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THE PIUS XI GOLD MEDAL AWARD

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Summary of Scientific Activity

I received my first exposure to serious laboratory work in synthetic organic chemistry in the laboratory of P.Y. Johnson as an undergraduate at Johns Hopkins University. In my last year, I was exposed to the mysteries of DNA chemistry by Michael Beer in the Biophysics department and I believe it was this (and having read "The Double Helix" a few years earlier) that inclined me towards working with this substance over the next twentysome years. As a graduate student at the California Institute of Technology, starting in 1974, I had the good fortune to work with DNA and RNA in two separate laboratories – first with Eric Davidson on hybridization analysis and "gene counting" strategies and then with Leroy Hood in using molecular cloning techniques to isolate and characterize rearrangements in immunoglobulin heavy chain genes. In 1980 I finished my Ph.D. and began working with William Paul at the National Institutes of Health (NIH). As work with antibody genes was winding down I thought that it would be interesting to combine what could be done with nucleic acid hybridization with the search for interesting genes in the immune system. This could be done by exhaustively hybridizing complementary DNA (cDNA) from one messenger RNA population with RNA from another. Previously, this had only been attempted with very different types of cells and tissues (liver versus kidney etc.) and large differences in gene expression had been seen, equivalent to thousands of different genes. From the natural history of lymphocytes, however, it seemed that they shared a similar origin and morphology such that I thought that T and B cells might differ by only a few genes, making the isolation of these relatively easy. After a few months of work at NIH, I was able to show that T and B cells indeed shared 98% of their gene expression and thus only 100-200 genes were expressed in one and not the other. With tremendous support and encouragement from Dr. Paul, I built up a small laboratory

at NIH and set out to use these findings to isolate important genes in the immune system, particularly the T cell receptor for antigen, the equivalent of the antibody molecule for T lymphocytes. In 1983, we were successful in isolating the first of what later turned out to be four T cell receptor genes, just at the time that my wife, Yueh-hsiu Chien, also a scientist and I moved to take a faculty position at Stanford. We published the first T cell receptor paper in early 1984, in a dead heat with Tak Mak who had the human equivalent, and later that same year, mostly through the efforts of Chien, we published a paper describing the second chain of the heterodimer, this time in a photo-finish with Susumu Tonagawa, who had joined the fray.

Since the mid-eighties, my work has gradually shifted its focus from nucleic acid chemistry and characterization, to protein structure and biochemistry, cell biology and even to medical issues involving T lymphocytes. In this first area we were able to demonstrate direct T cell receptor binding to its peptide/MHC ligands and to link the strength of binding to the density of cell-surface clustering (with Michael Dustin). I also became curious about the high degree of sequence diversity in the center of the T cell receptor molecules and we were able to show that this region (the CDR3 loops) is the driving force behind peptide specificity. More recently we have also shown this to be true with immunoglobulins. An unexpected byproduct of our biochemical efforts was the realization that while T cell receptor binding was very weak in the micromolar range, it was nonetheless highly specific. This suggested that labeled multimers of peptide/MHC might be good “tags” for T cells with interesting specificities. After a few false starts, we made “tetramers” of peptide/MHC and these are able to stain T cells of just about any degree of specificity. This technique is becoming quite useful for clinical applications, allowing physicians to “follow” specific T cells responses to viral, cancer or autoimmune antigens quickly and easily.

More recently, we have used this approach to show that while tumor specific T cells do arise, sometimes in large numbers in patients with Melanoma, they seem almost completely non-functional compared with T cells of other specificities in the same patients.

The major interest in the lab currently is to follow the fate of labeled membrane proteins on live T cells during the recognition process, in order to discern the underlying chemistry. Interesting facts have emerged from this work about the nature of co-stimulation and the formation of what has been called “the immunological synapse”.