Dankesrede

von

Prof. Dr. Tim R. Mosmann

anlässlich der Verleihung

des Paul Ehrlich- und Ludwig Darmstaedter-Preises

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Es gilt das gesprochene Wort.

Dear President of the Federal Republic of Germany
Dear Ministry of Higher Education, Research and the Arts
Dear Secretary of State in the Federal Ministry of Health
Dear Mayor of Frankfurt
Dear Mr. Kopper, Chairman of the Scientific Council of the Paul Ehrlich-Foundation
your Excellencies, and dignitaries,
Ladies and Gentlemen

It is a great honor to receive the Paul Ehrlich and Ludwig Darmstaedter prize, particularly because of the remarkable breadth of the discoveries of Paul Ehrlich, and the strength of his insights. I feel very honored that the selection committee has considered our research to be worthy of this great tradition.

The research that led to the identification of different types of immune T cell responses took place in an unusual setting, at a small company in California. In 1981, Alex Zaffaroni set up DNAX Research Institute, a startup Biotech company in Palo Alto. With help from a very distinguished Advisory Board, Alex initially recruited seven molecular biologists and immunologists to perform adventurous research and make discoveries that might lead to pharmaceutical products. I moved to DNAX at the beginning of 1982, understanding that there was a strong possibility that I would not easily be able to return to academe. Within six months, DNAX was acquired by Schering Plough, a large pharmaceutical company based in New Jersey. The DNAX mandate remained focused on discovery research.

I believe that the structure of DNAX was very important for the rapid progress that followed. Each scientist was expected to work partly on 'company' projects, but also partly on their own research projects. Laboratories were small, mostly one technician and one post-doc, which meant that the lab heads were intimately involved in the research. Facilities and supplies were excellent, and paperwork and other distractions were kept to a minimum. We quickly established a strong culture of discussion. The major initial project at DNAX was the identification of cytokines (proteins produced by T cells) using the relatively new technique of recombinant DNA cloning coupled with expression of functional proteins.

As part of this work we characterized T cell cytokines and developed functional screening assays for recombinant DNA clones. Our rapid MTT assay allowed us to measure cytokine functions in much more detail than had been possible previously. We also enjoyed wonderful collaborations with Bob Coffman, whose data on B cell antibody switching helped to define the T cell subsets, and who helped enormously with the development of the Th1/Th2 model and its implications; also with Martha Bond, who helped with biochemical separations; and with Ken-Ichi Arai and Frank Lee, who led the highly successful recombinant cytokine cloning program at DNAX. The large quantity of data that resulted from these studies enabled us to see patterns in the data that indicated more complexity in the cell lines than we had previously suspected. These patterns led in turn to the discovery of the Th1 and Th2 subsets.

The importance of rich datasets in this work must be emphasized. The immune system probably didn't evolve as a single entity, but rather as a patchwork of responses to block pathogen

mechanisms that continually challenge the existing immune defenses. Constant evolution of bacteria, viruses and other pathogens has allowed them to develop many ways to interfere with the immune system, and in turn the immune system has had to adapt so as to block the loopholes discovered by each pathogen. Thus the immune system is not easy to understand if we look only at the present system, and it is difficult to predict immune regulatory mechanisms from first principles. New immune mechanisms are often discovered as a result of recognizing patterns in data, rather than predictions from theoretical principles. This recognition of patterns in data is often a first step, to be followed immediately by the formulation of models that can be tested rigorously.

I believe that this interplay between pattern recognition and hypothesis-testing is a highly effective way for science to progress. Although many research grant panels acknowledge only hypothesis-driven research as 'rigorous science', in practice many breakthrough discoveries in immunology were made when an astute researcher recognized an unusual pattern that led in an unexpected direction. The very large genomic and proteomic databases now being created are opening up enormous possibilities for such discoveries.

While we discovered the Th1 and Th2 subsets mainly by recognizing patterns in the data, IL-10 was an example of the other kind of discovery, that proceeded directly from a hypothesis. Th1 and Th2 responses mutually inhibit each other, and the Th1 product Interferon gamma inhibits Th2 cells. We therefore searched for a factor with the opposite properties, i.e. a Th2 product that would inhibit Th1 cells, and were very pleased when this approach led us to IL-10, a cytokine with wide-ranging anti-inflammatory properties.

We were fortunate that our T cell subsets found ready acceptance, as they fit previously-described functional separations of T cells, and provided an explanation for the reciprocal regulation of different immune responses. Very different types of immune response are required to attack different types of pathogens, and the response that is suitable against, for example, tetanus, is ineffective against tuberculosis or leishmaniasis. Conversely, different types of damage can be induced by inappropriate responses, for example allergies by Th2 responses, and inflammation by Th1 or Th17 responses. Thus the choice of the type of response is critical for establishing immunity that destroys an infection while minimizing damage to host tissue.

This leads us to vaccines. Vaccination has been one of the most important contributions of immunology, and of medical science to world health. Effective as they are, many vaccines have been developed empirically, and most of the currently successful vaccines are probably based on antibody responses. Modern research has made enormous progress in understanding pathogens, and equally remarkable progress in defining the mechanisms of the immune response. However, we do not have effective vaccines or immune therapies for many major diseases such as tuberculosis, malaria, HIV, cancer, autoimmunity and some allergies. Vaccines or therapies targeting these diseases may require the activation or suppression of different types of immunity, not just antibodies. New understanding of immune responses offers the hope of designing vaccines more precisely, and therefore being able to tackle these complex diseases. Progress in adjusting vaccines to induce the best type of immune response must proceed side-by-side with research aimed at understanding the disease processes for each pathogen, so that we can design vaccines for the most effective attack on each pathogen, with the least damage to host tissue. An

early example of the principle of rational vaccine design was the design of the very successful ‘conjugate’ vaccines for Hemophilus influenzae and Pneumococcus, by using knowledge of the mechanism of T cell help for antibody production. I look forward to many more examples of rationally designed vaccines, built from the integration of information from basic research on antigens, innate immune stimuli and regulatory networks to induce exactly the right specificity of response, with exactly the right set of effector functions. I would be delighted if our initial studies on the definition of T cell subsets and functions can contribute to the design of many such vaccines and therapies.

I would like to close by expressing my heartfelt gratitude to Alex Zaffaroni for his vision in creating the research environment at DNAX, to my collaborators for their help in all aspects of the work, and to the Paul Ehrlich-Ludwig Darmstaedter selection committee for honoring this work today.