Max Planck The University of Tokyo Center for Integrative Inflammology

Report for project duration 1.1.2018 until 31.12.2018

Tadatsugu Taniguchi

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1. Short project description

Project name/-title Max Planck-The University of Tokyo Center for Integrative Inflammology
Project place / city Tokyo, Japan
Responsible person Tadatsugu Taniguchi
Main targets of project Inflammation is a complex biological response that is essential to protect the host from infection and other harmful stimuli. If left uncontrolled, however, inflammation can exacerbate illness, typically infection, allergy, autoimmunity, and cancer. In addition, inflammation underlies the development and/or aggravation of seemingly unrelated disorders such as cardiovascular, metabolic, and neuronal diseases. Therefore, the study of inflammation, and its linking together a multitude of research disciplines, is one of the most challenging and rapidly growing topics in medical research. Thus, the main targets of our Center are as follows. The Center consolidates seemingly distantly but inflammation-related research disciplines, which have previously been pursued by each individual organization by enhancing mutual cooperation between the two organizations. This facilitates a critical mass and concentrated research effort to spawn a highly attractive field we term “Integrative Inflammology”, the results of which contribute to the development of new methods for the diagnosis, prevention and treatment of inflammation-associated diseases. Thus, the Center expands and strengthens the mutual cooperation that exists between the Max Planck Socety and The University of Tokyo through joint symposia, research collaboration and education efforts by the participation of world-renown Principal Investigators (PIs) drawn from several institutions at the two parent organizations.

2. Project content

Realized project contents (1) The participating Pis. The Center is operated by the participation of the following Pis in cooperation with their colleagues. -From Max Planck Society-

Thomas Boehm (Max-Planck Institute of Immunology and Epigenetics); Member of the Consulting Board
Rudolf Grosschedl (Max-Planck Institute of Immunology and Epigenetics); Co-Director and Member of the Consulting Board
Hartmut Wekerle (Max-Planck Institute of Neurobiology); Member of the Consulting Board
Reinhard Fässler (Max-Planck Institute of Biochemistry)
Thomas Meyer (Max-Planck Institute for Infection Biology)
Stefan Kaufmann (Max-Planck Institute for Infection Biology); Member of the Consulting Board
Dietmar Vestweber (Max-Planck Institute for Molecular Biomedicine); Deputy Director and Member of the Consulting Board
-From The University of Tokyo (UT)-
Ung-il Chung (Graduate School of Engineering)
Masanori Hatakeyama (Graduate School of Medicine); Deputy Director and Member of the Consulting Board
Hiroshi Kiyono (Institute for Medical Science)
Tatsuhiko Kodama (Research Center for Advanced Science and Technology)
Toru Miyazaki (Graduate School of Medicine)
Yasuyuki Sakai (Institute of Industrial Science); Member of the Consulting Board
Takao Shimizu (Graduate School of Medicine and National Center for Global Health and Medicine); Member of the Consulting Board
Tadatsugu Taniguchi (Institute of Industrial Science); Co-Director and Member of the Consulting Board
Kazuhiko Yamamoto (Graduate School of Medicine); Member of the Consulting Board

(2) The projects
To effectively organize and run the Center, participants were broadly categorized into three groups on the basis of research activities, namely, those focusing on (A) development and interplay of inflammation-related cells, (B) regulation of inflammatory responses, and (C) infection and inflammation. It must be emphasized, however, that these groups were cohesive and complementary to each other, constantly sharing ideas, information and technologies, and commonly aiming at establishing the field of integrative inflammology, wherein the Center takes the initiative of coordinating all activities. Furthermore, the participants of all groups commonly seeked to better our understanding of various inflammation-associated diseases as well as develop new strategies for the diagnosis, prevention, and treatment of these diseases. The Center also aimed at coordinating an effective exchange of relevant materials and information for stimulating cooperation. Indeed, a participant was involved in more than one of these groups as cooperator.

(3) Joint meeetings
The Center organized joint symposia in Japan or in Germany on relevant topics in the context of inflammation and its associated diseases. All members of the two organizations, senior and junior researchers, actively participated. In addition, many graduate and undergraduate students attended these symposia.

(4) Exchange of scientists
The Center will establish programs to coordinate the mutual exchange of Pis and research scholars, who will exchange ideas or conduct research at the Center in order to stimulate and facilitate the active collaboration among the participating laboratories.

(5) Max Planck Junior Fellows
The Center provided a Max Planck Junior Fellowship(s), which is a non-tenure track position. Selection of the recipient(s) of this fellowship was first proposed by the Consulting Board of

the UTokyo side, and further evaluated and approved by the Consulting Board of the Max Planck side. We aimed at selecting indivisuals, each of whom is an exceptionally talented early-career researcher, e.g., the postdoctoral or Assistant Professor level. The fellows joined one of the labs of the Center, but worked largely independently.

(6) Science diplomacy
Science diplomacy may consist of three aspects of activities: (A) Science provides advice to inform and support foreign policy objectives. (B) Diplomacy facilitates international scientific cooperation. (C) Scientific cooperation improves international relations. As we believe in that our Center can enhance scientific cooperation between Germany and Japan, we aimed at interacting representatives of bureaucrats and politicians so as to mutually stimulate the above-mentioned activities.

3. Project targets

Which concrete targets have been achieved within the mentioned period by using which methods?

Overall, we believe that we made substantial achievements within the Center. These are all introduced in the website of our Center; http://mputc.com/index.html
We summarize below the targets and achievements.

-Research papers and exchange of researches-

We published more than 27 scientific papers in high-standard journals with the name of the Center. Joint symposium was held each year by the participation of PIs, young investigators and students (Berlin in 2014 and 2016, Tokyo in 2015 and 2017 and Kreuth in 2018); all these symposia were very successful, particularly by the active participation of young researchers and students.

As a result of these symposia, one of the young researchers from Prof. Grosschedl's lab visited our Institute in UTokyo in August, 2016 for collaboration on the transcriptional regulation in lymphocyte development; a joint paper between the two has been published in 2018 from Proc Natl Acad Sci U S A. (PNAS, 2018 May 15;115(20):5253-5258. doi: 10.1073/pnas.1803936115) Moreover one young researcher who finished his PhD at UTokyo has started his career in one of the Institute of Max Planck in 2017 and he joined our 2018 symposium to share his achievements.

-Max Planck Lecture series-

As many as 21 lectures, including one held in 2018, termed "The Max Planck Lecture Series", were held in UTokyo by inviting the world's most renown scientists in the related research fields, and all these lectures were attended very well with active discussions and information exchanges in the inflammology research.

-Max Planck Junior Fellows-

Regarding the Max Planck Junior Fellows, 5 junior fellows have been appointed in the reporting term of 01.01.2018-31.12.2018. They were selected among the applicants by the Consulting Board of the Mack Plank and UTokyo sides in 2014. They all presented their research achievements in one or more of the above-mentioned joint symposia. The names of the fellows and research summaries from each fellow are described below.

(1) Hiroko Nishikawa (Ph.D.):
(Research summary)

CagA is a bacterial oncoprotein produced by *Helicobacter pylori*, a gram-negative bacterium that chronically infects the stomachs of half of the world's population. CagA has been epidemiologically associated with the development of chronic gastritis, peptic ulcers, and gastric cancer. The oncogenic potential of CagA is augmented through its passive multimerization via PAR1b, a polarity-regulating kinase which exists as a multimer. However the nature of the PAR1b multimer had been unknown. I have discovered a novel mechanism by which PAR1b multimerizes and enhances it kinase activity. I am now in the process of preparing this project for publication.

(2) Hideyuki Yanai (Ph.D.):
(Research summary)
The sutdy is focused on high-mobility group box protein 1 (HMGB1) in inflammation and inflammatory diseases. HMGB1 is released from dying cells and damaged cells, and the released HMGB1 promotes inflammation through the activation of innate immune responses. I have generated HMGB1 conditional knockout mice and knockout cancer cells, and found that HMGB1 is required for the recruitment of granulocytes, critical mediators of inflammation, into the inflamed sites. In addition, I also worked on other molecules involved in the regulation of inflamation and oncogenesis.
(Publication)
1. Yanai H, Chiba S, Hangai S, Kometani K, Inoue A, Kimura Y, Abe T, Kiyonari H, Nishio J, Atarashi N, Mizushima Y, Negishi H, Grosschedl R. and Taniguchi. ; Revisiting the role of IRF3 in inflammation and immunity by conditional and specifically targeted gene ablation in mice. Proc Natl Acad Sci U S A. 2018;115(20):5253-5258.

(3) Yumiko Fujii (Ph.D.):
(Research summary)
Chronic infection with cagA-positive *Helicobacter pylori* is associated with gastric diseases including gastritis, metaplasia and carcinoma. My research aims to elucidate the inflammological and pathological effects on the stomach of CagA protein. We demonstrated that CagA induces precancerous mucosal lesion defined as spasmolytic polypeptide expressing metaplasia (SPEM) in mouse gastric corpus. We also revealed that CagA deregulates the phosphorylation status of E-cadherin cytoplasmic domain, which is involved in the strength of apical-junctional complex. Furthermore, we found that CagA binds to SHIP2, a phosphatidilinositol phosphatase, and consequently changes the phosphoinositide balance on the cell membrane of CagA-injected cells. We are currently preparing a manuscript to report these results in a scientific journal.

(4) Tomohisa Okamura (M.D., Ph.D.):
(Research summary)
Our study focused on the regulation of T cells and B cells by cytokines and other immunoregulatory molecules. In particular, the new subset of regulatory T cells, namely CD4+CD25-LAG3+ T cells originary indentified in our laboratory was the focus of my attention. We developed an integrative inflammology-based approach and revealed the requirement of Ltbp3 expression maintained by Egr2 and Egr3 for TGF-β3 production from the CD4+CD25-LAG3+ cells that also produce IL-10. Futhermore, recently, we reported TGF-β3 and IL-10 synergistically modulate transcriptional programs and suppressed cellular energetics of both glycolysis and oxidative phosphorylation in TLR-stimulated B cells, and improve lupus.
(Publication)
1. Okamura T, Yamamoto K, Fujio K. Early Growth Response Gene 2-Expressing CD4(+)LAG3(+) Regulatory T Cells: The Therapeutic Potential for Treating Autoimmune Diseases. Front Immunol. 2018;9:340.
2. Teruya S, Okamura T, Komai T, Inoue M, Iwasaki Y, Sumitomo S, Shoda H, Yamamoto K,

Fujio K. Egr2-independent, Klf1-mediated induction of PD-L1 in CD4+ T cells. Sci Rep. 2018;8(1):7021.
3. Komai T, Inoue M, Okamura T, Morita K, Iwasaki Y, Sumitomo S, Shoda H, Yamamoto K, Fujio K. Transforming Growth Factor-β and Interleukin-10 Synergistically Regulate Humoral Immunity via Modulating Metabolic Signals. Front Immunol. 2018;9:1364.
4. Komai T, Okamura T, Inoue M, Yamamoto K, Fujio K. Reevaluation of Pluripotent Cytokine TGF-β3 in Immunity. Int J Mol Sci. 2018;19(8). pii: E2261.

(5) Sho Hangai (M.D., Ph.D.):
(Research summary)
My research focused on the regulation of inflammation and oncogenesis by the self-derived molecule, termed "Damage-associated molecular patterns (DAMPs)". Previously the conventional wisdom was that DAMPs generally evoke pro-inflammatory responses. In my study, I identified prostaglandin E2 (PGE2) as an inhibitory DAMP (iDAMP) that is released from dead cells and negatively regulates immune responses. The study revealed the critical role of this iDAMP in the growth regulation of cancer cells in vivo. In addition, I also participated to other related projects.
(Publication)
1. Yanai H, Chiba S, Hangai S, Kometani K, Inoue A, Kimura Y, Abe T, Kiyonari H, Nishio J, Taguchi-Atarashi N, Mizushima Y, Negishi H, Grosschedl R, Taniguchi T.; Revisiting the role of IRF3 in inflammation and immunity by conditional and specifically targeted gene ablation in mice.; Proc Natl Acad Sci U S A. 2018;115(20):5253-5258.
2. Kimura Y, Negishi H, Matsuda A, Endo N, Hangai S, Inoue A, Nishio J, Taniguchi T, Yanai H.;Novel chemical compound SINCRO with dual function in STING-type I interferon and tumor cell death pathways.; Cancer Sci. 2018;109(9):2687-2696.

Book
1. Hangai S., Kimura Y., Taniguchi T., Yanai H.; Innate Immune Receptors in the Regulation of Tumor Immunity. In: Zitvogel L., Kroemer G. (eds) Oncoimmunology. 2018; Springer, Cham

Noteworthy event for this year was one of our Junior Fellows, Tomohisa Okamura
has been promoted to Project Associate Professor, Department of Functional Genomics and Immunological Diseases, Graduate School of Medicine, The University of Tokyo. The Department have been newly launched for the emerging research field of his study on integrative analysis of multi-omics data of multiple immune cell subsets from patients with autoimmune diseases.
He is the second Junior Fellow to be promoted to Project Associate Professor after Hideyuki Yanai. The outcome of two Junior Fellows' promotions, out of five, can be proudly evaluated.

-*Science diplomacy*-
As for the science diplomacy, we've worked uniquely to enhance scientific interactions between Germany and Japan.
As reported in the previous reports, we had guests from German and Japanese embassies for our symposia held in 2014 and 2015. In addition, in the 2016 symposium held in Berlin, Ambassador Takeshi Kimura of the Japanese Embassy gave the opening speech; former Ambassador Takeshi Nakane, who invited us in 2014 and now serves as Ambassador of Science and Technology of the Japanese ministry of Foreign Affairs, also kindly attended the symposium-related event. As part of the 2017 symposium held in Tokyo, we visited German embassy where Ambassador Hans Carl von Werthern kindly welcomed us. We presented our bilateral center and talked about future science and Center's activities.

In 2018, as we had a symposium in a special location of Ringberg castle, schedules of representatives from German or Japanese officials were unfortunately not available.

Strengthening the presence of our Center and its research field of Inflammation, we believe young scientists experienced the science is not only going on the bench but presenting, promoting and sharing science also matters.
We sincerely wish our notion of activities will be inherited by the next generation and will be cultivated in a different form of a center or a group while the research field continuously grows.

Were conceptual changes necessary within the project period with regards to the granted project?

There was no necessity to make any conceptual change.
The Co-Directors (Grosschedl and Taniguchi) and two Deputy Co-Directors, Vestweber and Hatakeyama discussed the activities of our Center whenever necessary. Some of the issues (e.g., joint meetings, appointment of the Max Planck Junior Fellows and future development of the Center) have also been periodically discussed among the Consulting Boards on both sides for the decision-making and/or official approval.
For the year 2018, one of our Junior Fellows, Tomohisa Okamura has been promoted to Project Associate Professor and due to the clerical reasons, he declined to receive monthly support from the Center. The Consulting Boards of UTokyo have discussed on the issue and agreed to have him as an honorary position.

What targets could not be achieved within the mentioned period?

As described above, we believe that we have made significant achievements in the Center during 01.01.2018 - 31.12.2018.
The future collaborations among the PI's laboratories have been discussed during our 2018 symposium.