Hilary Koprowski and the Viral Immunity Hub at the 1980s Wistar Institute: A T Cell Epitope Perspective

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IN JULY 1980 I SAT IN THE CROWDED AUDIENCE at the Palais des Congres in Paris on the final day of the Fourth International Congress of Immunology, keenly taking notes as distinguished authorities stepped forward to present their assessments of the major advances reported at the meeting. Being a post-doc at the National Institute for Medical Research at Mill Hill, London, studying influenza immunity with Brigitte “Ita” Askonas, I was fortunate to have landed a job back in my native USA—a junior position at The Wistar Institute to start the next year when my fellowship completed. So I felt a palpable surge of excitement as Hilary Koprowski, Director of The Wistar Institute, made his way to the podium—my first opportunity to hear the voice of my to-be Institute Director. I was not disappointed. His dynamic and straightforward message, delivered in his unique accented English, commanded attention and respect. Never mind that the summaries that day reflected the state of immunology in that era, an exciting time to enter the field, but with many essential principles and tools still to be established, and with many researchers streaming into blind alleys. I copied every complex diagram projected on the screen that revealed the latest intricacies about anti-idiotypic anti-sera (remember “internal images”?), antigen-binding suppressor factors (does “I-J” ring a bell?), and cleverly derived hints (mostly wrong) about the possible structure of the T cell receptor. Nevertheless, there was much hope in Koprowski’s viral immunology report that highlighted important new research about the role of viral replication in cytotoxic T cell recognition, differences between antibody and T cell epitopes, the need to understand the role of T cell-mediated pathology in viral infections, and the enormous potential of x-ray crystallography in understanding immune recognition of viral proteins.

Hilary Koprowski clearly impressed the audience that day with his energetic delivery, and also because he was known for shaping The Wistar Institute as a center of gravity for viral immunology research, populated by leaders that included the future Nobel Laureate Peter Doherty and monoclonal antibody and viral immunity innovator Walter Gerhard. And of course the vaccine accomplishments of Wistar researchers were known to all—Stanley Plotkin, Thad Wiktor, and Koprowski himself—had contributed enormously to public health with the inventions of the rubella⁽¹⁾ and the cell-based rabies vaccines.⁽²⁾ The Wistar Rabies Unit run by Thad Wiktor

was recognized internationally. The Wistar Institute was an impressive center where discoveries were made and resources were available, where standards were high and good scientists interacted—all planned and executed by Hilary Koprowski through strategic hiring, funding, and leadership.

At Mill Hill, Ita Askonas and visiting scientist Lin Yun-Lu had cloned a mouse class I MHC-restricted, IL-2-dependent cytotoxic T cell clone specific for influenza; I had used electron microscopy to study its interaction with target cells⁽³⁾ and had learned the vast potential of cloned T cells for detailed analyses of function and specificity. So I was thrilled that Walter Gerhard and Fritz Melchers, at the Basel Institute for Immunology, had cloned a murine class II I-E^d-restricted helper T cell that now was available for antigen recognition research. Gerhard elegantly showed that antigen recognition by this T cell clone was sensitive to an antibody-selected mutation in the H1N1 influenza PR8 hemagglutinin (HA) at position 115,⁽⁴⁾ a fortunate coincidence on the co-localization of a conformational antibody epitope and a linear T cell determinant. But this finding was only possible to demonstrate at Wistar because Gerhard and Jon Yewdell had assembled a very complete panel of monoclonal antibody-selected variants, having known amino acid changes in the HA. Today one would immediately order a synthetic peptide of that region and prove that the T cell recognized a linear epitope encompassing that residue, but at that time, over 30 years ago, there were no well-established examples of viral proteins being presented as peptides and few examples with model proteins; therefore other explanations, such as reduced stability of the variant HA molecule or conformational alteration of a distal epitope, seemed possible (which has been reported⁽⁵⁾). Collaboration between the Gerhard group and the Rabies Unit was essential in the identification of the epitope. Hilary strongly supported my collaborations with the Rabies group, which took the approach of applying knowledge of host responses to viral antigens for insights into new vaccines. This facilitated both intellectual and practical collaborations with the rabies investigators, principally with Bernhard Dietzschold, who had established state-of-the-art approaches in protein and peptide chemistry.

Because the epitope was preserved on the isolated, reduced, and alkylated HA1 chain of the viral hemagglutinin, Dietzschold was able to narrow down the epitope to smaller

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regions by HPLC separation and Edman degradation sequencing of cyanogen bromide fragments of HA1 cleaved at methionine and then tryptophan. Manual synthesis of multiple synthetic peptide homologs near position 115 ultimately proved that the helper T cell clone recognized residues 111–119 of the PR8 HA1.⁽⁶⁾ This finding was a significant contribution to the efforts at The Wistar Institute and in the larger field of T cell recognition; for example, the HA 111–119 helper epitope publication was cited by Alain Townsend in his landmark 1986 paper showing cytotoxic T cell recognition of synthetic peptides.⁽⁷⁾ The collaborative approach fostered by Hilary was also evident when Julia Hurwitz joined the Gerhard group, and, with the new Wistar staff member Ellen Heber-Katz, put in place the robust T hybridoma technology to probe T cell responses to influenza virus.⁽⁸⁾ Soon two additional new influenza class II-restricted T cell epitopes were mapped on the HA (Gerhard later showed that there are at least eight BALB/c class II MHC-restricted epitopes in PR8 HA⁽⁹⁾). Additional MHC class II-restricted T cell epitopes were mapped on the PR8 neuraminidase, nucleoprotein, and nonstructural protein 1, some in collaboration with Yewdell and Jack Bennink.^(10–12) In 1986 Hurwitz and I defined an I-A^b-restricted T cell epitope in PR8 HA that remained unpublished; however, 24 years later no one had reported an I-A^b epitope for influenza H1 HA, an important model system, so we submitted our finding in 2010 and it is now catalogued in the Immune Epitope Database (www.iedb.org/epId/128030). Andy Caton, who came from England to join the Gerhard group, created transgenes of a T cell receptor that recognizes the HA 111–119 epitope, leading to establishment of a powerful system to study self-T cell responses.⁽¹³⁾ Laurence “Ike” Eisenlohr based his doctoral research, performed in my lab at Wistar, and many excellent discoveries in his career, on understanding the mechanism by which these distinct influenza helper T cell epitopes are presented to T cells.⁽¹⁴⁾

I am indebted to Hilary Koprowski for his vision, and to Walter Gerhard and the “braintrust” of all of our Wistar colleagues in viral immunology for their insightful, intelligent, and critical discussions and for their helping hands that channeled this research along a pathway that continues to pay dividends.

This snapshot is just one example of how Hilary’s approach to hiring researchers with similar interests but different backgrounds and skills led to findings that have had long-lasting impact on the field. It was those intense and productive interactions that made those days at Wistar a unique environment for viral immunology.

Author Disclosure Statement

The author has no financial interests to disclose.

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