oxygen tension and are also bathed in high concentrations of surfactant. AMΦs alone among the all tissue MΦs are adapted to aerobic environment.

Inflammation of the lungs causes respiratory failure and interferes with life sustaining. Therefore, treatment of foreign antigens with AMΦs should be done without inflammatory response as much as possible. Thus precise mechanisms control the high anti-oxidant activity and the balance of pro- and anti-inflammatory responses are necessary for AMΦs to ensure an appropriate response to environmental agents. Here, recent findings on the origin and an essential role of granulocyte-macrophage colony-stimulating factor (GM-CSF)-peroxisome proliferator-activated receptor γ (PPARγ) axis in the development, surfactant homeostasis and anti-inflammatory activity of AMΦs are reviewed.

## Origin and self-renewal of AMΦs

In 1924, MΦs were defined by Aeschoff as cells of the reticulo-endothelial system (RES). This implied that macrophages originate from the tissue, and reside and renew within the tissue. In 1960, Ralph Van Furth proposed the concept of "the mononuclear phagocyte system (MPS)". According to the MPS, all MΦs, including all tissue-resident and inflammatory MΦs are derived from the bone marrow through circulating blood monocytes, and they are terminally differentiated cells. We previously showed the differences in the expression of asialo GM1, Mac-1 and the binding to FITC-LPS between AMΦs and PMΦs in the mouse[1)-3)]. AMΦs express asialo GM1$^{+}$, Mac-1$^{low}$ and do not bind to FITC-LPS, whereas PMΦs are asialo GM1$^{-}$, Mac-1$^{+}$ and bind to FITC-LPS. In agreement with the difference in FITC-LPS binding, PMΦs but not AMΦs activate tumor cytotoxicity by LPS stimulation[2)]. In 1981, we found that MΦs exist in fetal lung and fetal liver at E14, and the fetal lung MΦs are asialo GM1 positive as well as AMΦs obtained from adult mice. In 1988, we also found that AMΦs from adult mouse can proliferate and make colonies by stimulation with GM-CSF or M-CSF[3)]. These our studies strongly indicate that asialo GM1 positive lung MΦs already exist in fetus and maintenance of AMΦs in adulthood depend not only blood monocytes but also on the self-renewal.

Recent studies using the new method such as Fate-mapping elegantly showed that mouse tissue-resident MΦs in multiple organs, originate from embryonic progenitors such as primitive macrophages ($CX_3CR1^{hi}$ $F4/80^{hi}CD11b^{lo}$) in yolk sac (microglia) or fetal monocytes ($CX_3CR1^{-}$ $F4/80^{low}CD11b^{high}$) in fetal liver (MΦs in lung, spleen, liver, skin, kidney, gut), and can persist into adulthood and self-maintain by local proliferation[4)]. In 2013, Guilliams et al. reported that AMΦs originate from fetal monocytes within the first week of life,

mature by 3 days after birth and are long-lived cells[5]. The maintenance of them depends on their self-renewing capacity and circulating blood monocytes contribute minimally to the steady-state AMΦs pool[5]. Self-renewing capacity in human AMΦs was also detected by us[6]. In 2016, Nayak et al demonstrated that almost 100% of human AMΦs detected in BAL from the transplanted lungs are donor derived with a capacity to self-renewal[7]. However, monocytes can contribute to the AMΦs pool when AMΦs niche in lung is empty under extreme conditions of depletion or radiation injury[8]. In some tissues, embryo-derived MΦs show declining self-renewal activity and are replaced by monocyte-derived MΦs soon after birth (MΦs in intestine)[9] or with age (MΦs in the heart)[10].

**GM-CSF is a critical factor for the differentiation of AMΦs**

In 1988, we demonstrated that one of the mechanisms that control MΦs heterogeneity is the difference in colony-stimulating factor (CSF) by which MΦs differentiation is induced, and GM-CSF determine the phenotype of murine AMΦs, and M-CSF determine that of PMΦs[3]. Our results indicate that factor in the environment in which AMΦs locate determine the phenotype of AMΦs, because lung tissue is known to be rich in GM-CSF[11]. In 1994 and 1995, the essential role of GM-CSF in the functional differentiation of AMΦs was demonstrated from the studies of gene targeting of GM-CSF (GM-/-) and the common β-chain of the GM-CSF receptor (GMRβc-/-) in mice[12,13,14]. These gene-targeted mice develop pulmonary surfactant excess, which histologically resembles to the human pulmonary alveolar proteinosis (PAP). PAP is associated with a marked accumulation of foamy, lipid-filled MΦs, surfactant protein and lipids in the alveolar spaces of the lungs. Human PAP develops by the disruption of GM-CSF signaling caused by high levels of neutralizing anti GM-CSF antibodies in autoimmune PAP[15] or by mutations in *GM-CSFR* in congenital PAP[16]. Surfactant accumulation in these gene targeted mice and PAP patients is due to reduced clearance caused by reduced surfactant catabolism in AMΦs[17]. AMΦs from GM-/- mice and PAP patients also reduce the cell adherence, phagocytosis, bacterial killing, expression of cell surface receptors (TLR4, TLR2, CD14, mannose receptor, Fcγ receptor, M-CSF receptor, integrins) and LPS-mediated cytokine production, indicating that not only surfactant catabolism but also innate immune function in AMΦs are impaired[17]. In fact, these gene targeted mice and PAP patients are susceptible to respiratory infections[17]. In GM-/- mice, abnormality is observed only in AMΦs but not in other tissue MΦs, and the development of AMΦs stop at early AMΦs commitment from fetal monocytes[5].

In contrast to GM-CSF, M-CSF which is present at biologically active concentrations in the circulation and in most tissues is necessary for the development of many tissue MΦs including PMΦs, Kupffer cells, spleen MΦs, osteoclast in addition to blood monocytes. IL-34 produced from keratinocytes and neurons specifically promotes the development of Langerhans cells and microglias[18]. IL-34 and M-CSF share the receptor, Fms, but they bind different Fms domain, which cause different signal activation and bioactivities. These results taken together indicate that development of unique phenotype and functional properties in each tissue MΦs are largely specified by factors in the local environment in which the tissue MΦs exist.

**GM-CSF-induced human monocyte-derived MΦs become a model of human AMΦs**

Previously we demonstrated that human monocytes differentiate into 2 phenotypically and functionally distinct types of MΦs, dendritic cells and osteoclast-like multi-nucleated giant cells under the influence of M-CSF, GM-CSF and IL-4[19-25]. GM-CSF-induced human monocyte-derived MΦs (GM-MΦs) are the same as that of human AMΦs in morphology (fried egg-like shape) and the expression of cell surface antigens (c-fms$^{low}$, CD14$^{low}$, HLA-DR$^{++}$, HLA-DQ$^{+}$ CD71$^{+}$, 710F$^{+}$). In contrast, morphology (spindle-like and some cells remain small and round) and the expression of cell surface antigens (c-fms$^{high}$, CD14$^{high}$, HLA-DR$^{+}$, HLA-DQ$^{-}$, CD71$^{-}$, 710F$^{-}$) of M-CSF-induced human monocyte-derived MΦs (M-MΦs) resemble those of human PMΦs and inflammatory MΦs. As shown in table 1, other characteristics of GM-MΦs are the same as those of human AMΦs. These results indicate that GM-CSF is a critical factor for the differentiation and function of human AMΦs, and the environment that stimulate the development of AMΦs but not origin of AMΦs (fetal monocytes or adult blood monocytes) is important to decide the phenotype and function of AMΦs, and human monocyte-derived GM-MΦs become a model of human AMΦs. In agreement with our studies, recent study in mice show that transcriptome analysis of embryonic host-derived and postnatal donor bone marrow-derived AMΦs coexisting within the same

**Table 1. Characteristics of human monocyte-derived GM-MΦs and M-MΦs and human AMΦs**

| | Human AMΦs | GM-MΦs | M-MΦs |
|---|---|---|---|
| **Expression** | | | |
| C/EBPβ isoform | Small-isoform main | Small-isoform main | Large-isoform main |
| Hck | Not expressed | Not expressed | High |
| Bcl-2 family genes | Bcl-xL | Bcl-xL | Bcl-2 |
| **Functions** | | | |
| T cell proliferation | Suppress | Suppress | Suppress |
| IFNγ production | Not suppress | Not suppress | Suppress |
| IL-10 production | Low | Low | High |
| $H_2O_2$ production | Low | Low | High |
| $H_2O_2$ sensitivity | Resistant | Resistant | Sensitive |
| Catalase production | CSF-independent | CSF-independent | CSF-dependent |
| In vitro survival | CSF-independent | CSF-independent | CSF-dependent |
| HIV-1 infection | Resistant | Resistant | Susceptible |
| *M. tuberculosis* infection | Susceptible | Susceptible | Resistant |

mouse demonstrated >98% correlation, and overall functional analyses are similar[8].

GM-MΦs and human AMΦs, in contrast to M-MΦs, are highly resistant to $H_2O_2$ via the high basal level of catalase activity and a marked ability to express catalase in response to $H_2O_2$, indicating that GM-CSF but not M-CSF plays a critical role in the development of $H_2O_2$ scavenging ability via unique catalase producing activity in human MΦs[23]. A strong anti-oxidant mechanism of human AMΦs and GM-MΦs supported by high catalase activity may help them to be long survivors in an oxidant rich lung environment and contribute to lung homeostasis. In fact, human AMΦs and GM-MΦs are long-lived cells even in the absence of GM-CSF, and the survival depends on catalase produced in a CSF-independent manner[25]. Extracellular catalase has a novel role in the prevention of apoptosis through the dominant expression of BCL-$X_L$ in human AMΦs and GM-MΦs, and BCL-2 in M-MΦs[25].

**Critical roles of PPARγ in the development, surfactant homeostasis and anti-inflammatory function in AMΦs**

AMΦs from healthy mice and human but not from PAP patients and GM-/- mice express both PU.1 and PPARγ in nucleus, and the expression depends on GM-CSF. PU.1 has general roles in myelomonocytic development, and is expressed in many tissue MΦs. PU.1 in AMΦs is critical for the differentiation and the innate immune functions of AMΦs, whereas the role of PU.1 on the surfactant lipid catabolism in AMΦs is not yet clear[17]. In contrast to PU.1, PPARγ is indispensable for the development of AMΦs, and PPARγ-/- mice stop the AMΦs development at E17.5 as well as in GM-/- mice[26]. PPARγ was dispensable for the development of MΦs located in the peritoneum, liver, brain, heart, kidneys, intestine and fat. In these tissue MΦs, other transcription factors such as Spi-C in red pulp MΦs[27], GATA6 in PMΦs[28] NFATc1 in osteoclasts[29] and IRF8 in microglias[30] are known as tissue specific developmental factors.

PPARγ is a ligand-activated, nuclear transcription factor that regulates genes involved in lipid and glucose metabolism, inflammation, and other pathways. Reduced expression of both PPARγ and ABCG1 but not ABCA1 was observed in AMΦs from GM-/-mice and PAP patients (Table 2)[31]. ABCG1 and ABCA1 are ATP-binding cassette (ABC) lipid transporter that mediate cholesterol efflux from MΦs. ABCA1 mediate cholesterol efflux to ApoA-I and ABCG1 mediate cholesterol efflux to HDL. Instillation of lenivirus (lenti)-PPARγ to AMΦs in GM-/- mice restored the ABCG1 expression and reduced lipid accumulation in AMΦs and in BAL[32]. Instillation of lenti-ABCG1 to AMΦs in GM-/- mice reduced cholesterol accumulation in AMΦs and BAL, and improved the lung function[33]. In contrast, ABCG1-/- mice exhibited PAP-like pulmonary lipidosis with massive deposition of cholesterol in both AMΦs and BAL[34,35]. Thus the cholesterol efflux mediated by ABCG1 which is induced by GM-CSF via PPARγ is necessary for the surfactant homeostasis in AMΦs.

As well as GM-/- mice or PAP patients, mice that lack PPARγ in AMΦs cause lung inflammation and increase the Th1 type cytokines/chemokines production by BAL cells[35]. Interestingly, ABCG1-/- mice also induce lung inflammation with a marked recruitment of leukocytes and increased proinflammatory cytokine production by AMΦs[36,37]. In the atopic asthma model, ABCG1-/- mice display IL-17-mediated enhancement of neutrophilia in the airway following allergen sensitization and challenge[38]. The neutrophilic, high IL-17 asthma phenotype observed in ABCG1-/- mice resemble to that described in severe asthma in human subjects[39]. Thus GM-CSF-PPARγ-ABCG1 axis –mediated cholesterol homeostasis in AMΦs serves as an important negative regulator of pulmonary inflammatory responses, and the breakdown of this axis induces pulmonary inflammation. As shown in Fig.1, functions regulated by PPARγ in AMΦs are related to anti-inflammation or resolution of inflammation that are expressed in M2MΦs. As well as AMΦs, differentiation to M2MΦs depends on oxidative phosphorylation by expression and activation of PPARγ, and is inhibited in PPARγ deficient MΦs[40].

Pulmonary surfactant consists of ~10% neutral lipids including free fatty acids, which are precursors of PPARγ ligands. Thus surfactant-rich lung environment constantly stimulates AMΦs by endogenous PPARγ ligands, and probably maintains lung homeostasis by suppressing inflammation and controlling respiratory function necessary for maintenance of life. Lipoprotein lipase (LPL) hydrolyze neutral lipids to generate free cholesterol and free fatty acids, which are precursors of PPARγ ligands. Interestingly, expression of LPL is decreased in GM-/- mice as shown in Table 2. Important role of LPL was reported from gene targeting of lysosomal acid

**Table 2. Molecules expressed in alveolar macrophages from PAP patient, GM-/- mice, PPARγ-/- mice and ABCG1-/- mice**

| | GM-/- mice | PAP patient | PPARγ-/- mice | ABCG1-/- mice |
|---|---|---|---|---|
| PPARγ | ↓ | ↓ | None | → |
| PU.1 | ↓ | ↓ | → | → |
| ABCG1 | ↓ | ↓ | ↓ | ↓ |
| ABCA1 | ↑ | ↑ | ↑ | ↑ |
| LXRα | ↑ | ↑ | ↓ | n.d. |
| LXRβ | n.d. | n.d. | ↑ | n.d. |
| LPLA2 | ↓ | ↓ | → | n.d. |
| LPL | ↓ | n.d. | n.d. | n.d. |
| CD36 | ↓ | ↓ | ↓ | n.d. |
| GM-CSF | None | ↓ | ↑ | n.d. |
| M-CSF | ↑ | ↑ | ↑ | n.d. |

LXR: Liver X receptor.
LPLA2: Lysosomal phospholipase A2 specifically expressed in MΦs with predominance in AMΦs.
LPL: lipoprotein lipase.
n.d.: not determined.

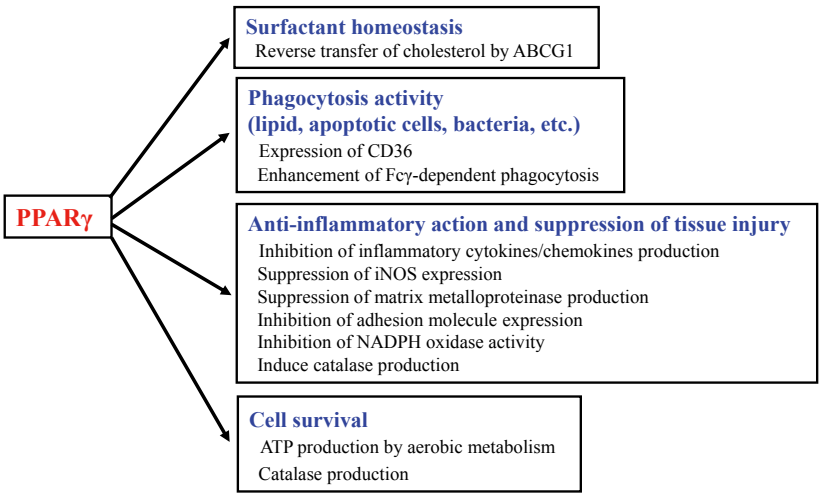


**Fig. 1. PPARγ regulates the functions of alveolar macrophages**

lipase (LAL) in mice. The LAL-/- mice results in respiratory inflammation, destruction in the lung with an increase in the number of foamy AMΦs and neutrophil infiltration, increase in proinflammatory cytokines/chemokines and matrix metalloproteinases in lung, and shows severe pathology of multiple organ failure[41]. MΦ-specific expression of human LAL or stimulation with PPARγ ligands corrects inflammation and pathogenic phenotypes in LAL-/- mice[41].

## Conclusions

The lungs are important organ responsible for the breathing functions essential to making the energy necessary for maintaining life. Inflammation of the lungs causes respiratory failure and interferes with maintaining life. AMΦs expresse PPARγ2, which is the same subtype as expressed in adipocytes, suggesting that the role of lipid metabolism of AMΦs is very important and necessary, since the AMΦs exist in the unique lung environment with lipid-rich surfactant ocean. Expression of both PPARγ and PU.1 in the nucleus of AMΦs by GM-CSF is an essential condition for AMΦs to maintain lung homeostasis. Well-balanced activity of PPARγ and PU.1 make it possible to maintain surfactant homeostasis and treat the pathogen and foreign matter entering the lung as much as possible without inflammatory reaction and terminate efficiently even if inflammation is induced. Abnormalities in surfactant lipid metabolism of AMΦs caused by breakdown of GM-CSF-PPAR γ-ABCG1 axis induce accumulation of cholesterol rich foamy AMΦs and inflammation of the lungs, and are involved in the development of many pulmonary inflammatory diseases such as PAP, asthma and COPD. New drug discovery that target the GM-CSF-PPARγ-ABCG1 axis is expected.

## Reference


1) Akagawa KS, et al. Microbiol Immunol 1981; 25: 1215-20.
2) Akagawa KS, et al. J Exp Med 1985; 162: 1414-19.
3) Akagawa KS, et al. J Immunol 1988; 141(10): 3383-90.
4) Gentek R, et al. Immunol Rev. 2014; 262(1): 56-73.
5) Guilliams M, et al. J Exp Med 2013; 210(10): 1977-92.
6) Nakata K, et al. J Immunol 1991; 147: 1266-72.
7) Nayak DK, et al. Am J Transplant 2016; 16(8): 2300-11.
8) Gibbings SL, et al. Blood 2015; 126(11): 1357-66.
9) Bain CC, et al. Nat Immunol 2014; 15: 929-37.
10) Molawi K, et al. J Exp Med 2014; 211(11): 2151-8.
11) Burgess AW, et al. J Biol Chem 1977; 252(6): 1998-2003.
12) Dranoff G, et al. Science 1994; Apr 29; 264(5159): 713-6.
13) Stanley E, et al. Proc Natl Acad Sci U S A 1994; 91(12): 5592-6.
14) Robb L, et al. Proc Natl Acad Sci U S A 1995; 92(21): 9565-9.
15) Kitamura T, et al. J Exp Med 1999; 190(6): 875-80.
16) Dirksen U, et al. J Clin Invest 1997; 100(9): 2211-7.
17) Trapnell BC, et al. Curr Opin Immunol 2009; 21(5): 514-21.
18) Wang Y, et al. Nat Immunol 2012; 13(8): 753-60.
19) Akagawa K.S, et al. Lymphokine Cytokine Res 1993; 12: 326.
20) Akagawa K.S, et al. BLOOD 1996; 88: 4029-39.
21) Akagawa K.S, et al. Int J Hematol 2002; 76: 27-34.
22) Mochida-Nishimura K, et al. Cell Immunol 2001; 214: 81-8.
23) Komuro I, et al. J Biol Chem 2001; 276: 24360-4.
24) Komuro I, et al. J Exp Med 2003; 198: 443-53.
25) Komuro I, et al. J Biol Chem 2005; 280: 41137-45.
26) Schneider C, et al. Nat Immunol 2014; 15(11): 1026
27) Haldar M, et al. Cell 2014; 156(6): 1223-34.
28) Leavy O, Nat Rev Immunol 2014; 14(6): 360.
29) Zhao Q, et al. Int J Biochem Cell Biol 2010; 42(5): 576-9.
30) Kierdorf K, et al. Nat Neurosci 2013; 16(3): 273-80.
31) Thomassen MJ, et al. J Lipid Res 2007; 48(12): 2762-8.
32) Malur A, et al. Am J Physiol Lung Cell Mol Physiol 2011; 300(1): L73-80.
33) Malur A, et al. Biochem Biophys Res Commun 2011 Nov 18; 415(2): 288-93.
34) Baldán A, et al. J Biol Chem 2006 29; 281(39): 29401-10.
35) Malur A, et al. J Immunol 2009; 182(9): 5816-22.
36) Baldán A, et al. J Immunol 2008; 180(5): 3560-8.
37) Wojcik AJ, et al. J Immunol 2008; 180(6): 4273-82.
38) Draper DW, et al. J Immunol 2012; 188(11): 5327-36.
39) Bullens DM, et al. Respir Res 2006; 7(1): 135.
40) Odegaard J.I, et al. Nature 2007; 447(7148): 1116-20.
41) Yan C, et al. Am J Pathol 2006; 169(3): 916-26.

PEER-REVIEWED ORIGINAL ARTICLE

# Role of Hypothiocyanous Acid on the Cytokine Production in Airway Epithelial Cells

Thuy Thu Nguyen, Shoichi Suzuki*, Ryuichi Sugamata, Fuyu Ito, Tomoko Yamamoto, Shoji Kawachi, and Kazuo Suzuki

Department of Health Protection, Graduate School of Medicine and Asia International Institute of Infectious Disease Control, Teikyo University, Kaga 2-11-1 Itabashi-ku,Tokyo 173-8605, JAPAN

Corresponding author (*)
Shoichi Suzuki
Asia International Institute of Infectious Disease Control, Teikyo University, Kaga 2-11-1 Itabashi-ku, Tokyo 173-8605, JAPAN
E-mail: shoichi3@med.teikyo-u.ac.jp

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## Abstract

**When influenza viruses infect to airway, it is thought that hypothiocyanous acid (HOSCN), an oxidant with anti-influenza virus activity, is produced by the catalysis of peroxidases such as myeloperoxidase (MPO) and lactoperoxidase (LPO). However, the actions of HOSCN on host cells are poorly understood. In this study, we examined the effects of HOSCN on the expression of cytokines in airway epithelial cells. Human airway epithelial (NCI-H292) cells were exposed to HOSCN that generated in LPO/glucose oxidase/$SCN^-$ culture system. The gene expression of cytokines was determined by quantitative polymerase chain reaction and the concentration of cytokines also was measured by ELISA method. We found that HOSCN induced the expression of pro-inflammatory cytokines such as IL-6, IL-8, TNF-α, IL-1β and M-CSF, but it did not do GM-CSF. The results suggest that HOSCN may contribute to the production of pro-inflammatory cytokines during influenza viral infection. And also it may impact on the balance of M1/M2 development of macrophages, because M-CSF plays an important role for the differentiation of macrophages toward M2 phenotype.**

## Introduction

Influenza virus infection leads to recruit neutrophils and monocytes to the infectious sites and produce inflammatory mediators including hydrogen peroxide ($H_2O_2$) to response against influenza virus infection[1,2,3]. Previously we showed that MPO, which is an enzyme released by activated neutrophils and monocytes, accumulated in the lung in the early phase after influenza virus infection[4]. In plasma, MPO is able to generate equal amounts of hypochlorous acid (HOCl) and HOSCN by catalytic oxidation of chloride ($Cl^-$) and thiocyanate ($SCN^-$), respectively, with $H_2O_2$[5]. In the airway, HOSCN is thought to be a major product by the MPO-catalytic oxidation, because airway surface liquid (ASL) covering the airway epithelium contains higher concentrations of $SCN^-$ than plasma[5]. In the presence of $H_2O_2$, it is also possible that $SCN^-$ may be oxidized to HOSCN by LPO, which is secreted into ASL by submucosal glands and goblet cells[6]. Therefore, we are focusing on roles of HOSCN during influenza virus infection.

As well as HOCl, HOSCN is an oxidant with anti-influenza virus activity[7,8]. However, the reactivity of individual oxidants is markedly different. HOCl reacts with the majority of functional groups in amino acids. In contrast, HOSCN is a much milder oxidant that reacts specifically with thiol and selenol residues, suggesting that HOSCN may act as a second messenger in redox signaling[9].

So far, effects of HOSCN on airway epithelial cells are poorly understood. A study showed that HOSCN activated NF-κB via PKA dimerization in airway epithelial cells, suggesting it may induce the gene expressions of various pro-inflammatory cytokines[10]. In this study, to clear the role of HOSCN on inflammation in the airway, we analyze its effects on the cytokine production in airway epithelial H292 cell line.

## Methods

*Cell culture*

H292 cells were cultured in RPMI-1640 medium (Sigma) supplemented with 10% heat-inactivated fetal bovine serum (FBS, GE Healthcare Life Sciences), 0.05 mg/mL gentamicin sulfate (Wako) at 37˚C in 5% $CO_2$ incubator.

*Exposure of cells to HOSCN*

H292 cells at 5 x $10^5$ cells/mL of concentration were cultured in RPMI medium at 37˚C for 1 day until 95% of the confluences. Cells were incubated in RPMI medium without red phenol (Gibco) plus 50 mM HEPES, 3 mM NaSCN, 5% FBS for 1 hr at 37˚C. Then, cells were exposed to HOSCN that produced in culture system containing 16 mU/ml GOX and 10 μg/ml LPO for 7 hr. Cells were collected for RNA isolation to quantify the mRNA expression of cytokine genes at 7 hr post exposure. The stimulated cells were incubated in RPMI medium containing 10% FBS until 24 hr at 37˚C, the cell culture supernatants were collected to measure the cytokine concentration.

*Isolation of RNA and quantification of the gene expressions*

Total RNA were isolated from cells by Isogen/chloroform extraction and isopropanol precipitation. The concentration of RNA was determined using Nanodrop. cDNA was synthesized with ReverTra Ace® qPCR RT Master Mix with gDNA remover (Toyobo). A 8 μl mixture containing 500 ng total RNA and 2 μl gDNA remover were incubated at 37˚C for 10 min. Then, 2 μl 5x RT Master Mix II was added in the reaction and incubated at 37˚C for 20 min, 50˚C for 10 min, 98˚C for 5 min. Gene expression was validated by Realtime-PCR (qPCR) using 10 μl 2X Power SYBR® Green PCR Master Mix (Applied Biosystems), 5 μl cDNA (5-fold dilution) and 10 pmol

specific primers of IL-6 (interleukin-6), IL-8 (interleukin-8), TNF-α (tumor necrosis factor-α), IL-1β (interleukin-1β), M-CSF (macrophage-colony stimulating factor), GM-CSF (granulocyte macrophage-colony stimulating factor) and G-CSF (granulocyte-colony stimulating factor) cytokine genes. The cycle conditions of qPCR were 95˚C for 20 s, 40 cycles of (95˚C for 3 s, 60˚C for 30 s), 95˚C for 15 s, 60˚C for 60 s.

*Measurement of the cytokine concentration*

Concentrations of Interleukin-6 and Interleukin-8 in cell culture fluids were determined using Human Interleukin-6 and Interleukin-8 immunoassay ELISA kit (Quantikine, R&D systems) following the manufacturer's instructions.

*Statistical analysis*

Data as presented as mean±standard deviation. Statistical analysis of results was performed by Student's t-test. Differences with $p$ values <0.05 were considered significant.

## Results

H292 cells were exposed to HOSCN for 7 hours to analyze the effect of HOSCN on the pro-inflammatory cytokine gene expressions. The mRNA expression levels of IL-6 and IL-8 were remarkably increased in H292 cells with HOSCN exposure in comparison to that in H292 cells without HOSCN exposure ($p$=0.002 and 0.0015, respectively) (Fig. 1a). And expression levels of TNF-α and IL-1β were slightly enhanced by HOSCN ($p$=0.047 and 0.028, respectively) (Fig. 1a). Therefore, we measured the amounts of IL-6 and IL-8 cytokines in the culture fluids. Concentration of IL-6 and IL-8 highly increased in H292 cells exposed to HOSCN than that in cells without HOSCN exposure for 7 hr ($p$=0.016 and 0.018, respectively) and 24 hr stimulation ($p$=0.01 and 0.004, respectively) (Fig. 1b). It was suitable to the mRNA level of IL-6 and IL-8 genes. These results confirmed that HOSCN induced the pro-inflammatory cytokine expression.

In addition, M-CSF was significantly increased (about 75 folds) in H292 cells exposed to HOSCN than that in cells without HOSCN exposure ($p$=0.048) (Fig. 1a). But, there was no difference of GM-CSF expression between cells with and without HOSCN exposure ($p$=0.2) (Fig. 1a). The expression of G-CSF was not detected.

## Discussion

It is thought that HOSCN is a major oxidant generated by MPO in the airway and its excessive or misplaced generation may contribute to lung diseases[10,11]. In this study, we found that the exposure of epithelial cells to HOSCN increases the mRNA level of IL-6, IL-8, TNF-α and IL-1β genes, which are driven by NF-κB, in concordance with previous data that it activates NF-κB[10]. These cytokines may enhance the recruitment and activation of neutrophils, resulting in amplifying the inflammation at early stages of influenza virus infection (Fig. 2).

At inflammatory sites during IFV infection, recruited monocytes differentiate to macrophages. Recent studies show that macrophages are divided into M1 and M2 phenotypes, characterized by pro-inflammatory and anti-inflammatory functions, respectively[12]. The polarization of M1/M2 macrophage differentiation depends on the cytokines in the environment where monocytes and macrophages reside. We observed the strong induction of M-CSF gene expression after exposure of airway epithelial cells (H292) to HOSCN. M-CSF is known to skew monocytes toward M2 macrophages via the activation of interferon regulatory factor 4, which is an important transcription factor for M2-phenotype related gene expressions[13,14]. Therefore, we speculate that HOSCN may impact on the balance of M1/M2 development of macrophages, skewing it toward M2 macrophages (Fig. 2). If our hypothesis is correct, the anti-inflammatory M2 macrophages increased by HOSCN are thought to dampen inflammation during IFV infection. Previous studies showed that it took around 6 days for the differentiation from monocytes to M2 macrophages[15]. Therefore, HOSCN may have a role for leading to converge inflammation at late stages of influenza virus infection.

In summary, under the oxidative stress with HOSCN, epithelial cells produced pro-inflammatory cytokines and simultaneously expressed M-CSF cytokine that may skew differentiates macrophage toward M2 phenotype to attenuate inflammation. That may be a defence mechanism of epithelial cells to HOSCN induced-inflammation.

## Acknowledgements

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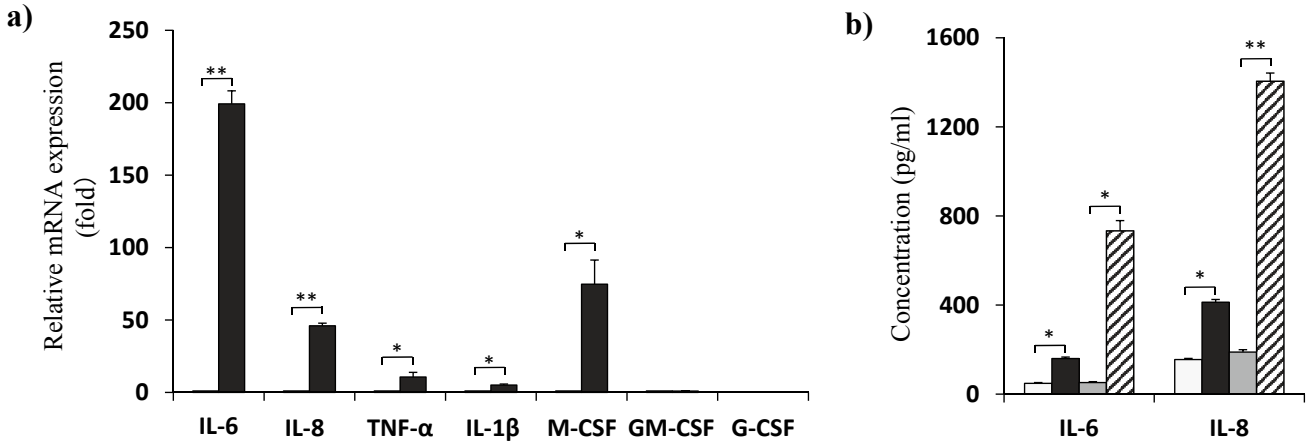



**Fig. 1. Induction of cytokines by HOSCN**

**a)** Relative mRNA level of cytokine genes of H292 cells (white bars), and H292 cells that exposed to HOSCN (black bars) after 7 hr stimulation.

**b)** Production of IL-6 and IL-8 cytokines of H292 cells at 7 hr (white bars), 24 hr (grey bars); and H292 cells that exposed to HOSCN at 7 hr (black bars), 24 hr (stripe bars) post stimulation. Data as presented as MEAN ± SD of the results of three independent experiments, *$p$< 0.05, **$p$< 0.01 (Student's t-test).

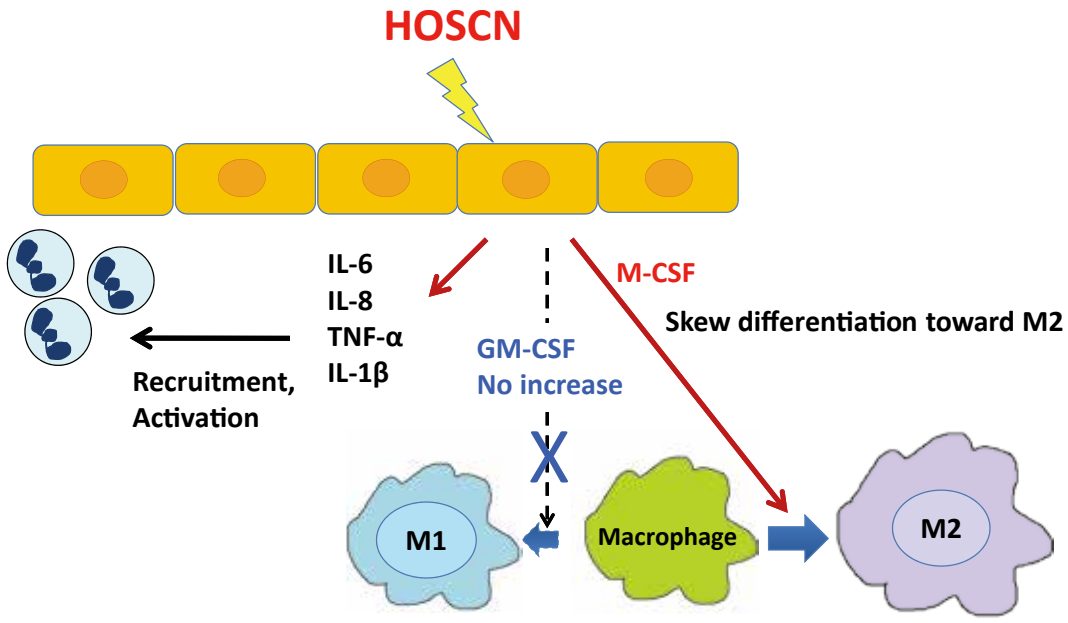



**Fig. 2. HOSCN may associate with the differentiation of macrophage and the inflammation of lung epithelial cells**
An excess generation of HOSCN induced the production of pro-inflammatory cytokines in the epithelial cells. These cytokines may recruit and activate neutrophils result in damage of cells. An excess generation of HOSCN also induced the production of M-CSF which may skew differentiates macrophage toward M2 phenotype to attenuate inflammation and epithelial damage.

Program from Japan Agency for Medical Research and Development, AMED (K. S.).

**Reference**

1) Camp JV and Jonsson CB. A Role for Neutrophils in Viral Respiratory Disease. Front Immunol. 2017; 8: 550.
2) Nicol MQ and Dutia BM. The role of macrophages in influenza A virus infection. Future Virol 2014; 9(9): 847-62.
3) Shi C and Pamer EG. Monocyte recruitment during infection and inflammation. Nat Rev Immunol 2014; 11(11): 762-74.
4) Sugamata R, Dobashi H, Nagao T, Yamamoto K, Nakajima N, Sato Y, Aratani Y, Oshima M, Sata T, Kobayashi K, Kawachi S, Nakayama T, and Suzuki K. Contribution of neutrophil-derived myeloperoxidase in the early phase of fulminant acute respiratory distress syndrome induced by influenza virus infection. Microbiol Immunol 2012; 56(3):171-82.
5) Barrett TJ and Hawkins CL. Hypothiocyanous Acid: Benign or Deadly? Chem. Res. Toxicol. 2012; 25: 263-73.
6) Fischer H. Mechanisms and Function of DUOX in Epithelia of the Lung. Antioxid Redox Signal 2009; 11(10): 2453-65.
7) Cegolon L, Salata C, Piccoli E, Juarez V, Palu G, Mastrangelo G, and Calistri A. In vitro antiviral activity of hypothiocyanite against A/H1N1/2009 pandemic influenza virus. Int J Hyg Envir Heal 2014; 217: 17-22.
8) Gingerich A, Pang L, Hanson J, Dlugolenski D, Streich R, Lafontaine ER, Nagy T, Tripp RA, and Rada B. Hypothiocyanite produced by human and rat respiratory epithelial cells inactivates extracellular H1N2 influenza A virus. J Inflamm Res 2016; 65: 71-80.
9) Arnhold J, Monzani E, Furtmuller PG, Zederbauer M, Casella L and Obinger C. Kinetics and thermodynamics of halide and nitrite oxidation by mammalian heme peroxidases. Eur J Inorg Chem 2006; 2006 (19): 3801-11.
10) Suzuki S, Ogawa M, Ohta S, Nunomura S, Nanri Y, Shiraishi H, Mitamura Y, Yoshihara T, Lee JJ and Izuhara K. Induction of Airway Allergic Inflammation by Hypothiocyanite via Epithelial Cells. J Biol Chem 2016; 291(53): 27219-27.
11) Lane AE, Tan JTM, Hawkins CL, Heather AK, and Davies MJ. The myeloperoxidase-derived oxidant HOSCN inhibits protein tyrosine phosphatases and modulates cell signaling via the mitogen-activated protein kinase (MAPK) pathway in macrophages. Biochem J 2010; 430: 161-69.
12) Martinez FO, Helming L and Gordon S. Alternative activation of macrophages: an immunologic functional perspective. Annu Rev Immunol 2009; 27: 451-83.
13) Lawrence T and Natoli G. Transcriptional regulation of macrophage polarization: enabling diversity with identity. Nat Rev Immunol 2011; 11(11), 750-61.
14) Eguchi J, Kong X, Tenta M, Wang X, Kang S and Rosen ED. Interferon regulatory factor 4 regulates obesity-induced inflammation through regulation of adipose tissue macrophage polarization. Diabetes 2013; 62(10): 3394-403.
15) Mia S, Warnecke A, Zhang XM, Malmstrom V and Harris RA. An optimized Protocol for Human M2 Macrophages using M-CSF and IL-4/IL-10/TGF-b Yields a Dominant Immuno suppressive Phenotype. Scand J Immunol 2014; 79(5), 305-14.

# サイエンスアゴラ SCIENCE AGORA 2017

November 24-26, 2017

## アジア×日本：高校生×留学生×研究者トークセッション
## “科学の力でアジアから未来を切り拓け！”

日時：平成29年11月25日(土) 10:30～13:00
場所：テレコムセンター８階 会議室B（東京都江東区青海2-5-10）
主催：JST 国際部、JST 理数学習支援部、AMED 国際事業部

ADC研究所に所属しているベトナムからの国費留学生Tran Huu Datさんが「サイエンスアゴラ2017」でJSTとAMEDの合同企画として開催された「アジア×日本：高校生×留学生×研究者トークセッション」に参加しました。

JSTの主催で2006年から行われているイベント「サイエンスアゴラ」。あらゆる人に開かれた、科学と社会をつなぐ広場を目指して毎年開催されています。今年のテーマは「越境する」。分野、年代、性別、職業、国籍の境界を越えて多様な人たちが集い、考え、明日への一歩につながることを目指す。その中で、アジアの国々、特にASEAN諸国と共同研究を推進する研究者、アジア諸国からの留学生、発展途上国/新興国との国際協力に関心のある高校生が、自身の経験を語り、それぞれが考える「国際人材」象について議論することで、勃興するアジアとの国際連携象と科学技術を通じた国際協力の重要性について理解を深めることを目的とし、トークセッションが開催されました。e-ASIAプロジェクトを主催したADC研 鈴木和男所長の国費留学生Tran Huu Datさんが参加することになりました。ベトナムでは小児科医であるDatさん。これまでの道のり、留学の動機や現在の研究内容、将来の目標について発表を行い、高校生や異分野の研究者と活発な議論を繰り広げました。

**スケジュール**

**＜第一部＞ トークセッション**

10:30 開会　10:40～11:40 プレゼンテーション　11:40～12:10 パネルディスカッション

**登壇者一覧**

| | | |
|---|---|---|
| 留学生 | Tran Huu Dat<br>帝京大学<br>（サポート）菅又龍一、相原初代（帝京大学） | Elaine Mission<br>熊本大学<br>（サポート）山福紗野、上野和華子（熊本大学） |
| 研究者 | 井上 公<br>防災科学技術研究所<br>災害リスク研究ユニット | Meng Ling Moi<br>長崎大学 |
| 高校生 | 斜面崩壊の研究<br>金村拓磨<br>(市川高校・千葉) | 蚊の研究<br>田上大喜<br>（京教大付高・京都） |

**＜第二部＞ ポスター発表**

Report

# SUMMARY OF SCIENCE AGORA MEETING IN 2017

大学院 医学研究科 2 年　Tran Huu Dat

**1. My current research:**

I have been working as a pediatric intensivist at Vietnam National Children’s Hospital. Since 2015, I have been studying at Teikyo University Graduate School of Medicine as a Ph.D. student supported by MEXT scholarship of Japanese Government. Our current research project is now focusing on Influenza A/H1N1 virus infection and development of new anti-influenza agents.

**2. Presentation at the Science Agora Meeting:**

The Science Agora is organized by AMED (Japan Agency for Medical Research and Development) and JST. Science Agora meeting was held on Nov. 25th, 2017 at Telecom Center Tokyo. There were 6 speakers and 8 poster presenters who came from Asian countries such as Japan, Vietnam, Philippines, Myanmar, and Indonesia. Most of us were the researcher, 2 others were super science high school students. The content of presentations regarding the prevention of earthquake, mosquito-related diseases, influenza virus infection, etc.

**3. Benefits from the Science Agora Meeting:**

The Science Agora Meeting gave me a great opportunity to share my current research project as well as my own impressions on Japan. It also helps me to communicate with international researchers around the Asia area. Moreover, the chance made me more motivated to study English and Japanese as well. We hope to have many collaborative projects between Japan and Vietnam in the future.

# ADC LABORATORIES-2

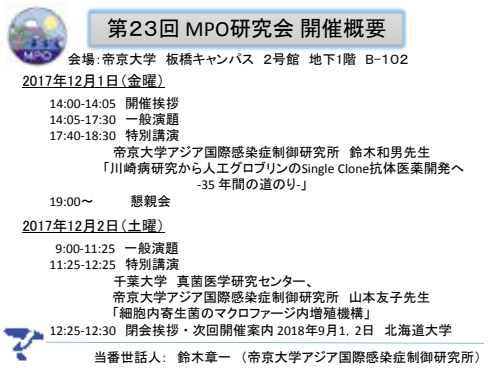
## 第23回　MPO研究会

December 1 - 2, 2017

2017年12月 1-2 日に第23回MPO研究会（世話人：ADC研 鈴木章一）が帝京大学 板橋キャンパスで開催されました。36人の参加者と21演題の発表、2 つの特別講演があり、活発な討議がなされ、充実した 2 日間となりました。

また、次回のMPO研究会は、2018年 9 月 1-2 日、北海道大学 石津明洋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 23rd MPO meeting in Teikyo University from Dec. 1st to 2nd. There were 36 attendees and 21 presentations and we had lively discussions. Next MPO meeting will be held in Hokkaido on Sep. 1st-2nd, 2018 with the chair of Prof. Akihiro Ishizu (Hokkaido Univ).




Attendee of the 23rd MPO Meeting

**【Special Lectures】**

- Studies for 35 years on Kawasaki disease and development of antibody drug for vasculitis using single clone of IgG ScFv
  Kazuo Suzuki
- Survival Mechanism of Intracellular Parasitic Bacteria in Macrophages
  Tomoko Yamamoto

**【ADC Staff's Research Presentations】**

- Successful treatment of pneumonia-induced severe ARDS complicated with DIC in two infants using recombinant human thrombomodulin
  Kawachi S, *et al.*
- The regulatory role of Duox1-derived hydrogen peroxide ($H_2O_2$) in primary B cells
  Sugamata R, *et al.*
- Untoward effects of hypothiocyanite on airway epithelial cells
  Suzuki S, Nguyen TT, *et al.*
- The inhibitory effect of Azithromycin on proliferative activities of 2009 pandemic influenza A/H1N1 virus
  Tran HD, *et al.*
- Moesin expression level of MPO-ANCA associated vasculitis mouse
  Ito F, *et al.*

# INTERNATIONAL MEETING AND SYMPOSIUM

**開催したイベント（2017.7.1～2017.12.31）**

| 日程 | イベント名 | 演者など | |
|---|---|---|---|
| 2017年 12月1日（金）～12月2日（土） | 第23回 MPO研究会 | ADC | 帝京大学 板橋キャンパス |
| 2017年 10月18日（水） | 第1回 バイオセーフティ講習会 | ADC, 感染研 棚林清先生 | 大学棟 セミナー室 |
| 2017年 10月16日（月）～10月24日（火） | SAKURA Science Plan 2017 | Vietnamから6名の研修生 | |
| 2017年 9月27日（水） | 危機管理と防災 | 防災訓練 | 大学棟 |
| 2017年 9月1日（金） | TAVP 報告会 | 医学部5年生 9名 | 本部棟 2F |
| 2017年 8月21日（月）～8月27日（日） | TASP Training for 10 Students（5-year） | NHP and Bacmai Hospital | Hanoi, Vietnam |

**今後のイベント情報（2018.1.1～2018.6.30）**

| 日程 | イベント名 | 演者など | |
|---|---|---|---|
| 2018年 6月22日（金） 15:00 ～ | ADC 5th Anniversary Symposium | ADC, International Collaborators | 本部棟 会議室 |
| 2018年 5月 | 危機管理と防災 | 板橋キャンパス危機管理委員会, ADC | 臨床大講堂 |
| 2018年 2月 | 危機管理 | 金谷泰宏 | 大学棟 |
| 2018年 1月末 | バイオセーフティ講習会 | ADC, 感染研 棚林清先生 | 大学棟 セミナー室 |
| 2018年 1月15日（月） | 平成30年新春講演会 | 日本私立大学協会 | 鈴木和男 |

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