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Online links

DATABASES

The following terms in this article are linked online to:

LocusLink: http://www.ncbi.nlm.nih.gov/LocusLink/*AIRE* | CD117 | CD25 | CD4 | CD44 | CD8 | delta-like 1 | delta-like 4 | MCSF | Notch 1

FURTHER INFORMATION

Juan Carlos Zúñiga-Pflücker's homepage: http://www.immunology.utoronto.ca/Faculty/INDIV_Faculty_Page/zuniga-pflucker.html

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OPINION

Translational research in immunology: Japanese perspectives

Robert Triendl

Japan has a formidable tradition in immunological research, starting with Shibasaburo Kitasato (1852–1931), who, after returning to Japan from his studies with Robert Koch, went on to build almost single-handedly a research tradition in investigative medical research, while engaging himself in the fight against infectious diseases[1]. Over the past few decades, Japanese immunologists have been involved in many important discoveries at the forefront of immunological research, yet, when it comes to the translation of new discoveries into clinical innovations and new therapies, Japan's track record seems more modest.

Despite the tremendous output and high visibility of basic immunological research in Japan today, when it comes to the translation of basic science into new therapies or pharmaceutical products, Japanese immunologists are hardly leaders. Even though the new approaches of 'evidence-based medicine' and 'translational research' have also arrived in Japan, a recent study indicates that whereas research output in the biomedical sciences in Japan has increased considerably over the past two decades, the same is not true in many clinical fields[2]. For example, a literature study finds evidence for only one randomized, controlled trial in the field infectious diseases in Japan between 1991 and 2000 (REF. 3). Although this might understate the reality, it is true that the proportion of case-controlled and cohort studies from Japan is indeed smaller than from other countries.

The problem that breakthrough discoveries in basic research do not easily translate into new therapies is hardly limited to Japan — or to the field of immunology[4,6]. However, it is true that, in the case of immunology, society demands have been mounting, and not only in developing countries. With the increasing resistance to antibiotics, the emergence of severe acute respiratory syndrome (SARS) and West Nile Virus, we have been reminded that the eradication of infectious disease is unlikely to occur. At the same time, the prevalence of allergies has been rising rapidly in many industrialized countries. And, at least in the United States, terrorist threats have led to increased spending on biodefence research, with a good deal of it flowing into the field of immunology.

In Japan, the Research Centre for Allergy and Immunology (RCAI) (BOX 1) — a new initiative launched in 2001 — aims to promote a systematic perspective in research on immunological disorders and immune regulation. However, there is a different background to the creation of this new organization.

Although the focus at the RCAI is on basic research, its political patrons have also bestowed a more practical mission on the centre — to contribute actively to the development of new therapies for common allergic conditions, such as Japanese cedar pollen allergy[5]. In some sense, the RCAI is an exemplary case. After two decades of unprecedented growth in research funding for life sciences, today, scientists in Japan are increasingly asked to deliver research results that are socially 'relevant' and the time seems ripe to initiate a debate on how to better link biological research to clinical applications.

What are the reasons for the continuing lack of integration of basic science and clinical or pharmaceutical applications in Japanese medical research, and especially in immunology? Here , I argue that the lack of cooperation between scientists, who work in basic research, and clinicians is largely the result of the reaction to a given set of incentives and circumstances, rather than a conscious choice. For scientists working towards a professorship and a research career at a large national university, there are few real incentives to engage in translational research, whereas for clinicians, to engage in clinical research at the 'cutting edge' of science typically means little more than inflated risks without much prospect for additional merits. Yet, over the next few years, to engage more aggressively in translational research could turn out to be crucial for basic immunologists in Japan to maintain funding and perhaps also research productivity.

Medical or biomedical research?

As Floyd E. Bloom argued in this year's presidential address at the annual meeting of the American Association for the Advancement of Science, the United States healthcare system seems ill-prepared to reap the benefits of the present advances in biological research[6]. The same is true with respect to Japan. As a former health ministry official observed in a comparative study on medical research policy published in the early 1990s, the health-care policy in Japan has never been integrated with science policy[7]. Despite a number of changes, numerous reports and policy documents, this remains true today. There are several reasons for this fact. First, research has not been high on the agenda of the Ministry of Health, Labour and Welfare (MHLW), which also manages Japan's national health insurance and pension systems — two of the largest budget items for the government. The MHLW also regulates drug approval and decides prizes for new pharmaceuticals; however, research is at best a minor occupation for the ministry. In fact, there are numerous cases in which health ministry officials have actively opposed more aggressive moves by other ministries to support innovation in medical science and technology[8].

The inherent conservatism of the MHLW is not without it's reasons. Although there is much to criticize about Japan's healthcare system and the quality of medical treatment, Japan provides its citizens with universal access to healthcare and boasts one of the lowest child mortality rates and perhaps the highest life expectancy of industrialized countries. Although rising healthcare costs in Japan are as much an issue of debate as elsewhere, it remains a fact that at barely 8% of gross domestic product (GDP), Japan spends much less on healthcare than most other Organization for Economics Cooperation and Development (OECD) countries — and so has less to spend on clinical research[9].

But, the conservatism of the MHLW benefits one of the major clients of the ministry, the Japanese Medical Association (JMA). In Japan's cooperative regulatory system, regulatory decision making is highly dependent on the relationship between ministries and their 'clients' in industry or the general public[10]. For the health ministry, the JMA — a powerful lobby group with tight connections with the ruling Liberal Democratic Party (LDP) — remains perhaps its most important client. The JMA has repeatedly taken the position that there can be no separation between medical therapy and medical research, and that any kind of activity carried out with the eventual goal of helping patients should be labelled as medical, rather than as research. The JMA has also taken an increasingly aggressive stance towards privacy protection in medical research[11]. One practical implication of such

Box 1 | The RIKEN Research Centre for Allergy and Immunology (RCAI)

Formally announced in 2000, the Research Centre for Allergy and Immunology (RCAI) located at the Yokohama campus of RIKEN, the Institute of Physical and Chemical Research, will eventually open its doors in early 2004. The name of the institute and its affiliation with Japan's foremost basic research organization are indicative of a political compromise; scientists behind the centre, as well as its main advisor, Kimishige Ishizaka, had stressed the importance of funding curiosity-driven basic research. However, some of the centre's political patrons saw it more as a step towards accomplishing their political crusade to overcome pollinosis and other allergies. The result of this compromise is a mix of unconditional support for basic science and efforts to accelerate the pace of discovery and innovation through common facilities, and a focus on research technologies to facilitate the transfer of new findings to the clinic.

A major research focus of the centre is on regulatory lymphocytes and other cells with regulatory functions, such as natural killer T (NKT) cells[27], regulatory T cells[28] or regulatory dendritic cells (DCs)[29]. The centre also supports research on developmental immunobiology[30,31], cell signalling[32] and autoimmune diseases[33]. Laboratories directed by younger investigators are specializing in various topics, including the role of impaired phagocytosis in inflammatory disorders or autoimmune diseases[34], the role of IgA in mucosal homeostasis[35], regulation of the T helper 1 (T_H1)/T_H2-cell balance by DCs, the link between innate and adaptive immunity[36], cytokine signalling that controls the T_H2/IgE balance[37] and chaperones involved in antigen processing–degradation pathways. These research activities are supported by groups that specialize in developmental genetics and techniques for embryo manipulation, genomics, proteomics and bioinformatics, forward-genetic approaches, single-molecule studies and nano-imaging (FIG 2). Programmes on fundamental research technologies are undertaken in cooperation with other organizations — such as the Kazusa DNA Research Institute or the RIKEN Genomic Sciences Centre — and various public hospitals. More applied topics studied at the centre include the mechanisms that control T-cell activation in immune dysfunctions, elucidation of the mast-cell transcriptome and strategies to combat Japanese cedar pollen allergens. The present focus in clinical research is carried out in collaboration with various universities and includes pollinosis, rheumatoid arthritis, the prevention of graft-versus-host disease, as well as studies on the application of BCG (*Mycobacterium bovis* Bacillus Calmette-Guerin) vaccines in rhinitis and the therapeutic use of NKT cells in cancer immunotherapy.

The RCAI faces challenging organizational issues — for example, as a branch of Japan's foremost basic science research institute, the centre has no direct access to internal hospital facilities, but has to depend on collaboration with adjacent hospitals in Tokyo to get access to human materials or patients for clinical studies. In many ways, the issues that the centre is facing are indicative of the present state of immunological research in Japan and, given the prominence of the centre, the solutions are likely to have broad repercussions.

Figure 1 | **Pioneer: Shibasaburo Kitasato.** Pictured during his stay at Robert Koch's laboratory (Image courtesy of the Kitasato Institute).

a position concerns research funding: control over funding in clinical research is typically given to the medical practitioners involved, not the scientists.

Research funding

Most research funding for medical sciences in Japan continues to come from the MHLW. But, despite this important role of the MHLW, the ministry is only a minor player in research funding in Japan, especially when compared with the Ministry of Education, Culture, Sports, Science and Technology (MEXT). Furthermore, research funding at the ministry is highly fragmented. With the exception of a relatively modest research grants programme, accounting for about 10% of the ministry's research and development budget, which is administered by a handful of officials in the minister's bureau, research funding at the MHLW is typically paid out directly by the ministry's various offices or spent within the ministry's research institutes. Moreover, several competitive research programmes are administrated by MHLW-related organizations, such as the Organization for Pharmaceutical Safety and Research (OPSR) or the Japanese Health Science Foundation (JHSF).

As the MHLW, similar to all of the Japanese funding agencies, lacks staff for programme management, research projects are usually organized as 'research groups', typically under the leadership of a senior academic. For the ministry, putting money into research groups rather than individual projects is a simple way to distribute funding effectively and without major administrative costs[12]. Yet, if one is to believe an informal review of the competitive research programmes undertaken by members of the Council for Science and Technology Policy (CSTP) in 2002, this is hardly an efficient system. The success of research groups in fostering collaborations seems to be limited. There are surprisingly few cases in which the ministry actually specifies that projects need to address links between basic research and clinical evaluation. The highly hierarchical structures that are still prevalent in medical research, in some cases, further impede innovative research[13]. Although other ministries, and notably the Ministry of Education — Japan's largest supporter of scientific research — also provide important funding for biomedical research, funding for clinical research remains largely the domain of the MHLW. A lack of coordination between the two agencies means that follow-up studies on research funded by the Ministry of Education, which are aimed at more translational research activities, are rare.

Technology transfer

In general, the transfer of knowledge and new discoveries from academia to industry — technology transfer — is not an area where Japan excels. In fact, in one of the world's most sophisticated economies, academic researchers have, for many years, been discouraged to work with industry[14]. For scientists, the concern was with observing the rules; in fact, there have been several cases in which prominent scientists, including a former chairman of the Japanese Society for Biochemistry, were arrested for illegal transfer of research money or results from companies to public universities.

Several legal bills passed over the past few years have provided university-based scientists with considerable freedom and have attempted to fundamentally rework technology transfer activities at public sector research organizations in Japan[15]. According to data published by the Ministry for Economy, Trade and Industry (METI), the number of new companies created by Japanese university professors has surged over the past few years after implementation of the new legislation. Still, the numbers remain modest and it is unclear whether Japanese industry has changed its approach to working with academia[16]. Conservatism and a reluctance to invest in new areas of research are widespread. For Japanese scientists working in areas of high commercial interest, such as transplant immunobiology, inquiries from biotechnology firms in the United States typically outnumber those from domestic pharmaceutical companies.

Companies have tended to build links with academic institutions through small allocations of money in the form of scholarships or grants to academic institutions. But, the overall amount of such payments is small and, rather than a contractual relationship, they signify little else than mutual good will — the implication being that the company that finances the work has privileged access to intellectual property. In one prominent recent case, a former president of Osaka University, Tadamitsu Kishimoto, announced his return to the laboratory bench through an affiliate laboratory at Osaka University, sponsored by a grant of three million US dollars from a pharmaceutical company.

Interestingly, a study of industry–academia relations in Japan covering all fields of science found that the growth in publications that are co-authored by scientists from academia and industry in Japan is comparable to other industrialized countries, including the United States[17]. Although these data have to be interpreted with care, there might be more collaborative research going on between industry and academia than some would admit. Yet, this indicates little about the actual content of such research and the real amount of transfer of knowledge from academia to industry. Despite recent changes

in the regulations for technology transfer and the reorganization of public sector research — what Japan's major economic newspaper refers to as 'universities entering the licensing business' — the incentives for scientists to engage with industry have hardly changed.

Regulatory environment

Regulatory agencies or bodies, such as the United States Food and Drug Administration (FDA) or the Recombinant DNA Advisory Board of the National Institutes of Health (NIH), are a constant target for criticism by industry groups or scientists. However, as the violent clashes over genetically modified organisms in Europe remind us, regulations can be important tools for building public confidence in science[18]. In contrast to the arcane rules and regulations that have governed technology transfer practices in Japan, there have been relatively few attempts, so far, to regulate the content of research. Instead, the regulation of biomedical research in Japan has followed a rather cautious path and, if anything, regulators have tended to favour permissiveness rather than restriction. Perhaps the only real exception is a somewhat unusual bill that outlaws human cloning, eventually introduced in 2001, and that some scientists would prefer to see revised and replaced by more flexible regulations[19].

The reluctant approach by regulatory agencies to biomedical research is not without problems. In controversial areas of research, such as xenotransplantation, the health ministry has simply postponed decisions, or in effect delegated them to Institutional Review Boards (IRBs), knowing that university IRBs are incapable of handling a complex regulatory decision such as the safety of xenotransplantation. The outcome has been that, while not forbidden, clinical trials with xenotransplantation seem highly unlikely in Japan until the ministry drafts some sort of safety guidelines. A negligent approach to bioethics rules can backfire too, and the introduction of the principle of informed consent is a typical example[20]. It was only after the international harmonization of pharmaceutical approval procedures that informed consent practices became enforced in Japan, in 1996. The effects were predictable. During the 1990s, enrolment in clinical trials in Japan declined steadily. In fact, in areas where regulation remains unclear, such as the harvesting of human cells and tissues for research use, the result has often been paralysis rather than 'anything goes'[21].

Society issues in research

For many scientists in Japan, there are few incentives to alter the present situation and its mix of relatively liberal regulations and a virtual absence of public concern about what goes on inside the laboratory. It is easy to see why. For example, there are no animal rights activists who attack animal facilities and this is not because Japanese scientists use less animals for research or because animal facilities are in better shape in Japan than elsewhere — if anything, the contrary tends to be true.

Yet, there is a clear downside to this absence of society coalitions or interest groups that are concerned with science and research. As Vololona Rabeharisoa and Michel Callon[22] have shown in an interesting study, the French Muscular Dystrophy Society — an organization of patients and their families that provides generous funding for research — has had an important role in establishing the first large-scale genetic research centre in France, the Généthon. In the United States, there are numerous lobby groups that urge increased medical research spending, and research charities and foundations in the United Kingdom account for a sizeable portion of overall medical research funding. But, with few exceptions, research has not been a major concern for patient organizations in Japan. In Japan, spending on research by foundations (which are taxed similar to ordinary corporations) is modest at best. In practice, this means that medical researchers in Japan depend highly on either the education ministry, the health ministry or both.

Similarly, whereas research on AIDS, immune tolerance in transplantation or biodefence have been important instigators of immunological research, particularly in the United States, the situation is different in Japan, where AIDS is a 'non-issue', as one observer put it[23], and where the number of solid organ transplants per year is still negligible[24]. Biodefence is not a topic on the agenda of immunologists in Japan. Also, there are few visible pressure groups for medical research spending and there has been little interest in research policy by politicians — by far the most effective lobbyists in Japan. But this has been changing slowly over the past few years and there are now a few prominent politicians who have spoken out about research. One of them, Omi Koji, has even written several highly readable books on science and science policy[25]. Also, in a rare move, several years ago a group of politicians formed an alliance to support research on common allergies and autoimmune diseases, which has provided support for the establishment of the new RIKEN centre. Certainly, alliances between scientists and politicians are rare and there are few Japanese politicians with a deep understanding of science and research. But, then, many scientists are only starting to learn how to best navigate Japan's political and bureaucratic world.

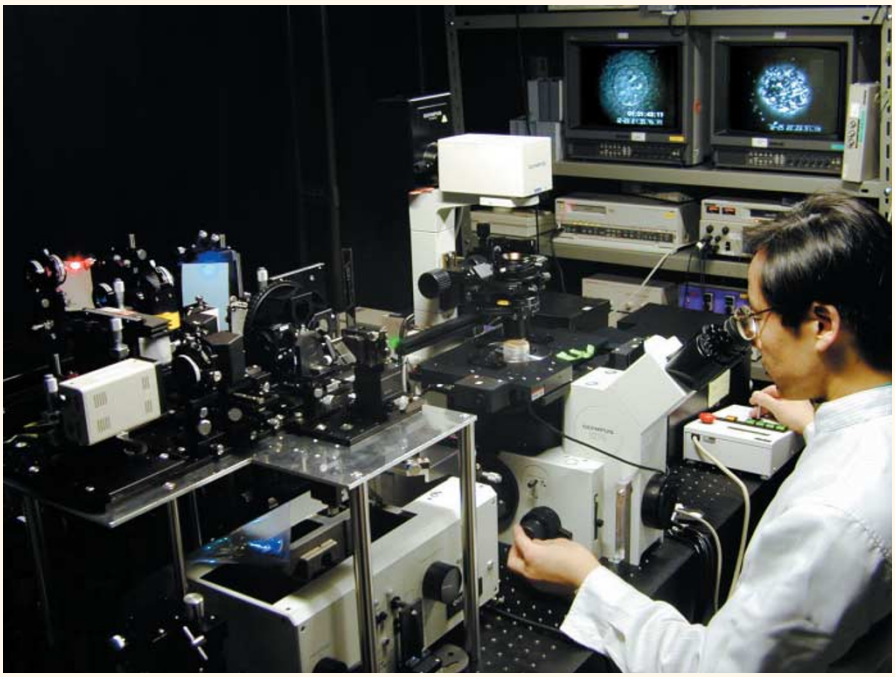

Figure 2 | **Frontiers in immunology.** This total internal reflection fluorescence microscope system is optimized for single-molecule studies in living cells and was built by Makio Tokunaga (Image courtesy of RIKEN/RCAI and NIG).

Future perspectives

Postwar Japan has often been characterized as a country with a sophisticated approach to industrial innovation, rather than a country where basic scientific research is held in high esteem[26]. In the case of immunobiology, scientists in Japan have shown considerable achievements in basic science, yet efforts to translate these findings into therapeutic innovations seem to have been much less prevalent, let alone fruitful. If leading immunologists in Japan have not chosen to pursue clinical development more aggressively, this can be explained by several external factors including; the organization of medical research in academia; research policy and research funding practices; a clinical environment that is hostile to therapeutic innovation; a peculiar technology transfer regime; regulatory uncertainty, as well as a lack of expression of society demands on research. What is needed is not only a better physical infrastructure for biomedical research, as opposed to biological or medical research and clinical studies, but also more marked changes in Japan's research funding regime and in Japanese academic institutions to provide scientists with the right incentives to engage in clinical and translational research activities.

Funding agencies can do much to improve the situation by providing more funding for research networks that include both molecular biologists and clinicians, or by designing programmes that specifically target links between basic research and clinical innovation. Several such programmes have been launched over the past few years, including the 'Research Revolution 2002' initiative, which has provided funding for translational research in areas such as the development of the BCG (*Mycobacterium bovis* Bacillus Calmette-Guerin) vaccine, transplant immunobiology and cancer immunosurveillance. Still, in the long-term, a fundamental reorganization of research funding and the creation of a dedicated funding body for biomedical research, independent from the ministries, might well be inevitable in Japan. But, so far, the Japanese scientific community has not been very outspoken on this issue, perhaps because those in control have few incentives to change the system. Still, there can be little doubt that, in the end, it will be up to the scientists themselves to alter the prevailing situation.

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Competing interests statement
The author declares that he has no competing financial interests.

Online links

FURTHER INFORMATION
The RIKEN Research Centre for Allergy and Immunology web site: www.rcai.riken.go.jp
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