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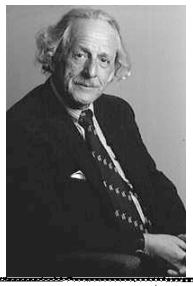

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Citation Analysis Highlights the Key Role in Antibody Diversity Research Played by Susumu Tonegawa, the 1987 Nobel Laureate in Medicine

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Using the *Science Citation Index*® and ISI®'s research-front database, we reviewed the data for Susumu Tonegawa, the 1987 Nobel laureate, and others who have pioneered the field of immunogenetics. In particular, these data highlight Tonegawa's impact on research concerning the generation of antibody diversity.

The 1987 Nobel Prize in physiology or medicine was awarded to Susumu Tonegawa, Department of Biology and Center for Cancer Research, Massachusetts Institute of Technology (MIT), Cambridge, for his work showing how the body manufactures the multitude of antibodies it uses to fight off disease.[1]

Born in 1939 in Nagoya, Japan, Tonegawa received his undergraduate degree in chemistry from Kyoto University in 1963. He earned his doctorate in biology at the University of California, San Diego (UCSD), in 1968. He remained at UCSD for two years doing postgraduate work before moving to the Salk Institute, also in San Diego, where he worked for another two years. In 1971 he moved again, to the Basel Institute for Immunology, Switzerland, where he and his colleagues did most of the work that eventually earned him the Nobel Prize. He returned to the US in 1981 to accept a position as a professor at MIT's Department of Biology and Center for Cancer Research, where he has remained since.

The Mystery of the Immune Response

Tonegawa's work is invaluable in understanding one of the greatest mysteries in immunology: how the white blood cells known as B lymphocytes manage to produce such a staggering variety of antibodies. Each antibody binds specifically to a single antigenic determinant, which may be a part of an invading organism (or antigen); this marks the invader as foreign and targets it for destruction by the immune system. The antibody-producing genes of each B lymphocyte can direct the manufacture of only one specific type of antibody, yet the number of unique types of antibodies present in the body exceeds the number of theoretical combinations of B-lymphocyte genes.[1]

Two competing theories had been put forward to explain how diversity of antibody production is achieved. One, the germ line theory, hypothesized that the genetic instructions for manufacturing each type of antibody were present in the sperm and egg cells from which the body developed.[2] However, the genome contains only about 100,000 genes—not enough to contain the instructions for building a human being and also for coding the roughly one billion different types of antibodies the body is capable of producing.[1]

The alternative explanation, known as a somatic theory, proposed that a limited number of antibody-producing genes could produce the observed variety of antibodies by genetic changes that occur during the life of an individual organism on demand to meet the body's immune-response needs.[3] Tonegawa's work, which confirmed the theories of the somatic school of thought, can be traced back to the immunological work of 1960 Nobel Prize winner Frank Mac-

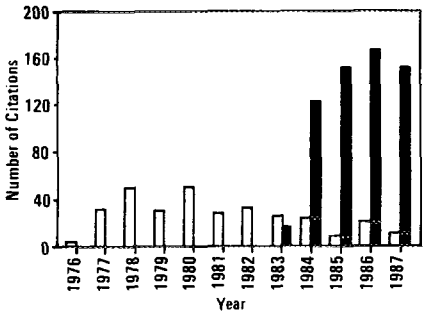


Figure 1: Year-by-year citations to Tonegawa S. *Nature* 302:575-81, 1983 (black bar) and Hozumi N & Tonegawa S. *Proc. Nat. Acad. Sci. USA* 73:3628-32, 1976 (white bar).

farlane Burnet.[4] His work is also linked to a specific version of germ line theory that was proposed in 1965 by W.J. Dreyer and J.C. Bennett, California Institute of Technology (Caltech), Pasadena.[5] In this model, cited in over 370 publications, the authors suggested that antibody genes undergo rearrangement. At the time, however, the mechanism by which this proposed rearrangement could occur was unknown.[2]

The Generation of Antibody Diversity

Each antibody is normally composed of four polypeptide chains, two heavy (or long) and two light (or short), that form a Y-shaped, symmetrical molecule. The heavy chains, which are identical, pair up with the light chains, which are also identical; the pairs of heavy and light chains are joined by "bridges" of sulfur molecules. Antibodies are classified by variations in the sequence of the amino acids in their heavy chains; the types have been designated M, D, G, A, and E. This forms the basis for the immunoglobulin classifications, such as IgM, IgD, IgG, and so on.[1] (The IgE class of immunoglobulins figured prominently in a recent essay we published on venom research, since these form the basis of the severe allergic reaction some people have to bee stings.[6])

Analysis showed that the sequence of amino acids that forms the antibody can be subdivided into one region (the "stem" of the Y) that remains constant for all chains of a particular immunoglobulin class and another region (the "arms" of the Y) that can vary widely. The variable region is the part of the molecule that binds to an antigen; once the antibody has bound to an invader, the constant region sends out a signal, much like an antenna, that alerts the macrophages to close in for the kill.[1]

In the mid-1970s, Tonegawa published several articles specifically addressing the somatic mutation theory of antibody diversity. Two of these—published in the *Proceedings of the National Academy of Sciences of the USA* (*PNAS*) in 1974 and 1976—appear in Table 1, which lists Tonegawa's most-cited works; they have been cited 73 and 104 times, respectively, and helped lead to his breakthrough discovery, also published in *PNAS* in 1976. (Tonegawa, incidentally, has been a foreign associate of the US National Academy of Sciences since 1981.) The paper provided the first direct evidence that the constant and variable regions of light-chain immunoglobulin cells in mouse embryos were rearranged—coded separately in different parts of the embryonic cell and later joined as development progressed. The Nobel Assembly of the Karolinska Institute described the paper as "convincing and elegant" proof of Dreyer and Bennett's theory.[1]

Citation Data

Although this 1976 *PNAS* paper, published with Nobumichi Hozumi, Basel Institute, is the one most often singled out for recognition, it is only one of Tonegawa's highly cited papers. A glance at Table 1 shows that it ranks eighth among Tonegawa's works, with 296 citations.

The most-cited paper on the list is a review of the process of antibody production that puts almost 20 years of work by various authors in this field into perspective. Cited in almost 600 publications, it was published in *Nature* in 1983. Figure 1 shows a graph comparing the citation rate of this paper with Tonegawa's 1976 *PNAS* paper just mentioned. Although the *PNAS* paper accrued citations at a respectable rate, they occurred in a more or less conventional pattern; the

Table 1: A selection of highly cited papers by Susumu Tonegawa. A = number of citations. B = bibliographic citation. The *SCI*® research fronts to which the paper is core are included in parentheses.

A	B
592	**Tonegawa S.** Somatic generation of antibody diversity. *Nature* 302:575-81, 1983. (86-0667, 85-6623, 84-3207)
566	**Gillies S D, Morrison S L, Oi V T & Tonegawa S.** A tissue-specific transcription enhancer element is located in the major intron of a rearranged immunoglobulin heavy-chain gene. *Cell* 33:717-28, 1983. (86-1674, 85-1677, 84-1737)
469	**Sakano H, Huppi K, Heinrich G & Tonegawa S.** Sequences at the somatic recombination sites of immunoglobulin light-chain genes. *Nature* 280:288-94, 1979. (83-3219, 82-0064, 81-0104, 80-0502)
431	**Sakano H, Maki R, Kurosawa Y, Roeder W & Tonegawa S.** Two types of somatic recombination are necessary for the generation of complete immunoglobulin heavy-chain genes. *Nature* 286:676-83, 1980. (86-0667, 85-0178, 84-3207, 83-3219, 82-0064, 81-0104)
385	**Brack C, Hirama M, Lenhard-Schuller R & Tonegawa S.** A complete immunoglobulin gene is created by somatic recombination. *Cell* 15:1-14, 1978. (84-3207, 83-3219, 82-0064, 81-0104, 80-0502, 79-0114)
366	**Tonegawa S, Maxam A M, Tizard R, Bernard O & Gilbert W.** Sequence of a mouse germ-line gene for a variable region of an immunoglobulin light chain. *Proc. Nat. Acad. Sci. USA* 75:1485-9, 1978. (82-0064, 81-0104)
322	**Bernard O, Hozumi N & Tonegawa S.** Sequences of mouse immunoglobulin light chain genes before and after somatic changes. *Cell* 15:1133-44, 1978. (82-0064, 81-0104, 80-0502, 79-0114)
296	**Hozumi N & Tonegawa S.** Evidence for somatic rearrangement of immunoglobulin genes coding for variable and constant regions. *Proc. Nat. Acad. Sci. USA* 73:3628-32, 1976. (83-3219, 79-1716)
261	**Sakano H, Rogers J H, Huppi K, Brack C, Traunecker A, Maki R, Wall R & Tonegawa S.** Domains and the hinge region of an immunoglobulin heavy chain are encoded in separate DNA segments. *Nature* 277:627-33, 1979. (81-0104, 80-0502, 79-0114)
256	**Saito H, Kranz D M, Takagaki Y, Hayday A C, Eisen H N & Tonegawa S.** Complete primary structure of a heterodimeric T-cell receptor deduced from cDNA sequences. *Nature* 309:757-62, 1984. (86-0633, 85-0178, 84-0171)
240	**Saito H, Kranz D M, Takagaki Y, Hayday A C, Eisen H N & Tonegawa S.** A third rearranged end expressed gene in a clone of cytotoxic T lymphocytes. *Nature* 312:36-40, 1984. (86-0633, 85-0178)
219	**Brack C & Tonegawa S.** Variable and constant parts of the immunoglobulin light chain gene of a mouse myeloma cell are 1250 nontranslated bases apart. *Proc. Nat. Acad. Sci. USA* 74:5652-6, 1977. (81-0104, 80-0397, 79-0114, 78-0656)
183	**Raulet D H, Garman R D, Saito H & Tonegawa S.** Developmental regulation of T-cell receptor gene expression. *Nature* 314:103-7, 1985. (86-0633)
160	**Maki R, Roeder W, Traunecker A, Sidman C, Wabl M, Raschke W & Tonegawa S.** The role of DNA rearrangement and alternative RNA processing in the expression of immunoglobulin delta genes. *Cell* 24:353-65, 1981.
158	**Sakano H, Kurosawa Y, Weigert M & Tonegawa S.** Identification and nucleotide sequence of a diversity DNA segment (D) of immunoglobulin heavy-chain genes. *Nature* 290:562-5, 1981. (82-0064)
154	**Kurosawa Y, von Boehmer H, Haas W, Sakano H, Traunecker A & Tonegawa S.** Identification of D segments of immunoglobulin heavy-chain genes and their rearrangement in T lymphocytes. *Nature* 290:565-70, 1981.
149	**Ephrussi A, Church G M, Tonegawa S & Gilbert W.** B lineage-specific interactions of an immunoglobulin enhancer with cellular factors in vivo. *Science* 227:134-40, 1985. (86-1674)
132	**Alt F W, Yancopoulos G D, Blackwell T K, Wood C, Thomas E, Boss M, Coffman R, Rosenberg N, Tonegawa S & Baltimore D.** Ordered rearrangement of immunoglobulin heavy chain variable region segments. *EMBO J.* 3:1209-19, 1984. (86-0677)
125	**Hayday A C, Saito H, Gillies S D, Kranz D M, Tanigawa G, Eisen H N & Tonegawa S.** Structure, organization, and somatic rearrangement of T cell gamma genes. *Cell* 40:259-69, 1985. (86-0633)
116	**Hayday A C, Gillies S D, Saito H, Wiman K, Hayward W S & Tonegawa S.** Activation of translocated human c-*myc* gene by immunoglobulin gene associated transcriptional enhancer element. *Nature* 307:334-40, 1984.
116	**Tonegawa S, Brack C, Hozumi N & Schuller R.** Cloning of an immunoglobulin variable region gene from mouse embryo. *Proc. Nat. Acad. Sci. USA* 74:3518-22, 1977. (78-1520)
107	**Maki R, Traunecker A, Sakano H, Roeder W & Tonegawa S.** Exon shuffling generates an immunoglobulin heavy chain gene. *Proc. Nat. Acad. Sci. USA* 77:2138-42, 1980. (82-0064, 81-0104)
105	**Maki R, Kearney J, Paige C & Tonegawa S.** Immunoglobulin gene rearrangement in immature B cells. *Science* 209:1366-9, 1980. (82-0051)
105	**Tonegawa S, Hozumi N, Matthyssens G & Schuller R.** Somatic changes in the content and context of immunoglobulin genes. *Cold Spring Harbor Symp. Quant. Biol.* 41:877-89, 1977. (79-1716, 78-0977)

104 **Tonegawa S.** Reiteration frequency of immunoglobulin light chain genes: further evidence for somatic generation of antibody diversity. *Proc. Nat. Acad. Sci. USA* 73:203-7, 1976. (78-0977, 77-1031)

98 **Saito H, Hayday A C, Wiman K, Hayward W S & Tonegawa S.** Activation of the c-*myc* gene by translocation: a model for translocation control. *Proc. Nat. Acad. Sci. USA* 80:7476-80, 1983. (86-0547)

97 **Kranz D M, Saito H, Heller M, Takagaki Y, Haas W, Eisen H N & Tonegawa S.** Limited diversity of the rearranged T-cell γ gene. *Nature* 313:752-5, 1985. (86-0633)

73 **Tonegawa S, Steinberg C, Dube S & Bernardini A.** Evidence for somatic generation of antibody diversity. *Proc. Nat. Acad. Sci. USA* 71:4027-31, 1974. (77-1031)

paper in *Nature*, on the other hand, has been cited at a remarkable rate since its publication. It is reasonable to suppose that this is a tribute not only to the completeness and elegance of the review but also to the increased interest in the topic and the growth in the field.

Our annual studies of the most-cited papers in the life sciences have often listed papers by researchers who have either won the Nobel Prize or go on to win one. For example, the list of 1983 life-sciences papers most cited in 1983 and 1984[7] included works by four Nobelists—including Tonegawa.

His most-cited work, for instance, was on the 1983 life-sciences list.[7] The fourth most-cited paper in Table 1, a description of the somatic recombination necessary to form one type of immunoglobulin gene (published in 1980 with colleagues at Basel), appeared in our study of the most-cited life-sciences articles of that year.[8] And Tonegawa's fifth most-cited paper, again published with colleagues at Basel, was listed among our 1978 articles.[9] In addition, a 1977 paper by Tonegawa and Christine Brack, also of the Basel Institute, was one of the most-cited articles of that year.[10] And most recently, two papers published by Tonegawa and colleagues—one in *Science*, the other in *Nature*—appeared in our study of 1985 papers.[11]

Research-Front Data

In awarding him the Nobel Prize, the Nobel Assembly joined numerous others in recognizing Tonegawa. By 1983 Tonegawa's work in the genetics of antibody diversity had begun to accumulate accolades at an impressive rate. To name but a few: in 1982 Tonegawa received the Louisa Gross Horwitz Prize from Columbia University, New York; he was given the Gairdner Foundation International Award (Toronto, Canada) the following year and the Bristol-Myers Award for Distinguished Achievement in Cancer Research in 1986. And in 1987, just prior to winning the Nobel Prize, he was honored with the Albert Lasker Basic Medical Research Award, which he shared with Philip Leder, chairman, Department of Human Genetics, Harvard Medical School, Boston, Massachusetts, and Leroy Hood, chairman, Division of Biology, Caltech.[12] We have highlighted these prizes, which often forecast the Nobel, in past essays.[13,14]

ISI®'s citation and research-front data confirm the Nobel committee's statement that Tonegawa has "completely dominated this area of research."[1] As Table 1 shows, many of Tonegawa's papers are core to numerous fronts, some of which go back to 1977. To put some of Tonegawa's contributions into context, we created a multidimensional scaling map showing the relationship between two of the 1986 research fronts for which Tonegawa's papers are core (#86-0633 and #86-0667) and other research fronts in immunogenetics (see Figure 2). The lines connecting the research fronts are related to co-citation strength—the shorter the line, the stronger the coupling between the fronts.

As Figure 2 shows, front #86-0667 is most closely related to front #86-0633; through the front entitled "T_4 antigens and induction of tolerance" (#86-2514), they are also related to such fronts as "B-cell immune response antigens" (#86-6993), "Activation of antigen expression" (#86-3809), "T-cell subsets" (#86-8172), "Immunoregulatory T-cell subpopulations" (#86-8432),

Figure 2: IMMUNOGENETICS AND THE MOLECULAR BIOLOGY OF ANTIBODIES. A multidimensional scaling map for C2-level research front #86-0048. Numbers in parentheses indicate the numbers of core/citing papers in each research front.

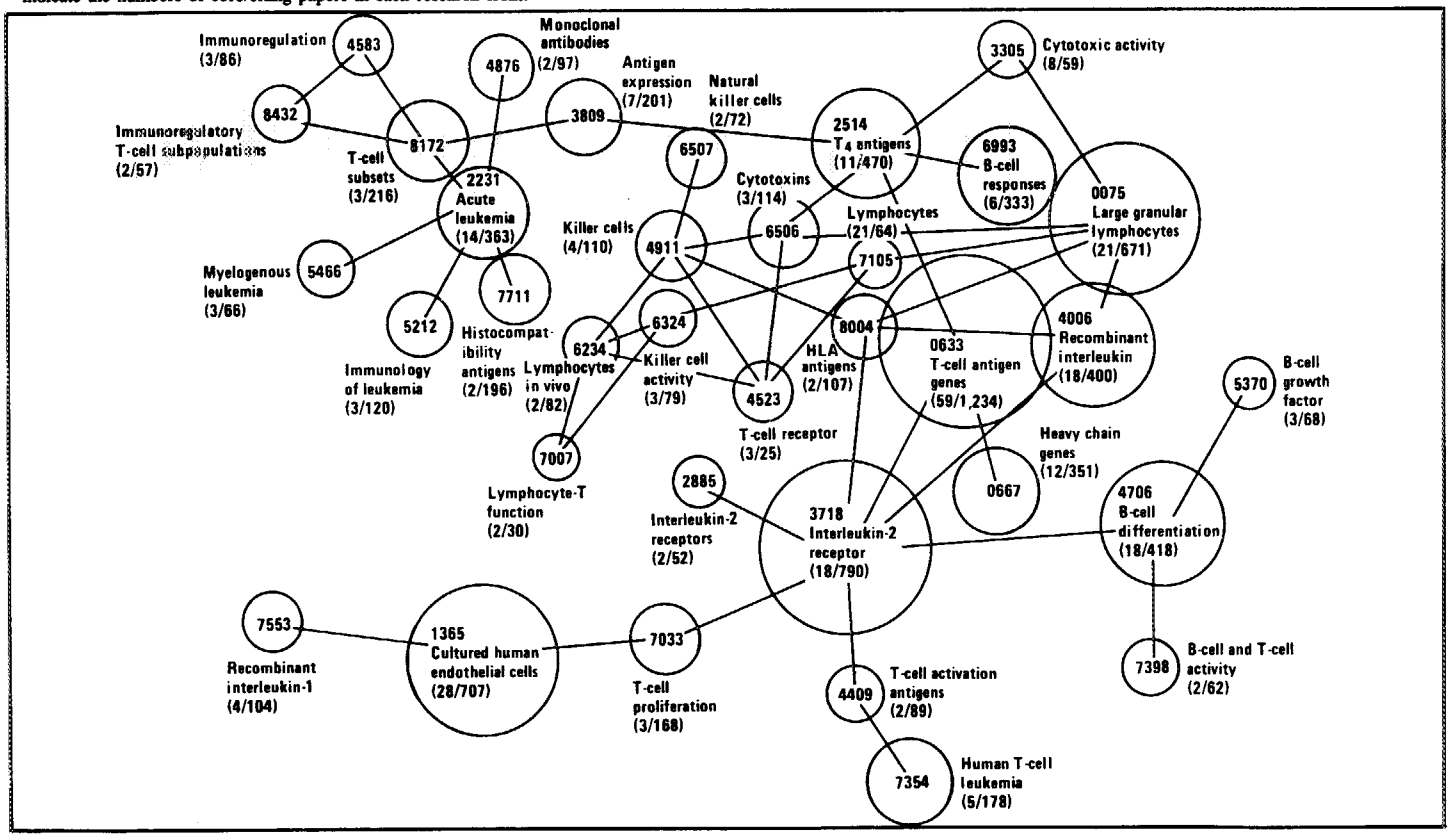
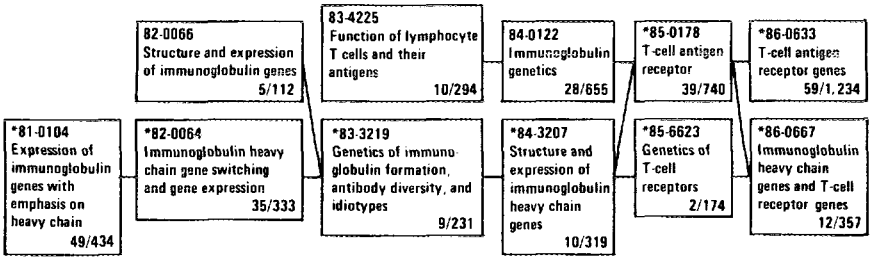


Figure 3: RECENT DEVELOPMENTS IN THE GENETICS OF IMMUNOLOGY. Historiograph showing developments in this research. Numbers of core/citing papers are indicated at the bottom of each box. Asterisks (*) indicate research fronts in which S. Tonegawa is a core author.



and "Immunoregulatory T-cell subsets" (#86-4583). The map also shows that the fronts on T cells are closely related to the group of fronts on leukemia and histocompatibility at left of center. Another related cluster of fronts concerns interleukin-2, below and to the right of center. More than 8,300 published papers identify the research fronts in Figure 2; these papers, in turn, are but a slice of the over 14,100 papers published on various aspects of immunology covered in the 1986 *Science Citation Index®*.

Whereas the map in Figure 2 gives a "snapshot" of the current shape of a field, the historiograph in Figure 3 provides a historical perspective. Papers by Tonegawa and his colleagues are core to each of the fronts in the lower string of boxes and to the 1985 and 1986 fronts in the upper string. Among Tonegawa's papers, common to fronts #86-0633 and #85-0178, is the 1984 *Nature* article he published with Haruo Saito, MIT, and colleagues on "Complete primary structure of a heterodimeric T-cell receptor deduced from cDNA sequences." His 1979 and 1980 *Nature* articles (third and fourth on the list in Table 1) are core to fronts #81-0104, #82-0064, and #83-3219. The 1980 *Nature* article, in addition, is also core to #86-0667, #85-0178, and #84-3207. Tonegawa's most-cited paper is one of only two core papers in front #85-6623; it is also core to #86-0667 and #84-3207. Both fronts #81-0104 and #82-0064 have seven papers by Tonegawa and colleagues in their cores; #83-3219 has four, #84-3207 has three, and #86-0667 has two.

Are Others in the Field of Antibody Diversity *of Nobel Class*?

Although the awarding of the Nobel to Tonegawa was universally praised, there was some surprise in the scientific community that it was given to him alone. Many expected the prize to be shared by Tonegawa and Leder and Hood, the two scientists with whom he shared the Lasker award. The award announcement from the Albert and Mary Lasker Foundation cited the three researchers for their closely related but independent work on the genetic basis for the immune system's incredibly flexible response to invaders.[12] While Tonegawa's research proved that antibody diversity is due to the rearrangement of genes, Leder was cited for research showing that certain cancers arise from mistakes in the rearrangement of such genes, and Hood was honored for identifying three separate genes that are involved in specifying components of antibody molecules.

This raises the issue of whether Leder and Hood are *of Nobel class*.[15] This term is used to characterize individuals who are "peers of prizewinners in every sense except that of having won the award."[16] Although citation frequency itself is not a sufficient measure, we would expect those who

are *of Nobel class* to have published several papers of high impact that are consistently cited for long periods. And in fact, both have distinguished citation records.

Leder has over 60 papers that have been cited 50 or more times, making him 1 of the 300 most-cited authors from 1961 to 1976[17] as well as 1 of the 1,000 scientists most cited from 1965 to 1978.[18] He and his colleagues[19] were identified in a study of 1972 papers most cited in 1972.[20] Another work[21] appeared in our study of 1972 articles most cited from 1972 to 1975.[22] Leder's most-cited work, a 1975 report on the effects of a carcinogen on cell genetics,[23] has been cited in over 450 publications. Subsequent to 1972, Leder, with various colleagues, published almost 50 papers that have been cited 50 or more times. His 1983 paper on genetic changes in human antibodies caused by cancer[24] was core to the 1986 research front on "C-*myc* protooncogene expression, cellular oncogenes, and n-*myc* genes" (#86-0547).

Hood has published 50 papers cited 50 or more times. Among these he coauthored seven 1980 papers[25-31]—including five on immunogenetics[25-29]—that appeared in our study of the most-cited papers published in that year.[8] Four additional papers by Hood and colleagues[32-35] appeared in our study of 1981 articles.[36] Hood's most-cited work, a description of the similarity between simian sarcoma virus and normal proteins involved in cell growth that was published in 1983,[37] has already accumulated more than 600 citations. Another paper that year, on the immunogenetics of mice,[38] is core to the 1986 research front on "Major histocompatibility complex class I genes, E-beta genes, and recombinational hot spots in the murine MHC" (#86-6653).

The citation record confirms that Tonegawa was a dominant worker in antibody diversity. Leder and Hood are also clearly *of Nobel class*, but neither they nor the hundreds of other scientists of similar impact can be guaranteed the ultimate recognition of the Nobel committee. As Harriet Zuckerman, Columbia University, put it, "Inevitably more scientists occupy the 41st chair than can receive Nobel recognition."[39]

Tonegawa's Prize and Japanese Science

Since Tonegawa is the first Japanese scientist to win the prize in physiology or medicine (although he is the seventh Japanese to be recognized by a Nobel Prize), his Nobel also raised issues concerning the development of Japanese science. As reported in *THE SCIENTIST*™,[40] Stephen Kreider Yoder, a staff reporter for the *Wall Street Journal*, has argued that the awarding of the Nobel to Tonegawa actually is an implicit criticism of Japanese science. Tonegawa left Japan early in his career to work in the US and Switzerland, claiming that Japan's scientific working environment stifles creativity.[41]

Whatever the weaknesses and strengths in the organization and funding of Japanese science, it is absurd to generalize about an entire country based on the example of a single—and singular—scientist. Our recent review of data on Japan's scientific output showed that Japan is among the world's leaders in many areas of basic research.[42]

As I concluded in my column in *THE SCIENTIST*, the 1987 Nobel Prize demonstrates that Tonegawa "is a brilliant researcher whose discovery of the somatic theory of the immune system constituted a true breakthrough of revolutionary impact."[40] Perhaps one of the important, if unintended, benefits of international prizes like the Nobel is that they can sometimes shake the complacency of established bureaucracies. However, important changes in the atmosphere for basic research in Japan will ultimately depend on regular exposure of Japanese scientists to other Nobel-class scientists, wherever they may be.

* * * * *

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