Speech of
PROFESSOR TAK WAH MAK
Co-winner of the 1995 King Faisal International Prize
for Medicine (Molecular Immunology)

Your Royal Highness Prince Sultan ibn Abd Al-Aziz,
Your Royal Highnesses,
Your Excellencies,
Distinguished Guests,

I am delighted and honoured to be a Co-recipient of The King Faisal International Prize for Medicine. I would, of course, like to thank The King Faisal Foundation for acknowledgment of our work, and for recognizing immunology as an important area of modern medical science. Obviously, our work on T Cell recognition and development is only a small part of a much greater effort to understand how T Cell can influence the immune system and consequently impact on a variety of different diseases, like those of tissue transplantation, tumor rejection, autoimmune diseases and infection.

The King Faisal Foundation has previously demonstrated its understanding of the urgency and importance of research on infectious diseases such as malaria and AIDS. The support given here to me, and thus to the field of immunology, is indeed an indication that the scientific community believes in the importance of immunology to new progress in the cure of disease throughout the world. With the continuing threat of AIDS, the emergence of drug-resistant diseases like tuberculosis, and the failure to eradicate vector-born diseases in equatorial regions, there is indeed ever greater significance to unraveling the basic mechanisms of the immune system in protection and pathology of disease.

Modern biological science is an overlap of many different fields and specialities, which allows investigators like myself to move across disciplines. Like many others in the 1970s, I began my training as a virologist, in. my case working on picornovirus with Roland Rueckert and John Colter. Later I worked on hematopoiesis and retroviruses with E. A. McCulloch and Howard Temin. During those years I had the opportunity to learn many of the then new techniques of molecular biology, which gave me the tools to venture into the rapidly expanding field of immunology in the early 1980s. I began with the attempt to clone genes involved in T Cell differentiation and antigen recognition. I was motivated by the knowledge that many T cell-specific gene-products were expressed at various stages of T cell development, and that these molecules were undoubtedly involved in T cell antigen-recognition and selection.

Without a doubt, the most elusive and intriguing genes in T cells were those coding for antigen recognition. However, being a relatively small laboratory with no prior achievements in immunology, it would have been foolhardy—and indeed difficult to justify—a research project that had as its sole objective the cloning of the T cell receptor genes. We simply set out to isolate T cell specific genes involved in differentiation and function. If this approach was to work, we had to assume that the T cell receptor genes were T cell specific; in addition, we had to rely on DNA subtraction, a method with little previous application in eukaryotic genetics. We certainly could not count on our strategy delivering us the T cell receptor. So it was with great astonishment, and after the isolation and characterization of thousands of T cell-specific clones, that Yusuke Yanagi and myself cloned the T cell receptor in. 1983. In modern science it is uncommon that any one laboratory is working alone on an important project. As it happened, that very year the group of Mark Davis at Stanford University cloned the same T cell receptor gene using an approach identical to ours.

Cloning the T cell receptor did turn out to be. of significance to the field of immunology. It was very important, for example, to clearly establish a one receptor model for T cells - a paradigm that relied heavily on structural data for MHC-peptide complexes. But perhaps the most exciting employment of TCR genes was in the delineation of thymic selection events and mechanisms of immune tolerance, developments made possible in part by the advent of T cell receptor transgenic mice. Now TCR genes are used

as standard tools to study T cell recognition development and T cell malignancies.

Towards the end of the 1980s our laboratory became involved in a theme that has preoccupied us eversince – we have been producing and analyzing genetically modified mice**.** The ability to generate these animals was made possible in the 1980s by new advances in the manipulation of embryonic stern (ES) cells, and by the discovery that ES cells injected into blastocytes would contribute to germ cell embryogenesis and allow transmission of genetic material. In the past five years we have produced a number of interesting animal models for the study of immunology. Our efforts continue along these lines today.

Our laboratory's work is only one small part of a very large effort to better understand T cell development, amid recognition. Collectively, however, I hope these explorations into T cell function will help us in our efforts to silence or augment specific T cell responses, and allow us to control autoimmunity and transplant rejection, win the fight against infectious disease,. and succeed in the development of immunologically-based therapies against cancer.

Today's award must not recognize only my efforts, but must also pay tribute to the many people who have been associated with the laboratory throughout the last 15 years - whom I am indebted. Acknowledgment should also be given to the Ontario Cancer Institute, the University of' Toronto, and the granting agencies in Canada which have supported our work. I ant also grateful to my wife and children for their understanding, and for graciously tolerating a hectic and unending schedule.

Thank you.