# 1

# Recent Trend of Immunology

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## 1.1 Introduction

The immune system is a biophylactic tool that is essential for humans living in symbiosis with various pathogenic microorganisms. Immunology is a science to understand and control the immune system. The development of immunology is expected to contribute not only to understanding basic life science, that is, search for life phenomena, but also to applications in the medical area such as clarification and conquest of infections, and immunological and allergic diseases, etc.

At the Kyushu & Okinawa Summit held in July 2000, measures against infections became one of the principal themes. Particularly, with regard to HIV/AIDS, tuberculosis and malaria, the reduction target up to 2010 was turned into a numerical goal, and the strengthening of measures to realize it was agreed on. The necessity of infection control and development of vaccines, etc., is still considerable throughout the world. In Japan, one out of three people has some type of allergy, and immunological intractable diseases (e.g., rheumatoid arthritis) attributable to the collapse of the immune system are increasing, representing one of the significant problems for modern medicine. To solve these problems, it is necessary to further promote immunological researches.

In the promotion strategy of prioritized areas (decided by the Council for Science and Technology Policy on September 21, 2001) based on the Science and Technology Basic Plan 2001-2005 (decided by Cabinet Meeting on March 30, 2001), "Clarification of the biophylactic mechanism dealing with environmental factors threatening Japanese people's health, prevention of diseases, and development of therapeutic techniques" was selected as one of the subjects in the field of life science, and the necessity for promoting immunological researches was indicated.

In this article, we will introduce the achievements of recent immunological researches, and, in addition, consider measures to further promote immunological researches.

## 1.2 Summary of immunology and achievements of recent researches

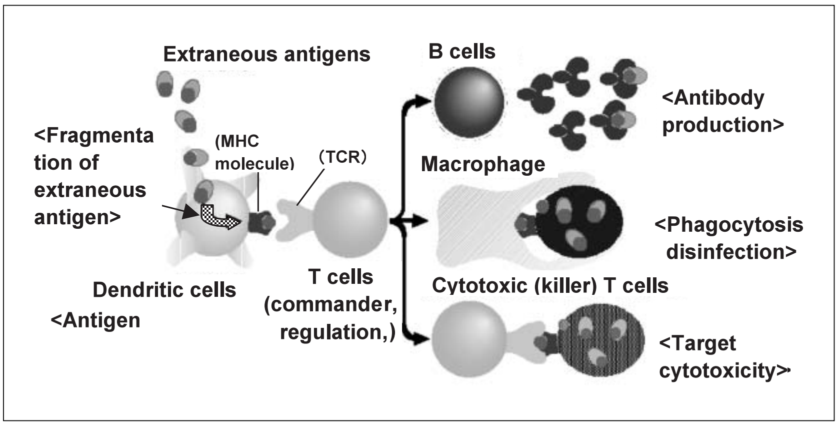
### 1.2.1 *Immune functions*

The immune system is a surveillance network distributed throughout the whole body as a self-defense against extraneous antigens (pathogenic microorganisms and foreign proteins, etc.), and has the function of attacking a foreign body for exclusion.

The cells involved in the immune response are white blood cells in blood. Of white blood cells, the principal cells involved in the immune response and the mechanism of the immune response are shown in Figure 1.

The extraneous antigens that invade into the body are fragmented into small peptides by antigen presenting cells such as dendritic cells, and are presented to helper T cells by major histocompatibility complex (MHC) molecules expressing on the surface of dendritic cells. Helper T cells that recognize this through T cell receptors (TCR) control B cells that produce antibody (immunoglobulin) specifically binding to antigen, macrophages that phagocyte antigen and disinfect, and cytotoxic T cells (killer T cells) that directly kill infectious cells such as those infected with a virus, in order to conduct the comprehensive regulation, etc., of the immune response. In addition, molecules called cytokines play an important role in the functions of

**Figure 1:** Main cells in charge of immune response

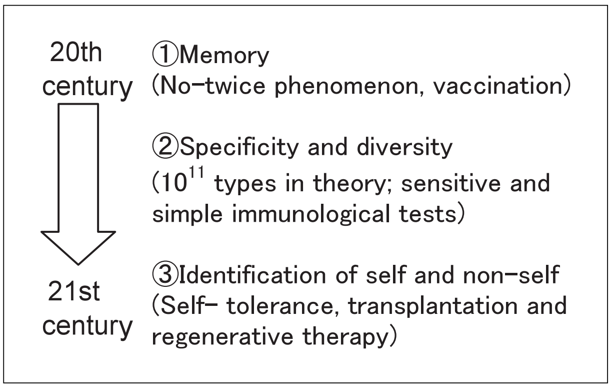



Source: The material prepared by prof. Yousuke Takahama of the Instute for at the Institute for Genome Research, University of Tokushima

differentiation, proliferation and interactions of these immunocytes.

The immune system builds up a complicated network system in which these cells and molecules are highly controlled. A large number of various immunocytes and cytokines were identified owing to the progress of immunology up to now, and the principal functions, etc., were clarified.

**Figure 2:** Three characteristics of the immune system




Source: The material prepared by prof.Yousuke Takahama of the Instute for at the Institute for Genome Research, University of Tokushima

### *1.2.2 Development of Immunology and Characteristics of the Immune System*

Immunology originated in researches on the prevention of infections, and has been developed. With the development, various characteristics of the immune system have been revealed (Figure 2).

**(1) Memory**

In 1789, based on the empirical fact that if a person's disease can be cured once, the person never develops the same disease again (no-twice phenomenon: immune memory), Edward Jenner (England) discovered that inoculation (vaccination) of pus of bovine smallpox in children could prevent the development of smallpox. In the late 19th century, based on the

**Table 1:** Diseases decreased through by vaccination in the United States

| Disease name | Number of patients (persons) | | Decrease rate (%) |
|---|---|---|---|
| | Maximum | 1997 | |
| Diphtheria | 206,939 | 4 | 99.99 |
| Measles | 894,134 | 138 | 99.98 |
| Mumps | 152,209 | 683 | 99.55 |
| Pertussis | 265,269 | 6,564 | 97.52 |
| Polio | 21,269 | 0 | 100.00 |
| Rubella | 57,686 | 181 | 99.69 |
| Congenital rubella syndrome | 20,000 * | 5 | 99.98 |
| Tetanus | 1,560 # | 50 | 96.79 |
| Influenza (< 5 years of age) | 20,000 * | 165 | 99.18 |

* Estimate, # No. of deaths

Source: Authors' compilation on the basis of the Nature Reviews Immunology, 2000 method of vaccination, Louis Pasteur (France) discovered that various livestock diseases could be prevented by using attenuated bacteria (vaccine therapy).

After that, the understanding of the phenomenon of immune "memory" that had been established up to the early 20th century and the spread of vaccines made great contributions toward saving many people throughout the world from various infections (Table 1).

**(2) Specificity and diversity**

The immune system produces antibodies specifically responding to numerous antigens. Since the latter half of the 1970s, genetic engineering was introduced into immunology, and it was proved that the mechanism to produce diverse antibodies was attributed to gene re-organization (a phenomenon in which recombination of gene fragments occurs to organize new genes). This achievement was brought about by Dr. Susumu Tonegawa, the first Japanese to win the Nobel Prize in Physiology and Medicine.

For human antibodies, if the number of diverse types is calculated from combinations of the number of gene locus (domain V, domain D, domain J), there are 2.6 x 106 types. Considering the addition of N sequence and the diversity (there are various theories of 105 to 1010) due to very frequent variations of somatic cells, a diversity of more than at least 1011 is likely.

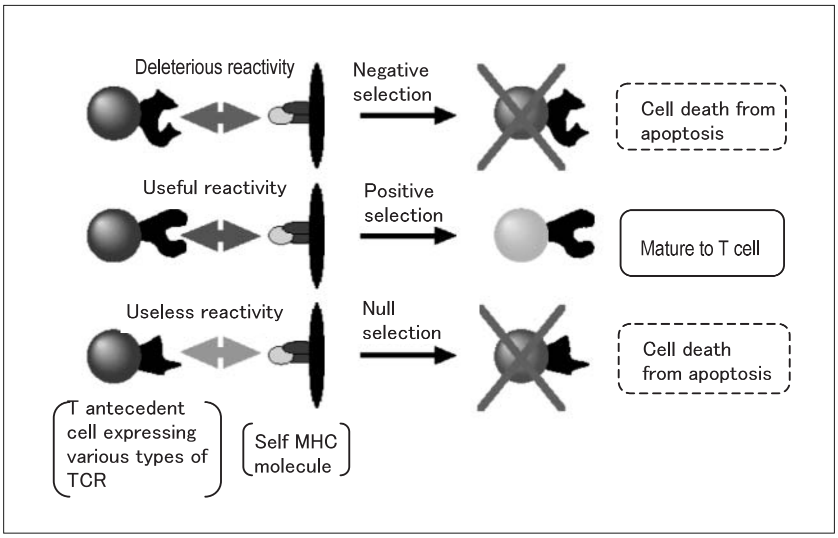
The clarification of the specificity and diversity of the immune system was a significant achievement of immunology in the 1970s to the latter half of the 1990s. The achievement is being utilized in many forms including clinical examinations such as cancer screening, detection of food poisoning bacteria, and tests for environmental chemical substances.

**(3) Identification of self and non-self**

Identification of "self" and "non-self" in the immune system is an important characteristic of such system. Clarification of the mechanism of self-tolerance, which excludes "non-self" but does not react to "self," is one of the greatest targets of modern immunology. When the mechanism of self-tolerance, which normally functions within the immune system, happens to collapse, an autoimmune disease may develop, and, as such, if it becomes possible to control the self-tolerance mechanism, the problem of rejection in transplantation and regenerative medicine may be resolved.

T cells, which play the most important role in the identification of "non-self," are produced in the thymus. Of hematopoietic stem cells produced in bone marrow, those that enter the thymus repeat rapid division and proliferation to produce a large quantity of early T cells. The early T cells are selected based on the reactivity of emerged T cell receptors (TCR) against the major histocompatibility complex (MHC) that is self

**Figure 3:** Selection of T cells in the thymus




Source: The material prepared by prof. Yousuke Takahama of the Instute for at the Institute for Genome Research, University of Tokushima molecule, and only those that received a "positive selection" mature to T cells (Figure 3).

The cells with a strong reactivity to MHC may possibly react to "self" in the future, and are judged as deleterious and receive a "negative selection" resulting in death. The cells without reactivity to MHC are judged as useless for future immune responses, and receive a "null selection" resulting in death. The cells with a moderate reactivity to MHC are judged possible to work and useful in the future, and receive a "positive selection" maturing to T cells. At that time, if the reactivity to MHC is too low, the cells cannot survive. Such strict selection in the thymus excludes more than 90% of early T cells.

If the process does not function well, it may become a cause of autoimmune disease, etc. A self-tolerance mechanism like this exists in peripheral lymphatic tissues other than the thymus, and such an abnormality in the immune control system may become a cause of developing autoimmune disease.

In recent years, researches on regenerative medicine and gene therapy are being conducted as important subjects. However, a significant problem that remains unsolved is that the medical techniques including embryonic stem cells (ES cells) and vectors (e.g., virus as a vector of gene) for gene introduction are rejected as "non-self."

At present, the rejection is suppressed by immunosuppressants, but there are many problems such as side effects due to the reduction of the patient's entire immunity, and the necessity for continuous treatment with the drugs. Thus, a solution from a new approach not dependent on immunosuppressants is being sought.

As a result, research attempting to solve the problem by clarifying the immune control mechanism, based on lymphocytes and the immune control molecules, in order to control the functions is currently one of the hottest themes.

### *1.2.3 One example of recent achievements in immunology*

**(1) Immune control system**

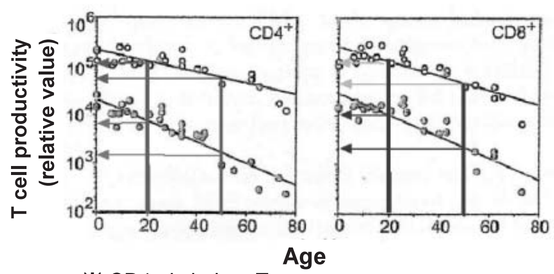
In recent years, the existence of T cells specializing in immune control was revealed, and as achievements of Japanese researchers, two types of immune control T cells ($CD25^+CD4^+$ T cells and NKT cells) were discovered. The functions of immune control T cells are maintenance of the take in organ transplantation, inhibition of the development of cancer and inhibition of allergy, and, further, their contribution to the inhibition of the development of autoimmune diseases was also revealed. Therefore, this discovery is expected to contribute to the resolution of immunological intractable diseases that remain unsolved up to now.

**(2) Induction of acquired immune tolerance**

The induction of acquired immune tolerance represents research to try to specifically induce immune tolerance by introducing a "non-self" ingredient (graft or vector) to the thymus and attempting re-programming of "self" postnatally. However, to realize this, the thymic functions must be working even in adults.

In the past, thymic functions in adults had been doubted because the establishment of "self" and "non-self" was said to occur during childhood, and after puberty the thymus was said to be replaced by fat tissue. However, a recent research by Douek (currently transferred to the National Institutes of Health, U.S.A.), who had belonged to Texas University South-Western Medical Center et al., using the TREC (a parameter to presume how much time passed after production of a certain T cell group in the thymus) revealed that the adult thymus is not completely replaced by fat tissue, and it continuously produces new T cells (Figure 4). Like this case, the basic concept of thymic functions began to be reviewed.

**Figure 4:** Age dependence of T cell productivity in the thymus




※ CD4+ is helper T cell.
CD8+ is cytotoxic (killer) T cell.

※ The two decreasing lines were measured

Source: Douek, et al.: Nature (1998)

**(3) Molecular mechanism related to the thymic formation and functions**

Researches to clarify the characteristics of the thymus have rapidly progressed. For example, some molecules such as a molecule involved in the maintenance and regeneration of thymic functions in the adult body, and a molecule involved in the thymic formation were known. However, the mechanism to form the thymus itself was not yet known.

Then, for example, among variants of medaka (*Oryzias* : ex., killifish), using a variant having no thymic development, an attempt to clarify the mechanism of the molecular structure that controls the formation of the thymic organ, its regeneration or development was started (a collaborative research by Professor Yousuke Takahama at the Institute for Genome Research, University of Tokushima, and Kondo's Induction and Differentiation Project, Exploratory Research for Advanced Technology (ERATO), Japan Science and Technology Corporation).

### *1.2.4 Entire picture of immunological researches*

In Figure 5, the entire picture of immunological researches is shown.

Immunology has to date clarified many basic concepts including individual cells and molecules involved in the immune response, and the functions and relationship between immunity and diseases. Based on the achievements, clinical application of them was generally conducted including the prevention of infections and realization of transplantation therapy through the development of vaccines and immuno-suppressants, and the development of immune therapy using the immune response.

However, there are many new problems that remain unsolved. For example, it is still an important problem for the future to tackle emerging infectious diseases threatening today's people such as AIDS, and re-emerging infectious diseases such as malaria and tuberculosis.

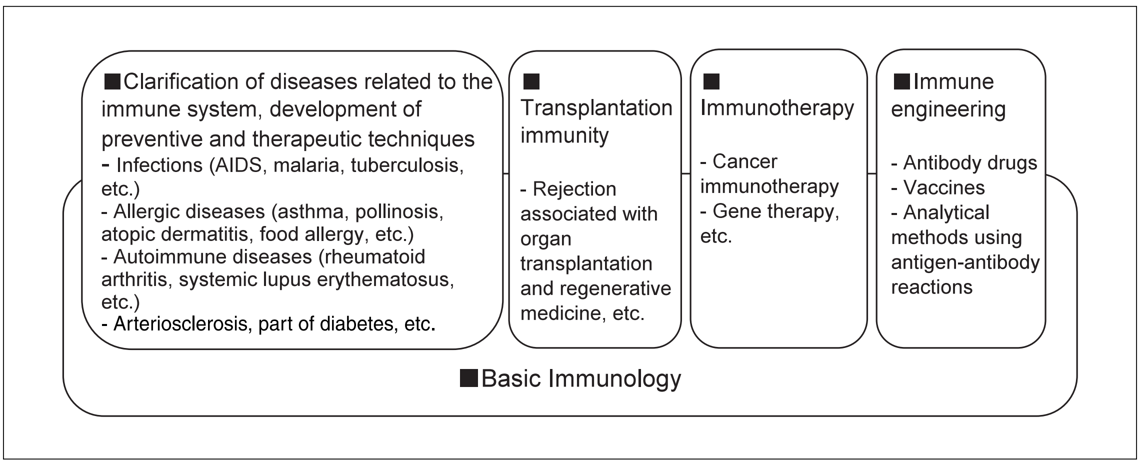
Allergic diseases and immunological intractable diseases have a tendency of increasing, and, in the therapies, development of a radical treatment based on the immune system is desired instead of the symptomatic therapy currently being conducted. As causes of the onset of allergic diseases, multiple factors such as stress and air pollution are considered to be involved, and it is necessary to clarify these in the future.

In the practical use of regenerative medicine and gene therapy, the problem of rejection in the immune system is an important problem to be solved.

In the future, it is necessary to promote research and development on the problems to meet the clinical needs, as well as the development of base technology such as database build up specifically for the immune system. In addition, it is imperative to promote translational researches that apply the results of exploratory basic researches to clinical studies.

In basic immunology, many areas remain to be clarified. Following this, it is necessary to promote individual immunological researches based on original ideas in order to understand the entire picture of the complicated immune system.

**Figure 5:** Entire picture of immunological researches



## 1.3 Research promotion system of immunology

### 1.3.1 Immunological researches in Japan

In our country, basic immunological researches have been promoted mainly by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), and measures against infections and related clinical researches by the Ministry of Health, Labour and Welfare (MHLW). As a budget related to researches of immunology and allergy for fiscal 2002, approximately 5,300 million yen was allotted by MEXT, and approximately 1,300 million yen (Grant-in-Aid for Health Science Basic Research) was allotted by MHLW. In this other, 1,500 million yen was appropriated to emerging and re-emerging infectious diseases research, and 1,800 million yen was appropriated to AIDS countermeasure research.

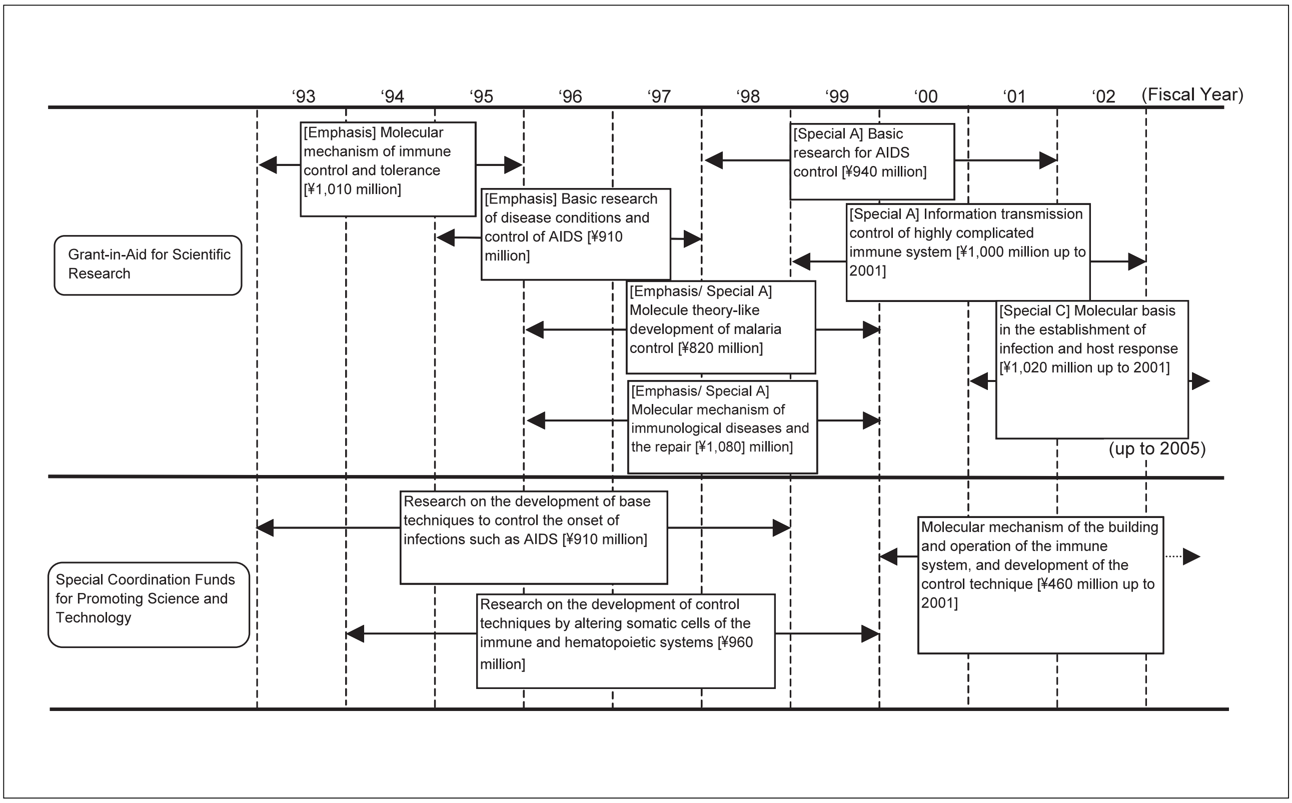
In Figure 6, the main achievements by the recent Grant-in-Aid for Scientific Research and the Special Coordination Funds for Promoting Science and Technology (SCF) are shown. In addition, as one of the researches of the Core Research for Evaluational Science and Technology (CREST) of the Japan Science and Technology Corporation, "Advanced medical techniques for immunological intractable diseases and infections, etc." was started in fiscal 2001.

In fiscal 2001, as the first public research organization in Japan established specifically for researches of immunology and allergy, the Research Center for Allergy and Immunology (RCAI) was started in the Institute of Physical and Chemical Research (RIKEN). RCAI has a similar form to that of American institutes, and all the staff from the head of the Center to the technicians are non-regular contract employees, and they are evaluated every 5 years in terms of achievements by an outside evaluation committee. RCAI aims to establish base technology such as development of DNA chips and building up of a database specifically for immunology, and to promote subject-setting-type of basic researches including allergy control and control of the onset of autoimmune diseases.

### 1.3.2 Immunological researches in the United States

Immunological researches in the United States are being conducted centering on the National

**Figure 6:** Achievements by the Grant-in-Aid for Scientific Research and the Special Coordination Funds for Promoting Science and Technology

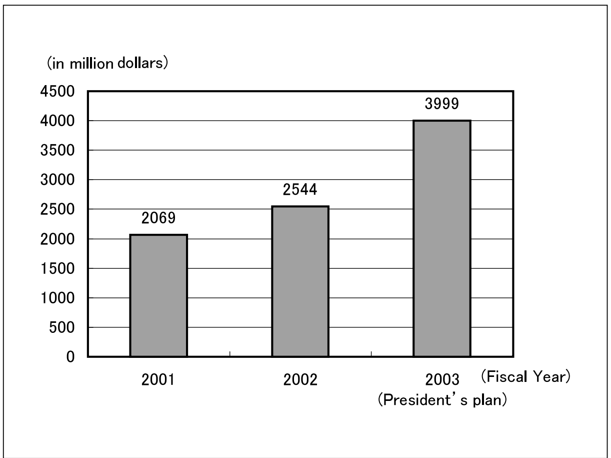


Institute of Allergy and Infectious Diseases (NIAID), which belongs to the National Institutes of Health (NIH), and the Centers for Disease Control (CDC).

The NIAID is conducting researches related to infections such as AIDS, immunity-related diseases such as allergy and asthma, and vaccine development, together with other supporting researches.

In the President's budget plan for fiscal 2003, due to the situation that 2003 is the final year of the 5-year double budget campaign of NIH started in 1999, the budget of NIH for research and development was substantially increased by 17.5% compared to the previous year. In particular, NIAID is an organization at NIH that takes the initiative in measures against biological terrorism and AIDS research, and, among the institutes of NIH, the budget of NIAID was substantially increased* by approximately 4 billion dollars (approx. 480 billion yen), which corresponds to approximately a 57% increase compared to the previous year (Figure 7).

**Figure 7:** Fluctuation of the budget of NIAID




Source: Authors' compilation on the basis of the home page of NIAID

Details of the NIAID's budget for fiscal 2001 are shown in Figure 8. Research grants, such as research project grants, are usually for basic researches, and are grants for researches based on ideas of researchers at universities or research institutes. Not only the NIAID but also other institutes of NIH allot approximately 70% of their total budget to research grants.

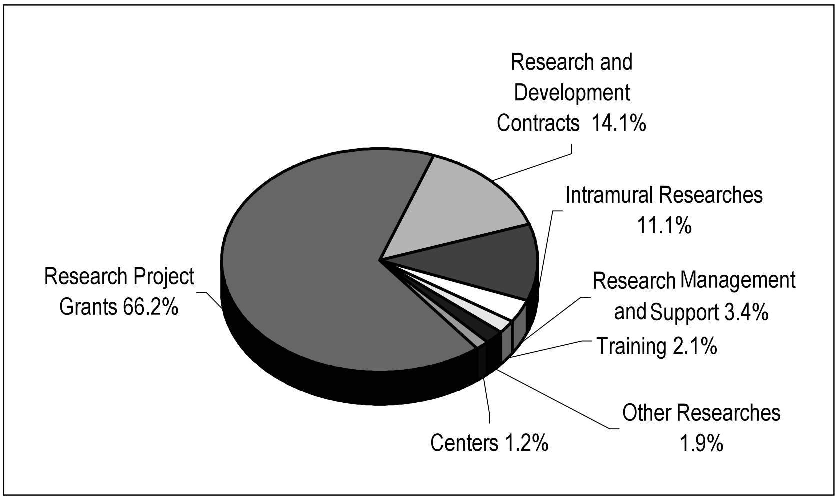
*Tomoe Kiyosada, The Trend of the R&D Policy in the US - Transition of priority areas in the R&D budget allocation of the federal government —; Science & Technology Trends — Quarterly Review, No.4 (December 2002).

## 1.4 Conclusion

### *1.4.1 Directivity of the development of immunology*

Today, in the field of immunology, there are many problems that remain unsolved including control of refractory infections such as AIDS, development of vaccines, clarification of the onset of allergic diseases and immunological intractable diseases, and development of preventive methods and therapies. High expectations are placed on regenerative medicine and gene therapy as state-

**Figure 8:** The Details of the budget for 2001 in NIAID




Source: NIAID Profile: Fiscal Year 2001

of-the-art therapies, but in order to put them to practical use it is necessary to develop a technique to control the self-tolerance mechanism. Following this, it is necessary to solve problems and develop base techniques to satisfy the clinical needs.

Immunology has clarified many basic concepts up to now including individual cells and molecules involved in the immune response, and the functions and relationship between immunity and diseases. However, many phenomena remain to be solved, and it is necessary to build up basic knowledge and findings further. In addition, it is necessary to comprehensively understand the entire picture of the immune system formed by the individual cells and molecules through their complicated mutual relationship.

### *1.4.2 Measures for promotion of immunology*

In order to solve problems that would satisfy clinical needs, i.e. research and development related to immunological and allergic diseases and infections, as well as those that are politically emphasized, it is necessary to promote the following organized research and development.

- Depending on the problem (e.g., clarification of environmental factors in the onset of allergy), attempt to seek efficiency by means of project-type researches such as genome researches.
- Promote human resource exchange and research exchange by attempting to establish cooperation between main institutes such as RIKEN Research Center for Allergy and Immunology, and universities.
- In order to understand the entire picture of the immune system including genome information, extend efforts to promote the development of basic technology such as database build up specifically for the immune system.
- Promote measures for translational researches that apply the results obtained from basic researches to clinical practice, for example, by promoting cooperation between research organizations and the hospitals belonging to them, etc.

In order to develop basic immunology that can clarify unsolved phenomena of the immune system, it is necessary to promote personal-idea-type researches based on personal intellectual curiosity or original ideas. To realize this, it is necessary to enrich research aid such as the Grant-in-Aid for Scientific Research, which gives a large degree of freedom to individual researchers.

Immunology in Japan has to date shown achievements focusing on cytokine researches, which are highly appreciated throughout the world. It is necessary to improve the evaluation system in order to aim at promoting researches having international competitiveness and to develop a new area in immunology. For example, it would be necessary to make public the review sheet for evaluations in an attempt to open up such evaluations, and to seek greater internationalization by adding foreign researchers to the judges of evaluations.

**Acknowledgements**

Together with our investigation, this article was compiled based on the lecture "Recent trends of immunology" (given by Yousuke Takahama, Ph.D., professor at the Institute for Genome Research, University of Tokushima and team director of the Laboratory of Immune System Development, RIKEN Research Center for Allergy and Immunology) at the Institute for Science Technological Policy on June 5, 2002.

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