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This Week's Citation Classic

Doherty P C, Blanden R V & Zinkernagel R M. Specificity of virus-immune effector T cells for H-2K or H-2D compatible interactions: implications for H-antigen diversity. *Transplant. Rev.* **29**:89-124, 1976. [Wistar Inst. Anat. Biol., Philadelphia, PA; Dept. Microbiol., John Curtin Sch. Med. Res., Canberra, Australia; Dept. Exp. Pathol., Scripps Clinic and Res. Found., La Jolla, CA]

We summarised here the concepts resulting from our discovery two years earlier that the so-called strong transplantation antigens function as recognition sites for self-monitoring cytotoxic T lymphocytes. This work drastically changed thinking about both the nature of histocompatibility and immunological surveillance. [The *SCI*® indicates that this paper has been cited in over 650 publications since 1976.]

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"The basic outline of this solicited review was written on a delayed British Airways flight to London, en route to spending six years at the Wistar Institute, Philadelphia. It presented the first comprehensive account of ideas and data generated during two years of intensive experimentation, starting with the discovery of major histocompatibility complex (MHC) restricted virus-immune cytotoxic T cell function by Rolf Zinkernagel and me in Canberra in October 1973.[1] Similar findings were made at about the same time by Gene Shearer at the National Institutes of Health, Bethesda, for the lymphocyte response to trinitrophenyl (TNP)-modified cells.[2] However, apart from the work in Shearer's laboratory, the isolation of Australia undoubtedly contributed to our having a 12-month-lead before the realization that a biological *raison d'être* had at last been found for the so-called strong transplantation antigens registered with the major groups in the Northern Hemisphere. The topic was dominating much of the debate in cellular immunology by the time that this article was published and it was immediately a key reference in the T cell field.

"The then current paradigm in the US was that the so-called immune response genes, which mapped to the I region of MHC, encoded part or all of the T cell receptor. We initially thought that we were studying something rather similar. However, we also proposed an alternative hypothesis that the virus-immune T cells might be recognising either some complex of virus and histocompatibility antigen, or a virus-induced alteration of MHC molecules themselves. This 'altered-self model, which quite unknown to us reflected an earlier proposal made by Sherwood Lawrence[3] to explain the binding of transfer factor, came easily enough to mind when thinking about virus infections and focused attention onto the target/stimulator cells. A completely novel set of arguments could thus be made about the nature of alloreactivity, differential responsiveness, and MHC gene polymorphism. However, we gained the impression that our ideas were considered heretical by the established immunological community, who were then rolling on a different bandwagon.

"At the stage that this review was written, we found ourselves almost totally unable to generate any support at all for the idea that MHC genes were coding directly for the T cell receptor. Key experiments that were described here showed quite clearly that different sets of virus-immune T cells were associated with H-2K and H-2D, and that mere expression of a particular MHC product on the immune lymphocyte did not allow for recognition of virus-infected target cells. Also, the fact that mutations in relatively small pieces of DNA coding for the structural MHC gene product completely modified the spectrum of T cell recognition could not readily be accommodated with the earlier T cell receptor model for MHC. However, I still felt that we needed to be rather circumspect in the writing of this article, as there seemed no particular need to make powerful enemies. We had already argued a much more extreme case for the 'altered-self model in an article written earlier for the 'Hypothesis' format of *Lancet*.[4] What we did not realise was that our ideas had made an impact: some of the leading proponents of the MHC-T cell receptor idea were already changing their ground and there would be evidence of a new emphasis at the Cold Spring Harbor meeting held early in 1976. Zinkernagel and I shared the Paul Ehrlich Prize for Medicine in 1983."

1. **Zinkernagel R M & Doherty P C**. Restriction of in *vitro* T cell-mediated cytotoxicity in lymphocytic choriomeningitis within a syngeneic or semiallogeneic system. *Nature* **248**:701-2, 1974.
2. **Shearer G M.** Cell-mediated cytotoxicity to trinitrophenyl-modified syngeneic lymphocytes. *Eur. J. Immunol.* 4:527-33, 1974.
3. **Lawrence H S.** Homograft sensitivity: an expression of immunologic origins and consequences of individuality. *Physiol. Rev.* **39**:811-59, 1959.
4. **Doherty P C & Zinkernagel R M.** A biological role for the major histocompatibility antigens. *Lancet* **1**:1406-9, 1975.