Global Station for Zoonosis Control

Global Institution for Collaborative Research and Education(GI-CoRE)

Hokkaido University

Final Evaluation Report

北海道大学　国際連携研究教育局

人獣共通感染症グローバルステーション

外部評価報告書

July 2020

2020年7月

Final Evaluation Report
(brief version in Japanese)

外部評価報告書（日本語・概要版）

もくじ（日本語版）

はじめに

国際連携研究教育局（GI-CoRE）は、北海道大学の強みや特色を活かした国際連携研究教育の推進と、部局が独自に進める国際連携研究教育の支援を目的とし、世界トップレベルの教員を国内外及び学内から結集した総長直轄の教員組織です。

GI-CoRE 内には研究領域ごとの活動拠点である「グローバルステーション（GS）」を置き、各 GS において、原則 5 年間の設置期間内に重点的に研究教育活動を進めています。これまでに、延べ７つの GS（下記※を参照）を設置し、研究活動を推進するとともに、最先端の研究成果を大学院教育などに還元してきました。

GI-CoRE では、GS の設置期間満了を迎える年度に、各 GS でのこれまでの活動を振り返るとともに、今後、より強固かつ持続可能な研究教育体制を確立していくため、国内外の有識者により構成される外部評価委員会において、評価を実施することとしています。

この外部評価報告書は、2018 年 7 月に実施した人獣共通感染症 GS の自己点検成果報告書及び外部評価結果を一冊に収録した、いわばGS の研究教育活動の集大成です。

なお、設置期間を満了した人獣共通感染症 GS は、関連部局等に定着化し、2020 年 4 月以降も「GI-CoRE 協力拠点」として、GI-CoRE と連携しながら研究教育活動を継続しています。

本学では、外部評価結果を踏まえ、より充実した研究教育活動を実践していくことにより、世界の課題解決に貢献していきたいと考えております。

北海道大学 国際連携研究教育局
局長代行（総長代行）
笠　原　正　典

※これまでに設置したグローバルステーション（GS）

GS 名	設置期間（年度）	主な学内連携部局等
量子医理工学	2014～2019	医学研究院、大学病院ほか
人獣共通感染症	2014～2019	人獣共通感染症リサーチセンター、獣医学研究院
食水土資源	2015～2019	農学研究院ほか
ソフトマター	2016～2020	先端生命科学研究院ほか
ビッグデータ・サイバーセキュリティ	2016～2020	情報科学研究院ほか
北極域研究	2016～2020	北極域研究センターほか
バイオサーフィス創薬	2019～2023	薬学研究院ほか

国際連携研究教育局(GI-CoRE)
人獣共通感染症グローバルステーション
外部評価委員

*国際医療福祉大学塩谷病院　倉田　毅　教授

アメリカ合衆国　セント・ジュード小児研究病院　　ロバート・ウェブスター教授

オーストラリア　モナシュ大学　ベン・アドラー　名誉教授

*委員長

国際連携研究教育局(GI-CoRE)
人獣共通感染症グローバルステーション
外部評価委員会実地調査要領

１．調査日程

平成 30（2018）年 7 月 19 日（木）～20 日（金）

２．詳細スケジュール

7 月 19 日（木）	
13:30～14:30	趣旨説明・笠原 GI-CoRE 副局長（理事・副学長）との懇談
14:50～15:20	施設見学（人獣共通感染症リサーチセンター）

7 月 20 日（金）	
14:00～15:30	関係教員のヒアリング
15:30～16:30	評価委員の打合せ
16:30～17:00	評価委員による講評

国際連携研究教育局(GI-CoRE)
人獣共通感染症グローバルステーション
外部評価調書の概要（参考和訳）

総合評価：S

（評価コメント）

新興感染症の多くは人獣共通感染症である。北海道大学 GI-CoRE 人獣共通感染症グローバルステーション（GSZ）は、国際社会の課題である人獣共通感染症の克服に向け、極めて優れた対策を推進している世界に類のない組織であり、内外に高く評価されている。 また、GSZ は“One Health-One World”の概念の下、獣医学、医学、生態学分野を融合した新学術領域を創成し、人獣共通感染症の早期発見とその抑制に向けた、予防、診断、治療法の開発および、宿主間伝播機構の解明を目的とする国際連携研究プログラムを遂行している。さらに、人獣共通感染症対策に資する人材育成を目指して、国際感染症学院を創設し、また博士課程大学院生を対象とした教育プログラムを推進している。

GSZ は世界トップレベルの研究者を、国内外から招聘することにより、人獣共通感染症の研究、教育、国際連携ネットワークの構築を達成している。ジカ熱等の新興感染症を対象とした研究も、国内外の研究者との共同研究により推進している。人獣共通感染症の発生が多い発展途上国との共同研究を重視し、アジア、アフリカ、南アメリカにおける研究を進めており、GSZ を中心とする国際共同研究は世界規模となっている。GSZ の研究が世界一流であることは、高水準の学術雑誌への論文投稿、および社会への貢献から判断される。国際感染症学院でも、発展途上国出身の学生の教育を重視しており、多くの博士課程修了者を国際社会に輩出していることも高く評価される。

GSZ の推進者である喜田統括が、WHO（世界保健機関）や OIE（国際獣疫事務局）の委員を務めており、GSZ が国際社会において重要な役割を担っていること、また発展途上国における研究発展と人材育成を目的とする教育訓練の場を提供していることが評価される。

将来展望として、現在長崎大学に BSL-4 施設が建設されているが、人獣共通感染症リサーチセンタに BSL-4 施設が必須と思われる。また、感染症発生現場で新興感染症の発生に対応できる人材を育成することを念頭に置いているので、獣医師と医師を共に募集することが必要である。

以上、総合評価において、GSZ は日本および国際社会における貢献度が高いことから「S」と判定した。

評価者は全員一致で GSZ の活動を高く評価しており、今後も GSZ が継続して貢献することを強く求める。

Final Evaluation Report
(original version in English)

外部評価報告書（英語・オリジナル版）

Contents

Foreword

Hokkaido University established the Global Institution for Collaborative Research and Education (GI-CoRE) as a faculty organization under the direct control of the President that brings together world-class researchers from around the world and within the University. It aims to promote international collaborative research and education that leverages the University's strengths and distinctive features as well as to provide support for international collaborative research and education promoted by faculties and centers, respectively.

Under the GI-CoRE system, a research and education hub known as a Global Station (GS) is implemented for each research field. GSs have a finite implementation period of five (5) years in principle to conduct intensive research and education activities. Thus far, seven (7) GSs in total (see * below) have been implemented to further develop research activities and contribute the resulting cutting-edge research outcomes to graduate school education.

In the final year of the GI-CoRE project period, a Final Evaluation is conducted by the External Evaluation Committee composed of global experts outside Hokkaido University for each GS to not only review GS activities from past years but also build a stronger and more sustainable research and education system in the future.

This Final Evaluation Report contains the Research Progress Report of GS for Zoonosis Control (GSZ) conducted in July 2018 and the evaluation results. This report is a compilation of the research and education activities of GSZ.

After the implementation period, GS projects are transitioned into affiliated faculties and centers, then certified as "GI-CoRE Cooperating Hubs" to continue research and education activities in cooperation with GI-CoRE after April 2020.

Hokkaido University remains committed to continuing its efforts to contribute to resolving global issues by conducting advanced research and education activities based on evaluation results.

Professor Masanori Kasahara, M.D., Ph. D.
Interim Director
Global Institution for Collaborative Research and Education (GI-CoRE)
Hokkaido University
(Interim President, Hokkaido University)

*The Global Stations (GSs) implemented thus far.

Name of the GS	Implementation Period (FY)	Main Internal Affiliation
Quantum Medical Science and Engineering	2014–2019	Faculty of Medicine, University Hospital, and others
Zoonosis Control	2014–2019	Research Center for Zoonosis Control and Faculty of Veterinary Medicine
Food, Land and Water Resources	2015–2019	Research Faculty of Agriculture and others
Soft Matter	2016–2020	Faculty of Advanced Life Science and others
Big Data and Cybersecurity	2016–2020	Faculty of Information Science and Technology and others
Arctic Research	2016–2020	Arctic Research Center and others
Biosurfaces and Drug Discovery	2019–2023	Faculty of Pharmaceutical Sciences and others

Global Station for Zoonosis Control
Global Institution for Collaborative Research and Education(GI-CoRE)
External Evaluation Committee

*Professor Takeshi Kurata,
International University of Health and Welfare, Shioya Hospital (Japan)

Professor Robert G. Webster,
St. Jude Children's Research Hospital (United States of America)

Emeritus Professor Ben Adler,
Monash University (Australia)

*Chair

別記様式

委 員 長 就 任 承 諾 書

平成３０年３月22日

国立大学法人北海道大学国際連携研究教育局長　　名　和　豊　春　殿

氏名 倉田 毅 印

私は，北海道大学国際連携研究教育局（GI-CoRE）人獣共通感染症グローバルステーションに係る外部評価委員会に委員長として就任することを承諾します。

以上

学校法人国際医療福祉大学　塩谷病院検査部
倉田　毅　教授

Attachment

Letter of Acceptance

23/03/2018

To Director Toyoharu Nawa of the Global Institution for Collaborative Research and Education (GI-CoRE), the National University Corporation Hokkaido University.

I hereby accept my appointment to serve as a member of the External Evaluation Committee for the Global Station for Zoonosis Control at the Global Institution for Collaborative Research and Education (GI-CoRE), Hokkaido University.

Signature 

Professor Robert G. Webster

Professor Robert G. Webster
Emeritus Faculty / Rose Marie Thomas Chair
Depts. of Virology and Molecular Biology / Infectious Diseases, Div. of Virology
at St. Jude Children's Research Hospital

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Signature 

Professor Ben Adler

Professor Ben Adler
Emeritus Professor of Microbiology
Department of Microbiology
Monash University

Global Station for Zoonosis Control
Global Institution for Collaborative Research and Education(GI-CoRE)
Schedule of the External Evaluation Committee

1. Date of Implementation
   Thursday, July 19 - Friday July 20, 2018

2. On-site Investigation Schedule

Thursday, July 19	
1:30pm - 2:30pm	Greeting and brief overview from Vice Director. Masanori Kasahara, GI-CoRE
	Break
2:50pm - 3:30pm	Facility tour

Friday, July 20	
2:00pm - 3:30pm	Interview Session with GI-CoRE Faculty members
3:30pm - 4:30pm	Discussion among committee members
4:30pm - 5:00pm	Review from the committee to the faculty members

Results of the Evaluation Committee

Evaluation Committee
Global Station for Zoonosis Control
Global Institution for Collaborative Research and Education (GI-CoRE)
Hokkaido University

October 2018

Summary Report

The Global Institution for Collaborative Research and Education (GI-CoRE) Global Station for Zoonoses Control that has been established at Hokkaido University is fulfilling an unmet global need, and is absolutely outstanding. The program is a credit to the faculty concerned, to the University, and is unique in the world. The recognition that most of emerging infectious diseases of humans and domesticated animals come from environmental and zoonotic threats is being addressed by this program. It brings together the fields of ecology, veterinary and human public health under the "One Health-One World" concept. The GI-CoRE program at Hokkaido University has established international cooperative research programs elucidating the fundamental mechanism of interhost transmission with the development of vaccines, diagnostics and therapeutics aimed at rapidly detecting and controlling diseases that could be catastrophic. The program also recognizes the need for trained personnel and has implemented a world class graduate program.

The program is completely meeting the goals of research, education and the establishment of a framework for international cooperative research and education. The strong points of the program are the achievements in attracting world class researchers, both within Japan and internationally. Cooperation between the researchers has enabled the program to address newly emerging infectious diseases, including zika and MERS-CoV. Expansion of the program to Asia, Africa and South America with a strong focus on underdeveloped countries shows the global reach of the program. The high level of productivity and quality of publications in the leading scientific journals attests to the program's high standard of research and demonstrates that it serves society by developing strategies to rapidly control emerging infectious diseases. The graduate school deserves special mention, for it has already graduated 19 PhDs, with a strong focus on students from international and developing countries.

Participation of the director of the GI-CoRE program in the World Health Organization (WHO), and the World Organization for Animal Health (OIE) adds to the strength of the GI-CoRE program. The GI-CoRE program provides unique strengths and training at human-animal-environmental interface with special emphasis on international research and training in undeveloped countries.

Future expansion of the program would benefit from having its own BSL4 facility; while the current needs of the program will be met by the BSL4 laboratory being constructed at Nagasaki, in the longer term it would be beneficial to have such a facility onsite. The recruitment of additional MDs would also be beneficial, especially if future goals are to provide trained personnel to respond to emerging zoonotic disease outbreaks in the field.

The overall evaluation is that the GI-CoRE program is outstanding (S), it serves both Japan and the world. The reviewers' unreservedly and enthusiastically recommend continuation of this important program.

Professor Takeshi Kurata
International University for Health and Welfare

Professor Robert G. Webster
St. Jude Children's Research Hospital

Professor Ben Adler
Monash University

Global Station for Zoonosis Control
Global Institution for Collaborative Research and Education (GI-CoRE)
Final Evaluation

External Evaluation Committee Member Name: Takeshi Kurata .

Choose one of the five Evaluation Ratings options below as explained by the Evaluation Explanation for each Evaluation Item on the form.

Evaluation Ratings	Evaluation Explanation
S	Achieved outcomes surpassed the original plan (Outstanding)
A	Good progress has been maintained and expected outcomes have been achieved (Excellent)
B	Most expected outcomes have been achieved with some slight delays (Good)
C	Although certain outcomes were achieved, overall results were insufficient (Satisfactory)
D	No expected outcomes were achieved (Unsatisfactory)

I. Research

1. Has construction of an international research and education center capable of attracting outstanding researchers from around the world (including from HU) been achieved?

Evaluation Results and Reasons

(Your Evaluation Results)

Ⓢ/ A / B / C / D (circle one)

(Reasons)

The Research Center for Zoonosis Control of Hokkaido University has excellent long-term collaboration system for zoonosis control activity with 32, 6 developed and 26 developing countries. Graduated PhD students are 19, including 7 Japanese during past 4 years (2014-2018). In addition, PhD course students are 37 including 16 Japanese and 21 foreign ones. They have published excellent scientific papers on zoonosis control.

Scientific activity of the staffs at Hokkaido University Research Center for Zoonosis Control is rapidly expanding from Asian countries to Russia, Europe, African and South American countries. The research activity contributes much for One Health of local to worldwide. I was indeed impressed by their presentations and active discussion made at the 6th Meeting of the Consortium for the Control of Zoonoses.

In addition, the publication record of the Research Center for Zoonosis Control is superb both in the point of view of numbers and quality.

As a member of the present External Evaluation Committee, I learned that outstanding international

collaborating programs are successfully ongoing in this GI-CoRE Program.

(Outstanding points)

It is surprising that first class researchers from three well known universities in the world gathered in the Research Center for Zoonosis Control at Hokkaido University and are proceeding important programs in collaboration with the members of the Center. Researchers from the University of Melbourne are carried out with the members of the Unit for the Development of Vaccine and Biologicals. Researchers from the University College Dublin are collaborating with the members of the Unit for Exploration of Pathogens, and the researchers from King Abdullah University of Science and Technology are concentrating into genome-function analyses of pathogens with the members of the Unit of Bioinformatics.

To integrate research activities towards the goal of controlling zoonoses, the Consortium for the Control of Zoonoses, where all three units members meet together and exchange information, has been established and is working successfully with effective and functional manner.

(Suggestions for improvement)

No specific points for improvement.

2. Is world-leading cutting-edge international cooperative research underway?

Evaluation Results and Reasons

(Your Evaluation Results)

Ⓢ/ A / B / C / D (circle one)

(Reasons)

Outstanding researchers, Profs H Kida, H Sawa and C Sugimoto at Hokkaido University Research Center for Zoonosis Control, Profs DC Jackson, LE Brown and E Hartland at the University of Melbourne, Prof W Hall at the University College of Dublin and Prof A Pain at the King Abdullah University of Science and Technology gathered together at Hokkaido University and formed the Consortium for the Control of Zoonosis. I believe that this consortium is the outstanding and strongest team for the control of zoonoses in the world.

Excellent publication record also indicate that their research activity is outstanding.

Specific points

(Outstanding points)

As stated above.

(Suggestions for improvement)

No specific points for improvement.

3. Are research outcomes from GI-CoRE being actively utilized to solve social issues?

Evaluation Results and Reasons

(Your Evaluation Results)

Ⓢ/ A / B / C / D (circle one)

(Reasons)

Identification of natural host animals of and the routes of transmission of the pathogens is the base for the control of zoonoses. The members of this GI-CoRE program have been developed several cheap and conventional diagnosis kits and methods for the detection of novel viruses and bacteria by genetic and immunologic analyses. By using these technology, many novel viruses and antibiotic resistant mycobacteria have been found.

Specific points

(Outstanding points)

Since the present Consortium is composed of first class researchers from multidisciplinary fields such as virology, bacteriology, immunology, entomology, molecular biology, bioinformatics, ecology, pharmacology and medical and veterinary clinics and they are cooperating effectively, the programs for the control of zoonoses are fulfilled effectively, and thus successful.

(Suggestions for improvement)

Nothing particular.

II. Education

Is the educational system and curriculum designed to help develop researchers who possess specialized knowledge and are capable of working internationally?

Evaluation Results and Reasons

(Your Evaluation Results)

Ⓢ/ A / B / C / D (circle one)

(Reasons)

Plans to create an educational structure and courses have been undertaken with the objective of fostering personnel who will cope with emerging and re-emerging infectious diseases. The present GI-CoRE program is looking ahead to take steps to foster global human resources. Establishment of the Graduate School of Infectious Diseases accelerates to strengthen and expand the educational scheme for postgraduates and develop specialists internationally contributing to global health solutions. The Graduate School provides the opportunity to obtain practical communication skills in English and will access the international research community consisting of collaborating scientists from more than 30 countries.

Specific points

(Outstanding points)

GI-CORE members are involved in educational program at the Graduate School of Infectious Disease. They are leading world-class international experts in the research field of infectious diseases. It is assured that they educate students to become the next generation of leaders who have broad vision, innovative ideas and the necessary skills to solve the problem of infectious diseases.

(Suggestions for improvement)

Current number of researchers at GI-CORE are rich in veterinary doctors, of which the reason is the Center has been based the part of School of Veterinary Medicine at Hokkaido University. It is recommended to invite excellent medical researchers who can collaborate with other field scientists on zoonotic diseases in the Research Center for Zoonosis Control.

III. Establishment of Framework

Are the necessary systems and frameworks being established in order to conduct international cooperative research and education?

Evaluation Results and Reasons

(Your Evaluation Results)

Ⓢ / A / B / C / D (circle one)

(Reasons)

The system and framework have been established at a high level by strong collaborative relationships with three research units; the University of Melbourne, University College Dublin and King Abdullah University of Science and Technology under the Global Station for Zoonosis Control. The Consortium for the Control of Zoonoses consisting of four research units is working successfully on the basis of unique and outstanding concept of GI-CoRE. The GI-CoRE management system supports the research and educational activities of Global Station for Zoonosis Control financially and systematically.

Specific points

(Outstanding points)

The GI-CoRE has an attractive system to accept world-class leading international researchers. Implementation cross-appointment and an annual-salary system is well thought.

(Suggestions for Improvement)

Nothing particularly.

IV. Overall Evaluation

The risks of incidence of arising emerging and re-emerging infectious diseases are increasing. More than 30 viral diseases, 15 bacterial and parasitic infectious diseases have emerged in the last 20 years. More than a half of the new diseases are zoonotic. One Health authorities are required urgently to increase the budgets and official personnel to control these new emerging infectious diseases. In such circumstances, the establishment of the Global Station for Zoonosis Control at Hokkaido University is of great significance in the research fields of infectious diseases. The Global Station for Zoonosis Control is a unique organization that aims to conduct research and response to zoonosis outbreaks. The activities of research and practical counter-measures are at quite a high level of global standards. Also, the Global Station for Zoonosis Control is accepting researchers and materials from over the world. It is clear that these materials sometimes must contain high biosafety level pathogens. It is strongly recommended that in addition to biosafety level 3 containment facility, Biosafety Level 4 facility and well-trained experts are crucially needed at the Research Center for Zoonosis Control.

Forming a consortium to promote research and education on zoonosis control in collaboration with the research units, Hokkaido University, the University of Melbourne, University College of Dublin and King Abdullah

University of Science and Technology is quite nice and smart. The consortium is enhancing the collaboration of all research units for the control of zoonoses and developing measures for diagnosis, disease prevention and therapy for infectious diseases.

Finally, the present reviewer strongly recommend for the Research Center for Zoonosis Control to establish a BSL-4 facility as soon as possible, to ensure safer practice with any materials from abroad and to lead One Health Institutes in the world.

Overall, the activities of Global Station for Zoonosis Control is evaluated as outstanding without hesitation. We are looking forward to seeing the next stage of the GI-CoRE program of excellence on their collaborative and educational activities.

Global Station for Zoonosis Control
Global Institution for Collaborative Research and Education (GI-CoRE)
Final Evaluation

External Evaluation Committee Member Name: Robert G. Webster .

Choose one of the five Evaluation Ratings options below as explained by the Evaluation Explanation for each Evaluation Item on the form.

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I. Research

1. Has construction of an international research and education center capable of attracting outstanding researchers from around the world (including from HU) been achieved?

Evaluation Results and Reasons

(Your Evaluation Results)

Ⓢ/ A / B / C / D (circle one)

(Reasons)

From a research perspective it is clear that an outstanding collaboration of researchers from The University of Melbourne-Drs. Brown, Jackson, Hartland; from The University of Dublin-Drs. Hall, Carr and Gordon, and from the King Abdullah University of Science and Technology, Saudi Arabia- Dr. Pain, together with an impressive group of researchers from Hokkaido University led by Professors Kida has established an outstanding collaborative research and education programme (GI-CoRE) at Hokkaido University for zoonoses control. This collaboration enables the researchers within and outside the university to conduct research on a wide range of emerging and reemerging infectious disease agents that are a continuing threat to veterinary and human public health, both within Japan and globally.

(Reasons)

The coverage of environmental threats to humanity is extremely impressive, including not only the known

environmental threats, but also the search for novel agents in Zambia, threats to public health in Nepal, Myanmar, and Thailand as well as expansion of the program to Vietnam, Brazil and Cuba. The rapid inclusion of research on Zika and chickungunya and the development of methodology for diagnosis by sequencing illustrating the flexibility of the programme and inclusion of novel emerging threats.

The productivity from the international collaboration with 118 peer reviewed papers in international journals covering the complete field of zoonotic threats attests to both the quality and the productivity at an international level.

Specific points

(Outstanding points)

The application of next generation sequencing and portable sequencing utilizing low-cost real time portable sequencing provides the possibility of rapid detection of emerging infectious agents in the field. The use of genomic analysis to elucidate horizontal gene transfer in protozoan parasites, and elucidation of the genes in legionella that subvert host cell transcriptional responses attests to the wisdom of genomic analysis of emerging zoonotic agents.

An important challenge is to convince the global influenza community about the potential advantages of moving back to whole influenza virus vaccines which would be absolutely essential in the face of an extremely severe influenza pandemic, there would be a great need for antigen sparing to save lives potentially in under developed countries. These studies together with improved adjuvants and the ability to predict the severity of an influenza pandemic address an unmet global need.

(Suggestions for improvement)

Overall the Consortium for the Control of Zoonoses is very and no improvement are suggested. Reducing the costs of sequence analysis in the field is a minimal aim.

2. Is world-leading cutting-edge international cooperative research underway?

Evaluation Results and Reasons

(Your Evaluation Results)

S /Ⓐ/ B / C / D (circle one)

(Reasons)

The productivity from the consortium members, with a high number of publications (118), the high number of invited oral presentations (51), patent applications (4), awards received (6), and external grants (2) attests to the world class cutting edge cooperative research that is underway. The cooperation is attested to throughout the program with collaborations between each of the international groups with scientists at Hokkaido University.

(Outstanding points)

Particularly good points include the genomic driven approaches in the studies of zoonotic malaria, development of novel drugs for Ebola, and the multiple collaborations with the University of Zambia gives access

to a potential wealth of novel agents.

(Suggestions for improvement)

The high level of productivity and the extent of international collaboration as well as the world class cutting edge research ongoing at Hokkaido University indicates that there is little room for improvement. It is encouraging that the difficulties encountered in the expansion of the program to Cuba are being worked through, and that this site is being developed despite the difficulties, for Cuba represents and under evaluated global resource.

3. Are research outcomes from GI-CoRE being actively utilized to solve social issues?

Evaluation Results and Reasons

(Your Evaluation Results)

(S) / A / B / C / D (circle one)

(Reasons)

Each of the programs in the GI-CoRE address social issues of importance related to the emergence and control of zoonoses. For example the studies on the neuropathology of prion diseases has the potential to lead to a treatment of prion diseases and neurodegenerative disorders of both humans and lower animals, for these are unresolved issues. A case could be made for each and every one of the projects. An example to illustrate the contribution to society would be the development of an anthrax vaccine; a safe and effective anthrax vaccine for humans is not available. The studies on the dimerized PAD-1 vaccine based on computational design together with the immuno-stimulatory molecules of the Pam2Cys from the University of Melbourne with David Jackson has the potential for providing a safe and highly efficacious vaccine for both humans and animals. This illustrates the value of the international collaboration and the potential benefits they bring to society.

Specific points

(Outstanding points)

The capacity to be prepared when novel agents emerge, and to have the methodologies and trained personnel available for the control of zoonoses are invaluable programmes to protect society.

(Suggestions for improvement)

In the presentation of their programs it would be beneficial for the staff to emphasize the contributions each section of the program is making to global society.

II. Education

Is the educational system and curriculum designed to help develop researchers who possess specialized knowledge and are capable of working internationally?

Evaluation Results and Reasons

(Your Evaluation Results)

Ⓢ/ A / B / C / D (circle one)

(Reasons)

One of the really impressive components of the GI-CoRE is the graduate school that trains students from all over the world in the control of zoonoses. This is a prestige program that Hokkaido University can be justifiable proud of. It fulfills a need for trained personnel that is not met anywhere else in the world. The extent of international collaboration is extremely impressive with students from 32 countries with a special emphasis on developing countries.

Specific points

(Outstanding points)

Nineteen students have already graduated with PhDs-twelve from international countries, and seven from Japan, again emphasizing the focus on international collaboration. While eight of the graduates have obtained positions in Japanese universities the majority of students (eight) have obtained positions in foreign universities.

It is notable that the staff of the graduate school comes from international countries (five) with three being members of the GI-CoRE staff. There are currently thirty-seven PhD students studying for a PhD. In the time that the graduate school has been in existence this is a laudatory achievement.

(Suggestions for improvement)

The reviewers had to ask for the details of the graduate school. Since the Graduate School is a major strongpoint for the program it is suggested that these details are included in future program reports.

III. Establishment of Framework

Are the necessary systems and frameworks being established in order to conduct international cooperative research and education?

Evaluation Results and Reasons

(Your Evaluation Results)

S /Ⓐ/ B / C / D (circle one)

(Reasons and Specific Points)

The framework for establishment of the global collaborative research and education program for conducting international cooperative research and education has most certainly been established. The written reports, site visit of the facilities, and presentations by the scientists involved establish that the international collaborative program is already addressing the major zoonotic threats and is providing the infrastructure and training for future threats to both human and animal health. The framework covers key regions of the world where emerging and re-emerging

zoonoses appear, and has the flexibility and trained personnel to deal with the zoonotic emergencies. The coverage of current methodologies in genomic analysis in future diagnosis and control is impressive.

(Suggestions for improvement)

While the number of collaborating institutions throughout the world could be extended, this does not necessarily add to the strength of the program. The framework is in place to deal with the development and measures for diagnosis, prevention, and most importantly for the fundamental understanding of the pathogenesis of emerging zoonoses.

IV. Overall Evaluation

Up to 65% of the threats to human and animal health come from environmental and zoonotic threats. While the global organizations through the World Health Organization and Food and Agriculture Organization of the United Nations/ World Organization for Animal Health recognize the importance of "One Health-One World" there is still a paucity of organizations that are aimed specifically at the control of zoonoses and the training of personnel. The Global Institution for Collaborative Research and Education (GI-CoRE) established at Hokkaido University, Sapporo fills this global need, not only from the detection of such agents throughout the world, but understanding the methodologies for rapid detection, the understanding of the molecular basis of their pathogenesis, and the development of anti-microbial agents and vaccines for their control. The GI-CoRE at Hokkaido University fulfills a global need, and it looks to the future in the establishment of a graduate school for the training of students who will undertake the research needed for the development of control strategies.

The strength of the Gi-CoRE at Hokkaido University is based on the successful international collaboration of world class scientists that provide not only the collaboration in the various fields, but also make their own facilities available for student and faculty exchange, increasing the strength and breadth of each institution.

The facilities and equipment at the global station for zoonotic control in Hokkaido University are world class, with an emphasis on biosafety and biosecurity, that is essential for research on organisms that are a threat to humanity. While the facilities at Hokkaido University do not have a BSL4 facility, one such facility is available to the group in Japan when such facilities are needed.

The productivity and quality of the research is emphasized by the high number of publications, invitations to national and international meetings, grants and awards that have been achieved since 2014. Hokkaido University can be justly proud of their GI-CORE, the concept and success of the program should be considered as a flagship program that is too be continued for the future, for it serves both Japan and the entire world.

Global Station for Zoonosis Control
Global Institution for Collaborative Research and Education (GI-CoRE)
Final Evaluation

External Evaluation Committee Member Name: Ben Adler .

Choose one of the five Evaluation Ratings options below as explained by the Evaluation Explanation for each Evaluation Item on the form.

Evaluation Ratings	Evaluation Explanation
S	Achieved outcomes surpassed the original plan (Outstanding)
A	Good progress has been maintained and expected outcomes have been achieved (Excellent)
B	Most expected outcomes have been achieved with some slight delays (Good)
C	Although certain outcomes were achieved, overall results were insufficient (Satisfactory)
D	No expected outcomes were achieved (Unsatisfactory)

I. Research

1. Has construction of an international research and education center capable of attracting outstanding researchers from around the world (including from HU) been achieved?

Evaluation Results and Reasons

(Your Evaluation Results)

A

(Reasons)

Absolutely yes. The Center has clearly attracted world class researchers from HU, from other institutes in Japan, and internationally. With highly regarded researchers from Australia, Ireland, USA and several other countries, the Center has built a profile such that it is a place to which scientists actively want to come to work and collaborate with scientists from within Japan and from abroad. It is apparent that the Center has become a nucleus for workers on zoonotic infections. As such, it is unique in Japan and one of perhaps only a handful of such centers worldwide. After speaking with some of the international collaborators, it was quite evident that the reasons were twofold, encompassing the scientific reputations of the personnel and the very impressive array of state-of-the-art equipment and facilities available, or being established, at the Center.

It was equally pleasing to see the level of international collaboration with scientists from many so-called "developing countries". This is an important initiative, as many of the zoonotic infections under study are the causes of major public health problems in these countries.

Specific points

(Outstanding points)

We especially commend the Director for the initiative of outreach to developing countries.

We also congratulate the Director and his staff on establishing a center with world class equipment and facilities.

(Suggestions for improvement)

Of course, one should never rest on one's laurels and there is scope for additional international collaboration However, in order to not dilute the available resources, such expansions will need to be carefully targeted towards appropriate zoonotic infections.

2. Is world-leading cutting-edge international cooperative research underway?

Evaluation Results and Reasons

(Your Evaluation Results)

S

(Reasons)

Again here, the answer is a very clear yes. We were very impressed with the quality of the science and the presentations at the Sixth Meeting of the Consortium for the Control of Zoonoses. These ranged from fundamental research aimed at understanding the mechanisms of pathogenesis of the zoonotic agents under study through to translational research directed towards the development and/or improvement of vaccines, diagnostic tools and new treatment regimens. The applied research components are of particular relevance to global regions which may not have the necessary resources to undertake this development. In this context, the range of over 30 countries involved can only be described as impressive and remarkable. The fact that approximately 75% of the collaborating countries are from resource poor regions is commendable.

The publications flowing from the research are excellent, both in terms of numbers and also in terms of quality. A high proportion of the papers is in highly-ranked discipline-specific journals or in top multidisciplinary journals. Of course, publications should not be the only criterion used to assess the quality and value of the research. The applied research within the Center (as is the case worldwide) may not necessarily result in high impact papers, but the public and social benefit of for example a more accurate diagnostic test or an improved vaccine cannot be overstated.

Overall therefore, the cooperative research in the Center is viewed as outstanding.

Specific points

(Outstanding points)

The spread of basic and applied research

The involvement of a high number of developing countries.

(Suggestions for improvement)

3. Are research outcomes from GI-CoRE being actively utilized to solve social issues?

Evaluation Results and Reasons

(Your Evaluation Results)

A

(Reasons)

The basic ethos of the research in the Center is to solve social issues. Infectious diseases remain a major cause of morbidity and mortality worldwide. At least 70% of these infections have a zoonotic origin. Any research that has the potential to alleviate this suffering will therefore have very significant social impact. This is especially important in the current context of the emergence of major problems of resistance of bacterial and parasitic pathogens and the ongoing difficulties of specific antiviral therapeutic agents. As such, a component of the research program seeks to specifically address these issues. This is relevant and appropriate.

Specific points

(Outstanding points)

The emphasis on vaccines, diagnostics and therapeutics.

(Suggestions for improvement)

None that could be achieved without a massive increase in funding.

II. Education

Is the educational system and curriculum designed to help develop researchers who possess specialized knowledge and are capable of working internationally?

Evaluation Results and Reasons

(Your Evaluation Results)

S

(Reasons)

Absolutely outstanding! The fact that 19 PhD students have already graduated from the Center is a superb early outcome. Notably, 12 of these were international students, with 10 of them from developing countries. Members of his latter category are now all employed at universities or institutes outside Japan, commensurate with the social ethos of appropriate transfer of specialist knowledge within Japan and abroad.

Equally impressive is the number of currently enrolled 37 PhD students. Here again importantly, 21 of these are from abroad and will be able to contribute expertise locally after graduation.

The establishment of a formal Graduate School of Infectious Diseases is commended and will certainly enhance the education and training of young researchers.

Specific points

(Outstanding points)

The number, quality and international spread of graduated and current post-graduate students

(Suggestions for improvement)

Keep going as you are.

III. Establishment of Framework

Are the necessary systems and frameworks being established in order to conduct international cooperative research and education?

Evaluation Results and Reasons

(Your Evaluation Results)

A

(Reasons)

The reasons in terms of high quality research and post-graduate training have been outlined in previous sections. One additional point warrants mention here. The Center is clearly a major international player in zoonosis research. This is evidenced by the number of international collaborators and the fact that many researchers come to spend time in the Center, for both short term and long term visits. This will provide a global network of scientists with expertise in zoonotic diseases. Ongoing mentorship of this network will be critical to maintain and enhance the research and education framework.

Specific points

(Outstanding points)

The superb facilities available within the Center.

The future international network that will develop from graduating students and visiting staff.

(Suggestions for improvement)

Not really a point for improvement, but rather a comment. It will be important for the Center to establish a mechanism to retain contact with the various national and international staff and students after they return to their own countries or institutions, in order to maintain the network. This could almost be viewed as a network of Center "alumni".

This could just as easily have received an **S**. The only reason it has got an **A** is that there is always room for improvement.

IV. Overall Evaluation

We were mightily impressed with what has been achieved so far and encouraged by the future vision of the Director. The Center has established itself as a major international player which has attracted top quality staff and students. The scope of research is quite broad and covers fundamental and translational aspects of zoonosis control. While this is to be commended, at some future time it may be necessary to prioritise the research focus. We note that some of the research areas are quite peripheral to the concept of zoonoses.

Overall, we congratulate the Director, staff and students and we recommend unreservedly and enthusiastically the continuation of funding for the Center.

Global Station for Zoonosis Control
Global Institution for Collaborative Research and Education (GI-CoRE)
Hokkaido Univeristy

Research Progress Report
(Project Period: Academic Year 2014-2019)

Contents

I. Overview

■ Name of Global Station (GS)

Global Station for Zoonosis Control

■ Project Period

2014-2019 academic years (5 years)

■ Aims and Goals

The objectives of the Global Station for Zoonosis Control at Hokkaido University are to promote research for the control of zoonoses thorough collaboration with leading international researchers and to establish a collaborative research network at a global level.

Our major targets, outlined below, are to develop strategies for zoonosis control based on the results of the collaborative research and to make proposals to the global community.

Our aims are:

1. to reveal the perpetuation mechanisms and transmission routes of zoonotic pathogens by conducting global epidemiological studies on infectious diseases to improve existing prevention and control strategies.
2. to study the genetics of pathogens and the factors responsible for their pathogenicity and host range.
3. to develop databases of information of the above results and to make freely available to reserachers and the public.
4. to develop and disseminate globally practical measures for the diagnosis, prevention and treatment of zoonoses.

Research subjects

I. Development of Vaccines and Biologicals

- I-A Development and practical use of seasonal influenza vaccines of global standard
- I-B Transcriptomics in bacterial infection and immunity
- I-C Management of influenza virus library
- I-D Development of bacterial vaccines

II. Exploration of Pathogens

- II-A Novel virus detection and characterization
- II-B Molecular pathogenesis of viral diseases and development of antiviral drugs
- II-C Genomic analysis of antimicrobial resistance

III. Pathogen Genomics

- III-A Linking genes to phenotypes in malaria parasites by classical genetics and genomic technologies
- III-B Analysis of horizontal gene transfer in protozoan parasite genomes
- III-C Development of point-of-care diagnostic systems in resource-poor settings
- III-D Additional activities under the framework of GI-CoRE

The GI-CoRE units of each of the participating universities all collaborate to achieve these goals.

■ Necessity and Urgency

Emerging and re-emerging infectious diseases, for example, influenza, Ebola virus disease, Middle East respiratory syndrome (MERS), tuberculosis, trypanosomiasis and Zika virus disease, now occur worldwide and have become a major threat to public health. Most of these diseases are zoonoses caused by agents transmitted from their natural wild animal hosts, to other animal species, including humans (Figure 1).

Recent rapid changes in the global environment have wreaked havoc on the ecologies of reservoir hosts and led to expanded opportunities for pathogens to invade human societies. Rapid development of global networks for mass human travel and food supplies, further exacerbate the problem by providing opportunities for pathogens to spread worldwide within a short time period. The net result of all these factors is a drastic increase in zoonoses in the 21st century, with the certainty that even greater numbers of humans will be exposed to infectious diseases in the future, resulting in major economic and societal costs from the associated morbidity and mortality.

It is obvious from occurrences of zoonoses that even a single outbreak has significant impacts on the global economy and society. Clearly, control measures that extend beyond national borders are necessary to control these trans-boundary infectious diseases highlighting the need for the formation of international research networks.

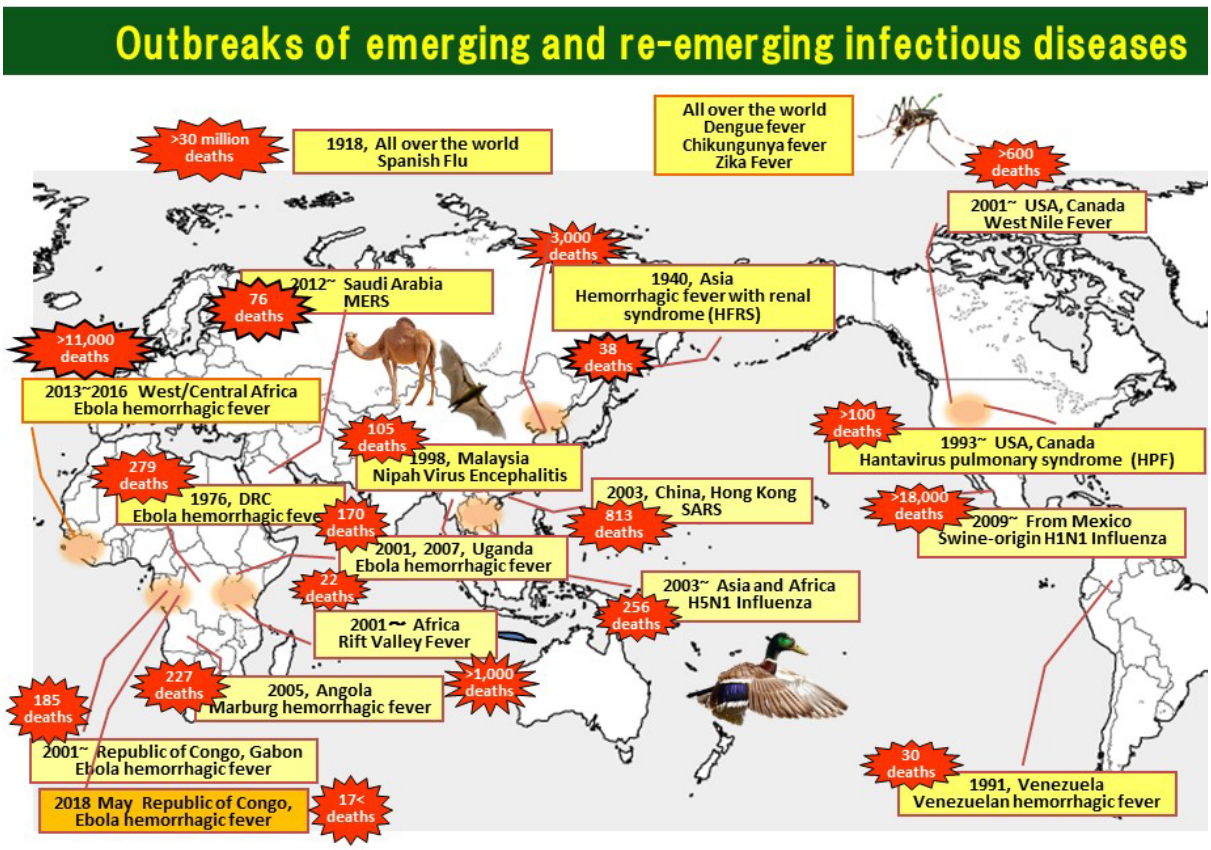


Figure 1

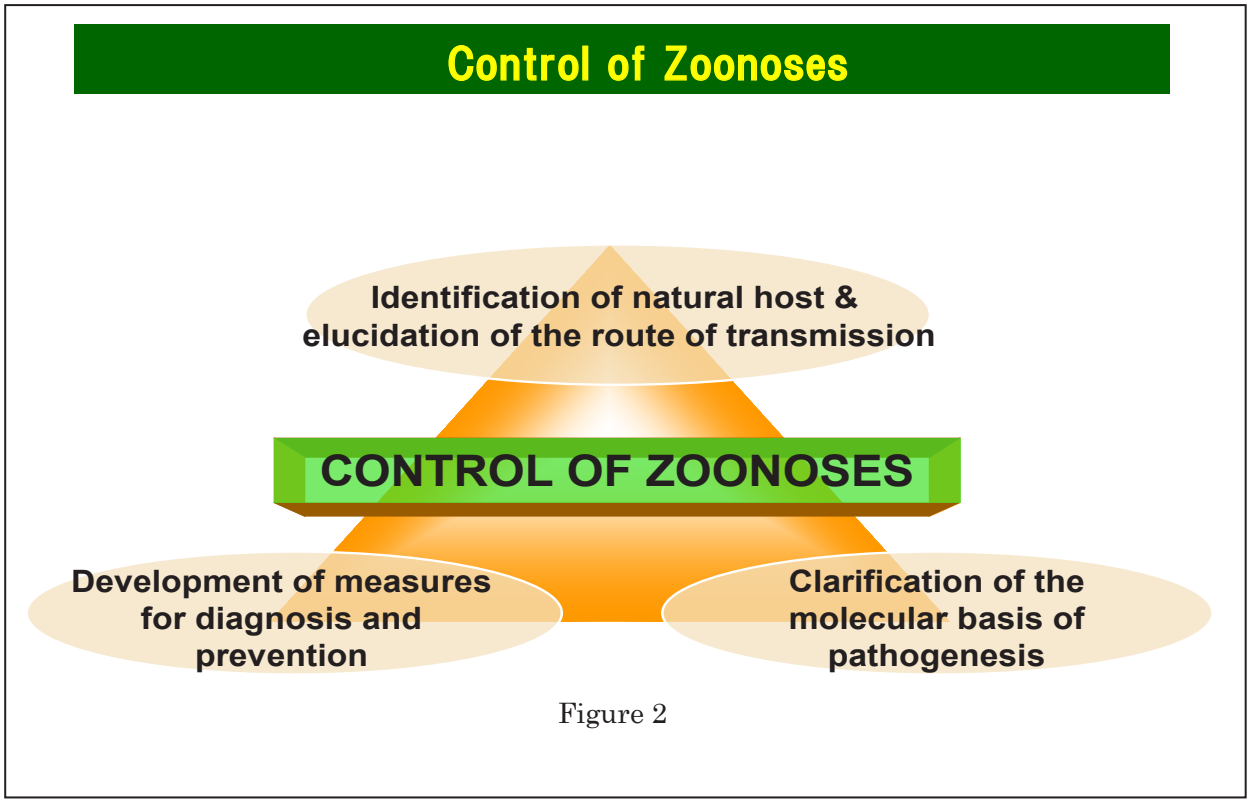


Figure 2

For the control of zoonoses, the rapid identification of natural host animals and their transmission routes is essential. The technologies to detect microorganisms in nature and the basic research techniques used to determine host ranges, ecology and pathogenicity, are, however, currently insufficient. Furthermore, there is a lack of expertise and organizations that conduct and coordinate strategic research for the prediction, prevention and control of zoonoses with the capabilities to implement control measures into disparate societies around the world.

Recently, the threat to economies and societies has significantly increased due to the emergence and re-emergence of trans-boundary infectious diseases. As a result, domestic and international demand for development of human resources capable of conducting infection research and control measures has increased significantly.

Due to these circumstances, the Japanese government formulated "*The Basic Policy on Strengthening Countermeasures for Infectious Diseases that Pose a Threat to Global Society*" at the meeting of the Ministerial Council on the Response to Infectious Diseases held in February 2016. The policy states that in order to confine infectious diseases at an early stage and, in particular, to prevent infection spreading from a localized epidemic to a pandemic, the development of an organization to foster measures to mitigate these threats is an urgent issue.

If a global framework is established that encompasses health governance, basic research activities designed to reveal the ecology of pathogens and the molecular basis of pathogenicity, in addition to applied research programs to devise new methods of diagnosis, prophylactic and therapeutic approaches, then it must be conducted at a level which transcends academic barriers and national borders (Figure 2).

■ Originality, Novelty, etc.

The Research Center for Zoonosis Control was established in Hokkaido University (HU) in 2005 as an institute specializing in the promotion of research directed towards the control of zoonoses. In particular, through gathering researchers from medical science, veterinary medicine, basic science and information science, the University has created new opportunities and developed innovative areas of research. Much progress has already been made in the areas of global surveillance of influenza, the comprehensive search for and discovery of new viruses, the studies of drug-resistant tuberculosis, and the development of rapid diagnostic methodologies. Furthermore, extensive international collaborative research has been conducted on viral, bacterial and parasitic zoonoses, and a global research network has been established. As such, the Research Center for Zoonoses Control has become a unique institute in the world.

In December 2010, the Research Center for Zoonosis Control hosted the regional workshop on collaboration between human and animal health sectors for the prevention and control of zoonoses, in which members from the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO), and the World Organisation for Animal Health (OIE) gathered together for the first time.

In November 2011, WHO designated the Hokkaido University Research Center for Zoonosis Control as the “WHO Collaborating Centre for Zoonoses Control” up to 2015 and Professor Kida became Head of the WHO Collaborating Centre for Zoonoses Control. The inauguration ceremony and “the regional forum of collaborating/reference centres on emerging infectious diseases and zoonoses” were held in December 2011 (Figure 3). In October 2015, WHO re-evaluated and redesignated as a “WHO Collaborating Centre for Zoonoses Control” until November 2019.

In a global context, the project promoted by the Global Station for Zoonosis Control with the Research Center for Zoonosis Control as a base, has provided an opportunity to attract leading researchers to the University and promote collaborative international research. The research conducted by each unit leads the world in each field. The four universities are at the forefront in their fields and the vibrant program of exchange of staff, students and research achievements amongst the members of GI-CoRE provides a model for others to follow.

Finally, in 2018, Hokkaido University will establish a Graduate School of International Infectious Diseases for the development of human resources in the fight against infectious diseases. The research activities at the Global Station for Zoonosis Control will provide the basis for promoting the process of globalization of education and research.

Figure 3

Ⅱ. Budget

Unit: 1,000 JPY

	Category	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018 (projected)	Total
Budget for Global Station for Zoonosis Control	Personnel cost	-	15,034	13,419	13,788	50,051	92,292
	Operating cost	-	32,191	45,908	45,539	9,276	132,914
	Facility cost	-	31,361	0	0	0	31,361
GI-CoRE establishment of framework	Personnel cost (for researchers from overseas)	5,054	22,685	32,291	30,946	60,000	150,976
	Administrative cost*	24,113	23,316	20,630	18,826	24,275	111,160
	Operating and research cost	68,349	78,215	58,392	57,373	33,275	295,604
Total		97,516	202,802	170,640	166,472	176,877	814,307

*Including travel expenses for invited international researchers

III. Detailed Results

● Framework of the Global Station for Zoonosis Control

The current situation with regards to the sharing of roles and cooperation between HU and affiliated universities is shown in Figure 4. The global station comprises three research units, in each of which principal investigators (PIs) are responsible for research projects as listed in the figure below. Each unit conducts its own research projects independently, but interactions and collaborations between units are encouraged. To integrate research activity toward the goal of "control of zoonoses", we have constructed the "Consortium for the Control of Zoonoses" where all unit members meet together and exchange information. Consortium meetings are held annually with frequent interactions fostering further collaborative projects.

The Research Center for Zoonosis Control, HU is responsible for provision of office and laboratory space for those invited from international universities. GI-CoRE members are free to access facilities and equipment such as Biosafety Level-3 (BSL-3) laboratories, BSL-3 animal facilities, core laboratories where flow cytometry-cell sorting systems, next generation sequencers, cell imaging systems, ultracentrifuges and other analytical equipment are installed. Support staff for laboratories and core facilities are also allocated by Hokkaido University.

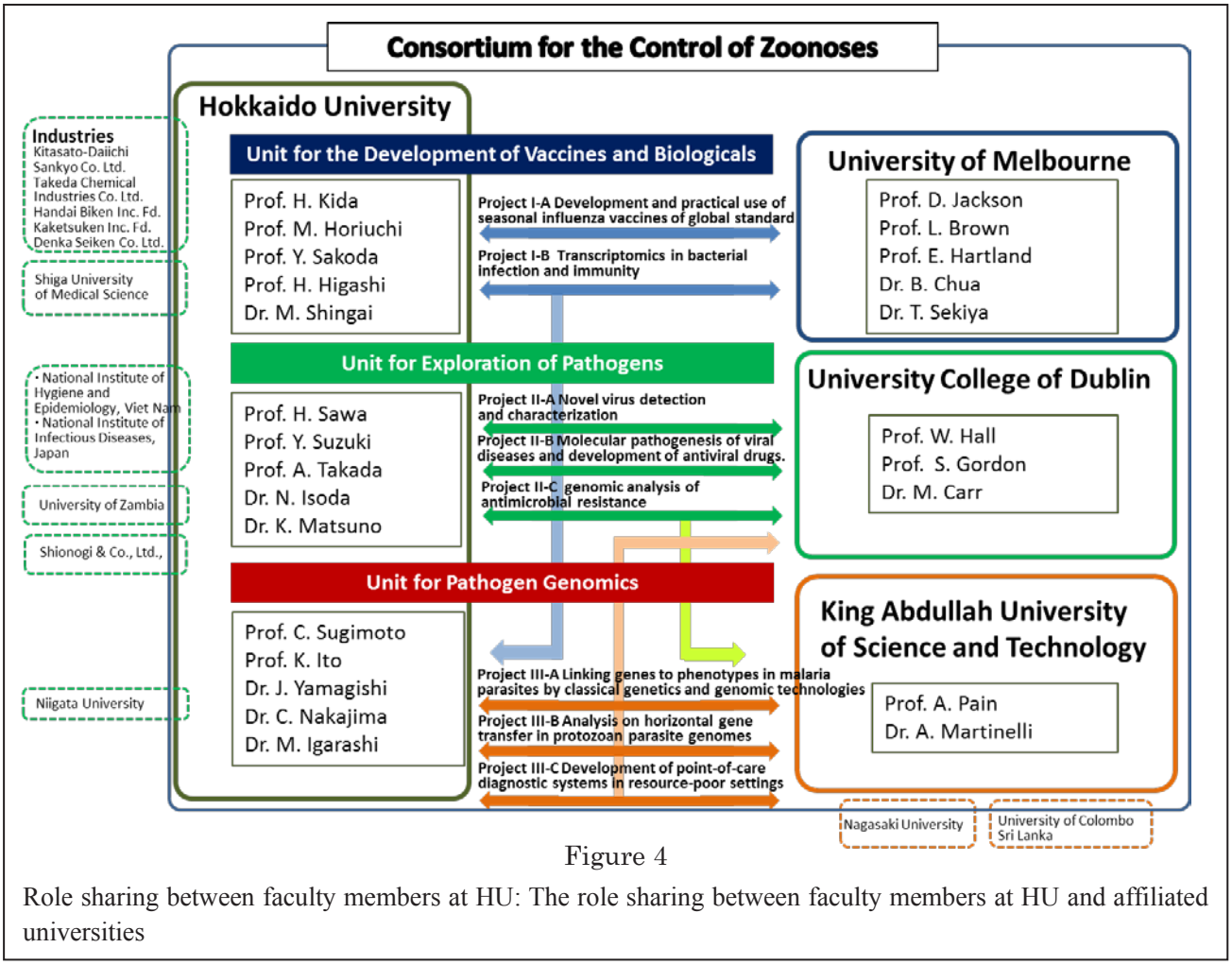


Figure 4

Role sharing between faculty members at HU: The role sharing between faculty members at HU and affiliated universities

●Future developments

Currently, a solid structure has been formed to conduct research activities within each unit. Based on GI-CoRE activity, a research network, the “Consortium for the Control of Zoonosis”, has been organized in order to promote collaborations among the affiliated universities. Once a year, the global station organizes the consortium meeting in order to facilitate information exchange and more active collaboration among members. We also invite members from institutions (universities, research institutes, companies, etc.) other than the affiliated universities to expand our research network. This network activity will be expanded toward our goal of developing a structure for a Global Center for Zoonosis Control.

Detailed Results for the **"Unit for the Development of Vaccines and Biologicals"**

1. Research

1.1 Goals

As the "Unit for the Development of Vaccines and Biologicals", University of Melbourne (UM) and HU (Research Center for Zoonosis Control and the Graduate School of Veterinary Medicine) conduct research on the development and practical use of seasonal influenza vaccines of global standard in collaboration with industries, universities and governmental organizations for the preparedness of future pandemic influenza. Vaccines against bacterial diseases, including anthrax, are also developed. In addition, we analyze mucosal innate immune responses that contribute to pathogen clearance and disease pathology using mouse infection models of bacterial pathogens.

1.2 Current Progress/Future Developmen

1.2.1 Construction of base

● Role sharing with affiliated universities

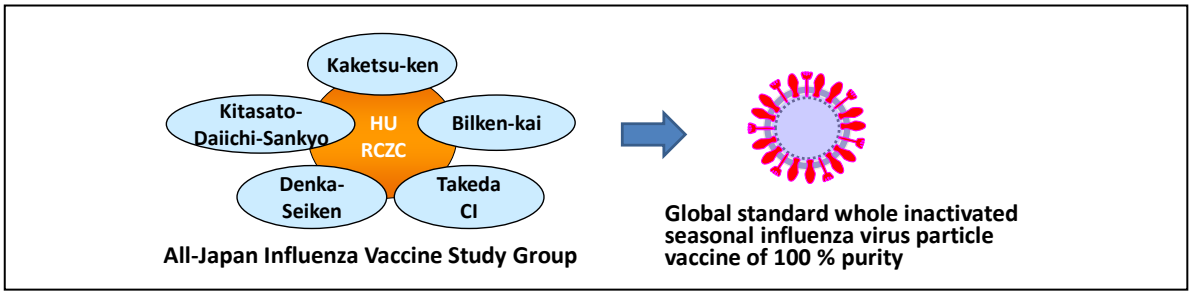
Affiliated institutions	Researcher name	Description of research
University of Melbourne, Australia Department of Immunology and Microbiology	Professor David Jackson Professor Lorena Brown Asst. Professor Brendon Chua Asst. Professor Toshiki Sekiya (Based at HU) Dr. Edin Mifsud	・Evaluation of proprietary adjuvants ・Analysis of immunological and biological responses following administration of vaccine candidates ・Development of bacterial vaccines
	Professor Elizabeth Hartland	・Transcriptomics in infection and immunity
Hokkaido University, Japan		
Research Center for Zoonosis Control	Professor Hiroshi Kida Assoc. Professor Masashi Shingai	・Comparison of immunogenicity and safety of whole virus particle vaccine with split vaccines ・Route of inoculation of vaccines ・Pre-clinical and clinical tests ・Revision of the biological standard of influenza vaccines for human use
	Professor Hideaki Higashi	・Development of bacterial vaccines
Graduate School of Veterinary Medicine	Professor Motohiro Horiuchi Professor Yoshihiro Sakoda	・Transcriptome analysis of innate cell-mediated immunity in infectious and inflammatory diseases ・Management of influenza virus library ・Bioinformatic analysis of influenza virus strains

In collaboration with

Professor Kazumasa Ogasawara, School of Medicine, Shiga University of Medical Science

Collaborating industries, the member of the All-Japan Influenza Vaccine Study Group:

1) Kitasato-Daiichi Sankyo Co. Ltd., 2) Takeda Chemical Industries Co. Ltd., 3) Handai Biken Inc. Fd., 4) Kaketsuken Inc. Fd., 5) Denka Seiken Co. Ltd.



1.2.2 International Collaborative Research

● Current progress in meeting initial research goals

Project I-A: Development and practical use of seasonal influenza vaccines of global standard

The current split seasonal influenza virus vaccine was developed in 1972 in Japan. This split vaccine is still used today due to reduced pyrogenicity and decreased adverse reactions following vaccination. However, the efficacy of split vaccines is extremely low and, importantly, does not protect high risk groups (infants and the elderly) from severe disease associated with influenza virus infection.

Because the immunological potency of the current split vaccine is limited, efforts have been made to enhance immunogenicity by using the following methods;

1) to annually update the vaccine to protect against the influenza viruses most likely to spread in the upcoming season,
2) to use higher doses (up to four times) of the vaccine which have been approved for people aged 65 and older in the US and Canada,
3) to apply intradermal administration of vaccine using a much smaller needle than normally used,
4) to use an adjuvanted seasonal influenza vaccine for people 65 years of age and older and vaccines formulated with MF59 or AS03 (oil-in-water adjuvants) approved in Europe and the US, and
5) to use live attenuated nasal-spray vaccines which have been demonstrated to have higher efficacy in children in studies in the US where it has been approved for people from two to 49 years of age.

These are interim measures, and not ideal solutions for effective vaccination for influenza. Therefore, the seasonal influenza vaccines need to be significantly improved.

Whole virus particle vaccines induce effective immune responses but have the potential to induce adverse reactions due to the enhanced innate immune response elicited. Therefore, the aim of this study is to compare the immunogenicity of whole virus particle vaccines to split vaccines in order to develop the vaccines as the new gold standard for a seasonal influenza vaccine.

To achieve this purpose, we have established an All-Japan Influenza Vaccine Study Group in which all five influenza

vaccine manufacturers in Japan have participated since April 2015. The goals of the program are;

1) to compare the immunological potency and safety of whole virus particle influenza vaccine to the current split virus vaccine provided by each company,
2) to perform pre-clinical and clinical trials of the test vaccines developed, and
3) to evaluate proprietary adjuvants and the route of vaccine inoculation.

Status of the Study

1) In April 2016, a material transfer agreement was exchanged with each of the participant vaccine producers.
2) Whole virus particle and ether-split vaccines were prepared by each of the All-Japan Influenza Vaccine Study Group members. Each of the members is assessing the immunological potency, safety and other properties of their own test vaccine products.
3) HU, Shiga University of Medical Science, and UM teams are analysing the immunological and biological responses *in vitro* and *in vivo* (mice and cynomolgus monkeys) following administration of each of the vaccine candidates. Subcutaneous administration of whole virus particle vaccine induced significantly higher neutralization titers for influenza virus in C57BL/6 mice compared with that of split vaccine (Figure 5).
4) HU and UM teams have started to study the effect of the vaccine inoculation route and the use of adjuvants on vaccine efficacy.
5) The third to seventh meetings of the All-Japan Influenza Vaccine Study Group were held in June 2016, December 2016, March 2017, June 2017 and December 2017 and the eighth meeting of the All-Japan Influenza Vaccine Study Group will be held on June 8th, 2018.
6) Kaketsuken, as a representative of the All-Japan Study Group, has prepared prototype vaccines for pre-clinical study.
7) The All-Japan Study Group has almost finished pre-clinical study and have started prior consultation to the Pharmaceuticals and Medical Devices Agency (PMDA) based on our pre-clinical study results.
8) Kaketsuken, as a representative of the All-Japan Study Group, is preparing an investigational new vaccine for clinical trials (phase I and II).

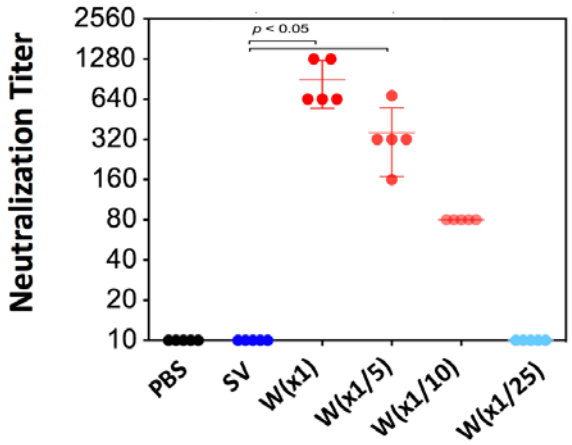


Figure 5
Whole virus particle vaccine (WV) diluted up to 10 fold induced significantly higher neutralization titers for influenza virus in mice compared with split vaccine (SV).

Project I-B: Transcriptomics in bacterial infection and immunity

Host innate defense relies on the activation of signaling pathways that regulate inflammation and cell death. The subversion of these pathways by microbial pathogens is a common step in the pathogenesis of many infections. In this way, pathogens may manipulate the innate immune response in infected cells. We are using mouse and amoebae infection models and the pathogens, such as, *Legionella pneumophila* (*L. pneumophila*) and *Citrobacter rodentium* to understand the mucosal

innate immune responses that contribute to pathogen clearance and also disease pathology.

Status of the Study

These collaborative studies were undertaken using next generation sequencing and data analysis platforms at HU.

1) The aim of this study was to understand the contribution of SnpL, which is one of effector proteins transported to the host cell nucleus, to *Legionella* infection and its effect on host cell transcription. This was achieved using a stable, inducible macrophage cell line expressing SnpL and RNA sequencing (RNAseq) to identify perturbations to the transcriptional profile of macrophages. A manuscript describing the function of SnpL is currently in review at Cellular Microbiology and this data was used to obtain funding from the Australian Research Council (AU$ 414K over three years), to investigate nuclear localized effector proteins of *Legionella*. This application included GI-CoRE as a partner investigator.
2) Infection with *L. pneumophila* induces massive infiltration of monocyte-derived dendritic cells (moDCs) into the lung. moDCs are an inflammatory dendritic cell type that are not major antigen presenting cells, but little is known about the signaling pathways, specific transcription factors activated in moDCs and their function during lung infection. Global transcriptional responses in primary moDCs from lung infection was examined by RNAseq to understand the pathways needed to respond to *L. pneumophila* infection. We identified multiple guanylate binding proteins (GBPs) that were upregulated in response to interferon gamma. We are currently generating knockout mice by the CRISPR system to determine if GBPs contribute to innate defense against *L. pneumophila* infection. This data was used to obtain funding from the Australian National Health and Medical Research Council (AU$ 628K over three years), investigating the role of GBPs in lung defense against *L. pneumophila*. This application included GI-CoRE as an associate investigator.
3) We have discovered new pathways and immune cell types that contribute to host defense against *Citrobacter rodentium*, an enteropathogenic *Escherichia coli* (EPEC)-like pathogen of mice. Our previous work aimed to dissect the contribution of RipK3, Casp8 and RipK1 in protection against acute colitis using double and triple knockout mice. RNAseq analysis of the pathogen-infected colon tissue from triple knockout mice showed that expression levels of serum amyloid protein were altered, but this was inconsistent when tested by qRT-PCR. No other differences in gene expression were observed among knockout mice, suggesting that the susceptibility of animals may not result from defects in colonocyte signaling. Continuing work is testing the susceptibility of the knockout mice to other pathogens, such as, *Salmonella* which is a systemic pathogen.
4) A new project to examine the transcriptional response of amoebae to *L. pneumophila* infection is under way. Amoebae serve as the environmental host for *L. pneumophila* replication, but little is known about amoebae defense pathways against *L. pneumophila* infection. We have performed RNAseq on *L. pneumophila*-infected amoebae at different stages of the life cycle to understand how *L. pneumophila* leads to amoebae cell death.

Project I-C: Management of influenza virus library

It is now believed that each of the past pandemic influenza viruses is a genetic reassortant generated in a pig between avian influenza virus and the preceding human strain. We have shown that pigs are susceptible to infection with each of avian and mammalian influenza viruses of different hemagglutinin (HA) subtypes, generating reassortants with human receptor specificity. Since each of the influenza A viruses of all known subtypes perpetuates among migratory ducks and

their nesting lake water and avian viruses of any subtype can contribute genes in the generation of reassortants in pigs, thus, none of the combinations of the 16 HA and 9 neuraminidase (NA) subtype viruses can be ruled out as potential candidates for future pandemic strains. Therefore, global surveillance of avian, swine and human influenza and drastic improvement of flu vaccines are clearly of crucial importance for the preparedness for forthcoming pandemics.

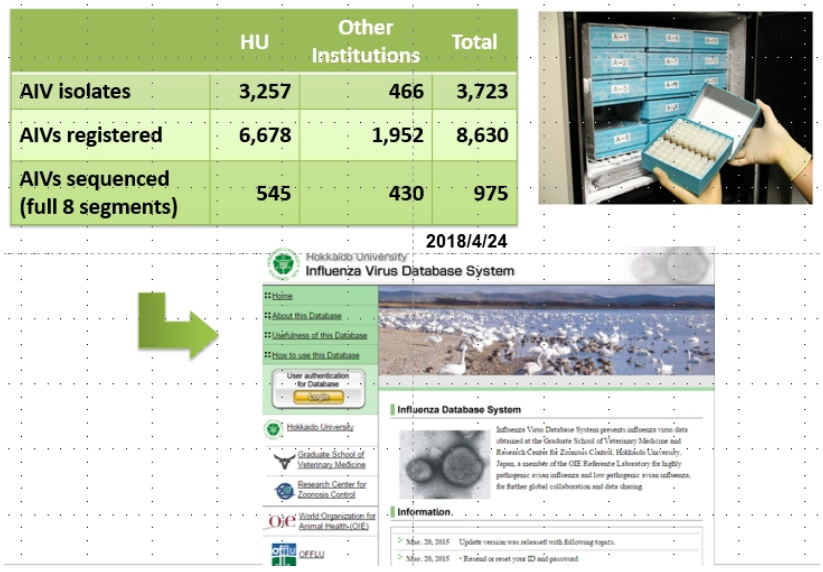


Figure 6
Influenza virus library and database

Status of the Study

Since each of the HA genes of past pandemic virus strains originated from a duck influenza virus that is antigenically and genetically highly stable, we have established a library of more than 3,000 low pathogenic avian influenza virus strains of the 144 possible combinations of the 16 HA and 9 NA subtypes for vaccine strain candidates and diagnostic usage (Figure 6). Virus stocks and their information including nucleotide sequence for candidate library are now available at HU in preparation for influenza pandemics (http://virusdb.czc.hokudai.ac.jp).

Project I-D Development of bacterial vaccines

Inhalation anthrax, resulting from exposure to aerosolized spores of *Bacillus anthracis* (*B. anthracis*), is a serious threat to both humans and animals. The toxicity of anthrax is dependent on three proteins; protective antigen (PA_{83}, which binds to the host cell surface through the anthrax receptor ANTXR2), lethal factor (LF) and edema factor (EF) which individually are non-toxic. Following removal of a 20 kDa fragment from the N-terminus of PA_{83}, the resulting PA_{63} associates to form a heptamer which then transports a complex formed between EF and LF to the cytosol of infected cells resulting in cell death.

Antibodies (Abs) directed against PA have been shown to mediate protection against *B. anthracis* in animal models of inhalation anthrax. The protection correlates with the ability of the antibodies to neutralize anthrax lethal toxin (LeTx) *in vitro* using a toxin neutralisation assay. Currently licensed vaccines in the US and UK consist of acellular culture filtrates of *B. anthracis* formulated with aluminium-based adjuvants. These vaccines induce PA-specific neutralising antibody which underlie their protective efficacy. The extensive immunisation protocol required for the establishment and maintenance of immunity for *B. anthracis* and the severity of potential sites of injection motivates the development of a new generation of anthrax vaccines.

Peptide sequences can be used to represent target epitopes of intact proteins potentially allowing for precise direction of immune responses to that target. Peptide-based vaccine candidates also have the advantages of (i) eliminating the potential risk of reversion to virulence, (ii) minimisation of the presence of deleterious sequences by judicious selection of the peptide sequence and (iii) overcoming limited availability of antigens (Ag). Furthermore, because of the methods of

chemical synthesis that are used in their manufacture, peptides lend themselves conveniently to chemical modification such as the attachment of carbohydrate antigen, lipid moiety and other biologically active groups, including adjuvants. Following analyses of the quaternary structures of PA and LF, we selected four peptides from PA and one peptide from LF as target epitopes for evaluation as vaccine candidates against *B. anthracis*. The five peptide sequences that we investigated are described as follows:

1) *Helix*: the peptide sequence ^{555}DQQTSQNIKNQ^{565} of PA_{63} was chosen because it is in a region of PA_{63} which is involved in the association of neighbouring subunits of the PA_{63} heptamer. It was reasoned that assembly of the PA_{63} heptamer could be prevented by antibodies directed against this helix thereby inhibiting correct formation of the toxin.
2) *Loop1*: the peptide sequence ^{269}IILSKNEDQSTQNTDSETRTISK^{291}of PA_{63} was chosen because it is in a region of PA_{63} which is involved in contacting the cell surface receptor, ANTXR2. It was reasoned that antibodies directed against this region of PA would prevent the attachment of PA to the cell surface receptor thereby inhibiting the toxins effects.
3) *Loop2*: the peptide sequence ^{648}DTEGLKE^{654} derived from PA_{63} was chosen for the same reasons as described above for *Loop1*.
4) PA_{30}: The 30-residue peptide ^{168}STSAGPTVPDRDNDGIPDSLEVEGYTVDVK^{197} located at the N-terminus of PA_{63} was chosen because we hypothesized that antibody raised against this peptide may stop the furin-like protease from cleaving the first 20 residues peptide to generate the active form of PA_{63}.
5) $LF^{679\text{-}701}$: this peptide sequence, ^{679}NDSEGFIHEFGHAVDDYAGYLLDK^{701}is located at the binding site of lethal factor which binds to the mitogen-activated protein kinase kinase substrate (MAPKK) a region necessary for its toxicity. We reasoned that antibodies directed to this region of the molecule would contribute to Ab-mediated inhibitory effects of an anthrax vaccine.

A T helper cell epitope with the sequence ALNNRFQIKGVELKS which is derived from the light chain of hemagglutinin of influenza virus A was incorporated into all vaccine constructs. This T helper cell epitope has been shown to be active in BALB/c mice which was used in this study. A TLR2 agonist, 2,3-dipalmitoyl-S-glycerylcysteine (Pam2Cys), was also incorporated into each of the vaccine constructs as a built-in adjuvant to create self-adjuvanting lipopeptide vaccine candidates. Each of the vaccine candidates were constructed using a modular approach developed by us (Zeng, W. *et al*. J. Biol. Chem. 2011).

Groups of five BALB/c mice were used in animal studies to determine the antibody responses following inoculation of peptide constructs. Each of the lipopeptides, Helix, Loop1, Loop2 and $LF^{679\text{-}701}$ assembled using the modular approach were administered subcutaneously by tail vein injections in saline. A group of mice also received a mixture of Helix, Loop1, Loop2 and PA_{30}-based lipopeptide constructs. PA30 alone was administered to mice in the presence of Freund's adjuvant. Mice were inoculated on days 0 and 21 and sera were prepared from blood taken on Days 21 and 35 and used in an ELISA to determine the titres of primary and secondary antibody responses. PAD-1 obtained from GI-CoRE at HU and characterised to be of a high quality was administered to a group of mice using Freund's adjuvant to determine its ability to induce antibody responses.

Status of the Study

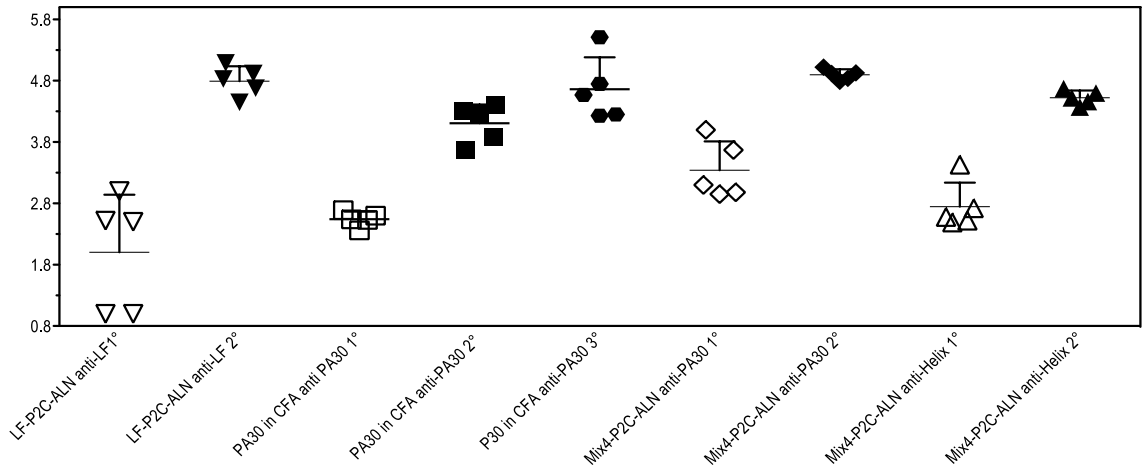


Figure 7

Anti-peptide antibody responses in mouse sera determined by ELISA following inoculation of peptide-based vaccine constructs. Each of the immunogens was given on two separate occasions on days 0 and 21 and sera prepared from blood taken on days 21 and 35 were used for determination of the Ab titres against each individual Ag.

Helix-based vaccine construct not only induced a strong antibody response against itself measured by an enzyme-linked immunosorbent assay (ELISA), but these antibodies also bound to PA_{63} from which its sequence is derived. The Loop1 peptide-based vaccine candidate induced a strong antibody response against itself but not to PA_{63}. The Loop2 peptide-based vaccine did not elicit any significant antibody response against itself or against PA_{63}. The lipopeptide based on $LF^{679\text{-}701}$ induced a strong anti-$LF^{679\text{-}701}$ antibody response following two inoculations of antigen. PA_{30} in complete Freund's adjuvant administered to mice in three separate doses elicited a high anti-PA_{30} antibody titre (Figure 7). The group of mice which received the mixture of Helix, Loop1, Loop2 and PA_{30} lipopeptide constructs in saline elicited a strong anti-Helix and anti-PA_{30} antibody responses. Anti-Loop1 and anti-Loop2 antibody responses were not determined in this experiment. Inoculation of mice with PAD-1 induced strong anti-PAD-1 responses following three injections and also a strong anti-PA_{63} antibody response. The anti-sera obtained from inoculation of PA_{30} in Freund's adjuvant and the mixture of Helix, Loop1, Loop2 and PA_{30} lipopeptide constructs in saline also elicited a strong anti-PA_{63} antibody response.

An *in vitro* toxin neutralisation assay was used to assess the ability of the various anti-sera to neutralise toxins. Anti-Helix, Loop1 and Loop2 antibody sera showed little or no toxin neutralisation activity in comparison to the anti-PA_{63} sera which was raised against PA_{63} and showed a very high toxin neutralisation activity. We also examined the ability of the anti-PA_{30} and anti-PAD-1 sera for their abilities to neutralise anthrax toxins. Anti-PA_{63} antisera possesses high toxin neutralisation activity. In contrast, anti-PA_{30} and anti-PAD-1 sera demonstrated only slightly higher toxin neutralisation activity than normal mouse sera.

In this study, we selected five target epitopes from PA and LF based on their crystal structures and successfully synthesised five lipopeptide vaccine constructs based on these target sequences. Animal studies show that two of these lipopeptide-based vaccines not only induced strong and specific antibody responses against the immunizing antigen but

also strong antibody responses again intact PA, as determined by ELISA. Although these anti-sera did not perform as well in the *in vitro* toxin neutralising assay as the anti-intact PA antibody, nevertheless, the detection of cross-reactive antibody responses to PA with anti-Helix and anti-PAD-1 is encouraging. Clearly additional studies need to be performed to further develop the appropriate target epitope(s), including Helix and PAD-1 that will not only will induce strong antibody responses towards PA or LF but also induce antibodies that can neutralise toxin activity and perform well in an animal challenge assay. It is possible that by increasing the length of Helix and/or $LF^{679-701}$**,** which also possess helical structure within the native structure, improved vaccine candidates may be obtained. An additional avenue to follow will be to assemble chimeric structures such as Helix-PAD-1 conjugates. A further advantage associated with the lipopeptide technology described in this study is that these Pam2Cys-based vaccine constructs are self-adjuvanting and can be successfully delivered intranasally as we have shown previously. This route of inoculation may be more appropriate to establish an effective defence against inhalation anthrax.

Detailed Results for the **"Unit for Exploration of Pathogens"**

1. Research

1.1 Goals

The "Unit for Exploration of Pathogens", comprising HU (Research Center for Zoonosis Control and Graduate School of Veterinary Medicine), University College Dublin, Ireland and the National Institute of Hygiene and Epidemiology, Hanoi, Viet Nam conduct surveillance to identify natural animal reservoirs and transmission routes of zoonotic pathogens, and to delineate pathogenicity determinants and the host range of the pathogens. The research outcomes are employed for the development of diagnostic technologies and therapeutic strategies directed against zoonoses, in collaboration with the pharmaceutical sector. Research is also conducted on bacterial pathogens, with particular reference to genomic analysis and drug resistance profiling.

Both of HU and University College Dublin also conduct the education and training of young, early-stage researchers to become qualified "Zoonosis Control Experts" who are responsible for the control of zoonotic diseases worldwide.

1.2 Current Progress/Future Developments

1.2.1 Construction of base

● Role sharing with affiliated universities

Affiliated institutions	Researcher name	Description of research
National Virus Reference Laboratory, University College Dublin, Ireland	Professor William W. Hall Asst. Professor Michael Carr (Based at Hokkaido University)	・Development and establishment of international collaborative research among global institutions ・Analysis of pathogenicity of zoonotic viruses
Hokkaido University, Japan		
Research Center for Zoonosis Control	Professor Hirofumi Sawa Professor Ayato Takada Assoc. Professor Noriyuki Isoda	・Conduct surveillance to identify natural host animals and transmission routes of zoonotic pathogens ・Development of diagnostic technology and therapeutic strategy against zoonotic pathogens ・Development of point-of-care diagnostic systems in resource-poor settings (Collaboration with KAUST unit)
	Professor Yasuhiko Suzuki	・Molecular basis of antimicrobial resistance
Graduate School of Veterinary Medicine	Lecturer Keita Matsuno	・Analysis of pathogenicity of zoonotic pathogens ・Conduction of surveillance to identify natural host animals and transmission routes of zoonotic pathogens
Department of Immunology and Molecular Biology, National Institute of Hygiene and Epidemiology, Vietnam	Professor Nguyen Thi Lan Anh	・Conduct surveillance of zoonotic pathogens using human samples ・Development of point-of-care diagnostic systems in resource-poor settings (Collaboration with KAUST unit)

Main Collaborating research institutes
- School of Veterinary Medicine, University of Zambia, Zambia
- Discovery Research Laboratory for Core Therapeutic Areas, Shionogi & Co., Ltd., Japan
- Laboratory of Zoonotic Diseases, Faculty of Applied Biological Sciences, Gifu University, Japan
- Graduate School of Pharmaceutical Science, Tokushima University, Japan
- Laboratory of Organic Chemistry for Drug Development, Center for Research and Education on Drug Discovery, Faculty of Pharmaceutical Sciences, HU, Japan
- The Faculty of Veterinary Medicine, Bogor Agricultural University. Indonesia

1.2.2 International Collaborative Research

● Current progress in meeting initial research goals

Project II-A: Novel virus detection and characterization

Since fiscal year 2014, the "Unit for Exploration of Pathogens" has undertaken extensive collaborative scientific research with domestic and international partners which has led to the discovery of many new mammalian viruses with zoonotic potential. This research greatly improves our understanding of viral diversity and epidemiology and the nature of species specificity of viruses in mammalian hosts. These findings have been disseminated by publication in international, peer-reviewed scientific journals and presentation at international conferences. With regards to the epidemiological research activities, surveillance has been undertaken to identify natural host animals and transmission routes of zoonotic pathogens in collaboration with academic institutions in foreign countries.

Status of the Study

The human immunodeficiency virus type 1 pandemic arose following cross-species transmission of simian immunodeficiency viruses (SIVs), which naturally infect African non-human primates (NHPs), and subsequent zoonotic transfer and then establishment and spread in the human population. Therefore, surveillance of SIVs and discovery of new SIVs in NHPs is critical to improve the monitoring and attempt to mitigate future cross-species transmission of these agents. In collaboration with the University of Zambia (UNZA), we have screened African green monkeys (AGMs; *Chlorocebus* spp.) and baboons (*Papio* spp.) employing an SIV consensus PCR and detected SIV pol gene fragments in 18.9% (18/95) from AGMs and 1.9% (2/105) of DNA samples from baboons in genomic DNA obtained from splenic tissue. We have established a replication-competent SIV isolate in different human CD4+ T-cell lines following co-culture *in vitro* with AGM peripheral blood mononuclear cells. Whole genome characterization was performed by next-generation sequencing of these isolates which demonstrated this novel SIV (SIVagmMAL-ZMB) was distinct from other known SIV strains and, also, ancestral to vervet monkey SIV. Specific screening assays demonstrated SIVagmMAL-ZMB viral RNA in 3.2% (3/94) of malbroucks (*Chlorocebus cynosuros*) collected in Zambia with no positives samples from baboons (0/105; 0%). Our results improve our understanding of the evolutionary history of SIV in NHPs.

Bats harbor greater numbers of zoonotic viruses than rodents per individual species and often live in large colonies, which may contribute to pathogen transmission and, by virtue of being the only flying mammalian genus, can disseminate infectious agents over wide geographical areas. Polyomaviruses (PyVs) are genetically highly stable and are known to be highly host specific in mammalian species with no convincing evidence demonstrating host-switching between mammalian species. For better understanding of the nature of virus-host specificity in different bat host species, in collaboration with

UNZA, we have investigated the diversity of PyVs in different Zambian insectivorous and fruit bat species and annotated ten novel PyV genomes. We have identified evidence of recombination in the newly described African PyVs and also in human, bat, NHP and other mammalian and avian species of PyV. The recombination events were non-random, with hot spots encompassing the structural regions encoding the viral capsid proteins with cold spots within the nonstructural gene regions (Figure 8). We have proposed that intergene recombination of structural regions between PyVs encompassing the capsid proteins may have facilitated altered tropism(s) and species-jumping events. Strikingly, we found evidence that two PyV species in different horseshoe bat hosts (*genus Rhinolophus*) were 99.9 and 88.8% identical with each other over their respective large T antigen coding sequences and therefore represent the same virus species in different bat hosts. Our findings demonstrate that PyVs are capable of host-switching events in horseshoe bats and have implications for zoonotic transmission involving high-consequence pathogens in this bat host.

In addition, we have identified novel PyVs from fruit bats in Indonesia in collaboration with the Faculty of Veterinary Medicine, Bogor Agricultural University, the Gorontalo State University and the Veterinary Investigation and Diagnostic Center in Indonesia. Using broad-spectrum PCR-based assays, we screened PyV DNA isolated from spleen samples from 82 wild fruit bats captured in Indonesia. Eight full-length PyV genome sequences were obtained using an inverse PCR method. A phylogenetic analysis of eight complete viral genome sequences showed that BatPyVs form two distinct genetic clusters that are genetically different from previously described BatPyVs. One group of BatPyVs is genetically related to the primate PyVs, including human PyV9 and trichodysplasia spinulosa-associated PyV. This study has identified the presence of novel PyVs in fruit bats in Indonesia and provides genetic information about these BatPyVs relatedness to human pathogens.

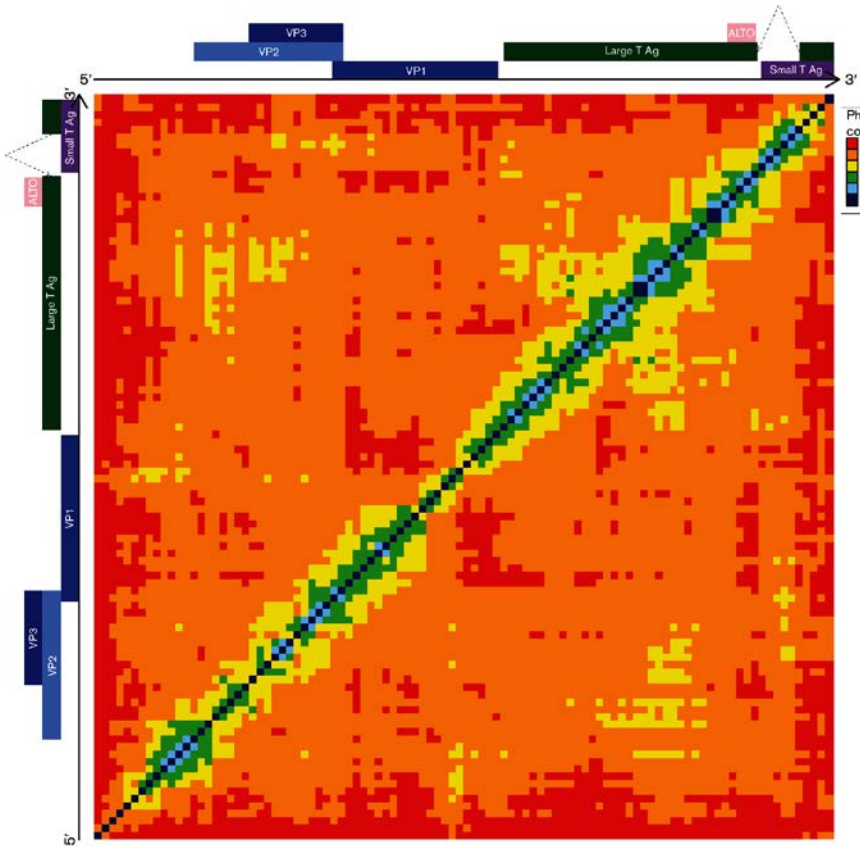


Figure 8

Recombination analysis of species of PyV. The horizontal axis shows the positions adjusted to *Rousettus aegyptiacus polyomavirus 1* as a reference and colour-coding of each panel is shown in the respective legends to the right. Phylogenetic compatibility matrix over the species of PyV. Each cell in the matrix reflects the normalized Robinson–Foulds distance between two neighbour-joining trees corresponding to the respective regions in the PyV alignment. The vertical axis corresponds to the positions adjusted to the genome of *Rousettus aegyptiacus polyomavirus 1*.

Rotaviruses exert a profound burden of diarrheal disease in children with estimates ranging from 120,000-215,000 deaths per annum; however, despite this the role of zoonotic transfer is poorly studied. We have identified a new strain of

group A rotavirus in the intestinal contents of a horseshoe bat in Zambia. Whole genome sequencing revealed that the identified virus, named RVA/Bat-wt/ZMB/LUS12-14/2012/G3P[3], possessed the genotype constellation G3-P[3]-I3-R2-C2-M3-A9-N2-T3-E2-H3. Several genome segments of LUS12-14 were highly similar as those of group A rotaviruses identified from humans, cows and antelopes, indicating interspecies transmission of rotaviruses between bats and other mammals with possible multiple genomic reassortment events.

In addition, we have screened wild animals for other viruses, such as coronavirus (CoV), herpesvirus and bufavirus, and identified novel bat CoV genes in Indonesian Moluccan naked-backed fruit bats. Phylogenetic analysis suggested that these bat CoVs are related to members of the genus betacoronavirus. We have previously isolated a novel alphaherpesvirus in fruit bats in Indonesia, and established the presence of viruses belonging to other taxa of the family Herpesviridae. We screened fruit bat DNA extracts by pan-herpesvirus PCR and discovered 68 sequences of novel gammaherpesvirus, designated 'megabat gammaherpesvirus' (MgGHV). A phylogenetic analysis of approximately 3.4 kbp of continuous MgGHV sequences encompassing the glycoprotein B and DNA polymerase genes revealed that the MgGHV sequences are distinct from those of other previously reported gammaherpesviruses. Further analysis suggested the existence of co-infections of herpesviruses in Indonesian fruit bats. We also performed nested-PCR screening and identified bufavirus from 12 megabats in Indonesia. We have determined the near full genome sequence of a novel megabat-borne bufavirus, tentatively named megabat bufavirus 1. Phylogenetic analyses showed that megabat bufavirus 1 clustered with known protoparvoviruses, including human bufavirus but represented a distinct lineage of bufavirus. Our analyses also inferred phylogenetic relationships among animal-borne bufaviruses recently reported by other studies. It is suggested that megabat bufavirus 1, as the first protoparvovirus discovered from megabats, indicates high genetic divergence of bufaviruses.

We investigated zoonotic orthopoxvirus (OPXV) infection among wild animals in Zambia to assess the geographical distribution of OPXV. Serological analysis indicated that rodents (14.7%), shrews (33.3 %) and non-human primates (2.1 %) had antibodies against OPXV, suggesting that wild animals living in rural areas of human habitation in Zambia have been infected with OPXV.

Shrews are small insectivorous mammals that are distributed worldwide. Similar to rodents, shrews live on the ground and are commonly found near human residences. We investigated the enteric virome of wild shrews captured in Zambia using a sequence-independent viral metagenomics approach. A large portion of the shrew enteric virome was composed of insect viruses, whilst novel viruses including cycloviruses, picornaviruses and picorna-like viruses were also identified. Several cycloviruses, including variants of human cycloviruses detected in cerebrospinal fluid and stools, were detected in wild shrews at a high prevalence rate. The identified picornavirus was distantly related to human parechovirus, which is associated with severe neurologic disease, inferring the presence of a new genus in this family. The identified picorna-like viruses were characterized as different species of calhevirus 1, which was identified previously in human fecal samples. Complete, or near complete, genome sequences of these novel viruses were determined and then were subjected to further genetic characterization. This study provides an initial view of the diversity and distinctiveness of the shrew enteric virome and highlights unique novel viruses related to human feces-associated viruses. Viral metagenomic analysis identified a new parvovirus genome in the intestinal contents of wild shrews in Zambia. Related viruses were detected in spleen tissues from wild shrews and non-human primates. Phylogenetic analyses showed that these viruses are related to human bufaviruses, highlighting the presence and genetic diversity of bufaviruses in wildlife.

Zambia is located in Southern Africa with a favourable climate for vector mosquitoes and the potential for arbovirus disease epidemics in both human and animal populations. While malaria is recognized as the major mosquito-borne disease

in Zambia, human or animal cases of arthropod-borne virus (arbovirus) diseases, including flavi- and alphavirus infections have not been extensively studied. In order to investigate arbovirus infections in Zambia, we have carried out surveillance studies to identify mosquito-borne viruses. So far, we have collected more than 13,000 female mosquitoes which are the target for arbovirus screening, as they ingest the blood of mammals for production of their eggs. We have identified many novel viruses from collected mosquitoes, including arboviruses and mosquito-borne viruses. We have recently described the isolation of a novel West Nile virus from mosquitoes and are examining the pathogenicity of the isolated virus *in vivo* (Figure 9).

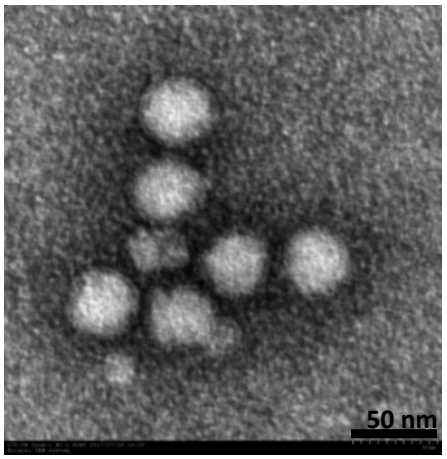


Figure 9
Transmission electron micrograph showing spherical (~40-nm diameter) and pleomorphic particles of the newly isolated West Nile virus from captured Zambian mosquitoes.

In summary, our research group have identified more than 40 viruses from wildlife, including more than 20 novel viruses and pathogenic zoonotic viruses, such as WNV from mosquitoes and the results were reported in 24 in the international journals (Transbound Emerg Dis 2018, Virus Res 2018, J Gen Virol 2017, Sci Rep 2016, Emerg Infect Dis 2015, J Gen Virol 2015, Nat Commun 2014, and so on) in collaboration with the counterparts in foreign countries. This research activity is important to provide an evidence base to better inform preemptive measures to mitigate the occurnce of zoonoses. For that purpose, it is necessary to identify the natural animal hosts carrying potential and known human pathogens and to better elucidate the routes by which the pathogens make the transition from those animals to other animals, including humans. In the future, we will further expand these epidemiological research activities in further countries, including Viet Nam, Sierra Leone, Taiwan and other international partners.

Project II-B: Molecular pathogenesis of viral diseases and development of antiviral drugs

Molecular pathogenesis of viral diseases

For the effective control of zoonoses, it is imperative to investigate the pathomechanisms underlying interactions between host-infected cells and pathogens. Therefore, we also focus on the interactions of host proteins with pathogen-derived pathogens and their impact on various stages of the viral life cycle and pathogenesis. For that purpose, we employ methods, such as RNA interference to knockdown mRNAs encoding host proteins of interest and examine the efficacy of infection in those cells. Alternatively, we also perform transcriptome analysis in pathogen-infected cells and control cells.

Status of the Study

We have sought to determine which Rab proteins, which belong to the Ras superfamily and play essential roles in regulating many aspects of vesicular trafficking, are involved in the intracellular trafficking of nascent West Nile virus (WNV) particles. RNA interference (RNAi) analysis revealed that Rab8b plays a role in WNV particle release. We found that Rab8 and WNV antigen were colocalized in WNV-infected cells, and that WNV infection enhanced Rab8 expression

in the cells. In addition, the amount of WNV particles in the supernatant of Rab8b-deficient cells was significantly decreased compared with that of wild-type cells, and WNV particles accumulated in the recycling endosomes in WNV-infected cells. These findings suggest that Rab8b is involved in trafficking of WNV particles from recycling endosomes to the plasma membrane.

Another host protein, valosin-containing protein (VCP) is classified as a member of the type II AAA+ ATPase protein family. VCP functions in several cellular processes, including protein degradation, membrane fusion, vesicular trafficking and disassembly of stress granules. Moreover, VCP is considered to play a role in the replication of several viruses, albeit through different mechanisms. We have investigated the role of VCP in WNV infection by inhibition of endogenous VCP expression using VCP inhibitors and by siRNA knockdown. We have shown that the inhibition of endogenous VCP expression significantly inhibited WNV infection. The entry assay revealed that silencing of endogenous VCP caused a significant reduction in the expression levels of WNV-RNA compared to control siRNA-treated cells. This indicates that VCP may play a role in early steps, such as, the binding or entry steps of the WNV life cycle. Using WNV virus-like particles and a WNV-DNA-based replicon, we demonstrated that perturbation of VCP expression decreased levels of newly synthesized WNV genomic RNA. These findings suggest that VCP is involved in early steps and during genome replication of the WNV life cycle.

We have also established new methods to examine the efficacy of virus-infected cells using subviral particles (SVPs) and viral-like particles (VLPs). SVPs self-assemble and are released from cells transfected with expression plasmids encoding flavivirus structural proteins. Flavivirus-like particles (VLPs), consisting of flavivirus structural proteins and a subgenomic replicon, can enter cells and cause single-round infections. Neither SVPs nor VLPs possess complete viral RNA genomes, therefore are replication-incompetent systems; however, they retain the capacity to fuse and bud from target cells and follow the same maturation process as whole virions. We have developed quantitative methods for the detection of cellular entry and release of SVPs and VLPs by applying a luciferase complementation assay based on the high affinity interaction between the split NanoLuc luciferase protein, LgBiT and the small peptide, HiBiT.

We introduced HiBiT into the structural protein of WNV and generated SVPs and VLPs harboring HiBiT (SVP-HiBiT and VLP-HiBiT, respectively). As SVP-HiBiT emitted strong luminescence upon exposure to LgBiT and its substrate, the nascently budded SVP-HiBiT in the supernatant was readily quantified by luminometry. Similarly, the cellular entry of VLP-HiBiT generated luminescence when VLP-HiBiT was infected into LgBiT-expressing cells. These methods utilizing SVP-HiBiT and VLP-HiBiT will facilitate research into life cycles of flaviviruses, including WNV.

Rabies virus (RABV) is the causative agent of fatal neurological disease. As with other viruses, cellular attachment is an initial step in RABV infection. Viral attachment factors are host molecules that facilitate viral adhesion on the cell surface and enhance infection but do not trigger endocytic entry and membrane fusion of viruses. The glycoprotein (G) of RABV, the only transmembrane protein of RABV, binds to the entry receptors and plays critical roles during RABV entry. RABV G also binds various cell membrane components, such as membranous proteins, gangliosides, and lipids. These prior studies suggested the existence of the attachment factor(s) that contribute to efficient adhesion of RABV; however, the molecules that serve as attachment factors for RABV infection are unidentified, and the mechanism of cellular attachment of RABV remains unclear. RABV uses several host membrane molecules as entry receptors, including the nicotinic acetylcholine receptor, neural cell adhesion molecule (NCAM), and nerve growth factor receptor p75NTR. Although characterization of the interaction of RABV with these receptors has facilitated our understanding of RABV infection, the mechanism of cellular attachment and entry of RABV remained to be elucidated. Heparan sulfate (HS), a

glycosaminoglycan with a disaccharide repeating unit of glucosamine and uronic acid, is abundant on cellular surfaces as a component of HS proteoglycans. HS is involved in various biological events through interactions with cytokines, growth factors, proteases, and membrane proteins. Previous work has shown that HS also binds certain viruses and mediates target cell infection. Soluble forms of HS and heparin, a highly sulfated HS analog, can neutralize infection with viruses that use HS for cellular attachment by competitive inhibition for binding of cellular HS to the viruses. HS and heparin have also been shown to inhibit RABV entry; however, this observation has been explained by the assumption that HS antagonizes the binding of RABV to the entry receptor NCAM because HS also binds to NCAM. Thus, the tripartite relationship between RABV, HS and NCAM is still unclear.

We investigated the role of cellular HS on RABV infection and examined the interaction between HS and RABV and demonstrated that cellular HS supports RABV adhesion and subsequent entry into target cells. Enzymatic removal of HS reduced cellular susceptibility to RABV infection, and heparin, a highly sulfated form of HS, blocked viral adhesion and infection. Direct binding between RABV glycoprotein and heparin was demonstrated, and this interaction was shown to require HS N- and 6-O-sulfation (Figure 10). We also revealed that basic amino acids in the ectodomain of RABV G serve as major determinants for the RABV–HS interaction. Collectively, our study highlights a previously undescribed role of HS as an attachment factor for RABV infection.

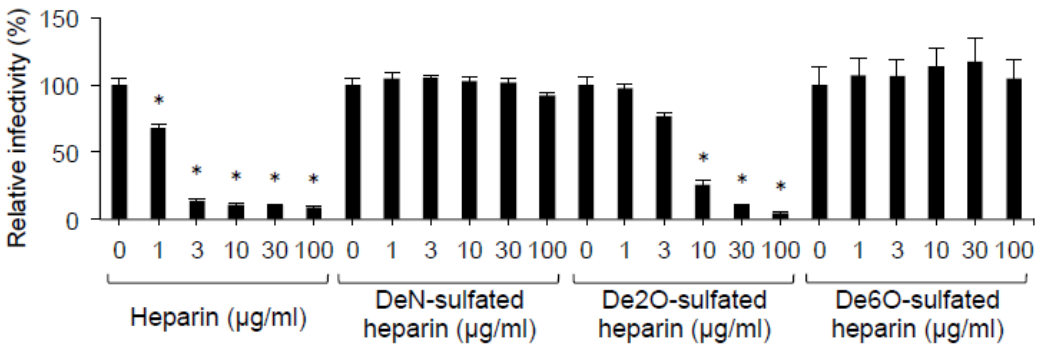


Figure 10

Rabies virus (RABV) was mixed with either heparin or the indicated forms of desulfated heparin and then inoculated to SK-N-SH cells. Cells were stained with anti-RABV N antibody and Hoechst 33342 and counted by imaging cytometry. Relative infectivity was calculated by setting the infectivity of mock-treated RABV to 100%.

Prion diseases are fatal neurodegenerative disorders, which show three types of disease presentation, infectious, inherited, and sporadic. In each type, these transmissible proteinaceous infectious particles devoid of nucleic acid, termed “prions”, are produced in the central nervous system (CNS). No adaptive immune responses are induced upon prion infection; however, the innate immune response is activated before the onset of the disease. The activation state of microglia influences pathophysiology of prion infection; however, the detailed mechanism(s) remain to be clarified. Macrophages, monocytes, and microglia are immune cells that play a key role in innate immunity. In infectious and inflammatory diseases and cancers, distinct acute and chronic innate immune responses are evoked which greatly influence the subsequent pathophysiological processes. Thus, the analysis of innate immune response and pathophysiology appears to contribute not only to a development of prophylactic and therapeutic interventions of infectious disease agents but also to an improvement

of the understanding of and development of treatment modalities in inflammatory diseases and cancers as chronic inflammation. A higher goal of our research is to clarify the roles and functions of macrophages/monocytes in infectious and inflammatory diseases to utilize this information in the development of novel prophylactic and therapeutic approaches. We are now collecting gene expression profiles of microglia employing next generation sequencing as one strategy to progress our research. We are focusing on analyzing the relationship between the pathophysiology of prion diseases during neuroinfection and neurodegeneration. Our recent studies have suggested that transplantation of mesenchymal stem cells (MSCs) influences the activation state of microglia in prion-infected mice. Thus in 2017, we have focused on the analysis of the activation state of microglia that were treated with MSCs *in vivo* and *in vitro*.

Recently, we reported that autologous transplantation of mouse compact bone-derived MSCs (mCB-MSCs) into prion Chandler strain-infected mice prolonged the survival of mice. Interestingly, the mCB-MSCs transplantation enhanced further microglial activation with up-regulation of some of the marker genes for M2-type microglia. In order to elucidate the mechanism for the control of microglial activation with mCB-MSCs, we analyzed how the pathological niche of prion diseases impacts upon on the activation of mCB-MSCs and the influence of factors produced from mCB-MSCs on microglial activation. Brain extracts from Chandler strain-infected mice stimulated mCB-MSCs with the up-regulation of COX-2 gene expression, suggesting that mCB-MCSs can adapt to prion diseases in the brain. When LPS-treated microglia were incubated with the conditioned media from mCB-MSCs that were treated with brain extracts from prion Chandler strain-infected mice, the expression of CD68, one of the microglial activation markers, was down-regulated. Additionally, the expression of IL-1β, a marker for M1-type microglia, was down-regulated, whereas the expression of Arg-1, a marker for M2-type microglia, was up-regulated. These results suggest that the mCB-MSCs treated with brain extracts from prion-infected mice have the ability to shift the activation state of LPS-treated microglia from an M1-type to an M2-type. However, unexpectedly, conditioned media from mCB-MSCs treated with brain extracts from mock-infected mice or without brain extracts also appeared to have the same ability. Similar tendencies, down-regulation of CD68 and IL-1β, but up-regulation of Arg-1, were observed when microglia isolated from the Chandler strain-infected mice were used. These results suggest that, regardless of their activation state, mCB-MSCs intrinsically secrete factors that shift microglial activation state from M1 to M2-type. We have already acquired RNA-seq data of those microglial cells and bioinformatics is now under way to find out any specific properties of microglia polarized to an M1 or M2 activation state.

Development of antiviral drugs

In order to control zoonoses, it is important to establish strategies for chemotherapeutic intervention measures against zoonotic infectious diseases in outbreak settings. Our research group has strongly collaborated with a pharmaceutical company, Shionogi & Co. Ltd. and the Laboratory of Organic Chemistry for Drug Development, Center for Research and Education on Drug Discovery, Faculty of Pharmaceutical sciences, HU.

Status of the Study

Rabies remains an invariably fatal neurological disease despite the availability of a preventive vaccination and post-exposure prophylaxis that must be immediately administered to the exposed individual before symptom onset. Antivirals which can inhibit RABV replication are identified through screening of small compounds; however, as RABV infection does not generate easily discernible cytopathic effects *in vitro*, cell viability assays may not be feasible to observe antiviral activity of small compounds against RABV. Therefore, we generated recombinant RABVs (rRABVs) encoding NanoLuc

luciferase (NanoLuc) to facilitate the screening of small compound libraries. NanoLuc expression was confirmed in single-step growth cures of virus infection and showed that the rRABVs were capable of viral replication without decrease of luciferase activity through ten serial passages. Furthermore, the rRABVs were able to quantify the antiviral activity of the nucleoside analogue ribavirin against RABV *in vitro*. These findings confirm the potential of the rRABV encoding NanoLuc system to facilitate screening of small compounds to inhibit RABV infection.

It has been reported by our group and others that ribavirin, a guanine nucleoside analog, is a potent inhibitor of RABV replication *in vitro* but lacks clinical efficacy in symptomatic rabies infection. Therefore, we attempted to identify potential ribavirin analogs with superior anti-RABV activity. Antiviral activity and cytotoxicity of the compounds were initially examined in human neuroblastoma cells. Among the tested compounds, two exhibited a 5- to 27-fold higher anti-RABV activity than ribavirin. Examination of the anti-RABV mechanisms of action of the compounds using time-of-addition and minigenome assays revealed that they inhibited viral genome replication and transcription. Addition of exogenous guanosine to RABV-infected cells diminished the antiviral activity of the compounds, suggesting that they are involved in guanosine triphosphate pool depletion by inhibiting inosine monophosphate dehydrogenase. Taken together, our findings underline the potency of nucleoside analogs as a class of antiviral compounds for the development of novel agents against RABV.

Chikungunya fever (CHIKF) is a re-emerging mosquito-borne zoonosis caused by CHIKV infection. The major symptoms of CHIKF are an acute febrile illness with arthralgia, myalgia, rash, lymphopenia, thrombocytopenia and gastrointestinal symptoms. In severe cases of CHIKF, encephalitis has been reported in neonates and fatal disease can occur, although rarely, in both the young and the elderly. The arthralgia is characterized by severe joint pain and can become chronic in significant numbers of patients persisting over years as a rheumatoid-like disorder. This painful, debilitating arthralgia is a major factor affecting the quality of life in convalescent CHIKF patients. Outbreaks of CHIKF have occurred worldwide since 2004, in Africa, Asia and North, Central and South America. It is thought that one factor in the re-emergence of CHIKF could be related to viral genome mutations which have resulted in an increased efficiency of viral transmission in different mosquito vectors and/or possibly an increased virulence in humans. Currently there are no licensed prophylactic vaccines or chemotherapeutic options available for prevention or treatment. Recently, two vaccine candidates have showed promising results in phase I clinical studies; however, the development of antiviral therapeutics is still in early development. Several studies have suggested that the development of chronic arthralgia may be related to the severity of the symptoms during the acute phase. Therefore, effective antiviral treatment during the acute phase could potentially reduce symptoms not only in the acute but also the chronic phases to diminish the rheumatoid-like sequelae. Recently, several candidates which can inhibit chikungunya virus (CHIKV) infection have been reported; however, the basis of their inhibitory effects have not been fully elucidated. We have identified an anti-CHIKV candidate which is effective at nanomolar concentrations and designated as Compound-A (Figure 11). Using whole genome sequencing of resistant clones, reverse genetics and CHIKV replicons, the

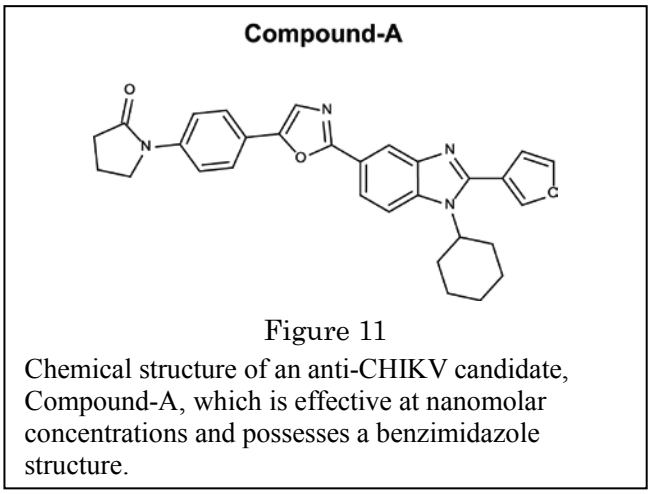


Figure 11
Chemical structure of an anti-CHIKV candidate, Compound-A, which is effective at nanomolar concentrations and possesses a benzimidazole structure.

viral target region was identified in the nsP4 and the anti-CHIKV candidate inhibits the RNA-dependent RNA-polymerase function of CHIKV.

Ebolaviruses and Marburgviruses are members of the family *Filoviridae*. These filoviruses are known to cause severe hemorrhagic fever in humans and nonhuman primates. There are no commercially available vaccines or therapeutics for viral hemorrhagic fevers, including Ebolavirus disease (EVD) and Marburgvirus disease (MVD). Although it has been reported that some antiviral drugs such as nucleotide analogues (e.g. T705), which are approved for clinical use for other viral diseases may also be beneficial against EVD, their efficacies in humans have not been definitively established, and concerns about adverse effects remain. Thus, the development of effective and safe therapeutics against EVD is of crucial importance. Using biological assays to analyze filovirus protein functions, we screen chemical compounds in this study, focusing on each replication step of filovirus infection.

Using vesicular stomatitis viruses pseudotyped with filovirus glycoproteins (GPs), we have previously obtained a lead compound that inhibits entry of filoviruses into target cells. This compound was further analyzed for structure-activity correlation with 77 newly synthesized derivatives and we have obtained two derivatives (derivative A and B) that show enhanced ability to reduce infectivity of pseudotyped viruses. We confirmed that derivative B efficiently reduced focus formation of all filoviruses tested. Anti-viral activity was also confirmed by demonstrating significantly reduced cytopathic effects of Vero E6 cells infected with these filoviruses in the presence of derivative B. Animal experiments and further characterization (i.e. pathomechanisms) of the compound are now ongoing. New chemical compound libraries will be screened soon, focusing on inhibition of viral RNA replication and budding of viral particles.

Project II-C: Genomic analysis of antimicrobial resistance (AMR)

Drug resistance in *Mycobacterium tuberculosis* (*M. tuberculosis*)

Our group have been collaborating with researchers in Zambia, Sri Lanka, Nepal, Bangladesh, Myanmar, Thailand, the Philippines and China on the prevalence of drug resistance in *Mycobacterium tuberculosis* (*M. tuberculosis*) clinical isolates in these countries in order to obtain the basic data useful for the development of rapid, simple and low-cost drug susceptibility test kits. Our group has elucidated the genetic mutations conferring rifampicin, isoniazid, streptomycin, pyrazinamide and levofloxacin resistance. In addition, our group has clarified that the tubercle bacillus with a specific genotype tended to more easily acquire a multidrug-resistant phenotype. However, drug-resistance associated mutations in specific genes were not found in 5 to 30 % of drug-resistant isolates during our international study. Based on this finding, it presented an opportunity to discover unidentified mutations conferring drug-resistance in *M. tuberculosis* clinical isolates which will be essential for the development of rapid, simple and low-cost drug susceptibility test kits. Hence, the goals of this research study are as follows:

1) To continue the elucidation of drug-resistance associated mutations in specific genes by using polymerase chain reaction and conventional Sanger DNA sequencing to identify *M. tuberculosis* clinical isolates without any previously described mutation(s) in the known drug-resistance associated genes.
2) To identify the mutations that correlate with drug resistance among *M. tuberculosis* clinical isolates without any mutation in the known drug-resistance associated genes by using next generation sequencing (NGS) technologies.
3) To establish rapid, simple and low-cost drug susceptibility test kits by combining the data from conventional Sanger DNA sequencing and NGS analyses.

4) To evaluate the established drug susceptibility test kits in Zambia, Nepal and Thailand to validate for the rapid detection of drug-resistance mutations in *M. tuberculosis*.

Status of the Study

To determine the frequency of pyarazinamide (PZA) resistance and its correlation with mutation in *pncA* in *M. tuberculosis* clinical isolated from patients in Lusaka, Zambia, BACTEC MGIT M960 was used for phenotypic PZA susceptibility testing while sequencing was used to determine resistance-conferring mutations in the *pncA*. Of all the 134 isolates analyzed, 33 were phenotypically resistant to PZA. Among multidrug-resistant *M. tuberculosis* (MDR-MTB) isolates, the frequency of PZA resistance was 22 of 38 (Table 1). And 28 of 33 PZA resistant isolates had mutations in the *pncA* that confer resistance. With BACTEC MGIT 960 as the reference standard, gene sequencing showed 84.8% sensitivity and 100% specificity (Table 2). Nine new mutations were identified and the single nucleotide substitution T104G and C195T were the most frequent mutations. However, they were observed in both susceptible and resistant strains indicating that they are non-resistance-conferring mutations.

Table 1: Phenotypic Drug Susceptibility profiles of the isolates

Drug resistance pattern	PZA-Resistant	PZA-Sensitive	Total
SHRE	7	2	9
SHR	6	11	17
HRE	5	2	7
HR	4	1	5
SHE	-	1	1
SH	-	1	1
SR	-	2	2
HE	-	1	1
S	-	3	3
H	3	12	15
R	1	1	2
Susceptible	7	64	71
Total	33	101	134

S-Streptomycin, H-Isoniazide, R-Rifampin, E-Ethambutol. Susceptible-not resistant to any drug

Table 2: Diagnostic value of mutation detection for PZA susceptibility testing

PZA resistant		PZ susceptible		Sensitivity% (95%CI)	Specificity% (95%CI)
with mutation	without mutation	with mutation	without mutation		
28	5	0	101	84.8 (68.1-94.9%)	100 (100-100%)

It has been demonstrated that PZA susceptibility testing is necessary, especially in patients infected with MDR-*M. tuberculosis*, as approximately half of the bacilli have PZA-resistant TB. Similar studies are required in other provinces to get a more accurate estimate of PZA resistance in Zambia. Mutations in *pncA* were the major mechanism of PZA resistance; however, the presence of mutations among phenotypically PZA-susceptible *M. tuberculosis* isolates makes it challenging to independently use genotyping methods for the determination of PZA resistance.

Characteristics of MDR-MTB clinical isolates in Nepal and Myanmar were also analyzed. In Nepal, the major lineage of circulating MTB was the Central Asian Strain (CAS); however, the Beijing genotype lineage was more prevalent among MDR-MTB. This year, we focused on the analysis of the CAS lineage of MDR-MTB. A total of 145 MDR CAS isolates collected in Nepal from 2008 to 2013 were characterized by spoligotyping, employing mycobacterial interspersed repetitive unit-variable number tandem repeat (MIRU-VNTR) analysis and drug resistance-associated gene sequencing. Spoligotyping analysis showed that the CAS1_Delhi SIT26 predominanted (60/145, 41.4%). By combining spoligotyping and MIRU-VNTR typing, 145 isolates were discriminated into 116 different types including 18 clusters with 47 isolates (clustering rate: 32.4%). About 50% of these isolate clusters shared the same genetic and geographical characteristics with

other isolates in each cluster. Some of them shared rare point mutations in *rpoB*, likely associated with rifampicin resistance, including a 3-codon deletion and amino acid substitution events, such as, double mutations like Asp516Phe (GAC→TTC) and Ser531Gln (TCG→CAG). The observed high diversity of the MDR CAS isolates in Nepal suggested the bacteria progressively acquired drug resistance and became MDR in each patient in the majority of the cases, although some cases were suggested to be possible transmissions of MDR-MTB. In Myanmar, the major lineage of circulating MTB was Indo-Oceanic lineage, but the Beijing lineage predominanted among MDR-MTB. A total of 212 MDR Beijing clinical isolates collected in Myanmar in 2010 and 2012 were characterized as a retrospective study by the same methodologies described above. MIRU-VNTR analysis differentiated the 212 isolates into 143 patterns including 37 clusters comprising 110 isolates. The number of isolates in a cluster ranged from 2 to 8 and most of the clusters consisted of less than 3 isolates. However, some of the isolates shared unique mutations, which were likely associated with rifampicin or isoniazid resistance, including mutations observed in *rpoC* suggesting the bacteria had recovered the enzyme function by acquiring the compensatory mutation. The high genetic diversity of isolates suggested a reduced likelihood of MDR-MTB outbreaks; however, the transmission of MDR-MTB was indicated in some instances, as was observed in the analysis of the Nepalese cases.

Drug resistant potential in *Enterobacteriaceae*

AMR is one of the major concerns in public health at a global level. In Thailand, we have isolated numerous *Escherichia coli* (*E. coli*) and *Salmonella* from both pig and pork showing drug resistant potential. Genes responsible for drug resistance and plasmid(s) encoding the resistant gene(s) should be detected to better understand plasmid-mediated transfer of drug-resistant potentials between *Enterobacteriaceae*. By comparing the plasmids conferring drug resistant potential among two *Enterobacteriaceae* but in identical individuals, we can elucidate the horizontal gene transfer of drug resistant potential between bacterial species. This project is a collaboration with Thammasat University, Thailand.

Status of the Study

A total of 120 samples including 60 fecal and 60 carcass swabs were collected in 3 slaughterhouses in Pathurnthani province, Thailand. A total of 67 samples, including retailed pork and cutting board samples, were collected in 2 markets in Pathurnthani province. All samples were tested to attempt to isolate *E. coli* and *Salmonella* by microbiological procedures following standard protocols established by the USFDA. Approximately, 10 isolates of suspected *E. coli* and suspected *Salmonella* per sample were collected for further biochemical identification. In slaughterhouses, 1,085 suspected *E. coli* isolates and 374 suspected *Salmonella* isolates were biochemically identified. The proportion of identified *E. coli* and *Salmonella*-positive isolates from 3 slaughterhouses were 76.9% (834/1085) and 93.1% (348/374), respectively. In markets, 610 suspected *E. coli* isolates and 193 suspected *Salmonella* isolates were biochemically identified. The frequency of identified *E. coli* and *Salmonella*-positive isolates from 2 markets were 74.9% (467/610) and 87.1% (168/193), respectively.

In slaughterhouses (A, B and C), a total of 120 tested samples (feces and carcass) were contaminated with *E. coli* in 100% (120/120) and *Salmonella* in 64.2% (77/120) of cases; and of 60 swine fecal samples, the detection rates of *E. coli* and *Salmonella* were 100% (60/60) and 53.3% (32/60), respectively. Among 60 carcass swab samples, the detection rates of *E. coli* were in 100% (60/60) and that of *Salmonella* were 75.0% (45/60). At slaughterhouse C, fecal and carcass swab samples were positive for *Salmonella* in lower percentages than those in slaughterhouse A and B. Overall, the detection rates of *Salmonella* isolates contaminated in carcass swab samples were significantly higher than those in fecal samples ($p < 0.05$). In markets, a total of 67 tested samples were contaminated with *E. coli* in 100% of cases and *Salmonella* was

detected in 94.0% of samples (63/67). Of pork samples, the detection rates of *E. coli* were 100% (43/43), whereas those of *Salmonella* were 93.0% (40/43). Of 24 cutting board swab samples, the detection rates of *E. coli* were 100% (24/24), whereas those of *Salmonella* were 96.8% (23/24). These results indicated that the detection rates of *Salmonella* contamination from pork and cutting board swab samples were comparably high percentages. One likely conclusion is that the cutting board is the source of *Salmonella* contamination in the fresh market. In the future, for *E. coli* isolates, pathogenicity-associated genes will be characterized to enumerate the proportion of pathogenic *E. coli* among the isolates. For *Salmonella* isolates, serotyping will be conducted by the WHO National Salmonella and Shigella Center Laboratory (NSSC), Nonthaburi, Thailand. In parallel, each of the isolates will be phenotypically and genetically investigated for their AMR potential against a total of 8 of antibiotic families. Both *E. coli* and *Salmonella* isolated from the same feces or pork sample will be characterised to find the phenotypic associations in the drug-resistant potential between these two bacteria, and then determine the correlation of the genes encoding the same drug resistant potential onto the plasmids in two bacteria.

Detailed Results for the **"Unit for Pathogen genomics"**

1. Research

1.1 Goals

As the "Unit for Pathogen Genomics", King Abdullah University of Science and Technology and Hokkaido University (Research Center for Zoonosis Control) conduct researches on zoonotic pathogens from a genomics perspective. The outcomes of the research are used for the development of diagnostic technologies and therapeutic strategies directed against the zoonosis caused by protozoan parasites.

1.2 Current Progress/Future Developments

1.2.1 Construction of base

● Role sharing with affiliated universities

Affiliated institutions	Researcher name	Description of research
King Abdullah University of Science and Technology, Saudi Arabia	Professor Arnab Pain Assistant Professor Axel Martinelli (Based at Hokkaido University)	・Linking genes to phenotypes in malaria parasites by classical genetics and genomic technologies
Hokkaido University, Japan		
Research Center for Zoonosis Control	Professor Chihiro Sugimoto Professor Kimihito Ito Assoc. Professor Junya Yamagishi Assoc. Professor Manabu Igarashi Assoc. Professor Chie Nakajima	・Analysis of horizontal gene transfer in protozoan parasites and their vectors ・Development of point-of-care diagnostic systems in resource-poor settings (Collaboration with UCD unit)
Other Collaborators Assoc. Professor Richard Culleton, Malaria Unit, Institute of Tropical Medicine, Nagasaki University Dr. Sisira Pathirana, Department of Parasitology, University of Colombo, Sri Lanka Assoc. Professor Takashi Abe, Institute of Science and Technology, Niigata University, Japan		

1.2.2 International Collaborative Research

● Current progress in meeting initial research goals

Project III-A: Linking genes to phenotypes in malaria parasites by classical genetics and genomic technologies

Malaria kills almost a million children every year. Despite significant financial investment and decades of research, we have no effective vaccine, and the drugs and anti-mosquito measures that are relied upon for control are failing. Recently, there have been reports that the malaria parasite is developing resistance against artemisinin, which is the most effective drug currently available. If resistance to this drug continues to emerge, and spread, it is conceivable that the burden of

malaria, currently intolerable, will increase further. Given this situation, new strategies to control the malaria parasite are urgently required. Of the six species of *Plasmodium* parasites that cause disease in humans, *Plasmodium vivax* (*P. vivax)* is the most widespread, and causes the highest burden of disease outside of tropical Africa. Despite this, there is currently very little *P. vivax*-specific vaccine research ongoing. Furthermore, malaria parasite species closely related to *P. vivax*, but parasitic on macaque monkeys have recently been observed infecting humans in areas of Southeast Asia [*Plasmodium knowlesi* (*P. knowlesi*) and *Plasmodium cynomolgi* (*P. cynomolgi*)], raising the spectre of zoonotic malaria. In recent years, with the spectacular advance in high-throughput genomic technologies, there is an increased opportunity to combine modern genomic technologies with classical genetics and bioinformatics-driven approaches to study biology of the parasite with a focus to look for candidate malaria vaccines in a genome-wide manner. It is now possible to apply classical genetic-cross experiments in malaria parasites with distinct phenotypes (e.g. differences in drug susceptibility, antigenicity, growth rate, relapsing behaviour etc.) and undertake a holistic approach by applying deep sequencing and statistical algorithms to identify genes for a given phenotype within a short period of time in genome-wide screens.

P. cynomolgi is one of the most closely related simian malaria species to *P. vivax* and has been used to model various aspects of human malaria, such as protective immunity and relapse. Furthermore, its zoonotic potential makes it medically relevant. The existence of protocols for genetic manipulation also makes it an ideal model for follow-up studies. One of the objectives of the proposed work is thus to identify genes for the target antigens of "strain"-specific protective immunity against blood and liver stage parasites of *P. cynomolgi*, using the Old World toque monkeys (*Macaca sinica*) as a model host. This is expected to identify genes that are targets for immunity and provide vaccine candidate proteins that will be effective against *P. cynomolgi*, and very likely against *P. vivax* and *P. knowlesi*. As a parallel and complimentary approach, we will establish *in vitro* cultures of *Plasmodium falciparum* (*P. falciparum*) and potentially *P. cynomolgi* in HU. The former will be used to perform *in vitro* selection of an available cross for *in vitro* growth rate and adaptation, chloroquine resistance and polyclonal-antibody immune mediated selection. The purpose of these experiments will be to apply the Linkage Group Selection (LGS) approach to *P. falciparum in vitro* for the first time and explore the nature of strain-specific immunity (SSI) in the most devastating human malaria parasite. These sets of *in vitro* and *in vivo* experiments will examine the viability of artificial genetic crosses in *P. cynomolgi* and, also, in *in vitro* cultures for LGS studies and partially remove the need for a vertebrate host, which will greatly facilitate future experiments with human and simian malaria parasites. Adapting *P. cynomolgi* parasites to *in vitro* cultures with human blood will both facilitate future transfection studies with the species (e.g. using the CRISPR-CAS system) and also allow us to study adaptation of a zoonotic species to infections in human hosts.

Status of the Study

Current efforts have been focused on establishing the facilities for the experimental work at HU while a pilot experimental cross in *P. cynomolgi* is being tried at the University of Colombo. This included establishing the necessary facilities for housing and maintaining mosquito colonies, obtaining relevant parasite strains, obtaining the necessary permits for experimental work with primates, malaria parasites and mosquitoes and hiring an experienced researcher for the *in vitro* and animal work.

·*P. falciparum:* HB3 genome assembly and *in vitro* application of LGS

LGS has been widely applied *in vivo* in both rodent models of malaria and against the human parasite *P. falciparum*.

However, thus far, there have been no test of its effectiveness *in vitro*. In order to test that, a pre-existing cross between two strains of *P. falciparum* (HB3x3D7) was grown *in vitro* and exposed to the antimalarial drug pyrimethamine (PYR). While HB3 is PYR resistant, 3D7 is susceptible. The mutation underlying PYR resistance in HB3 [S108A in the dihydrofolate reductase gene (DHFR) on chromosome 4] is well documented. The experiment thus aimed at identifying a corresponding signature of selection (referred to as a "selection valley") in a locus containing the DHFR gene on chromosome 4. As part of the experiment, the *de novo* assembly of the HB3 genome based on a combination of long PacBio and Oxford Nanopore Technologies (ONT) reads was performed. This produced a more consolidated assembly than the one currently available (50 vs 1194 scaffolds) and allowed a better filtering of the single nucleotide polymorphisms (SNPs) used as quantitative markers for the experiment. The final outcome shows the presence of a single significant selection valley against the sensitive 3D7 alleles on chromosome 4. The locus encompasses the DHFR gene, thus validating the application of the LGS methodology *in vitro* in malaria. This result is relevant for future plans to produce novel crosses of human malaria parasites using humanised mice to identify loci associated with antimalaria resistance in the field.

・Sequencing of *P. cynomolgi* genomes

Three strains of *P. cynomolgi* have been selected for the production of crosses in monkeys to study the relapse and SSI phenotypes in malaria. Relapses in malaria are due to the formation of a dormant stage (the hypnozoite) in the liver of the host, whose genetic basis is still unknown. During a collaboration with Prof. Pathirana in Sri Lanka, a strain of *P. cynomolgi* (which normally forms hypnozoites) that had never been observed inducing relapses was described. DNA from these strains, as well as that of two sporozoite-inducing strains was obtained and sequenced by Illumina technology. As part of an effort to assemble the genome and provide a complete picture of both the SNPs as well as more complex structural variations, work is currently underway to apply selective whole genome amplification (sWGA) to the DNA of the parasites to provide enough material for the production of long sequence reads by PacBio and/or ONT sequencing. sWGA has been successfully applied previously to various malaria species present at low quantities in host blood (as is the case with *P. cynomolgi*) to produce enough template for whole genome sequencing (WGS). By repeating the same procedure in *P. cynomolgi* for the first time, the goal is to produce reference genomes for each of the strains for further studies.

・Sequencing and assembly of a zoonotic *Plasmodium simium* (*P. simium*) genome

P. simium is a monkey parasite closely related to the human parasite *P. vivax* and found exclusively in South America. In fact, *P. simium* is thought to represent a case of anthroponosis of *P. vivax* from humans to monkeys. Recently, the case of a human infection with *P. simium* was reported from Brazil. A genome sequencing and assembly project of this zoonotic case of infection was started as a collaboration between KAUST in Saudi Arabia and the GI-CoRE within HU. Since no reference genome assembly of *P. simium* is currently available, this represents the first time such a genome will be sequenced, assembled and analysed. An initial assembly split into 2184 scaffolds based solely on short Illumina reads was produced and combined into 14 composite chromosomes by synteny with *P. vivax*, and efforts are currently underway to apply sWGA to produce enough DNA for long read sequencing. This should further consolidate the assembly into larger scaffolds and remove current gaps. The assembly will then be annotated and compared with the human *P. vivax* genome to both confirm its origin as an anthroponosis and to identify key mutations involved in host switching.

Project III-B: Analysis on horizontal gene transfer (HGT) in protozoan parasite genomes

Apicomplexan parasites exhibit a wide range of biological diversities. The free-living photosynthetic algae *Chromera*, which is the ancestor of apicomplexans, has evolved toward the parasitic life style by acquiring infectivity to non-vertebrates, and eventually to vertebrates. One of the crucial steps in the evolutionary path of apicomplexans is adaptation to arthropods which serve as vectors for the transmission between vertebrate hosts. Parasites utilize arthropods not only as compartments for the development and vehicles in transmission, but also as partners to exchange genetic material.

Horizontal gene transmission (HGT) is a well-studied phenomenon amongst bacteria; however, it sometime occurs beyond the kingdoms of Archae- and Eubacteria. HGT often results in "gain-of-function" of the organism that has acquired the genetic material. The recent report of HGT from mammals to ticks which facilitates the blood-suckling process is a good example of the significance of HGT in the host-adaptation of arthropods. Therefore, HGT is considered to be one of important driving forces in the evolution and acquisition of novel traits.

We are now trying to detect HGT in apicomplexan parasites and their vectors by a genome-wide approach (Figure 12). Traditionally, evidence of HGT have been detected through conventional tools, such as BLAST and phylogenomics. Once candidate HGT genes are found, homologous genes are identified by the BLAST and phylogenetic searches. However, this approach may be not so efficient to detect evidence of HGT in a genome-wide manner. In addition, in the case that the origins of the HGT are unknown organisms for which DNA sequences have not been well characterized, the conventional homology-based approaches have fundamental limits. For this purpose, Batch Learning Self-Organizing Mapping

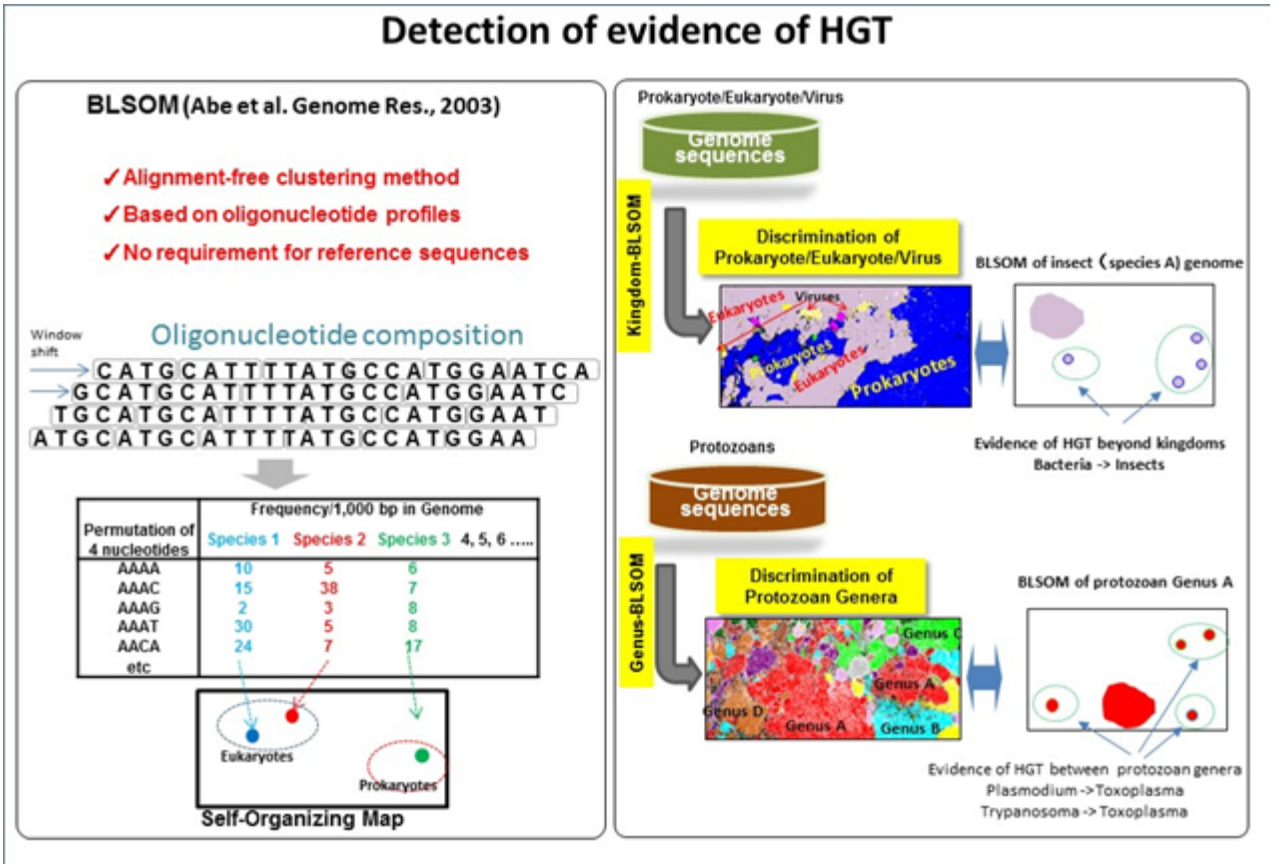


Figure 12

Principal of BLSOM and detection of the evidence of HGT in apicomplexan parasites and their vectors by a genome-wide approach.

(BLSOM), developed by Dr. T. Abe (Niigata University), can effectively find hidden signatures in genome sequences of target organisms based on oligonucleotide composition. This alignment-free clustering method which has been successfully applied for phylogenetic classification of bacterial populations and arthropods is a very powerful tool to find evidence of HGT in parasite and vector genomes. We expect that our approach can provide insights into the evolution of interactions between parasites and their vector arthropods.

Status of the Study

In order to evaluate clustering capacity of BLSOM, we obtained complete genome sequences of arthropods from 11 genera and 34 species, including tsetse fly (*Glossina morsitans*), protozoan parasites from 23 genera present in genome databases and analyzed by BLSOM. The sequences from the genome of *Glossina* clustered into a single node while several sequences were separated from this cluster. These non-clustering sequences were mapped on the bacterial genus level, which are therefore presumed to be of bacterial origins. These presumptive sequences included those from *Wolbachia*, endosymbionts in insects, *Rickettsia*, potential animal pathogens, and several other bacterial genera. To validate the accuracy of the BLOSM HGT predictions, the sequences presumably derived from *Wolbachia* were used as query sequences for BLAST (Figure 13). From a total of 38 sequences, 36 hit to known *Wolbachia* sequences in the gene database, resulting in an accuracy of 94.7 %. Genus level BLSOM maps have also been constructed by using genome sequence data from *Plasmodium*, *Toxoplasma*, *Trypanosoma*, and other protozoan genera. BLSOM analysis gave clear discrimination for each of the genera. In addition, mapping patterns by BLOSM are in good agreement with phylogenetic relationships analyzed by conventional homology-based analyses such as BLAST and Clustal Omega. From the clustering profiles, we could identify evidence of putative HGT between distant organisms, such as HGT between protozoans. Evidence of HGT in protozoan genomes from prokaryotes are also being analysed. In order to provide evidence that HGT has occurred during the course of parasite/vector evolution, further analyses are needed.

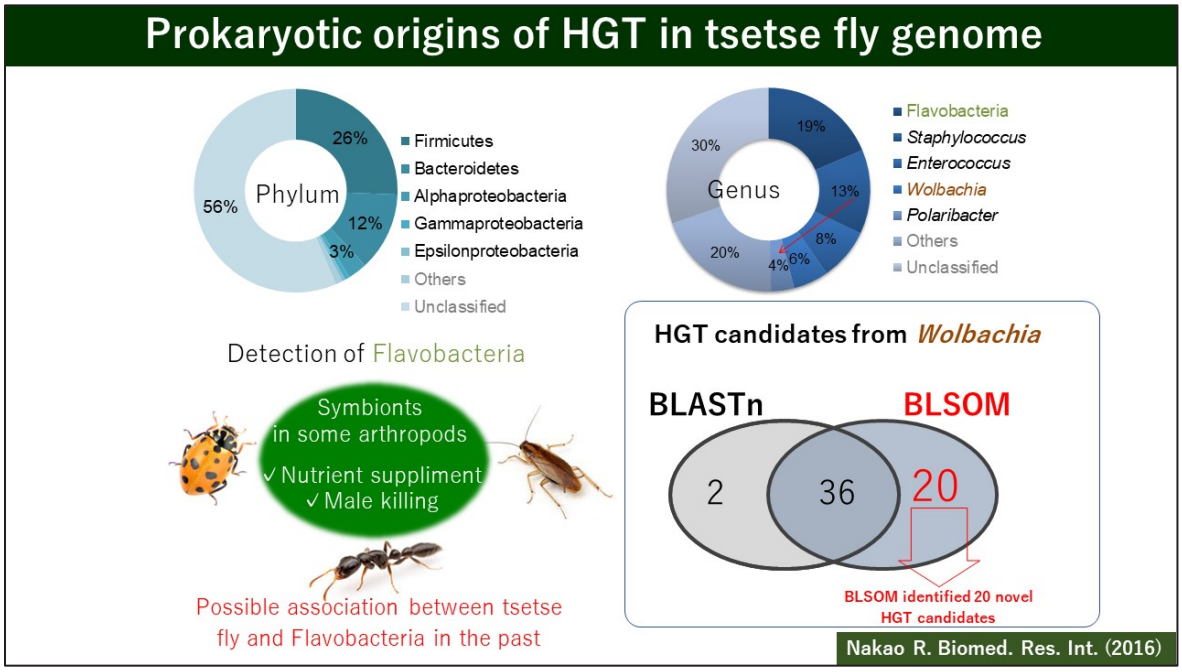


Figure 13
Schematic summary of potential HGT observed in tsetse fly genome.

1) Possibility of contamination of bacterial genomic DNA in the materials used for genome sequencing for parasites/vectors should be excluded. This can be done by analyzing flanking genome sequences of putative HGT regions.
2) Functional analysis of the genes obtained by HGT should be carried out. Coding regions in putative HGT regions should be determined and annotated. Possible role of the horizontally-acquired genes in metabolic pathways, parasitism and other biological activities will be analyzed. We also envisage undertaking gene knock out/down experiments in the target parasites/vectors in order to determine the biological significance of HGT.

Project III-C: Development of point-of-care diagnostic systems in resource-poor settings

Loop-mediated isothermal amplification (LAMP) is a rapid and sensitive tool used for the diagnosis of a variety of infectious diseases. One of the advantages of this method over polymerase chain reaction is that DNA amplification occurs at a constant temperature, usually between 60–65°C; therefore, expensive devices such as thermal cyclers are unnecessary for this step. However, LAMP still requires complicated sample preparation steps and a well-equipped laboratory to produce reliable and reproducible results, which limits its use in resource-poor settings in most developing countries.

Status of the Study

We have made several substantial modifications to the technique to carry out diagnosis at epidemiological hot spots or at point-of-care facilities for human African Trypanosomiasis (HAT). One of the improvements is that the LAMP reagents are air-dried in a single tube so that the activity can be retained for over 6 months at ambient temperatures. This ready-to-use LAMP provides an ideal diagnostic system in resource-poor settings and is now currently being tested at clinical laboratories in Zambia and Malawi as a point-of-care methodology. We are now also introducing a portable sequencing system for point-of-care diagnosis of various infectious diseases including HAT, dengue fever and chikungunya fever. The recent invention of a portable sequencer, “MinION” has drastically changed the way DNA sequencing outside specialized laboratories. MinION has been successfully miniaturized in the form of a portable, one-time use as a universal serial bus (USB) device connected to a laptop personal computer (PC) at a reasonable cost that covers both the device itself as well

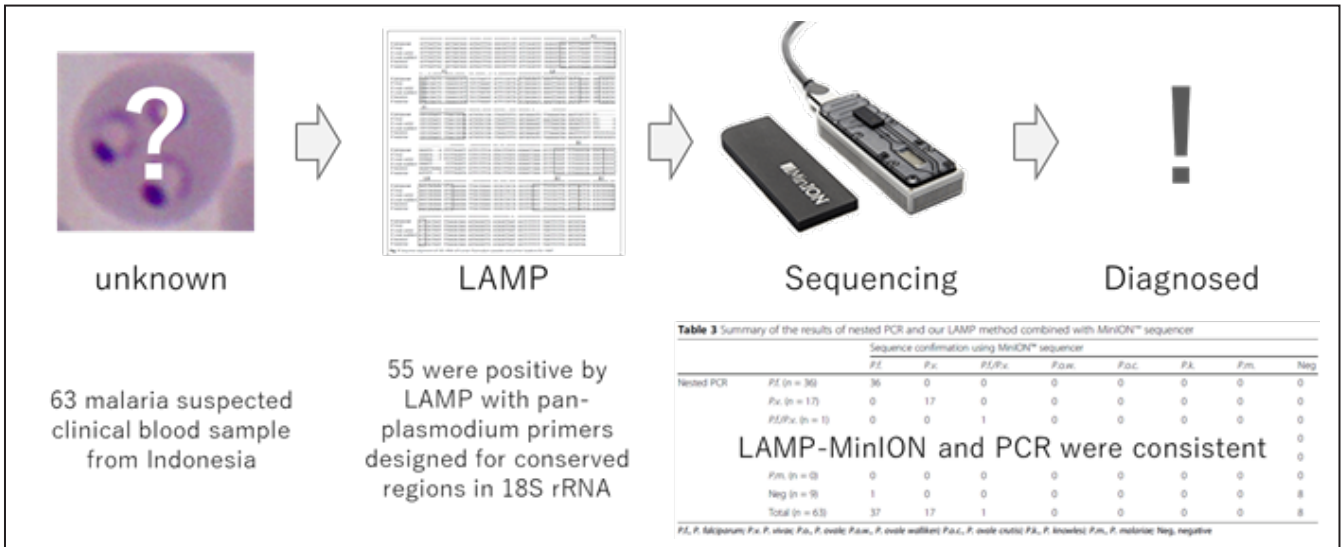


Figure 14
Schematic summary of point-of-care diagnostic systems based on LAMP-MinION system.

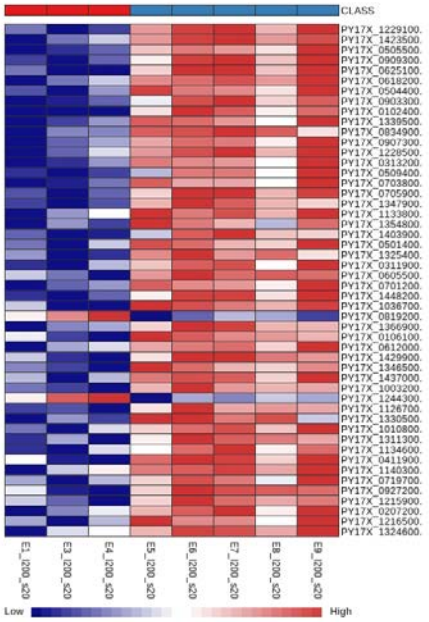
as consumables. Conversion of a sample to a sequencing template is also simple, consisting solely of adaptor ligation under isothermal conditions, which can be completed within 1-2 hours. One of the major advantages of the MinION sequencer lies in the fact that it does not require any installation of conventional laboratory equipment or the use of specific skills in molecular biological techniques in its sequencing procedure. These features of MinION in combination with LAMP have opened the opportunity to enable precise genotyping of pathogens in tropical diseases in rural hospitals or in field circumstances. In order to accommodate demand for the dried reagents, we have set up a small-scale factory with a semi-automated system by using an ink-jet printer at the Research Center for Zoonosis Control, HU. Reagents prepared by this system are now provided to the University of Zambia and the University Teaching Hospitals, Zambia and used for clinical diagnoses of HAT.

With the combination of MinION with isothermal amplification of viral RNA, we were able to amplify and sequence target viral genomes in a single day. The analysis of blood samples collected from 141 Indonesian patients demonstrated that this method enables the clinical identification and serotyping of the dengue virus with both high sensitivity and specificity. Similar analyses were conducted on 80 Vietnamese and 12 Thai samples with comparable performance standards. Based on the obtained sequence information, we have demonstrated that this approach is able to produce indispensable information for etiologically analyzing annual or regional diversifications of the pathogens (Figure 14, page 35). A pilot study of the clinical use of the LAMP-MinION system is also underway at the National Institute of Hygiene and Epidemiology (NIHE), Vietnam in collaboration with Prof. William Hall (University College Dublin). The MinION sequencing costs $500 per run; thus, it is affordable though still expensive for clinical use. To reduce the cost-per-test, we examined multiplex sequencing runs with indexed primers. We designed 9 indexes in the loop region of the forward inner primers and performed the LAMP assay with plasma obtained from patients. In total, we tested 72 plasma by LAMP and 18 amplicons were selected and MinION sequencing performed in duplicate. More than 20,000 primary reads were successfully obtained from each run and they were uploaded and a base calling process was conducted. Our approach is able to produce indispensable information for etiologically analyzing annual or regional diversifications of the pathogens.

Project III-D Additional activities under the framework of GI-CoRE

・Effects of the Pam2Cys adjuvant molecule on malaria parasites

Pam2Cys is a powerful vaccine adjuvant that has been previously shown to modulate strong immune responses in test subjects. Previous test has indicated that when provided as a preventive treatment it can inhibit the liver stage of malaria parasites of the rodent model *Plasmodium yoelii*. In an effort to understand both the antimalarial activity of Pam2Cys and possible countermeasures adopted by surviving parasites, the transcriptome of parasites emerging from the liver after Pam2Cys treatment was compared with that of control infections. Results have shown an inhibition of parasite transcription factors and of the expression of surface antigens, which suggests epigenetic adaptations to the selection pressures imposed by a stimulated immune system (Figure 15). Intriguingly, the pattern of transcriptional inhibition are remarkably similar to those recently observed in the transcriptomes of parasites, inducing severe malaria. This indicates that Pam2Cys may be inducing stressed conditions in the immune system similar to those observed during severe malaria and that parasite may be displaying similar adaptive mechanisms. This study was carried out in collaboration with Prof. Jackson and Dr. Chua (University of Melbourne).



ID	Name	P-value	FDR
GO:0044409	entry into host	0.01703831	0.0463936115
GO:0052192	entry into other organism involved in symbiotic interaction	0.01703831	0.0463936115
GO:0052126	movement in host environment		0.0463936115
GO:0002263	cell activation involved in immune response	0.029981398	0.0463936115
GO:0002252	immune effector process	0.029981398	0.0463936115
GO:0002312	B cell activation involved in immune response	0.029981398	0.0463936115
GO:0002285	lymphocyte activation involved in immune response	0.029981398	0.0463936115
GO:0002366	leukocyte activation involved in immune response	0.029981398	0.0463936115
GO:0042113	B cell activation	0.044637989	0.0463936115
GO:0046649	lymphocyte activation	0.044637989	0.0463936115
GO:0045321	leukocyte activation	0.044637989	0.0463936115
GO:0006955	immune response	0.044637989	0.0463936115

Figure 15

Analysis of the parasite transcriptome upon emerging from the liver shows the downregulation of 90 gene and upregulation of 2 genes. GO term analysis of downregulated genes highlighted terms associated with activation of the host immune system, consistent with the downregulation in the expression of several surface antigens. Various transcription factors and metabolic processes were also inhibited.

● Research achievements (FY 2014-2019)

1. International collaborative papers (peer reviewed)	Featured in journals: #210
2. Other publications	Featured in journals: #100
3. Books published	#5
4. Oral presentations	Keynote speeches/ invited lectures: #76 Other presentations: #18
5. Patent applications	Patent applications: #32 (#12 in Japan, #20 overseas) Patent registrations (of the above number): #26
6. Awards received	#7
7. External grants	#3
8. Gifts	#4
9. Science outreach activities	#31
10. Training	#2
11. Collaboration with institutions	#31

1. International collaborative papers (peer reviewed)

1.1 International collaborative papers co-authored with overseas affiliated universities：#75

i) Papers where "GI-CoRE" is stated as an affiliated institution

ii) Papers which mention "Hokkaido University" in the acknowledgements

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1.2 International collaborative papers：#135

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3 Published books

Number of books: #5

1) Carr MJ, Gonzalez G, Teeling EC, Sawa H: "Bat Polyomaviruses: A Challenge to the Strict Host-Restriction Paradigm within the Mammalian *Polyomaviridae.*" In *Bats and Viruses: Current Research and Future Trends*, Corrales-Aguilar E, Schwemmle M (ed), Caister Academic Press, U.K.: 87-118 (2020), ISBN: 978-1-912530-14-4 i)

2) Yamaguchi T, Nakajima C, Suzuki Y: "Acquisition of drug resistance by *Mycobacterium tuberculosis* –Tuberculosis and nontuberculous mycobacteriosis. The expert's lecture on recent findings useful for actual clinical activiries", *Respiratory Journal*,64(4): 650-656 (2018) i)

3) Villanueva MA, Mingala CN, Nakajima C, Suzuki Y: "Emerging Infectious Diseases in Water Buffalo – An economic and Public Health Concern." Intech Open Access Publisher, Rijeka, Croatia, doi: 10.5772/intechopen.73136 (2018) i)

4) Kongsoi S, Nakajima C, Suzuki Y: "Quinolone Resistance in Non-typhoidal *Salmonella.*" In *Current Topics in Salmonella and Salmonellosis,* Mares M (eds.), Intech Open Access Publisher, Rijeka, Croatia:115-135 (2017) i)

5) Thapa J, Nakajima C, Gairhe KP, Maharjan B, Paudel S, Shah Y, Mikota SK, Kaufman GE, McCauley D, Tsubota T, Gordon SV, Suzuki Y: "Wildlife tuberculosis: An emerging threat for conservation in South Asia." In *Global Exposition of Wildlife Management.* Cardona P-J (eds.), Intech Open Access Publisher, Rijeka, Croatia: 73-90 (2017) i)

4 Oral presentations

4.1 Keynote lectures/Invited lectures: #76

1) Ayato Takada: “Approaches for the development of therapeutics for Ebola virus disease”, University of Miyazaki, Miyazaki, Japan, Open seminar for infectious diseases, 2020.1.24 [Domestic conference] (invited speaker)
2) Yoshihiro Sakoda: “Classical swine fever outbreaks in Japan in 2018-2019 and related research activities”, Tamsui, Taiwan, Experience Exchange on Prevention Techniques and Training Course of Diagnosis of Classical Swine Fever, 2019.11.19 [International symposium] (invited speaker)
3) Yoshihiro Sakoda: “Classical swine fever outbreaks in Japan in 2018-2019”, China Institute of Veterinary Drug Control, Beijing, China, International Symposium for Classical Swine Fever, 2019.10.23-26 [International symposium] (invited speaker)
4) Yoshihiro Sakoda: “Classical swine fever outbreaks in Japan in 2018-2019”, Animal and Plant Quarantine Agency, Korea, Seminar for Classical Swine Fever, 2019.10.15 [International symposium] (invited speaker)
5) Hirofumi Sawa, William Hall: “Tactics for Global Infectious Diseases Control”, Tsukuba International Congress CenterTsukuba Conference, Ibaraki, Japan, Tsukuba Conference 2019, 2019.10.3 [International conference] (invited speaker)
6) Stephen Gordon: “One Health route to exploring virulence in the Mycobacterium tuberculosis complex”, The Grand Hall & Winter Gardens at The Drum at Wembley, London, UK, VALIDATE-BSI 2019 Conference, 2019.10.3 [International conference] (Invited Speaker)
7) Chie Nakajima, Yasuhiko Suzuki: “Genetic analyses of multidrug-resistant Mycobacterium tuberculosis clinical isolates collected in Asian countries.”, Awaji Yumebutai International Conference Center, Awaji, Japan, The 18th Awaji International Forum on Infection and Immunity, 2019.9.11 [International symposium] (invited speaker)
8) Ayato Takada: “Recent topics on Filovirus research”, Tsukuba international congress center, Tsukuba, Japan, The 162nd Meeting of the Japanese Society of Veterinary Science, Symposium “Infectious diseases threatening humans and animals”, 2019.9.10 [Domestic conference] (invited speaker)
9) Chie Nakajima: “Development of a Simple and Rapid Drug-resistant Campylobacter Detection Method Utilizing DNA-array Technique”, University of San Agustin, Ilo Ilo city, the Philippines, The 4th International Symposium on Livestock Biotechnology, 2019.7.15 [International symposium] (invited speaker)
10) William Hall: “Special lecture: Infectious diseases caused by flaviviruses,” Enyu Gakusya, Hokkaido University, Sapporo, Japan, Symposium and Workshop for Diagnosis-by-Sequencing using MinION, 2019.7.10 [International symposium] (invited speaker)
11) Ayato Takada: “Ebola and Marburg hemorrhagic fever”, Sapporo Convention Center, Sapporo Japan, The 8th Annual Meeting of the Japan Psychiatric Medical Conference, 2019.7.5 [Domestic conference] (invited speaker)
12) Yoshihiro Sakoda: “How to implement cooperation among Asian countries for the control of highly pathogenic avian influenza (HPAI)?”, National Institute for Environmental Studies, Japan, NIES_NIER_USGS International workshop 2019, 2019.5.21-23 [International symposium] (invited speaker)
13) Stephen Gordon: “Exploring the molecular basis of virulence in the Mycobacterium tuberculosis complex”, Sapporo Convention Center, Sapporo, Japan, The 92nd Annual Meeting of Japanese Society for Bacteriology, 2019.4.23 [International symposium] (Invited Speaker) *

14) Chie Nakajima, Yasuhiko Suzuki, Jeewan Thapa: “Development of new methods for the characterization of bacterial pathogens”, Sapporo Convention Center, Sapporo, Japan, The 92nd Annual Meeting of Japanese Society for Bacteriology, 2019.4.23 [International symposium] (invited speaker) *
15) Chie Nakajima: “Genetic analyses of multidrug-resistant *Mycobacterium tuberculosis*”, National University of Singapore, Singapore, Asia - Pacific Scientific Workshop 2019.3.5 [International symposium] (invited speaker)
16) Yasuhiko Suzuki, Chie Nakajima: “Molecular epidemiology of human and animal tuberculosis in Asian countries”, La Thanh Hotel, Hanoi, Vietnam, 21st International Conference on Emerging Infectious Diseases in the Pacific Rim, 2019.2.26 [International symposium] (invited speaker) *
17) Norikazu Isoda: “Antimicrobial resistance survey in Thailand”, Thammasat University, Rangsit, Thailand, 3rd One Health lecture Series on Antimicrobial Resistance, Faculty of Public Health, 2018.12.20 [International symposium] (invited speaker)
18) Takada Ayato: “Toward the control of viral zoonoses: Our SATREPS activity in Africa”, Nagasaki University, Nagasaki, Japan, The 59th Annual Meeting for the Japanese Society of Tropical Medicine, 2018.11.10 [Domestic conference] (invited speaker)
19) Stephen Gordon: “Zoonotic Tuberculosis: Comparative analyses of the human and bovine tubercle bacilli” , The Hague, Netherlands, The 49th Union World Conference on Lung Health, 2018.10.26 [International conference] (Invited speaker)
20) Yasuhiko Suzuki: “Zoonosis Control”, University of the Philippines Cebu, Cebu, The Philippines, 3rd International Livestock Biotechnology Symposium, 2018.7.16 [International symposium] (invited speaker) *
21) Ayato Takada: “Recent advances in Ebola virus research”, Nitori Cultural Hall, Sapporo, Japan, The 20th Annual Meeting of the Japan Society for Health Care Management, 2018.6.8 [Domestic conference] (invited speaker)
22) Chie Nakajima: “The current situation of multidrug-resistant tuberculosis in Asia and development of rapid genetic diagnostic methods”, Nippon Veterinary and Life Science University, Tokyo, Japan, The 45th Symposium of the Japanese Society of Antimicrobials for Animals, 2018.4.28 [Domestic symposium] (invited speaker)
23) Ayato Takada: “Recent Topics from Ebola virus Research”, Inner Mongolia Agriculture University, Hohhot, Inner Mongolia, Inner Mongolia Agriculture University Seminar, 2018.4.18 [International conference] (invited speaker)
24) Ayato Takada: “Filoviruses”, Fukuoka Convention Center, Fukuoka, The 91th Annual Meeting of Japanese Society for Bacteriology, 2018.3.27 [Domestic conference] (invited speaker)
25) Hirofumi Sawa: “Development of anti-viral compounds for zoonotic viral diseases”, Mahidol University, Bangkok, Thailand, International Joint Forum on Infectious Disease Research 2018, 2018.2.28 [International symposium] (invited speaker)
26) Hiroshi Kida: “For the cotrol of avian influenza and the preparedness for pandemic influenza”, Rangsit Campus, Thammasat University, Thailand, A special Lecture, 2017.12.4 (invited lecture)
27) Ayato Takada: “Recent advances in Ebola virus Research”, Keio Plaza Hotel, Tokyo, The 66th Annual Regional Meeting of the Japanese Association for Infectious Diseases, 2017.11.1 [Domestic conference]
28) Hirofumi Sawa, Keita Matsuno, Ryo Nakao, Michihito Sasaki, Yasuko Orba: “Discovery of diverse arthropod bunyaviruses in field-collected mosquitoes and ticks and their evolution”, Osaka International Convention Center, Osaka, Japan, The 65th Annual Meeting of the Japanese Society for Virology. 2017.10.26 [International symposium] (invited speaker)

29) Yoshihiro Sakoda: “Current situation of H5Nx highly pathogenic avian influenza epidemic in the world”, Beijing, China, China & Asia-Pacific Conference on Emerging Infectious Diseases (CAPEID), 2017.9.12-15 [International conference]

30) Keita Matsuno, Masahiro Kajihara, Nodoka Kasajima, Ryo Nakao, Shiho Torii, Hiroshi Shimoda, Ken Maeda, Ayato Takada, Hideki Ebihara, Hirofumi Sawa: “Genetic diversity among phleboviruses identified in ticks; implication of distinct evolutional pathways of phleboviruses”, Awaji Yumebutai International Conference Center, Hyogo, Japan, The 16th Awaji International Forum on Infection and Immunity. 2017. 9.8 [International conference] (invited speaker)

31) Keita Matsuno: “Genetic diversity among phleboviruses identified in ticks; implication of distinct evolutional pathways of phleboviruses”, Awaji, Hyougo, The 16th Awaji International Forum on Infection and Immunity, 2017.9.5-8 [International conference]

32) Ayato Takada: “Genetic Predisposition to Acquire a Polybasic Cleavage Site for Highly Pathogenic Avian Influenza Virus Hemagglutinin”, B-nest Pegasart, Shizuoka, The 31st Annual Symposium for Japanese Influenza Virologist, 2017.6.9 [Domestic symposium]

33) Axel Martinelli: “Detection of loci under selection using Linkage Group Selection (LGS) in vitro” Hokkaido University, Sapporo, The 86th Annual Meeting of the Japanese Society of Parasitology, 2017.5.29 [Domestic conference]

34) Ayato Takada: “Ebolavirus --Ecology and antiviral strategies--”, Korea University, Seoul, 11th Annual Meeting of Korean Society of Zoonosis, 2017.5.19 [International conference]

35) Ayato Takada: “Recent advances in Ebola virus Research”, Kobe Convention Center, Kobe, The 32nd Annual Meeting of Japanese Society for Infection Prevention and Control, 2017.2.25 [Domestic conference]

36) Yoshihiro Sakoda：“Challenges for providing technical training HPAI and LPAI: Research Center for Zoonosis Control, Hokkaido University (Japan)”, Tokyo, Japan, Regional Meeting of OIE Reference Centers in Asia and the Pacific, 2017.2.6-7 [International Conference]

37) Hiroshi Kida: “How to control avian influenza and how to prepare for future pandemics in humans”, Rangsit Campus, Thammasat University, Thailand, Keynote Lecture for Lecture Series on One Health First Meeting on Technical Cooperative Network, 2016.11.15 (invited lecture)

38) Michael Carr: "Identification of the same polyomavirus species in different African horseshoe bat species is indicative of short-range host-switching", Osaka International Convention Center, Osaka, The 65th Annual Meeting of the Japanese Society for Virology, 2016.10.26 [Domestic conference]

39) Hiroshi Kida: “We are prepared for pandemic influenza”, Sapporo Convention Center, Sapporo, Japan, The 8th International Global Virus Network Meenting, 2016. 10.25 [International conference]

40) Ayato Takada: “Neutralization and Antibody-Dependent Enhancement of Ebolavirus”, Sapporo Convention Center, Sapporo, 8th International Global Virus Network Meeting, 2016.10.25 [International conference]

41) Ayato Takada: “Biochemistry for sustainable global health, Recent advances in diagnostics and therapeutics for Ebola virus disease”, Sendai International Center, Sendai, The 89th Annual Meeting of the Japanese Biochemical Society, 2016.9.25 [Domestic conference]

42) Ayato Takada: “Ebolavirus Entry into Cells –Neutralization and Antibody-Dependent Enhancement–”, Awaji Yumebutai International Conference Center, Awaji, The 15th Awaji International Forum on Infection and Immunity, 2016.9.9 [International conference]

43) Hiroshi Kida: “Control of avian influenza and preparedness for pandemic influenza”. Asia-Pacific WHO/OIE/FAO Joint Workshop on Surveillance Prevention and Control of Zoonotic influenza, Paro, Bhutan, 2016.8.30 [International conference] (invited speaker)
44) Ayato Takada: “Influenza as a Zoonosis”, Izumi Garden, Tokyo, The 24th Meeting of Respiratory/Infectious Disease Study Group, 2016.8.20 [Domestic conference]
45) Brendon Yew Loong Chua:"Multi-tasking an influenza vaccine to provide rapid and long-term protection against influenza and secondary pneumococcal infection”, Albufeira, Portugal, Engineering Conference International on Vaccine Technology VI, 2016.7.16[International conference]
46) Hiroshi Kida: “We are prepared for pandemic influenza”, WHO Collaborating Centere Conference Room, Hokkaido University, Sapporo, Japan, The 4th Meeting of the Consortium for the Control Zoonoses, 2016.7.8 [Domestic conference]
47) Hiroshi Kida: “Pandemic influenza as an example of emerging zoonoses” University of Zambia School of Veterinary Medicine Veterinary School Main Lecture Theatre. Lusaka, Zambia, 2016.6.14 [International Conference] (invited lecture)
48) Hiroshi Kida: “Pandemic influenza as an example of emerging zoonoses”, Nagasaki University, Nagasaki, Japan, 2016 Training Course for Tropical Medicine, 2016.6.3 (invited lecture)
49) Ayato Takada: “Recent Topics on Zoonosis Research –Ebola hemorrhagic fever–”, Fukuoka Convention Center, Fukuoka, The 63rd Annual Meeting of the Japanese Society of Anesthesiologist, 2016.5.26 [Domestic conference]
50) Hiroshi Kida: “Looking back and forward on One Health Strategy - 40 years struggle for the control of zoonoses”, School of Veterinary Medicine, Hokkaido University, Sapporo, Japan, Special Lecture, 2016.5.2 (invited lecture)
51) Ayato Takada: “Recent Topics on Ebola Virus Research”, Sendai International Center, Sendai, The 90th Annual Meeting of the Japanese Association for Infectious Diseases, 2016.4.16 [Domestic conference]
52) Ayato Takada: “Recent Topics on Zoonosis Research –Ebola hemorrhagic fever and Influenza–”, Nagoya University, Nagoya, 45th Noyori Forum, 2016.4.15 [Domestic conference]
53) Arnab Pain: “Chromerid genomes reveal the evolutionary path and genomic adaptations from photosynthetic algae to obligate intracellular parasitism”, International House, Osaka, The 89th annual meeting of Japanese Society for Bacteriology, 2016.3.24 [Domestic conference]
54) Ayato Takada: “Ecology of Viruses”, Kokuyo Hall, Tokyo, Kickoff Symposium for the Inter-University Research Institute Corporation, National Institutes for the Humanities, 2016.3.19 [Domestic symposium]
55) Kimihito Ito: “On the analysis of genetic sequence data of influenza viruses”, JST Tokyo, Big Data Application International Symposium, 2016.3.4 [International symposium]
56) Axel Martinelli: “A multidisciplinary approach to uncover the genetic basis of selectable phenotypes”, JST Tokyo, Big Data Application International Symposium, 2016.3.4 [International symposium]
57) Ayato Takada: “A monoclonal antibody neutralizing all known ebola viruses”, National Institute of Allergy And Infectious Diseases (NIAID) National Institutes Of Health (NIH), Rockville, 2016 US–Japan Annual Medical Biodefense Research Symposium Theme: “Ebola And Emerging Pathogens”, 2016.1.14 [International symposium]
58) Hiroshi Kida: “Points for the control of avian influenza and preparedness for future pandemics.”, The Bethesda North Marriott Hotel and Conference Center, Bethethda, United States of America, The 18th Respiratory Infections (ARI) Panel Meeting, 2016.1.14 [International conference]

59) Yoshihiro Sakoda, “Characterization of avian influenza viruses recently isolated in Japan”, Tamsui, Taiwan 2015 International Conference on Prevention and Control of Avian Influenza, 2015.10.21 [International conference]
60) Ayato Takada: “Ebolavirus: ecology and antiviral strategies”, Davos Congress Centre, Davos, 3rd GRF One Health Summit 2015, 2015.10.5 [International conference]
61) Stephen Gordon: “Tuberculosis and One Health: defining host preference across the Mycobacterium tuberculosis complex,” Lecture Hall, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan, The 3rd Sapporo Summer Symposium for One Health 2015, 2015.9.16-17 [International symposium] (invited speaker)
62) Yoshihiro Sakoda: “Contributions on the zoonosis control from veterinary medicine”, Aomori, Japan, Aomori Branch of the Japan Veterinary Medical Association, 2015.9.12 [Domestic conference]
63) David Charles Jackson: “How to elicit immediate and long-term immunity against influenza”, Crown Plaza London, International Conference on Influenza, 2015.8.25 [International conference]
64) Hiroshi Kida: “For the control of avian and human influenza”, Crown Plaza London, International Conference on Influenza, 2015.8.24 [International conference]
65) Lorena E. Brown: “Inducing cross-reactive responses”, Crown Plaza London, International Conference on Influenza, 2015.8.24 [International conference]
66) Ayato Takada: “Ebola hemorrhagic fever”, Kyoto Terrasa Hall, Kyoto, The 62th annual meeting of Japanese Association for Laboratory Animal Science, 2015.5.28 [Domestic conference]
67) Yoshihiro Sakoda: “Research activities in Hokkaido University for the control of avian influenza”, Korea, International Workshop on Highly Pathogenic Avian Influenza and Bird Migration, 2015.5.27 [International conference]
68) Yasuhiko Suzuki: “Tuberculosis - clear and present danger at natural disasters”. Sendai City Hall, Sendai, Japan, The 3rd World Conference on Disaster Risk Reduction. 2015.3.18 [International conference]
69) Yoshihiro Sakoda: “Diagnosis and identification of highly pathogenic avian influenza viruses recently isolated in Asia”, Tamsui, Taiwan, 2015 International Conference on Prevention and Control of Avian Influenza, 2015.3.11 [International conference]
70) Ayato Takada: “Comparison of antiviral activity between IgA and IgG specific to influenza virus hemagglutinin: Increased potential of IgA for heterosubtypic immunity”, Academia Sinica, Taipei, "Improving efficacy of vaccines for ARI", Acute Respiratory Infections (ARI) Panel Meeting, 17th International Conference on Emerging Infectious Diseases (EID) in the Pacific Rim Emerging Viral Diseases, United States–Japan Cooperative Medical Sciences Program, 2015.1.28 [International conference]
71) Yasuhiko Suzuki: “Collaboration on tuberculosis control in Zambia”, Protea Hotel Stellenbosh, Stellenbosh, South Africa, Global Research Council Africa Summit, 2014.11.24 [International conference]
72) Yoshihiro Sakoda: “Characterization of highly pathogenic avian influenza virus recently isolated in Japan”, Tamsui, Taiwan, 2014 International Conference on Prevention and Control of Avian Influenza, 2014.11.18 [International conference]
73) Brendon Yew Loong Chua: “Harnessing innate and adaptive immunity against influenza and bacterial co-infections”, Melbourne, Australia, Australian Influenza Symposium, 2014.11.12 [International symposium]
74) William Hall: “One Health: Importance of virus infections and a focus on Vietnam,” Lecture Hall, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan, The 2nd Sapporo Summer Seminar for One Health (SaSSOH) 2014, 2014.9.24-25 [International conference] (keynote speaker)

75) Hiroshi Kida: “Control of avian influenza and preparedness for pandemic influenza”, Tokyo University, Tokyo, OIE Regional Workshop on Enhancing Influenza A virus National Surveillance Systems OIE/JTF Project for Controlling Zoonoses in Asia under One Health Concept, 2014.8.26 [International conference]
76) Ayato Takada: “Role of antibodies in protective immunity against filovirus infection”, Hotel Galvez, Galveston, 6th International Symposium on Filoviruses, 2014.4.2 [International symposium]

4.2 Other presentations:#18

1) Kosuke Okuya, Reiko Yoshida, Rashid Manzoor, Shinji Saito, Tadaki Suzuki, Osamu Ichii, Hideaki Higashi, Ayato Takada: “A potential role of non-neutralizing IgA antibody for cross-protective immunity against influenza A viruses”, Tower-Hall Funabori, Tokyo, The 67th Annual Meeting of the Japanese Society for Virology, 2019.10.31 [Domestic conference]
2) Keita Mizuma, Keita Matsuno, Masatoshi Okamatsu, Ayato Takada, Yoshihiro Sakoda: “A functional analysis of host RNAs binding with the nucleoprotein of severe fever with thrombocytopenia syndrome virus”, Tower-Hall Funabori, Tokyo, The 67th Annual Meeting of the Japanese Society for Virology, 2019.10.30 [Domestic conference]
3) Mao Isono, Wakako Furuyama, Makoto Kuroda, Tatsunari Kondoh, Manabu Igarashi, Masahiro Kajihara, Reiko Yoshida, Rashid Manzoor, Kosuke Okuya, Hiroko Miyamoto, Heinz Feldmann, Andrea Marzi, Masahiro Sakaitani, Ayato Takada: “Searching chemical compounds for development of the entry inhibitor against ebolavirus”, Tower-Hall Funabori, Tokyo, The 67th Annual Meeting of the Japanese Society for Virology, 2019.10.30 [Domestic conference]
4) Masahiro Kajihara, Katendi Changula, Bernard Hang’ombe, Hayato Harima, Hiroko Miyamoto, Yoshiki Eto, Kosuke Okuya, Mao Isono, Reiko Yoshida, Yongjin Qiu, Akina Mori-Kajihara, Yasuko Orba, Hirofumi Sawa, Hirohito Ogawa, David Squarre, Victor Mukonka, Aaron Mweene, and Ayato Takada: “Genetic analyses of marburgvirus in Egyptian fruit bats in Zambia”, Tower-Hall Funabori, Tokyo, The 67th Annual Meeting of the Japanese Society for Virology, 2019.10.30 [Domestic conference]
5) Keita Mizuma, Keita Matsuno, Masatoshi Okamatsu, Ayato Takada, Yoshihiro Sakoda: “Profiling RNAs binding with the nucleoprotein of severe fever with thrombocytopenia syndrome virus (SFTSV) revealed orchestrated replication of a segmented RNA virus”, Glasgow, United Kingdom, International meeting on arboviruses and their vectors (IMAV 2019), 2019.9.5-6[International conference]
6) Augustin Twabela, George Tshilenge, Thanh-Lam Nguyen, Keita Matsuno, Isabella Monne, Bianca Zecchin, Masatoshi Okamatsu, Yoshihiro Sakoda: “Characterization of H5N8 highly pathogenic Avian Influenza Virus isolated in democratic republic of Congo in 2017”, SUNTEC, Singapore, Options X for the Control of Influenza, 2019.8.28-9.1[International conference]
7) Yuto Kikutani, Masatoshi Okamatsu, Shoko Nishihara, Sayaka Takase-Yoden, Takahiro Hiono, Ryan Mcbride, Robert P. De Vries, Keita Matsuno, Hiroshi Kida, Yoshihiro Sakoda: “H6 chicken influenza virus recognizes sulfated α2,3 Sialylated glycans as the receptors”, SUNTEC, Singapore, Options X for the Control of Influenza, 2019.8.28-9.1[International conference]

8) Brendon Chua: “Development of TLR2-against-based immunostimulants against respiratory pathogens,” Lecture Hall, Faculty of Veterinary Medicine, Hokkaido University, Sapporo, Japan, Wise Program for One Health Frontier Graduate School of Excellence, 2019.2.27 [Special lecture]
9) Keita Matsuno, Masahiro Kajihara, Syun-ichi Urayama, Ryo Nakao, Miho Hirai, Yongjin Qiu, Takuro Nunoura, Aaron S Mweene, Bernard M Hang’ombe, Martin Simuunza, Masatoshi Okamatsu, Yoshihiro Sakoda, Hirofumi Sawa, Ayato Takada:“Discoveries of novel viruses in ticks and fruit bats by using FLDS method and MinION sequencer”, Osaka International Convention Center, Osaka, Japan, The 65th Annual Meeting of the Japanese Society for Virology, 2017.10.24-26 [International conference]*
10) Lam Thanh Nguyen, Kazunari Nakaishi, Keiko Motojima, Ayako Ohkawara, Takahiro Hiono, Keita Matsuno, Masatoshi Okamatsu, Ayato Takada, Hiroshi Kida, Yoshihiro Sakoda: “Rapid and broad detection of H5 hemagglutinin by an immunochromatographic kit using novel monoclonal antibody against a clade 2.3.4.4 highly pathogenic avian influenza virus”, Osaka International Convention Center, Osaka, Japan, The 65th Annual Meeting of the Japanese Society for Virology, 2017.10.24-26 [International conference]*
11) Nodoka Kasajima, Keita Matsuno, Shiho Torii, Takahiro Hiono, Masatoshi Okamatsu, Hideki Ebihara, Yoshihiro Sakoda: “Suppression of PKR signaling pathway by nonstructural protein of severe fever with thrombocytopenia syndrome virus”, Osaka International Convention Center, Osaka, Japan, The 65th Annual Meeting of the Japanese Society for Virology, 2017.10.24-26 [International conference] *
12) Masatoshi Okamatsu, Takahiro Hiono, Keita Matsuno, Lam Thanh Nguyen, Mizuho Suzuki, Yuto Kikutani, Hiroshi Kida,Yoshihiro Sakoda: “Characterization of H5N6 highly pathogenic avian influenza viruses isolated from wild and captive birds in the winter of 2016–2017 in northern Japan”, Osaka International Convention Center, Osaka, Japan, The 65th Annual Meeting of the Japanese Society for Virology, 2017.10.24-26 [International conference]*
13) Hirofumi Sawa, Shintaro Kobayashi, Hiroki Yamaguchi, Wallaya Phongphaew, Michihito Sasaki, Yasuko Orba: “Examination of neuronal injury by West Nile virus infection”, Royton Sapporo, Sapporo, Japan, The 59th Annual Meeting of the Japanese Society of Neurology”, 2017.5.23-26 [International conference] *
14) Arnab Pain: “Chromerid genomes reveal the evolutionary path and genomic adaptations from photosynthetic algae to obligate intracellular parasitism,” International House Osaka, Osaka, Japan, The 89th Annual Meeting of Japanese Society for Bacteriology, 2016.3.24 [International conference]
15) Shintaro Kobayashi, Wallaya Phongphaew, Kentaro Yoshii, Minato Hirano, Memi Muto, Yasuko Orba, Hirofumi Sawa, Hiroaki Kariwa: “Analysis of the accumulation mechanism of denatured proteins by West Nile virus infection,” Fukuoka International Congress Center, Fukuoka, Japan, The 63rd Annual Meeting of the Japanese Society for Virology, 2015.11.22-24 [International conference]
16) Yoshihiro Sakoda: “Host or virus derived secretory membrane binding proteins are involved in formation of infectious Flavivirus particles,” Fukuoka International Congress Center, Fukuoka, Japan, The 63rd Annual Meeting of the Japanese Society for Virology, 2015.11.22-24 [International conference]
17) Hirofumi Sawa: “Epidemiological and Basic Research Activities Targeting Polyomaviruses,” Awaji Yumebutai International Conference Center, Japan, The 14th Awaji International Forum on Infection and Immunity, 2015.9.8 [International conference]

18) Junya Yamagishi: “How to approach the diversity in transcriptiome, a key to elucidate host-parasite interaction in genomic era,” Awaji Yumebutai International Conference Center, Japan, The 14th Awaji International Forum on Infection and Immunity, 2015.9.11 [International conference]

5 Patent applications

Number of patent applications: # 32 (Japanese patents: # 12, overseas patents: # 20)

Number of patent registrations (of the above number): # 26

5.1 Registration information

1) Expression vector for producing protein derived from foreign gene in large quantity using animal cells, and use thereof, National University Corporation Hokkaido University, Fuso Pharmaceutical Industries Ltd, Canada Patent 2748011, 2018 11. 23. Tahara H, Suzuki Y, Yamamoto K, Kitahara Y, Suzuki Y.
2) Microneedle array containing inactivated whole-virus-particle vaccine and the administration method, FUJIFILM Corporation, National University Corporation Hokkaido University
Japan Patent 2018-39839, 2018.3.15, Koji Kuruma, Takayoshi Oyamada, Toshio Shimada, Yoshihiro Sakoda, Hiroshi Kida
3) Recombinant vaccinia virus coding hemagglutinin gene derived from a novel influenza virus, Tokyo Metropolitan Institute of Medical Science, The Chemo-Sero-Therapeutic Research Institute (Kaketsuken), National University Corporation Hokkaido University
Japan Patent 2016-178945, 2016.10.13, Michinori Kohara, Fumihiko Yasui, Toshio Murakami, Hiroshi Kida, Yoshihiro Sakoda
4) Protein substance having triple helix structure and manufacturing method therefor cell and use thereof, National University Corporation Hokkaido University, Fuso Pharmaceutical Industries, Ltd
Canada Patent 2748015, 2017.02.28, Suzuki Y, Yamamoto K, Suzuki Y, Tahara H
Korea patent 10-1686688, 2016.12.08, Suzuki Y, Yamamoto K, Suzuki Y, Tahara H
Hong Kong Patent HK1163153, 2015.09.18, Suzuki Y, Yamamoto K, Suzuki Y, Tahara H
EU Patent 2380979, 2015.04.15, Suzuki Y, Tahara H, Yamamoto K, Kitahara Y, Suzuki Y
Japan Patent 5645187, 2014.10.20, Suzuki Y, Tahara H, Yamamoto K, Kitahara Y, Suzuki Y
Australia Patent 2009331327, 2014.04.01, Suzuki Y, Tahara H, Yamamoto K, Kitahara Y, Suzuki Y
5) Expression vector for Mass production of foreign gene-derived protein using animal cell and use thereof, National University Corporation Hokkaido University, Fuso Pharmaceutical Industries, Ltd.
EU patent 2258843, 2016.11.11, Tahara H, Suzuki Y, Yamamoto K, Kitahara Y, Suzuki Y
Japan Patent 6022518, 2016.10.14, Suzuki Y, Yamamoto K, Suzuki Y, Tahara H
Korea patent 10-1655492, 2016.09.01, Tahara H, Suzuki Y, Yamamoto K, Kitahara Y, Suzuki Y
Hong Kong patent HK1155772, 2016.06.10, Suzuki Y, Yamamoto K, Suzuki Y, Tahara H
Korea Patent 10-1604502, 2016.03.11, Suzuki Y, Yamamoto K, Suzuki Y, Tahara H
Hong Kong Patent HK1161898, 2016.02.26, Tahara H, Suzuki Y, Yamamoto K, Kitahara Y, Suzuki Y
China Patent ZL200980114565.X, 2015.09.16, Suzuki Y, Yamamoto K, Suzuki Y, Tahara H

EU Patent 2385115, 2015.09.09, Tahara H, Suzuki Y, Yamamoto K, Kitahara Y, Suzuki Y
US Patent 9096878, 2015.08.04, Tahara H, Suzuki Y, Yamamoto K, Kitahara Y, Suzuki Y
Japan Patent 5704753, 2015.03.06, Tahara H, Suzuki Y, Yamamoto K, Kitahara Y, Suzuki Y
Hong Kong (China) patent HK1163739, 2014.11.14, Tahara H, Suzuki Y, Yamamoto K, Kitahara Y, Suzuki Y
Japan Patent 5648912, 2014.10.22, Suzuki Y, Yamamoto K, Suzuki Y, Tahara H
US Patent 8653249, 2014.10.11, Suzuki Y, Yamamoto K, Suzuki Y, Tahara H
Australia Patent 2009331326, 2014.09.08, Tahara H, Suzuki Y, Yamamoto K, Kitahara Y, Suzuki Y
China Patent. ZL200980157244.8, 2014.05.06, Suzuki Y, Yamamoto K, Suzuki Y, Tahara H
Australia Patent 2009218069, 2014.04.16, Suzuki Y, Yamamoto K, Suzuki Y, Tahara H

6) Gene amplification method and use thereof, National University Corporation Hokkaido University
Japan Patent 5688702, 2015.02.06, Chie Nakajima, Yukari Fukushima, Yasuhiko Suzuki

5.2 Application information

1) Japan patent application PCT/JP2019/13132, Novel K95-5901-1 substance and method for producing threof, 2019.03.27, National University Corporation Hokkaido University, The Kitasato Institute, Satoshi Omura, Mihoko Mori, Atsuko Matsumoto, Kazuro Shiomi, Yasuhiko Suzuki, Chie Nakajima, Tomoyuki Yamaguchi.
2) Japan patent application 2018-99704, Novel vectors and use thereof, 2018.05.24, National University Corporation Hokkaido University, FUSO Pharmaceutical Industries. Ltd, Yasuhiko Suzuki, Miki Nakagawa, Yayoi Kameda, Takashi Konnai, Tomohiro Okagawa, Naoya Maekawa, Shinya Goto, Yamato Saji, Kazuhiko Ohashi, Shiro Murata, Jo Kitahara, Keiichi Yamamoto.
3) International patent application 2017-535564, Monoclonal antibody neutralizing infectivity of all ebolavirus species, 2018.2.9, Hokkaido University, Kyowa Hakko Kirin, Co., Ltd., Ayato Takada, Reiko Yoshida, Wakako Furuyama, Hiroko, Miyamoto, Junki Miyamoto, Shigeru Iida, Shinya Ogawa
4) Japan patent application 2017-071729, Biaryl sulfonamide derivatives that inhibit filovirus entry into cells, 2017.3.31, Hokkaido University, Ayato Takada, Masahiro Sakaitani, Wakako Furuyama
5) Japan patent application 2015-161567, Monoclonal antibody neutralizing infectivity of all ebolavirus species, 2015.08.19, Hokkaido University, Kyowa Hakko Kirin, Co., Ltd., Ayato Takada, Reiko Yoshida, Wakako Furuyama, Hiroko, Miyamoto, Junki Miyamoto, Shigeru Iida, Shinya Ogawa
6) Japan patent application 2014-190530, Kits including markers to distinguish drug susceptibility and use thereof, 2014.09.18, Hokkaido University, Rakuno Gakuen University, Kanto Chemical, Co., Inc., Yutaka Tamura, Yasuhiko Suzuki, Chie Nakajima, Masaru Usui

6 Awards

Number of awards: #7

1) William Hall: “Robert C. Gallo Award for Scientific Excellence and Leadership in Medical Virology”, 2019. 6.9
2) Hiroshi Kida: “Person of cultural merits”, 2017.10.24
3) Hiroshi Kida: “The order of the sacred treasure, gold and silver star”, 2017.4.29

4) Ayato Takada: “Hokkaido University President’s Award for Outstanding Research”, 2017.1.31
5) Hiroshi Kida: “The Hokkaido distinguished service award”, 2016.10.31
6) Ayato Takada: “Hokkaido University President’s Award for Outstanding Research”, 2016.2.3
7) Ayato Takada: “Hokkaido University President’s Award for Outstanding Research”, 2015.2.23

7 External grants

Number of grants: #3

1) Core-to-Core Program, B. Asia-Africa Science Platforms, (Japan Society for the Promotion of Science), “Research Exhange toward social implementation of novel diagnosis method based on comprehensive sequencing”, 2019-2022, 7,040,000 JPY, Junya Yamagishi (PI), William Hall and Arnab Pain
2) Tropical Medicine Research Center General Collaborative Research Grant (Nagasaki University), “Applying Linkage Group Selection to *P. falciparum in vitro*”, 2017-2018, 300,000 JPY, Axel Martinelli (PI) and Chihiro Sugimoto
3) Grant-in-Aid for Scientific Research (C) (Japan Society for the Promotion of Science), "Long non-coding RNAs in viral infection", 2016-2018, 4,810,000 JPY, Michael Carr (PI) and Hirofumi Sawa

8 Gifts

Number of gifts: #4

1) TheAtlantic Philanthropies Director/Employee Designated Gift Fund (Atlantic Filanthropies), “the Development of New Methods and Training for the Detection of New Virus Diseases Project”, 2019.9.1, US$150,000, Hirofumi Sawa
2) TheAtlantic Philanthropies Director/Employee Designated Gift Fund (Atlantic Filanthropies),” immune therapy to treat coronavirus in the very early stages of infection,” 2019.3.31, US$10,000.00, Hirofumi Sawa
3) TheAtlantic Philanthropies Director/Employee Designated Gift Fund (Atlantic Filanthropies),” immune therapy to treat coronavirus in the very early stages of infection,” 2019.3.31, US$10,000.00, Hirofumi Sawa
4) The Atlantic Philanthropies Director/Employee Designated Gift Fund (Atlantic Filanthropies) “The development of new methods and training for the detection of new virus diseases”,2018.11.14, €50,000.00 , Hirofumi Sawa

9 Science outreach activities

Number of science outreach activities: #31

The following presentations were made in seminars for the public.

1) Ayato Takada: “Basic preventive measure of the novel coronavirus is to dilute it”, The Hokkaido Shimbun press, 2020.3.3 [Newspaper article]
2) Ayato Takada: “Diseases transmitted from animals to humans”, Asahi Shogakusei Shimbun, 2020.2.16 [Newspaper article]
3) Ayato Takada: “Virus is rogue?”, Science book cafe, Yomiuri Shimbun Building, Tokyo, Japan, 2019.9.10 [Science cafe]

4) Ayato Takada: “Detection/diagnosis/therapy of Ebola viruses”, JICA Yokohama, Yokohama, Japan, TICAD seminar: What we can do to fight Ebola virus, a possibility of contribution and challenge of industry, government and academia, 2019.6.16[Open lecture]
5) Hirofumi Sawa: “Observation of mosquito larva, pupa and imago. Making the mosquito specimen,” P2 Practical Room, Research Center for Zoonosis Controol, Hokkaido Universitym Sapporo, Hokkaido University Kids Laboratory 2019, 2019.03.25 [Special practicum]
6) Junya Yamagishi: “Why are diseases infected?”, Seminar Room, Institute for Genetic Medicine, Hokkaido University, Sapporo, Hokkaido University Kids Laboratory 2019, 2019.3.25 [Special lecture]
7) Hirofumi Sawa: “Zoonosis control measures contributing to One Health,” Conference Hall, Hokkaido University, Sapporo, Resaerch Center for Zoonosis Control extension course open to the public, 2019.1.12 [Extension course]
8) Yasuhiko Suzuki: “Activities torward the control of Zonosis,” Research Center for Zoonosis Control, Hokkaido University, Sapporo, SAKURA Exchange Program in Science, 2018.8.6 [Special lecture]
9) Keita Matsuno: “Viruses hiding in ticks”, Amami Branch of Kagoshima University Research Center for the Pacific Islands, Amami, 2018.3.1 [Open lecture]
10) Axel Martinelli: “An introduction to genomics”, Sapporo Higashi High School, Sapporo, Academic Fantasista, 2018.2.2 [Visiting lecture]
11) Yasuhiko Suzuki: “Tuberculosis: Never ending threat,” Auditorium, School of Agriculture, Hokkaido University, Sapporo, Research Center for Zoonosis Control extension course open to the public, 2018.1.20 [Extension Course]
12) Michael Carr: “What are viruses?”, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Academic Fantasista, 2017.12.12 [Open lecture]
13) Ayato Takada：“Viral Zoonosis Research in Africa”, JICA Research Institute, Tokyo, SATREPS Workshop, 2017.8.28 [Extension course]
14) Lorena Brown: “Preparedness for pandemic influenza” Hotel Mystays Sapporo Aspen, Sapporo, Strategy for the Control of Zoonoses, 2017 7.8 [Open seminar]
15) William Hall: “International contributions to our appreciation of new and emerging virus infections” Hotel Mystays Sapporo Aspen, Sapporo, Strategy for the Control of Zoonoses, 2017 7.8 [Open seminar]
16) Arnab Pain: “Latest trends in tracking pathogens by genomics” Hotel Mystays Sapporo Aspen, Sapporo, Strategy for the Control of Zoonoses, 2017 7.8 [Open seminar]
17) Keita Matsuno: “Interactive lecture of microbes and their researchers”, The 86th Annual Meeting of the Japanese Society of Parasitology, 2017.5.28-29 [Science Cafe]
18) Ayato Takada：“Recent Advances in Ebola Virus Research”, Sapporo Convention Center, Sapporo, Infection Control Doctor Lecture Course, 2016.10.25 [Extension course]
19) Ayato Takada：“Recent Advances in Virology –Topics from Influenza and Ebola–”, Hokkaido High Technology College, Eniwa, Heisei 28 Bio Lecture for High School Teachers, 2016.8.4 [Extension course]
20) Ayato Takada: “Zoonosis –Topics from Influenza and Ebola–”, Hokkaido University, Sapporo, Heisei En-yu Night School, 2016.8.2 [Extension course]
21) Ayato Takada：“Ecology of Viruses”, Hokkaido University, Sapporo, The 58th Hokudaisai Extramural Lecture, 2016.6.4 [Extension course]

22) Ayato Takada: “How do viruses survive?”, Marunouchi building, Tokyo, Keio Marunouchi City Campus Regular Seminar, Sekigaku50, 2015.11.18 [Extension course]
23) Ayato Takada: “Ebola virus”, Miyazaki Kanko hotel, Miyazaki, The 5th International Symposium at Miyazaki University, Preparation for impending infectious diseases, focusing on zoonoses, 2015.11.13 [Extension course]
24) Ayato Takada: “Ebola virus research: Current situation and future prospects”, The alumni *hall Frate* at school of medicine of Hokkaido University, Sapporo, Science Council of Japan, Second Section Meeting Of The Life Science Field, Public Academic Lecture, 2015.8.5 [Extension course]
25) Ayato Takada: “Recent advance in Ebola virus research”, Conference Hall, Hokkaido University, Sapporo, Hokkaido University extension course 2015, 2015.7.20 [Extension course]
26) Hiroshi Kida: “Strategy for the control of zoonoses”, Open Hall, School Of Engineering, Hokkaido University, The 1st GI-CoRE Open Forum, 2015.7.3 [Extension course]
27) Ayato Takada: “Ebola hemorrhagic fever, Current situation and future prospects for science research”, Satellite Campus of Gifu University, Gifu, Gifu University public lecture, 2015.3.2 [Extension course]
28) Ayato Takada: “Ebola virus research, Current situation and future prospects”, Fujita Health University, Toyoake, The200th seminar in medical science, 2014.10.1 [Extension course]
29) Ayato Takada: “Ebola hemorrhagic fever and BSL4”, Nagasaki City Library, Nagasaki, Institute of tropical medicine Nagasaki University, Extension special course open to the public, 2014.9.21 [Extension course]
30) Ayato Takada: “Activities of the Hokudai Center for Zoonosis Control in Zambia”, UDX Conference, Tokyo, J-GRID extension course open to the public, SFTS, MERS, Ebola hemorrhagic fever referred as recent topic of infectious diseases, 2014.8.23 [Extension course]
31) Hiroyuki Oshiumi: “Innate Immune response during viral infection,” Lecture Hall, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo, Seminar: Infecton, Pathogenesis and Immunity-For the Control of Zoonosis-, 2014.8.20 [Open seminar]

10 Training

Number of trainings: #2

1) Mariko Tanaka, Walter Muleya, Shiho Torii, Dayana Baker, Gabriel Gonzalez, Yongjin Qiu, Kyoko Hayashida, Keita Matsuno, Yasuko Orba, Ryo Nakao, Junya Yamagishi, Stephen Barker, Yuki Eshita, Sawa Hirofumi, William Hall: “Training course of infection, immunity, diagnosis, and pathogenesis of virus pathogens”, Practical Room, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Japan, 2019. 9.19-10.2
2) William Hall: “Chikungunya virus detection”, Instituto de Medicina Tropical Pedro Kourí, Havana, Cuba, The 15th International Dengue Course-Challenges of Zika and Chikungunya transmission, 2017.8.12-21

11 Collaborations with institutions (universities, research institutes, local government, companies, etc.) other than affiliated universities

Number of collaborations: #31

1) Department of Molecular Medicine, Mayo Clinic
   Dr. Hideki Ebihara (Associate Professor) is collaborating with Unit for Exploration of Pathogens on development of detection methods of tick-borne viruses.
2) Joint Faculty of Veterinary Medicine, Yamaguchi University
   Dr. Ken Maeda (Professor) and Dr. Hiroshi Shinmoda (Associate Professor) is collaborating with Unit for Exploration of Pathogens on detections of tick-borne phleboviruses.
3) Research and Development (R&D) Center for Marine Biosciences, JAPAN Agency for Marine-Earth Science and Technology (JAMSTEC)
   Dr. Takuro Nunoura (Deputy Director) is collaborating with Unit for Exploration of Pathogens on development of sequencing methods of tick-borne virus genome.
4) Asa Zoo, Hiroshima, Japan
   Dr. Noriyuki Nonoue (Veterinarian) is collaborating with Unit for Exploration of Pathogens on development of detection methods of tick-borne viruses and elephant-specific pathogens.
5) Department of Pathology, Shiga University for Medical Sciences
   Professor Kazumasa Ogasawara (Immunology) is collaborating with the Unit for the Development of Vaccines and Biologicals on animal experiments to test vaccine safety and efficacy.
6) Graduate School of Science and Technology, Niigata University
   Associate Professor Takashi Abe, who has developed BLSOM, is collaborating with Unit for Pathogen Genomics on the analysis of horizontal gene transfer in parasites and vectors.
7) Institute of Tropical Medicine, Nagasaki University
   Associate Professor Richard Culleton is collaborating with the Unit for Pathogen Genomics on malaria infections and parasite genetic cross.
8) School of Veterinary Medicine, University of Zambia
   Professors Aaron Mweene, Bernard Han'gombe and Boniface Namangala are collaborating with the Unit for Exploration of Pathogens on pathogen detection and characterization from animals and insects in sub-Saharan Africa.
9) University Teaching Hospital, Zambia
   Dr. Mwaka A. Monze is collaborating with the Unit for Exploration of Pathogens on pathogen detection and characterization from humans in sub-Saharan Africa.
10) Department of Parasitology, University of Colombo, Sri Lanka
   Dr. Sisira Pathirana, is collaborating with on with the Unit for Pathogen Genomics on malaria infections and parasite genetic cross in monkeys. Collaboration with industrial parties as shown in Fig.1 is also important for influenza vaccine development.
11) Laboratory of Virology at the Rocky Mountain Laboratories (RML), DIR NIAID, NIH
   Dr. Heinz Feldmann and Andrea Marzi are collaborating with the Unit for Exploration of Pathogens on the development of anti-filovirus therapeutics.
12) Institut National de Recherche Biomédicale
   Professors Steve Ahuka, Justin Masumu, Sheila Makiala and Jean-Jacques Muyembe are collaborating with the Unit for Exploration of Pathogens on the development of rapid diagnosis kits for hemorrhagic fevers.

13) State Central Veterinary Laboratory, Mongolia
Drs. Ulaankhuu Ankhanbaatar, Bodisaikhan Khishgee, Basan Ganzorig are collaborating with the Unit for Exploration of Pathogens on avian influenza surveillance in Mongolia.

14) Faculty of Veterinary Medicine, Hokkaido University, Japan
Dr. Satoru Konnai (Associate Professor) is collaborating on the development of therapeutic recombinant antibodies.

15) Faculty of Veterinary Medicine, Rakunogakuen University, Japan
Dr. Yutaka Tamura (Professor) and Dr. Masaru Usui (Associate Professor) is collaborating on elucidate the drug resistance acquisition mechanism by bacterial pathogens.

16) Leprosy Research Center, National Institute of Infectious Disease, Japan
Dr. Tetsu Mukai (Unit Head) is collaborating on development of rapid diagnostic methods for leprosy.

17) Japan BCG Laboratory, Japan
Dr. Kazuhiro Matsuo (Division Director) is collaborating on the genome analysis of *Mycobacterium bovis* BCG from patients.

18) Osaka Institute of Public Health, Japan
Dr. Aki Tamaru (Senior Research Officer) is collaborating on the molecular analysis of multi- and extensively drug resistant *Mycobacterium tuberculosis* clinical isolates.

19) Fuso Pharmaceutical Industries, Ltd., Japan
Dr. Keiichi Yamamoto (Deputy Division Director), is collaborating on the development of therapeutic recombinant antibodies.

20) Tohoku Bio-Array Co., Ltd., Japan
Dr. Mitsuo Kawase (Division Director), is collaborating on the development of rapid, simple and low-cost drug susceptibility test for tuberculosis.

21) Philippine Carabao Center, Department of Agriculture, The Philippines
Dr. Claro Mingala (Director of Biotechnology Center) and Dr. Marvin Villanueva (Section Head) are collaborating on the surveillance of drug resistant enterobacteria and leptospirosis.

22) National Institute of Health, Ministry of Public Health, Thailand
Dr. Benjawan Phetsukusiri (Section Director) is collaborating on the molecular analysis of multi- and extensively drug resistant *M. tuberculosis* clinical isolates in Thailand.

23) Faculty of Public Health, Mahidol University, Thailand
Dr. Fuangfa Utrarachkiji (Head Department) is collaborating on the surveillance of drug resistant enterobacteriaceae in Thailand.

24) Faculty of Public Health, Thammasat University, Thailand
Dr. Kanjana Changkaew (Lecturer) is collaborating on the surveillance of drug resistant enterobacteria in Thailand.

25) Department of Medical Research, Ministry of Health and Sports, Myanmar
Dr. Khin Saw Aye (Deputy Director General) is collaborating on the molecular analysis of multi- and extensively drug resistant *Mycobacterium tuberculosis* clinical isolates in Myanmar.

26) German-Nepal Tuberculosis Project, Nepal Anti-tuberculosis Association, Nepal
Mr. Bhagwan Maharjan (Head of Laboratory) is collaborating on the molecular analysis of multi- and extensively drug resistant *Mycobacterium tuberculosis* clinical isolates and zoonotic infection of *M. tuberculosis* complex in Nepal.

27) Faculty of Medicine Peradenia University, Sri Lanka
Dr. Chandika Gamage (Senior Lecturer) is collaborating on the molecular epidemiology of tuberculosis in Sri Lanka.

28) The University Teaching Hospital, The Ministry of Health, Zambia
Dr. Grace Mbulo (Head of Laboratory) and Mr. Eddie Solo (Senior Medical Scientist) is collaborating on the molecular analysis of multi- and extensively drug resistant *Mycobacterium tuberculosis* clinical isolates in Zambia.

29) Zambia Tuberculosis and Leprosy Trust
Ms. Charity Habeenzu (CEO) is collaborating on the survey of leprosy in Zambia.

30) The University of Zambia, Zambia
Dr. Bernard Hang'ombe (Professor) is collaborating on the zoonotic infection of *M. tuberculosis* complex in Zambia.

31) South Valley University, Egypt
Dr. Hassan Diab (Lecturer) is collaborating on the molecular epidemiology of tuberculosis in Egypt.

● Issues affecting the research and measures to overcome these/future developments

Currently, the global station does not face any major issues.

In addition to core funding from MEXT, the global station is supported by other funding, such as, Japan Initiative for Global Research Network on Infectious Disease (The Japan Agency for Medical Research and Development "AMED") and the International Collaborative Research Program for Tackling the NTDs (Neglected Tropical Diseases) Challenges in African countries (AMED). These funding sources have greatly supported overseas activity of the Research Center for Zoonosis Control, especially in Zambia, which provides significant resources to GI-CoRE, such as, materials for pathogen detection and characterization in tropical animals. Seamless interoperability of these resources and funding will be beneficial to all GI-CoRE affiliated members. In addition, technical assistance for enhanced capacity building for these institutions in developing counties will be an important task of GI-CoRE.

Researchers from the foreign universities who are based at Hokkaido University are eligible to apply for Japanese grants, such as "Kakenhi (Grant-in-Aid for Scientific Research)". Well-organized and sustainable support for their applications by Japanese academic staff will be needed, because their project schemes including accounting regulations are different from those in the EU and USA. Technical staff at the Research Center for Zoonosis Control are insufficient to support GI-CoRE activities, including DNA/genome analysis, cell imaging, and bioinformatics. Hokkaido University is required to address this staffing shortage.

2. Education (Graduate Schools to Foster Global Human Resources)

2.1 Establishment of a new graduate school; Graduate School of Infectious Diseases

● Background

The threat to economies and societies has significantly increased due to emerging and re-emerging infectious diseases and trans-boundary infectious diseases, such as the global spread of Ebola hemorrhagic fever, the SARS and MERS coronaviruses, and Zika fever. Domestic and international demand for increased research efforts into combatting infectious diseases, including development of control measures, has significantly increased. In order to maintain the health and development of humanity, outbreaks of zoonotic diseases demand an understanding of the health of animals and their ecosystems. There is therefore an urgent need to provide human resources which can respond immediately to new and emerging infectious diseases. An international deployment of human resources working towards the concept of "One Health" is and will continue to grow as human societies further encroach on wildlife habitats.

A culture of One Health will require the establishment of a robust framework for higher educational institutions. Well-balanced and carefully formulated educational schemes should provide the fundamentals of immunology, molecular biology and genomics which must be integrated with a program of applied sciences, including clinical microbiology, vaccinology, epidemiology and the practical skills necessary for diagnoses, prevention and treatment of disease at epidemic sites.

Integration and systemization of educational resources and the establishment of a new educational systems with a view to utilizing the human resources necessary for One Health are challenges facing our university. The number of educators and researchers working in the fields of infectious diseases at institutions in Japan, however, continues to decrease with a bias towards allocation of resources to scientific fields other than the study and control of zoonoses. It is therefore not a straightforward matter to establish the systems that are necessary for responding rapidly to the global threats to human health. The situation is further complicated because the origins of these infectious diseases are located mostly in developing countries in tropical and sub-tropical zones and there is no currently sustainable initiative for capacity and infrastructure building in these countries. These are urgent social needs and they require an education system which transcends conventional academic field barriers to provide specialists with a truly internationally-oriented One Health mindset.

Since 2010, the Graduate School of Veterinary Medicine, Hokkaido University has run the Program for Leading Graduate Schools: Fostering Global Leaders in Veterinary Sciences toward Contributing to "One Health" and has initiated the development of human resources to this end. In order to strengthen and expand this educational scheme for postgraduates, Hokkaido University established the "Graduate School for Infectious Diseases" in 2017 (Appendix 1).

The detailed information on the current program for leading graduate schools can be found at the following link: https://www.infectdis.hokudai.ac.jp/en/

2.2 Vision for fostering human resources at the proposed Graduate School of Infectious Diseases

An important task for the new Graduate School is to produce experts who will take on leadership roles in the prevention and control of infection as an increasing social problem. The School's aim is to produce graduates:

1) who have an academic, i.e. evidence-based background but who have a broad vision and practical skills in infection, immunity, epidemiology and related disciplines.
2) who can provide leadership across national boundaries to implement the One Health concept.
3) who hold Ph.D. level qualifications in infectious diseases or veterinary medicine.

Well-organized and systemic curriculum, including the interaction with the international health community through the "Internship Abroad" program at the Graduate School, which is designed to meet the above-mentioned missions and development of human resources (Appendix 2). Students can pursue either of two tracks in course studies towards a Ph.D. in infectious diseases or veterinary medicine. Actual number of enrollment at the Graduate School of Infectious Diseases is 14 in 2017 and 16 in 2018 and is exceeding the admission quota.

2.3 Educational affiliation with the GI-CoRE

A number of members appointed at GI-CoRE have already been participating in the education program at the new Graduate School. These members are recognized at the national and international level as experts in the fields defined above and together will provide a level of education that will provide the necessary skill sets for the next generation of One Health practioners (Appendix 3).

One of essential components of the new Graduate School will be globalization and to this end discussions are underway with the Graduate School of Veterinary Medicine of University College Dublin with a view to establishing a joint, or *cotutelle* (co-tutoring), Ph.D. degree. In preparation for this joint program both parties have been conducting exchange of faculty, staff and students since 2014.

Students of the Graduate School of Veterinary Medicine and Graduate School for Infectious Diseases (2017~) at Hokkaido University attended the lecture "Advances in Infection Biology" which has been held in University College Dublin since 2016 and professors of Hokkaido University delivered lectures on topics realting to zoonotic diseases and bioinformatics in the same course (Appendix 4). In addition, Hokkaido University invited graduate students from University College Dublin to Hokkaido University for two-three months and supervised their research topics. Based on their research at CZC, two co-authored papers in international, peer-reviewed journals have been produced (Appendix 5), which constitute an essential part of their thesis. Furthermore, UCD has secured an EU grant for graduate education, ERASMUS, to invite our faculty staff and graduate students. These bidirectional relationships can further strengthen educational links toward the establishment of the cotutelle/joint degree program.

Finally, researchers from each of the international units of the GI-CoRE who are based at Hokkaido University share the laboratories with young researchers and students on a daily basis engaging in collaborative research. These interactions also contribute to the improvement of English language skills for Japanese and overseas students from non-English speaking countries through seminars which provide skills for English oral presentations and writing. As the results of their academic interactions, several co-authored publications have already been produced (Appendix 6).

Since 2016, at the Summer Institute held at the Sapporo Campus, a faculty professor from University College Dublin delivers lectures on "Bioinformatics and Computational Biology" (Appendix 7), which attracted international as well as Japanese students from a wide range of academic backgrounds. Therefore, GI-CoRE also extends its activity to support globalization of the graduate and undergraduate education at Hokkaido University.

3. Establishment of Framework

3.1 Management System

The Global Institution for Collaborative Research and Education (GI-CoRE) was established in April 2014 as a faculty organization under the direct control of the Hokkaido University President, with the aim of promoting international collaborative research and education that leverages Hokkaido University's strengths and distinctive character. GI-CoRE is positioned as an independent educational and research organization managed by the President as its director. It brings together world-class teaching staff from around the world, within Japan and within Hokkaido University, based on a new idea to invite the world highest level research units. GI-CoRE's framework enables the conduct of international collaborative research and education systematically together with leading research units invited from overseas, rather than relying on international exchange promoted individually by researchers. Implementing this unprecedented way to accept overseas researchers, Hokkaido University reformed the management system and established the framework of GI-CoRE promptly under the President's powerful leadership. GI-CoRE appointed the President as the director, and Vice President for International Affairs as the deputy director. Under the President/GI-CoRE director, the GI-CoRE steering committee is established to discuss matters important to GI-CoRE and comprises the President, Vice Presidents for International Affairs and for Planning and Management, and faculty deans/research center directors who are appointed to serve as members to the committee in turn. The steering committee was held a total of 14 times, between April 2014 and March 2018, and discussed the following: 1) Matters regarding the personnel transfers of faculties; 2) Matters regarding the establishment, reform or termination of global stations; 3) Matters regarding the evaluation of the research and educational activities of global stations; 4) Matters regarding budgets; and 5) Other important matters pertaining to the administration of GI-CoRE, such as progress reports. To promote the collaborative research and education that capitalizes upon the distinctive characteristics of the university from a practical viewpoint, Hokkaido University place global stations (GSs) in GI-CoRE. Each GS has a designated station director who shall be one of the core teaching staff in the research field. Invited world-leading overseas research units are assigned to the GS so as to foster the promotion of international collaborative research and education together with the leading teaching staff within the university.

Member List of the Steering Committee *As of 1 April 2018

	Name	Affiliation 1	Affiliation 2
1	Toyoharu NAWA	President	Director, Global Institution for Collaborative Research and Education
2	Masanori KASAHARA	Executive / Vice President	Deputy Director, Global Institution for Collaborative Research and Education
3	Jyunji NISHII	Executive / Vice President	
4	Fumihiko YAMAMOTO	Dean / Professor, Graduate School of Letters	
5	Koichiro ISHIMORI	Dean / Professor, Faculty of Science	

6	Takeshi SAITO	Dean / Professor, Faculty of Health Sciences	
7	Toshiyuki NAKAGAKI	Director / Professor, Research Institute for Electronic Science	
8	Hiroki SHIRATO	Professor, Faculty of Medicine	Director, Global Station for Quantum Medical Science and Engineering
9	Hirofumi SAWA	Professor, Research Center for Zoonosis Control	Director, Global Station for Zoonosis Control
10	Takashi INOUE	Professor, Research Faculty of Agriculture	Director, Global Station for Food, Land and Water Resources
11	Jian Ping GONG	Professor, Faculty of Advanced Life Science	Director, Global Station for Soft Matter
12	Yoshikazu MIYANAGA	Professor, Graduate School of Information Science and Technology	Director, Global Station for Big Data and Cybersecurity
13	Natsuhiko OTSUKA	Professor, Arctic Research Center	Director, Global Station for Arctic Research
14	Ko HASEGAWA	Executive / Vice President	
15	Ryuichiro SHIMA	Director, International Affairs Department	

3.2 Establishment and Improvement of Acceptance System/Environment, and Future Prospects, etc.

Under the governance of the President, GI-CoRE has established the necessary system to accept overseas researchers and improved the environment to operate GI-CoRE tasks, as follows, in order to invite the world's top research units from external universities and institutions, and allow them to collaborate with the fine teaching staff in the related disciplines of the university.

1) GI-CoRE introduced the cross-appointment system with overseas universities and institutions before the system was implemented by the whole university. The cross-appointment system is to appoint top-class researchers from overseas and domestic institutions at Hokkaido University, while keeping their status at the host institutions and pay salaries to them based on the level of the effort at Hokkaido University.
2) The implementation of cross appointment system has produced more flexible personnel and salary system for the overseas faculty members such as choosing the annual salary system, relaxing the employment age restriction, and establishing a new title Distinguished Professor which shall be awarded in recognition of particularly important achievement in their fields of study.
3) For the overseas researchers who conduct education and research activities at Hokkaido University, GI-CoRE has set up a flexible system on travel expense and accommodation rental.
4) To utilize the exiting research resources in the university, GI-CoRE has also applied the cross-appointment system to the participating researchers of Hokkaido University who conduct international collaborative research and education, and appointed them to the positions both in their original departments and in GI-CoRE.

5) Upon conducting advanced international collaborative research and education, GI-CoRE has reviewed the point-based personnel system and applied flexible personnel distribution even in positions for researchers.
6) To secure the academic environment to concentrate on research, GI-CoRE faculty members are exempt from administrative tasks such as faculty meetings, etc.

The above-mentioned cross-appointment system, annual salary system for regular teaching staff and other relevant systems have been started as a pilot system for the other departments within the university. Other than the systems, GI-CoRE has provided rich research environments and extensive educational experiences to young researchers, and led to good effects as fusion of different research fields/interdisciplinary collaboration with diversified departments to cooperate in the project.

Through this virtuous cycle, the pilot systems at GI-CoRE have been gradually expanded to the whole university, and have started to reinforce the university's administrative function.

From now on, GI-CoRE will utilize the established network and achieved outcomes of collaborative research with institutions/organizations in order to further strengthen research projects which give the university a certain superiority over other research universities, and implement 'global postgraduate-level education by organic fusion of different fields' at graduate schools of related fields. For this promotion, besides the management expenses grants from the Japanese government, GI-CoRE aims to obtain various funds such as competitive funds as grants-in-aid for scientific research and donation, etc.

3.3 Administrative System

In order to support research and educational activities in each global station, administrative staff are required to strengthen their capabilities to handle international affairs. Considering this, Hokkaido University has set up a GI-CoRE-specialized administrative section in the International Affairs Department, distributed staff members with study/work abroad experiences to the section, and established bilingual (English) administrative support systems. Also, bilingual staff have been stationed in each global station office to support daily research activities conducted there.

Graduate School of Infectious Diseases, Hokkaido University

Education Appendix 1

Established in April 2017

Graduate School of Infectious Diseases

Major: Infectious Diseases

Enrollment capacity	Course terms	Degree to be awarded
12	4 years	Doctor of Philosophy in Infectious Diseases Doctor of Philosophy in Veterinary Medicine

- Graduate School of Veterinary Medicine
- Research Center for Zoonosis Control
- Graduate School of Medicine
- GI-CoRE

Schools and Institutes in charge

Urgent Need for Zoonosis Expertise

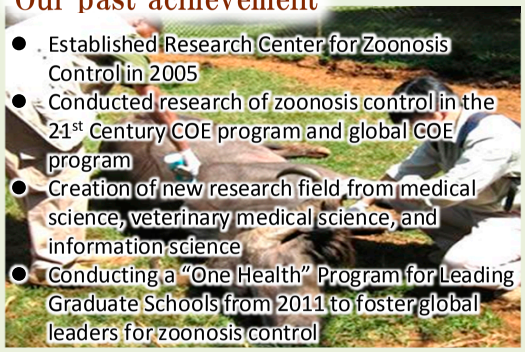
Emerging and re-emerging infectious diseases are appearing worldwide

- Infectious diseases; such as Ebola hemorrhagic fever, pandemic influenza, dengue fever, MERS coronavirus have become a major public health concern.

Lack of expertise and an absence of systematic educational training schemes

- Insufficient basic research of ecology, pathogenicity and transmission routes of zoonotic pathogens.
- There is an urgent need for the development of diagnostic, preventive and therapeutic methods to better tackle zoonoses.
- A lack of experts in the control of zoonotic diseases with relevant academic backgrounds.

Our past achievement



- Established Research Center for Zoonosis Control in 2005
- Conducted research of zoonosis control in the 21st Century COE program and global COE program
- Creation of new research field from medical science, veterinary medical science, and information science
- Conducting a "One Health" Program for Leading Graduate Schools from 2011 to foster global leaders for zoonosis control

Advanced education systems and unique curriculum

Development of practical skills activated on the international stage

- Supervision by leading professors in the relevant fields of microbiology, immunology and infectious diseases.
- Interdisciplinary learning in areas, such as, bioinformatics, mathematical modeling and risk analysis of infectious diseases.
- Support for **internship overseas** that aims to develop career paths at a global level.
- Development of practical skills in disease endemic spots
- Access to state-of-the art research facilities/equipment.

Collaboration with world-class leading organizations

- **Top level world scientists** from the University of Melbourne and University College Dublin as research supervisors.
- Improvement of scientific communication skills in English.

Development of experts for zoonosis control

- The School **certifies students expertise** (Zoonosis Control Expert, ZCE) based on the following criteria: practical experience in countries where infectious zoonotic diseases spread, research achievements and academic credits in relevant subjects.

Two types of degree provided in accordance with specialization

- **Enrolment of students who have various academic backgrounds** including relevant academic fields other veterinary medicine and medicine at the Graduate School of Infectious Diseases.
- The Graduate School covers a wide range of advanced subjects.
- The Graduate School grants a degree of **Ph.D. (Infectious Diseases)** or **Ph.D. (Veterinary Medicine).**

Diploma policy

Degrees are awarded to doctoral candidates who meet the following criteria:

- They have demonstrated an advanced knowledge and skills for the study of infectious disease and related subject areas and can practically apply this knowledge to practical research and control measures.
- Who have shown leadership on the international stage to implement a "One Health" policy for the improvement of the health of humans, animals and their environments.

Career Path

Ph.D. (Infectious Diseases) degree holders

- **Universities and research institutes** in Japan and overseas in academic areas of infectious diseases, public health, tropical medicine etc.
- **Government organizations** e.g. Ministry of Health, Labor and Welfare, Ministry of Agriculture, Forestry and Fisheries in Japan and overseas.
- **International organizations** which are responsible for international health control, such as WHO.

Ph.D. (Veterinary Medicine) degree holders

- **Universities and research institutes** in Japan and overseas in academic areas of veterinary medicine, microbiology, immunology, epidemiology etc.
- **Government organization**, such as, Ministry of Agriculture, Forestry and Fisheries etc. in Japan and overseas.
- **International organizations** which are responsible for infectious disease control in animals and food production and safety such as OIE, FAO.

Curriculum of PhD/ZCE course in Graduate School of Infectious Diseases

Education Appendix 2

Universities and Institutions worldwide （Infectious Diseases・Public Health・Tropical medicine・Veterinary Medicine）, Government Office （MHLW, *etc.*.）・International Organizations （WHO, OIE, *etc.*）

Universities and Institutions worldwide （Veterinary Medicine・Microbiology・Epidemiology・Government Office （MAFF, *etc.*）・International Organizations （FAO,OIE, *etc.*）

Ph.D. in Infectious Diseases/ZCE

Ph.D. in Veterinary Medicine/ZCE

Red Frame: Required

Blue Frame: Elective

Year 3・4

Management of Disease Control in International Settings
～Simulation, Risk Analyses, Control Measures, Management, etc.

Thesis Defense

Certification Examination for Zoonosis Control Expert(ZCE)

Pathobiology and Preventive Medicine of Infectious Diseases
～Zoonotic diseases, Transboundary Animal Infection, Animal diseases, Pathogen, Vital reaction, Diagnosis/Treatment etc.

3rd QE: Preliminary screening of the dissertation

Advanced Seminar on Infectious Diseases (2 credits)
（Laboratory seminar Research progress report.）

Research on Infectious Diseases IIA (8 credits)
（Theme of the dissertation Infectious diseases, Infection control, Simulation model for infectious diseases etc.）

Research on Infectious Diseases IIB （8 credits）
（Theme of the dissertation Transboundary pathogens, Development of method of prevention and diagnosis, Fundamental research of pathogenicity etc.）

Internships Abroad A （2 credits）
（Internship at international organizations for health and infection control (WHO etc)）

Internships Abroad B (2 credits）
（Internship at overseas field (such as epidemiological investigation at the on-site field), universities, research institutions, international governmental organizations, etc.）

Advanced Seminar on Infectious Diseases (2 credits)
（Laboratory seminar Research progress report.）

Year 2

2nd QE: Mid-term dissertation evaluation, Decision of the degree title

Research on Infectious Diseases I （8 credits）

Core Subjects on Infectious Diseases IIA (a minimum of 2 credits)
（Advanced Lecture on Risk Analysis
Advanced Seminar on One Health
Advanced Lecture on Mathematical Biology of Infectious Diseases）

Core Subjects on Infectious Diseases IIB （a minimum of 2 credits）
（Advanced Lecture on Pathology of Infectious Diseases
Advanced Lecture on Transboundary Diseases
Advanced Lecture on Pharmaceutical Development）

Research on Infectious Diseases I （8 credits）

Academic and career counseling

Recommended：Medical ethics （Subject of Graduate School of Medicine）
Practice on Epidemiology I （Inter-Graduate School Class）

Core Subjects on Infectious Diseases I （a minimum of 2 credits）
（Advanced Lecture on Pathogen Genomics, Advanced Lecture on Zoonosis Control, Advanced Lecture on Biological Defense）

Advanced and Comprehensive Studies on Zoonosis Control （5 credits）

Year 1

1st Quality Examination (QE): Career path inquiry, Academic advice

Recommended：Basic Medicine, Basic clinical Medicine Ⅰ （Inter-Graduate School Class）

Subjects on Fundamental Veterinary Science and Infectious Diseases （a minimum of 6 credits）
Advanced Lecture on Biostatistics, Practice on Analytical Machines, Advanced Lecture on Information Science,
Advanced Lecture on Immunology, Advanced Lecture on Parasitology, Advanced Lecture on Veterinary Public Health,
Advanced Lecture on Microbiology, Advanced Lecture on Veterinary Hygiene

Research Ethics Seminar （1 credit)/Academic English （2 credits）

Required subjects for acquiring Ph.D. in Infectious Diseases

Common Course

Required subjects for acquiring Ph.D. in Veterinary Science

Lectures at the Graduate School of Infectious Diseases

Education Appendix 3

University of Melbourne

Prof. David Jackson
Prof. Lorena Brown
Prof. Elizabeth Hartland
Assist. Prof. Brendon Chua

July 2018 ~

Host responses to microbial infection

1. Microbial infection and host responses (HIGASHI, **BROWN, CHUA**)
 - Bacterial infection
 - Virus infection
 - Parasitic infection
 - Immune system and inflammation
2. Infection prophylaxis with host defense systems (**BROWN**)
3. Microbial evasion mechanisms from host defense systems (**HARTLAMD)**
4. Exercise and presentation

Pharmaceutical development

1. Infectious diseases and antibiotics (HIGASHI, IGARASHI)
 - Anti-viral, bacterial and fungal agents
 - Anti cancer drugs
2. Infectious diseases and vaccines (**JACKSON**)
3. Molecular modeling to develop new drugs (IGARASHI)
 - Drug modeling from protein structures
 - Design of chemical compounds
4. Drug delivery systems (HIGASHI)
5. Drug development and clinical trials (HIGASHI)
6. Exercise and presentation (HIGASHI)

GI-CoRE-based Student exchange 1

Education Appendix 4

UCD DUBLIN

ADVANCES IN INFECTION BIOLOGY 2016

CO-ORDINATOR: PROF. STEPHEN GORDON
REGISTRATION: stephen.gordon@ucd.ie
MODULE CREDITS: 5
Venue: Vet Sciences Centre, Room 115
14TH-16TH MARCH 2016

Course Outline:
The aim of this graduate module is to provide students with an overview of current research developments in the infection biology area, and how these are translating into novel therapeutic modalities. Students will learn key concepts in Infection Biology from the "bottom up", starting with the molecular basis of host-pathogen interaction, moving to animal models, systems biology approaches, population level studies, issues in global health, and therapeutics and vaccines. The module comprises 6 sessions, morning and afternoon, running over three days at UCD.

Fiscal Year	No. of students	Academic staff from HU (No. of Lectures)
2015	9	5 (2)
2016	3	4 (2)
2017	7	3 (2)

GI-CoRE-based Student exchange 2

Education Appendix 5

Fiscal Year	No. of students	Exchange Period
2014	2	5 days
2015	2	3 months
2016	2	3 months
2017	1	2 months

Training outcomes (co-authored publications)

UCD Graduate student

GI-CoRE Professors

Gonzalez G, Sasaki M, Burkitt-Gray L, Kamiya T, Tsuji NM, Sawa H, Ito K. An optimistic protein assembly from sequence reads salvaged an uncharacterized segment of mouse picobirnavirus. Sci Rep. 2017 Jan 10;7:40447.

Donovan PD, Gonzalez G, Higgins DG, Butler G, Ito K. Identification of fungi in shotgun metagenomics datasets. PLoS One. 2018 Feb 14;13(2):e0192898.

Co-authored publications

Education Appendix 6

Graduate student **GI-CoRE non-Japanese members**

Torii S, Orba Y, Hang'ombe BM, Mweene AS, Wada Y, Anindita PD, Phongphaew W, Qiu Y, Kajihara M, Mori-Kajihara A, Eto Y, Harima H, Sasaki M, Carr M, Hall WW, Eshita Y, Abe T, Sawa H: "Discovery of Mwinilunga alphavirus: a novel alphavirus in Culex mosquitoes in Zambia", Virus Res, pii: S0168-1702(18)30098-4. doi: 10.1016/j.virusres.2018.04.005. [Epub ahead of print](2018)

Sasaki M, Anindita PD, Ito N, Sugiyama M, Carr M, Fukuhara H, Ose T, Maenaka K, Takada A, Hall WW, Orba Y, Sawa H: "Heparan sulfate proteoglycans serve as an attachment factor for rabies virus entry and infection", J Infect Dis, in press (2018)

Sasaki M, Anindita PD, Phongphaew W, Carr M, Kobayashi S, Orba Y, Sawa H: "Development of a rapid and quantitative method for the analysis of viral entry and release using a NanoLuc luciferase complementation assay", Virus Res, 243, 69-74 (2018)

Phongphaew W, Kobayashi S, Sasaki M, Carr M, Hall WW, Orba Y, Sawa H: "Valosin-containing protein (VCP/p97) plays a role in the replication of West Nile virus", Virus Res, 228, 114-123(2017)

Wada Y, Orba Y, Sasaki M, Kobayashi S, Carr MJ, Nobori H, Sato A, Hall WW, Sawa H: "Discovery of a novel antiviral agent targeting the nonstructural protein 4 (nsP4) of chikungunya virus", Virology, 505, 102-112(2017)

Anindita PD, Sasaki M, Nobori H, Sato A, Carr M, Ito N, Sugiyama M, Orba Y, Sawa H: "Generation of recombinant rabies viruses encoding NanoLuc luciferase for antiviral activity assays.", Virus Res, 215,121-8(2016)

Summer Institute

Education
Appendix 7

Bioinformatics and Computational Biology

2017 : 44 students enrolled (21 international students from 11 countries)

In order to deepen your understanding of the basic principle of computer algorithms, software and databases often used in life sciences, this course reviews these technologies from a point of view of information science, aiming to acquire the applicative skills necessary for doing advanced research.

- 26/June/2017 - 05/Jul/2017
- Level: Ph.D. Level
- Capacity: 30
- Language:English
- Organizing Institution: Graduate School of Infectious Diseases

Lecturers

Kimihito Ito
Professor
Hokkaido University

Des Higgins
Professor
University College Dublin, Ireland

Kanako Koyanagi
Associate Professor
Hokkaido University

Manabu Igarashi
Associate Professor
Hokkaido University

Ryosuke Omori
Assistant Professor
Hokkaido University

Program Overview

As a part of the future reform strategy towards the 150th anniversary of Hokkaido University (HU), the university launched the Hokkaido Summer Institute (HSI) in 2016, utilizing the climatic advantage of the summer in Hokkaido which is cooler than any other regions of Japan. HSI is a program that brings together leading researchers, with proven educational and research track records, from around the world and provides courses in collaboration with HU faculty members. In 2018, more than 160 researchers from over 110 universities/research institutes from all over the world will gather at HU.

HSI enables participants to expand their knowledge of subjects in cutting-edge research fields at HU that previously were open only to students of the university. Program participants have an opportunity to attend classes that employ attractive educational techniques, such as, field training in Hokkaido's extensive land resources and active learning activities, so as to develop into professionals capable of thriving on the world stage.

All instruction at HSI is in English. This provides international students with a stress-free learning environment without having to worry about language barriers, and also creates a special opportunity for Japanese students, who can audit classes taught by internationally acclaimed researchers. The university strongly hopes that HSI students will cultivate a better understanding of other cultures and improve their English-language proficiency and communication skills through exchanges with researchers and students from other countries. Off-campus events and field trips are also planned so participants can enjoy Hokkaido's beautiful summer.

References

Global Institution for Collaborative Research and Education (GI-CoRE) Final Evaluation for the Global Station for Quantum Medical Science and Engineering/Global Station for Zoonosis Control projects

1. Aims

The Global Institution for Collaborative Research and Education (GI-CoRE) shall implement an external evaluation of the research, education and organizational framework of the Global Station for Quantum Medical Science and Engineering/Global Station for Zoonosis Control projects which started on April 1, 2014. As the projects have welcomed the final (fifth) year of the implementation period upon the Fiscal Year 2018, the feedback of this evaluation shall be used to decide whether or not to renew the Global Station project for a further period and improve operations upon the renewed period.

2. Evaluation Structure

A "Hokkaido University Global Institution for Collaborative Research and Education External Evaluation Committee" shall be established in each of the Quantum Medical Science and Zoonosis Control Global Stations in accordance with the External Evaluation Implementation Guidelines for the Hokkaido University Global Institution for Collaborative Research and Education Global Station (Document 2). All evaluations and reports shall be undertaken in English.

☐ Global Station for Quantum Medical Science and Engineering External Evaluation Committee
Candidates from Quantum Medical Science GS: 2 foreign members, 1 Japanese member

☐ Global Station for Zoonosis Control External Evaluation Committee
Candidates from Zoonosis Control GS: 2 foreign members, 1 Japanese member

*When the evaluation is complete, the GI-CoRE Steering Committee shall receive a report from the Committee chair.

3. Evaluation Method

☐The External Evaluation Committee shall check the contents of the Research Progress Report (Document 3) sent in advance from HU before implementing the on-site investigation, and shall evaluate the evaluation items prescribed in Document 4.

☐A 5-level evaluation ratings (S to D) and comments shall be obtained for each "Evaluation Item".

Evaluation Ratings	Evaluation Explanation
S	Achieved outcomes surpassed the original plan (Outstanding)
A	Good progress has been maintained and expected outcomes have been achieved (Excellent)
B	Most expected outcomes have been achieved with some slight delays (Good)
C	Although certain outcomes were achieved, overall results were insufficient (Satisfactory)
D	No expected outcomes were achieved (Unsatisfactory)

4. Required Expenses

Travel expenses and honorarium shall be provided to the Evaluation Committee Members (in accordance with HU regulations). Other expenses required for the External Evaluation (as travel expenses, honorarium, evaluation report printing expenses, etc.) shall be funded by the budget (non-personnel cost) of each Global Station.

5. Publishing of Evaluation Results

Evaluation of this project shall be broadly announced, with the results both published on the relevant HU websites and published as booklets which are sent to external organizations such as the Japanese Ministry of Education, Culture, Sports, Science and Technology.

GI-CoRE Global Station External Evaluation Schedule

Year and Month	Agenda
Fiscal Year 2017 (2017)	
August to November	**Proposal of Evaluation Items and Evaluation Structure (Draft Fixed)**
December	**GI-CoRE Steering Committee #13** >> Fixing overviews of evaluation items, evaluation structure, schedule, etc. >> Starting to create the GI-CoRE Research Progress Report (in English)
	Selection/Arrangement of the Evaluation Committee Members *Criteria: 2 foreign and 1 Japanese members (candidates who can conduct evaluation in English) *Confirmation of affiliation, main achievements, contact details, etc.
March	**GI-CoRE Steering Committee #14** >> Fixing the Evaluation Committee Members and evaluation forms >> Official appointment request (by letters from the GI-CoRE Director)
Fiscal Year 2018 (2018)	
April	**Commencement of the Appointment as the Evaluation Committee Members**
May to June	**Completion of the Research Progress Report (in English)** >> Forwarding the report to the Evaluation Committee Members for their document screening
July to August	**On-site Investigation (by the External Evaluation Committee)** July 19 -20 (for GSZ) August 8 (for GSQ)
October	**Submission of the Report of the Final Evaluation** >> Evaluation Committee Members shall forward their reports of the final evaluation, based on the document screening and on-site investigation
	GI-CoRE Steering Committee #18 >> Report of the Final Evaluation by each Chair of the External Evaluation Committees of GSQ/GSZ on behalf of the three External Evaluation Committee Members >> Decision of the GSQ/GSZ projects period extension until FY 2019
Fiscal Year 2019 (2020)	
March	**Expiration of the GSQ /GSZ projects under the GI-CoRE system**
Fiscal Year 2020 (2020)	
April	**Internalization of the GSQ /GSZ projects into the affiliated faculty and center**
July	**Publication of the Final Evaluation Reports (in English)**

Hokkaido University
Global Institution for Collaborative Research and Education (GI-CoRE)
External Evaluation Implementation Guidelines for the Global Stations

December 15, 2015

Establishment of the Global Institution for Collaborative Research and Education Steering Committee

1. Purpose

These implementation guidelines shall provide the necessary matters for the implementation of evaluation of the Global Station by non-University affiliated persons (hereinafter the “GS External Evaluation”) of the Hokkaido University Global Institution for Collaborative Research and Education (GI-CoRE).

2. Committee

(1) The "Hokkaido University Global Institution for Collaborative Research and Education External Evaluation Committee (hereinafter the "Committee")" shall be established by GI-CoRE in order to perform the matters prescribed in each of the following items.

(i) Implementation of GS External Evaluation

(ii) Matters related to the creation and publishing of the report pertaining to the GS External Evaluation

(2) A Committee shall be established for each Global Station that is target for external evaluation.

3. Composition

(1) The Committee shall be composed of third parties other than constituent members of Hokkaido University, and designated by the Director of GI-CoRE from persons prescribed in each of the following items.

(i) Person designated by the Director of GI-CoRE who is an expert both within and outside Japan in the research field of the Global Station to be externally evaluated

(ii) Persons whom the Director of GI-CoRE deems necessary

(2) The Committee members prescribed in the preceding paragraph shall be commissioned by the Director of GI-CoRE after approval by the GI-CoRE Steering Committee.

4. Term of Office

(1) The term of office for Committee Members shall be 1 year. However, if a Committee Member vacancy occurs, the term of office of the successor shall be the remaining term of the predecessor.

(2) Committee Members may be reappointed.

5. Committee Chair

(1) A Committee Chair shall be appointed and selected through mutual election by the Committee members.

(2) The Committee Chair shall call a Committee meeting as required, and shall chair the said meeting.

6. Proceedings

(1) A Committee meeting may not be held unless a majority of the members are present.

(2) Committee meeting proceedings shall be decided by a majority of the attending members. In case of a tie, the Committee Chair shall decide the issue.

7. Implementation of GS External Evaluation

(1) The Committee shall implement the GS External Evaluation as prescribed in the following Article.

(2) The Committee may hear the opinions of persons concerned and implement firsthand investigations related to the implementation of the GS External Evaluation.

8. Evaluation Items

The Committee shall evaluate the items prescribed by GI-CoRE in each of the following items.

(1) Items related to research

(2) Items related to education

(3) Items related to the structure of the research and education center

(4) Other items deemed necessary by the Committee

9. Creation and Publishing of the Report

The Committee shall collate the evaluation results prescribed in the preceding paragraph and publish the results in a report.

10. Response to Evaluation Results

The Director of GI-CoRE shall promptly work to implement improvements in view of the report prescribed in the previous paragraph for items in which improvements are deemed necessary.

11. General Affairs

General affairs for the Committee shall be processed by the Division of International Relations, International Affairs Department.

12. Miscellaneous Provisions

Necessary matters concerning GS External Evaluation other than those prescribed within these implementation guidelines shall be prescribed separately by the GI-CoRE Steering Committee.

Supplementary Provisions

These guidelines shall come in force on 12 December 2017.

REGULATIONS FOR THE HOKKAIDO UNIVERSITY GLOBAL INSTITUTION FOR COLLABORATIVE RESEARCH AND EDUCATION

HU Doc. No.151
April 1, 2014

(Purpose)

Article 1 These *Regulations* shall prescribe the organization and administration of the Hokkaido University Global Institution for Collaborative Research and Education (hereinafter referred to as "the Institution for Research and Education"), based upon the *Rules Concerning the Organization of Hokkaido University* (HU Doc. No. 31 of 2004), Article 37(4).

(Objectives)

Article 2 The objectives of the Institution for Research and Education shall be to invite teaching staff from Japan and overseas with world-class education and research results, to promote international collaborative research and international collaborative education (hereinafter referred to as "international collaborative research and education") that capitalizes upon the distinctive characteristics of Hokkaido University (hereinafter referred to as the "University"), and to provide support for international collaborative research being furthered independently by faculties or schools.

(Employees)

Article 3 A Director and other necessary teaching staff shall be placed in the Institution for Research and Education.

(The Director)

Article 4 The President shall be appointed as the Director of the Institution for Research and Education.

2. The Director shall supervise the work of the Institution for Research and Education.

(The assistant director)

Article 5 An assistant director shall be placed in the Institution for Research and Education.

2. A vice president designated by the President shall be appointed as the assistant director.
3. The assistant director shall assist the Director in his or her duties and shall take over those duties in the event of the latter being incapacitated.

(Global stations)

Article 6 The following global stations shall be placed in the Institution for Research and Education to promote international collaborative research and education that capitalizes upon the distinctive characteristics of the University.

(1) The Global Station for Quantum Medical Science and Engineering
(2) The Global Station for Zoonosis Control
(3) The Global Station for Food, Land and Water Resources
(4) The Global Station for Soft Matter
(5) The Global Station for Big Data and Cybersecurity
(6) The Global Station for Arctic Research

2. Full-time teaching staff from the University (including specially appointed academic staff who come under each item of Article 3 of the *Hokkaido University Specially Appointed*

Academic Staff Regulations (HU Doc. No. 35 of 2006). The same applies to Article 7(2) below.) and teaching staff invited from Japan and overseas shall be placed in the Institution for Research and Education.

3. The period for which a global station is established shall be five years. However, this period can be extended within five years if the steering committee provided for in Article 8 deems it necessary.

(Global station leaders)

Article 7 A global station leader shall be placed in each of the global stations referred to in the items of Article 6(1).

2. The global station leader shall be one of the teaching staff of the said global station who has been designated by the Director.
3. The global station leader shall supervise the work of the said global station under the orders of the Director.
4. The term of office of the global station leaders shall be three years or less, and they can be reappointed.

(Steering Committee)

Article 8 A steering committee shall be placed in the Institution for Research and Education to deliberate important matters concerning the said institution.

2. The organization and administration of the steering committee shall be prescribed separately.

(Administration)

Article 9 The administrative work of the Institution for Research and Education shall be processed in the Division of International Planning, the International Affairs Department.

(Miscellaneous provisions)

Article 10 In addition to what is prescribed in these *Regulations*, necessary matters regarding the operation of the Institution for Research and Education shall be prescribed separately by the President after approval by the steering committee.

Supplementary Provisions

These *Regulations* come into force on April 1, 2014.

Supplementary Provisions

These *Regulations* come into force on April 1, 2015.

Supplementary Provisions

These *Regulations* come into force on April 1, 2016.

Supplementary Provisions

These *Regulations* come into force on July 1, 2018.

REGULATIONS FOR THE GLOBAL INSTITUTION FOR COLLABORATIVE RESEARCH AND EDUCATION STEERING COMMITTEE

HU Doc. No. 152
April 1, 2014

(Purpose)

Article 1 These *regulations* shall provide for the necessary matters concerning the organization and administration of the Global Institution for Collaborative Research and Education Steering Committee (hereinafter referred to as "the committee"), based upon Article 8(2) of the *Regulations for the Global Institution for Collaborative Research and Education* (HU Doc. No. 151 of 2014, "*Regulations for the Institution for Education and Research*" in Article 3).

(Topics for Deliberation)

Article 2 The committee shall deliberate on the issues set forth in item (6) through item (10) of Article 2 of the *National University Corporation Hokkaido University Agenda for Hearing with Faculty Council Rules* (HU Doc. No. 42 of 2015, referred to as "*Hearing Rules*" in the following paragraph) and deliver opinions to the President.

2. In addition to the matters specified in the preceding paragraph, the committee shall deliberate the following matters pertaining to the Hokkaido University Global Institution for Collaborative Research and Education (hereinafter referred to as "the Institution for Research and Education" in (5) below).

(1) Matters regarding personnel affairs of the faculty (excluding matters set forth in item (6) through item (10) of Article 2 of the *Hearing Rules*).

(2) Matters regarding the establishment, reform or termination of global stations.

(3) Matters regarding the evaluation of the educational and research activities of global stations.

(4) Matters regarding budgets.

(5) Other important matters pertaining to the administration of the Institution for Research and Education.

(Structure)

Article 3 The committee shall consist of the following members:

(1) The director of the Global Institution for Collaborative Research and Education (referred to as "the director" in Article 5)

(2) The assistant director of the Global Institution for Collaborative Research and Education (referred to as "the assistant director" in Article 5)

(3) One vice president designated by the President (excluding the person mentioned in the previous item)

(4) One dean or director from each of the following categories (a-d), each of whom shall be designated by the President

a) The Graduate School of Letters, the Graduate School of Law, the Faculty of Education, the Research Faculty of Media and Communication, the Faculty of Economics and Business, the Faculty of Public Policy

b) The Graduate School of Information Science and Technology, the Faculty of Fisheries Sciences, the Faculty of Environmental Earth Science, the Faculty of Science, the Research Faculty of Agriculture, the Faculty of Advanced Life Science, the Faculty of Engineering, the Faculty of Veterinary Medicine

c) The Faculty of Pharmaceutical Sciences, the Faculty of Health Sciences, the Faculty of Medicine, the Faculty of Dental Medicine, Hokkaido University Hospital

d) Each affiliated research institute, each research center, the Field Science Center for Northern Biosphere

(5) Each global station leader as prescribed in Article 7 of the *Regulations* for the Institution for Education and Research

(6) Other persons whom the President deems appropriate

2. The President shall appoint the committee members mentioned in the preceding item (6)

(Term of Office)

Article 4 The terms of office of the committee members indicated in paragraph 1(4) and paragraph 1(6) of the previous article shall be two years. However, the term of office of substitute committee members shall be the remaining term of office of the previous committee member.

2. The committee members indicated in the preceding paragraph may be reappointed.

(Committee Chair)

Article 5 The director shall be appointed as the committee chair.

2. The committee chair shall call committee meetings and preside over the said meetings.

3. The assistant director shall take over the director's duties in the event of the latter being incapacitated.

(Proceedings)

Article 6 The committee cannot validly convene unless at least two-thirds of the committee members are present.

2 Committee proceedings, other than those prescribed separately, shall be decided by the majority vote of the attending committee members.

(Attendance of Persons Other Than Committee Members)

Article 7 In cases deemed necessary by the committee, persons other than committee members may be permitted to attend committee meetings, and explanations or opinions of the said persons may be heard.

(Committees on Special Issues)

Article 8 Committees on special issues may be established within the committee when necessary in order to deliberate specialized matters.

(General Affairs)

Article 9 The administrative affairs of the committee shall be processed in the Division of International Planning, the International Affairs Department.

(Miscellaneous Provisions)

Article 10 In addition to what is prescribed in these *regulations*, necessary matters regarding the operation of the committee shall be prescribed by the said committee.

Supplementary Provisions

These *regulations* come into force on April 1, 2014.

Supplementary Provisions (HU Doc. No. 196 of April 1, 2015)

These *regulations* come into force on April 1, 2015.

Supplementary Provisions (HU Doc. No. 191 of October 1, 2016)

These *regulations* come into force on October 1, 2016.

Supplementary Provisions (HU Doc. No. 163 of April 1, 2017)

1. These *regulations* come into force on April 1, 2017.
2. The dean of the Graduate School of Dental Medicine who was specified as a committee member in c) of paragraph 1(4) of Article 3 prior to the revision (hereinafter referred to as "the former committee member" in this paragraph) shall be deemed to have been appointed as a committee member under the revised *regulations* in c) of paragraph 1(4) of Article 3 on the enforcement date of these regulations. The term of office of the said member shall be the remaining term of office of the former committee member on the enforcement date, notwithstanding the revised provisions of Article 4(1).

Supplementary Provisions (HU Doc. No. 182 of June 20, 2017)

These *regulations* come into force on June 20, 2017 and apply retroactively from April 1, 2017.

Supplementary Provisions (HU Doc. No. 98 of July 1, 2018)

These *regulations* come into force on July 1, 2018.

Final Evaluation Report

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