IMMUNOLOGY BOARDS

[Established 1981]

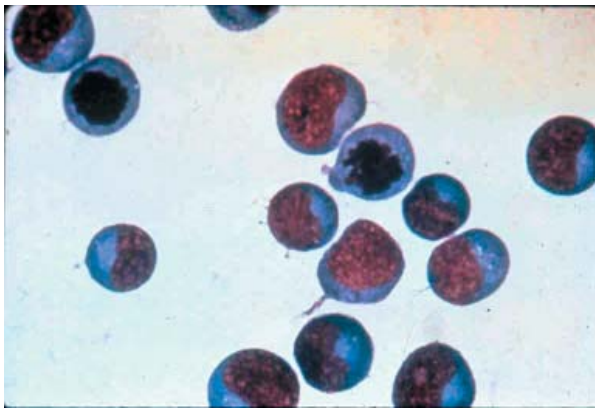
The establishment of the Japanese and U.S. Immunology Boards in 1981 represented a departure for the USJCMSP. It was the first time that members of the Joint Committee had decided to focus on a discipline-oriented area rather than a disease-oriented topic. The field of immunology was advancing rapidly, and new technological developments were allowing researchers to grow and study immunocompetent cells in long-term culture. The Immunology Boards were established to capitalize on this pioneering area of research, and to apply the knowledge gained in immunology to the diagnosis, treatment, and prevention of infectious diseases.[1]

In the United States, Dr. Richard Krause was director of the National Institute of Allergy and Infectious Diseases (NIAID), the NIH institute that funds immunology research. Dr. Krause served as a member of the U.S. Delegation from 1979 to 1984, and strongly advocated the formation of the Immunology Boards. "My particular interest was in streptococcal infections, but that kind of research was applicable to other bacterial infections," he said in a June 2004 interview. "I also did quite a bit of work in immunology, so I could see there was very important parallel work [in immunology] going on in the United States and Japan."

The discussion at the 13th meeting of the Joint Committee in 1977 to create the Immunology Boards preceded their actual initiation by several years, however:

> Further consideration was to be given to additional fields of biomedical science such as cellular immunology and immunogenetics aimed at improving treatment, diagnosis, and prevention of diseases, and how to incorporate these areas effectively into the Program.[2]

Two years later, at its 15th meeting, held at the NIH in Bethesda, Maryland, the Joint Committee recommended that a symposium on immunology be held in 1980. The plan was to consider whether immunology should be the USJCMSP's first discipline-oriented panel. The symposium paved the way for the formation of the Japanese and U.S Immunology Boards.



Normal T Cells

> The Joint Committee was pleased with the content of the [immunology] symposium, and enthusiastically recommended that the organizers prepare research guidelines as a preliminary step for including immunology as a new research area in the U.S.–Japan Program.[3]

Why did the USJCMSP refer to the new immunology groups as 'boards' rather than 'panels?' "The Japanese members had that idea," said Dr. Krause. "They said the panels should be reserved for disease topics."

"It's a very funny situation," said Dr. Tadao Shimao, in an August 2004 interview. Dr. Shimao was Chair of USJCMSP Japanese Delegation from 1992-2001, and a Delegation Member from 1977-1993. "The budgeting system is very different between the U.S. and Japan, but we still continue very well," he added. In Japan, support for USJCMSP activities had been the purview of two ministries. From the creation of the Program in 1965 until 1981, the Japanese Ministry of Health, Labour and Welfare supported the activities of the Panels, while

the Ministry of Foreign Affairs funded the meetings of the Delegation Committee and Subcommittee. But when the Immunology Board was established in 1981, the Japanese Ministry of Education, Culture and Sports undertook the support of its activities.

In the United States, financial support for the new Immunology Board fell to the NIAID, the NIH institute that supports the activities of all the USJCMSP Panels except for the Environmental Genomics and Carcinogenesis Panels (established in 1972 as the Environmental Mutagenesis and Carcinogenesis Panels), which is supported by the NIEHS, and the Nutrition and Metabolism Panel, which is supported by the NIDDK.

Although it is possible to think of immunology as a basic research discipline, many important aspects of the pathology, treatment, and prevention of parasitic and infectious diseases require an understanding of immunological responses that are induced, as well as responses that are actively inhibited by the pathogen. "For example, with the malaria parasite [*Plasmodium*], it is known that certain antigens induce immune tolerance," said Dr. John La Montagne, deputy director of NIAID and U.S. Program Director of the USJCMSP from 1998–2004, in a June 2004 interview. "The organism induces the host *not* to respond to certain malarial antigens. So there must be something about the absence of that immune response that is important in the ability of this organism to cause disease. We need to understand the basic mechanisms by which pathogenic organisms induce immune tolerance. I think this kind of work is going to require teams of people; it is not something one person could do."[4] Increasingly, he says, the USJCMSP encourages interdisciplinary meetings and workshops to explore ways in which one field of research can benefit another.

The long-term objectives of the Immunology Boards are to elucidate the cellular and molecular mechanisms of the immune response and the pathogenesis of immunologic disorders, to pursue areas of immunology that could help expedite vaccine development, and to develop new methods to prevent and treat immunologic diseases and cancer.

Scientists associated with the Japanese and U.S. Immunology Boards have made important scientific advances in B cell biology, T cell biology, and cytokine research. [See text box.] Bone marrow-derived (B) cells are destined to differentiation to memory and antibody-secreting cells. Once mature, B cells play a central role for the immune system by preventing infection from pathogenic microorganisms. Since 1981, when the USJCMSP Immunology Boards were established, members of the U.S. and Japanese Immunology Boards published many studies that helped clarify molecular mechanisms underlying B cell development, maturation, and signaling. In addition, the past 23 years have witnessed phenomenal progress in understanding T cell immunity. Collaborative research studies between Japan and the United States have proven particularly fruitful in the advancement of this field.

Scientists in both Japan and the United States have also contributed considerably to the understanding of cytokines, soluble factors produced by cells of the immune system that circulate in the bloodstream. The growth and differentiation of T and B lymphocytes, the two main cell types that direct immune responses, are regulated by cytokines. By the end of 1970, researchers had reported a variety of cytokines that regulate the immune response in humans and mice, but few were well characterized and the existence of many such molecules was doubtful. With the advent of techniques for molecular biology in the late 1970s, scientists began to clarify the obscure nature of these soluble factors. During the 1980s, investigators discovered and characterized approximately 20 different cytokines and their receptors. Cytokines produced by T lymphocytes are typically called interleukins (IL), followed by a number. These include IL-2, IL-4, IL-5, IL-6, and IL-18, which were cloned by Japanese researchers, many of whom have been associated with the U.S.–Japan Program.[5]

By the 1990s, recombinant proteins and "knockout" mice—which are genetically engineered to lack a specific gene or set of genes—had become widely available for exploring immune responses in model systems and yielded many unexpected findings in interleukin research. One of the most exciting discoveries is that one interleukin is not restricted to one function, and is thus a multi-functional (pleiotropic) molecule with a variety of activities, some of which overlap with those of other interleukins. The effect of a cytokine depends on its target cell(s), specifically on the cytokine receptors associated with the surface

membrane of the target cell type(s). The pleiotropy and redundancy of interleukins are specific to cells of the immune system, and also to other target cells and tissues, including those of the nervous system. The receptors for a given cytokine are made of different protein subunits; they not only allow the cytokine to bind to its target cell, they also transduce the chemical signal (the cytokine), thus triggering a biological response within the target cell.

Since their inception, the Japanese and U.S. Immunology Boards have contributed in important ways to the USJCMSP and to the field of immunology. "There has been an infusion of cellular and molecular biology – and immunology – into all aspects of the research agenda of the U.S.–Japan Program," Dr. Krause said. "This is something that has really given a major impetus to the Program." Also, there is an active exchange of research fellows. Many collaborative research projects have been established, and more than 10 Japanese postdoctoral fellows have been trained in laboratories of the U.S. Board members. Additionally, many Immunology Board members frequently exchange information and reagents.

"The Immunology Boards have very high-quality meetings," said Dr. La Montagne. "It is one of the strongest areas of research."

The pursuit of viable immune-based therapies is close at hand. In the years to follow, USJCMSP investigators will continue to make progress in understanding the immune responses to infections and the immunopathogensis of cancer and autoimmune diseases, through collaborations between Japan and the United States.

Following is a list of important science advances in immunology research to which USJCMSP scientists have contributed. The list is adapted from information supplied by Helen Quill (U.S. Immunology Program Officer) and Dr. Tasuku Honjo (member of the Japanese Immunology Board from 1988–present).

Immunology Boards
[Established 1981]

[The following advances, from 1981–2000, resulted from collaborations between members of the U.S. and Japanese Immunology Boards]

- Identification of autoimmune disease susceptibility genes in the MHC region of the genome
- Demonstration, in a mouse model of human rheumatoid arthritis, that B cells secrete arthritogenic immunoglublins that contribute to joint destruction

[The following advances, from 1981–2000, resulted from research in the laboratories of individual USJCMSP members:]

- Made major advances in understanding distinct signaling pathways in B and T lymphocytes and in identifying the molecules that transduce and transmit such signals during the course of immune responses to infections with bacteria and viruses. The signaling pathways elucidated include apoptosis pathways as well as those mediated by CD72-SHP-1, MyD88-NFkB, and OX-40.
- Cloned a receptor involved in cell death, Fas. Drs. Shin Yonehara and Shigekazu Nagata of Kyoto University and Osaka University, respectively, collaborated to clone the Fas receptor, and Dr. Nagata cloned the ligand for Fas (FasL) as well. The Fas receptor was the first example of extrinsic cell death receptors responsible for a variety of immune regulatory processes. The Fas-FasL system is involved in cell-mediated cytotoxicity, peripheral immune regulation, and host resistance against malignant tumors.
- Made major advances in understanding antigen processing pathways, how peptide epitopes interact with class I and class II MHC molecules, and how CD8 and CD4 T cells, respectively, are activated via T-cell receptors
- Improved understanding of the molecular mechanisms of generating diversity in genes for antibodies, and genes for T-cell antigen receptors. USJCMSP scientists helped explain VDJ recombination and somatic mutation of genes for antibody variable regions, as well as the molecular mechanisms by which antibody genes switch their constant regions to maintain specificity while modifying their functions. B cells are generated from pluripotent hematopoietic stem cells in the fetal liver and adult bone marrow. Decisive commitment to the B-cell lineage is championed by the V(D)J recombination that brings variable (V), diversity (D), and joining (J) segments of Ig-heavy chain (IgH) genes together to create a complete V gene. Dr. Leroy Hood of Systems Biology, who was a member of the U.S. Immunology Board from 1987 to 1994 and U.S. Board Chair from 1995 to 1996, made his prolific and imaginative

studies of somatic recombinations in the immune system, detailing in molecular genetics of antibody diversity. He demonstrated that the DNA sequence encoding a complete V region is generated by the somatic recombination of separate gene segments. For example, an IgH V gene is generated from three segments of DNA, VH, D and JH by which the joining of V and J gene segments creates antibody diversity. Dr. Tasuku Honjo of Kyoto University, and a member of the Japanese Immunology Board, mapped the entire V gene organization of the human IgH chain locus.

- Further elucidated the molecular mechanisms of V(D)J recombination. Each step of V(D)J recombination is programmed, ordered, and tightly regulated by a number of factors including cytokines provided by stromal cells. The regulation prevents generation of more than one copy of functional V exon in the heavy and light chain gene loci (allelic exclusion). V(D)J recombination is initiated by the lymphoid-specific RAG-1 and RAG-2 proteins that recognize recombination signal sequences (RS) that flank each V, D, and J segment and then introduce double strand breaks (DSB) between the gene segments and flanking RS. Dr. Fred Alt of Harvard University, and a U.S. Immunology Board member from 1991–1996, used gene-targeted mice to demonstrate that, besides RAG-1 and RAG-2, ubiquitously expressed DNA-modifying enzymes including Ku, DNA-dependent protein kinase (DNA-PKcs), XRCC4, TdT and DNA Ligase IV are involved in V(D)J recombination for double-stranded DNA repair, DNA bending, or the modification of the ends of the broken DNA strands.
- Helped demonstrate how pro-B cells differentiate into pre-B cells, and finally into mature B cells. Pro-B cells, the earliest stage of B-cell development, contain the germline pattern of IgH genes and express B-cell lineage characteristic surface phenotypes. Pro-B cells can differentiate into pre-B cells accompanied by the rearrangement of IgH genes and expression of cytoplasmic μ-chain. Pre-B cells proliferate, rearrange light (L) chain genes, and express surface IgM (sIgM) as antigen receptor giving rise to mature B cells. Dr. Max Cooper of the University of Alabama at Birmingham, who was a member of the U.S. Immunology Board from 1981–1987 and U.S. Board Chair from 1987–1989, contributed to study the development of humoral immunity in birds and defined the functions of the bursa that become antibody-secreting cells. He identified the μ+ pre-B cell and demonstrated its developmental origin in hematopoietic tissues, thereby identifying the "bursal equivalent" in mammals as the fetal liver and adult bone marrow. Dr. Cooper and his colleagues clarified the assembly and role of the human pre-B cell receptor and receptor editing in the development of B cells. They also demonstrated that all B cells initially express sIgM whose expression is a necessary step for continued differentiation along the B lineage.
- Clarified a second wave of genetic alterations important in B cell maturation. Mature B cells express IgM on the surface and migrate to the secondary lymphoid organs where they encounter antigens. They are destined to differentiate to memory and antibody-secreting plasma cells, and thereby proliferate vigorously in lymphoid follicles and germinal centers where the second wave of genetic alterations, namely class switch recombination (CSR) and somatic hypermutation (SHM), take place in the immunoglobulin gene loci. CSR replaces the immunoglobulin CH gene without changing the antigen specificity. Dr. Tasuku Honjo and his colleagues demonstrated that CSR and SHM require activation-induced cytidine deaminase (AID), a member of an RNA editing cytidine deaminase family. They further showed that AID expression alone could induce CSR or SHM, indicating that AID is the only factor required for SHM and CSR, and the remaining factors are ubiquitously expressed. They established and characterized AID transgenic mice, which die of T cell lymphomas that have accumulated a large number of mutations, particularly in the IgM gene variable region. The findings indicate that AID can be tumorgenic and implicate that aberrant expression of AID could cause tumors in human.
- Helped identify and characterized precursor lymphoid cells in the bone marrow. T cells develop from hematopoietic stem cells in the bone marrow through several thymic expansion, differentiation, and selection processes. Together with his colleagues, Dr. Irving Weissman of Stanford University, who was a member of the U.S. Immunology Board from 1985–1988 and Board Chair from 1989 to 1994, isolated and identified a common lymphoid progenitor cell population from the bone marrow. These precursor cells can differentiate into T, B, and NK cells following appropriate stimuli. Dr. Kazuo Sugamura of Tokyo University and his colleagues showed that IL-7 binds to a multicomplex receptor that includes the common γ chain, which is shared by receptors for at least six other cytokines. The differentiation of common lymphoid progenitor cells to pro-T cells is dependent on IL-7 signals. This implies that the common γ chain is an essential component for T cell development.
- Identified fundamental principles of T-cell development in the mouse thymus that lead to the selection of an appropriate repertoire of T-cell specificities to fight infections while removing harmful self-reactive T cells. Dr. Takehiko Sasazuki of the International Medical Center of Japan and his colleagues reported the results of T cell receptor (TCR) MHC/peptide interaction in T cell repertoire selection, by utilizing transgenic-knockout mouse cells lines. The results may also have a important implications for MHC-linked autoimmune disease.
- Helped deduce mechanisms of thymic selection, an important process in T cell maturation. In particular, negative selection plays a key role for central tolerance, which in turn regulates autoimmune responses. Recent studies by Dr. Diane Mathis

of Harvard Medical School and colleagues concerning the autoimmune regulator (Aire) protein have revealed new information for understanding the mechanism for central tolerance and the importance of central tolerance in controlling autoimmunity.

- Recognized the role of T-cell anergy in unresponsiveness, the involvement of two events in T-cell activation, and the role of co-stimulatory molecules in this process. The co-stimulatory molecules studied include CD28, B7-2, B7x, PD-1, and OX-40.
- Gained a better understanding of immune recognition mediated by T and B cell antigen receptors based on findings from the crystallization and structural analysis of Class I and II major histocompatibility complex (MHC) proteins at the atomic level.
- Helped explain the complex interactions between T cell receptors (TCR) and an antigen/MHC complex on antigen presenting cells (APC), which are crucial steps for generating T cell responses. Working with his colleagues, Dr. John Kappler of the National Jewish Center for Immunology and Respiratory Medicine, who became a member of the U.S. Immunology Board in 1987, analyzed the structure of the antigen/MHC complex and discovered that the actual number of antigen peptides captured by MHC is strictly regulated. Dr. Mark Davis of Stanford University and his colleagues conducted a detailed investigation of an "immunological synapse," which is formed by T-cell-APC interactions, and increased understanding of the mechanisms behind antigen presentation. The immunological synapse contains not only TCR/MHC but also T cell accessory molecules, such as CD28 and CTLA-4. Dr. James Allison of the Howard Hughes Medical Institute at Children's Hospital, who has been a member of the U.S. Immunology Board since 1998, showed that CTLA-4, a CD28 homologue, is an important regulator for T cell activation, and that inhibitory signals mediated by CTLA-4 regulate unwanted T cell responses to self, which leads to peripheral suppression of autoimmunity.
- Described the target cell receptor systems for various interleukins. For example, the IL-2 receptor system consists of IL-2–specific alpha chain (cloned by Dr. Honjo), beta chain (cloned by Dr. Tadatsugu Taniguchi of Tokyo University, and common gamma chain (cloned by Dr. Kazuo Sugamura). IL-2 common gamma-chain is shared by receptors for IL-4, -7, -9, and -15. The IL-6 receptor system is also composed of IL-6–specific receptor and gp130 common receptors (both receptors were cloned by Dr. Tadamitsu Kishimoto, who was a member of the Japanese Immunology Board from 1981–1985 and Board Chair in 1986), the latter of which is shared by receptors for IL-11, leukemia inhibitory factor, oncostatin M, and ciliary neurotrophic factor.
- Helped elucidate the intracellular signaling pathways triggered by interleukins and cloned genes of key molecular mediators. Studies, many of which used mice as a model system, of the intracellular signaling pathway via interleukin receptors showed that many interleukins use Jak-Stat signaling pathways. Each interleukin activates one or several STAT proteins that work as both signal transducers and transcriptional activators. Dr. Tadamitsu Kishimoto cloned Stat3 as a signal transducer of IL-6. The Jak-Stat pathway is tightly regulated by a negative feedback system, whereas activated STAT induces gene transcription of a negative regulator that binds to the interleukin receptors and inhibits their function (called the SOCS/SSI/CIS family). Drs. Kishimoto and Akihiko Yoshimura of Kyushu University, working independently, cloned this family of interleukin receptor inhibitors.
- Characterized the Toll-like receptors (TLR), which recognize components of infectious pathogens and are therefore essential for detecting infectious pathogen invasion and for triggering innate, interleukin-mediated immune responses against bacteria and viruses. Each TLR recognizes a different microbial component and triggers different immune responses against invading pathogens. In particular, TLR 2, 4, and 7 were characterized. Ligand identification of TLRs and studies of their signaling pathways was done by USJCMSP scientist Dr. Shizuo Akira.

[Science Advances: 2000 –2004]

- Demonstrated the unique role of MHC susceptibility genes in selecting the repertoire of autoreactive CD4+ T cells (cloned from NOD mice) that react against a specific antigen occurring in pancreatic islet cells. The authors of the study argue that the MHC haplotypes, which confer susceptibility to the autoimmune form of diabetes (in NOD mice), may work in the thymus to positively select the repertoire of CD4+ T cells that specifically destroys pancreatic islet cells, which make insulin. USJCMSP scientists Drs. Hitoshi Kikutani and Diane Mathis, together with other Japanese and U.S. investigators, collaborated on the project.[6]

Footnotes — Immunology Boards

[1] Two Decades of Progress: The United States–Japan Cooperative Medical Sciences Program. The Fourth Five Years: 1980–1985. Department of State Publication 9429: East Asian and Pacific Series 219. Bureau of Oceans and International Environmental and Scientific Affairs. Released July 1985.

[2] The United States–Japan Cooperative Medical Science Program: Third Five Year Report: 1975–1980. Department of State Publication 9127: East Asian and Pacific Series 217. Bureau of Oceans and International Environmental and Scientific Affairs. Released July 1980. p.2.

[3] Two Decades of Progress: The United States–Japan Cooperative Medical Sciences Program. The Fourth Five Years: 1980–1985. Department of State Publication 9429: East Asian and Pacific Series 219. Bureau of Oceans and International Environmental and Scientific Affairs. Released July 1985.

[4] See also: Ocana-Morgner C, Mota MM, and Rodriguez A. Malaria blood stage suppression of liver stage immunity by dendritic cells. *J. Exp. Med.* 2003 Jan 20;197:143–51.

[5] Dr. Tadatsugu Taniguchi cloned IL-2. Dr. Tasuku Honjo, a member of the Japanese Immunology Board from 1988–present cloned IL-4. Another Board member, Dr. Kiyoshi Takatsu, collaborated with Dr. Honjo to clone IL-5. Dr. Tadamitsu Kishimoto, member of the Japanese Immunology Board from 1981 to 1985, and Chair in 1986, and Dr. Toshio Hirano cloned IL-6. Another member of the Japanese Immunology Board, Dr. Ko Okamura, cloned IL-18.

[6] Stratman T, Martin-Orozco N, Mallet-Designe V, Poirot L, McGavern D, Losyex G, Dobbs CM, Oldstone MB, Toshida K, Kikutani H, Mathis D, Benoist C, Haskins K, and Teyton L. Susceptible MHC alleles, not background genes, select an autoimmune T cell reactivity. *J Clin Invest*. 2003;112:902–14.