


## Reinstalling Tissue Immune Tolerance and Homeostasis in Autoimmune and Inflammatory Diseases

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### Purpose and Significance of the Research

#### ●Overcoming diseases caused by immune system abnormalities!

The immune system functions to protect the human body from external pathogens by regulating the balance between an activation mechanism and a suppression mechanism. However, recent years have seen a growing incidence of diseases caused by abnormal immune states due to imbalances between these opposing mechanisms, such as an overly active activation mechanism or weak suppression mechanism. Applied and interdisciplinary research will be conducted using state-of-the-art technologies to elucidate the human immune mechanism. Furthermore, restoring the balance between activation and suppression will lead to innovative therapies for human autoimmune and inflammatory diseases that are currently difficult to treat.

#### ●Using state-of-the-art technologies to elucidate human immune mechanisms

Immune mechanisms have so far been elucidated in detail using mice, which however, are not identical to those in humans. Human-derived samples need to be used in research to overcome human diseases, but analyses of small amounts of human-derived samples were impossible using conventional research technologies. Recently, rapid progress in single-cell analysis using next-generation sequencing and informatics analysis technologies has made it possible to conduct sufficient analysis even with these small samples and expectations are high for research into the mechanisms underlying the human immune system and the resulting development of therapies. This research aims to elucidate novel mechanisms through interdisciplinary research including imaging technology, and to develop treatments for human diseases using an international research network.

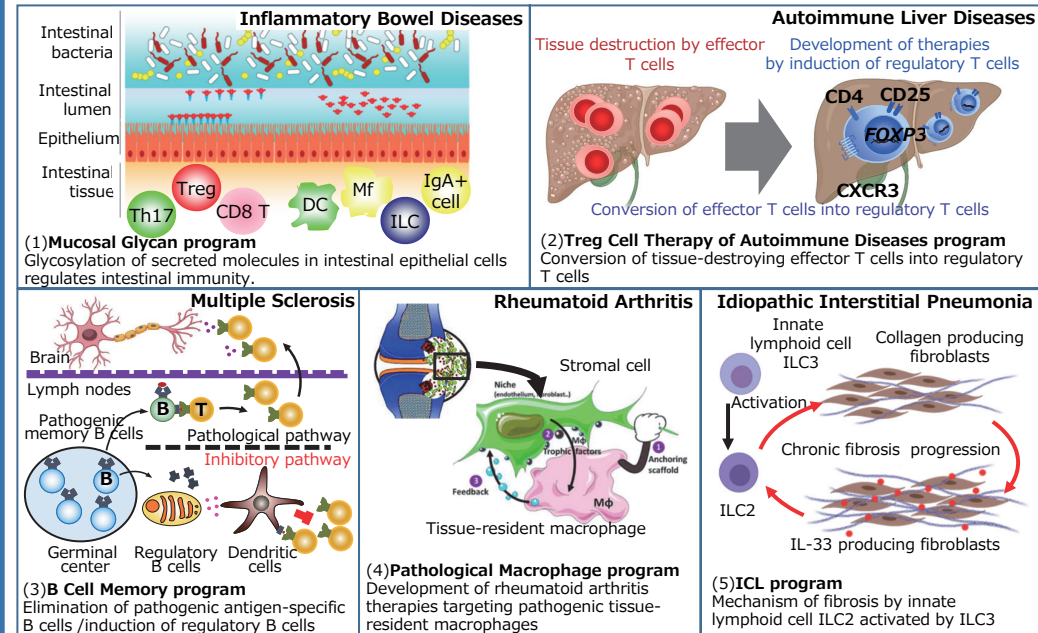


Fig.1 Five programs to be conducted in this project

### Organization of the Project Team

#### ●International research network comprising Japanese basic immunology researchers and overseas clinical immunology researchers

Researchers from Japan belong to the Osaka University Immunology Frontier Research Center (IFReC), where world-class basic research on immunology is conducted mainly using cells and mice. TAKEDA Kiyoshi, a principal investigator and a significant contributor in the field of immune regulation by gut bacteria, leads collaborations with many international research organizations as IFReC's Director. The research group includes SAKAGUCHI Shimon, the discoverer of regulatory T cells and a world authority in this field; KUROSAKI Tomohiro, a pioneering researcher of memory B cells; ISHII Masaru, who discovered pathological bone-destroying cells using a novel imaging method; and MORO Kazuyo, who discovered innate lymphocytes and contributes to the elucidation of their functions. From overseas, the clinical researchers have outstanding research achievements involving diseases caused by immune disorders, and the microbiology or basic immunology researchers conduct research from a different perspective from the Japanese researchers. This interdisciplinary study has basic researchers receiving patient-derived samples from clinical researchers and conducting detailed analyses that were previously impossible, the generated idea from which will be verified through mice experiments and other means to clarify the human immune mechanisms involved in disease, then be applied in clinical research.



Fig. 2 International research network centered on IFReC at Osaka University that makes this research possible

### Plan for Fostering Early-career Researchers

On the Japanese side, 17 young researchers belonging to five globally recognized teams in basic research will participate in the project. For these young researchers to lead the next generation of immunologists, it is necessary for them to broaden their research through direct contact with diverse ideas and technologies and to form their personal networks. To this end, they will be dispatched overseas on a long-term basis to collaborating institutions so they can gain research experience abroad. By acquiring the expertise and technical knowledge of the research institutes to which they belong both in Japan and overseas, they will develop as unique researchers, which is a significant advantage in their career development. The project will encourage the young researchers to implement their original research related to this research topic, allocate research funding for their research, and encourage and support the active acquisition of external funding. Meetings of research groups with young researchers will be held semi-annually, where young researchers will report on their research progress and will be mentored by senior researchers. Mentoring is also provided to postdoctoral researchers in particular from the perspective of research management to encourage their independence. IFReC organizes the International School on Advanced Immunology to attract extremely talented young researchers. Useful for building long-term personal networks of peers of the same generation, active participation of the young researchers in this project is encouraged. Outstanding young researchers will be recruited and fostered as IFReC provides them with travel support and promotes them to independent researchers.



Fig. 3 International School on Advanced Immunology: Bringing together the world's best young researchers