it conceivable that a TCR:MHCpep complex can wait around long enough for another such complex to find it and become crosslinked to it?

An alternative view is that crosslinking of TCRs does not occur, but that the key initial event is an interaction between the TCR complex and the CD4 or CD8 antigens that respectively bind to MHC class II or MHC class I antigens. The TCR complex is not alone at the cell surface but is in a loose complex with CD2, CD4 or 8, CD5 and the tyrosine kinases $p56^{lck}$ and $p59^{fyn}$ (refs 7,8).

The figure illustrates possible molecular interactions. The CD4 and CD8 antigens look much more like classical signal transduction molecules than do any of the TCR or CD3 chains. To a cell biologist a classical receptor has an extracellular binding domain, a transmembrane segment and a tyrosine kinase cytoplasmic domain, and this is exactly the case for CD4 and CD8 with the kinase being non-covalently attached[9]. It may be that when CD4 and TCR bind the same MHCpep, the kinase domain is orientated to other cytoplasmic domains of the TCR multi-molecular complex such that a primary triggering event occurs. T-cell receptors and CD4 are present at cell surfaces at about $2\times10^4$ molecules per cell, and as they exist in preformed complexes it is imaginable that dual binding of these molecules to MHCpep might frequently occur within the time in which a single TCR and MHCpep are associated.

It might be argued that there are examples of T-cell triggering with cells that are CD4 or CD8 negative, and CD4 negative cells were used by Weber *et al.*[2]. However it could be that the cells in question express CD4 at a few hundred molecules per cell and that this is sufficient for triggering on T hybridoma cells that are poised to respond. The key question is whether T-cell triggering involves crosslinking of the TCR molecules, or whether activation occurs by perturbation of a TCR multi-molecular complex by a single MHCpep. □

*†It is a matter of great regret to record that Alan F. Williams, Director of the MRC Cellular Immunology Unit, Sir William Dunn School of Pathology, University of Oxford, died of cancer earlier this month, shortly after completing this article. He was 46. Albertus D. Beyers is in the same unit.*


1. Matsui, K. *et al. Science* **254**, 1788–1791 (1991).
2. Weber, S. *et al. Nature* **356**, 793–796 (1992).
3. Demotz, S., Grey, H. M. & Sette, A. *Science* **249**, 1028–1030 (1990).
4. Harding, C. V. & Unanue, E. R. *Nature* **346**, 574–576 (1990).
5. Sayre, P. H. *et al. J. exp. Med.* **169**, 995–1009 (1989).
6. Dustin, M. L. & Springer, T. A. *Nature* **341**, 619–624 (1989).
7. Beyers, A. D., Spruyt, L. L. & Williams, A. F. *Proc. natn. Acad. Sci. U.S.A.* **89**, 2945–2949 (1992).
8. Dianzani, U. *et al. J. Immun.* **148**, 678–688 (1992).
9. Rudd, C. E. *et al. Proc. natn. Acad. Sci. U.S.A.* **85**, 5190–5194 (1988).


OBITUARY

# Peter Mitchell (1920 – 1992)

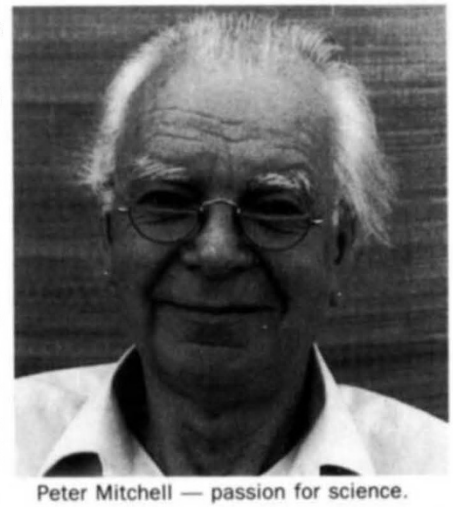
**PETER Mitchell, biochemist and Nobel laureate for chemistry in 1978, died from cancer on 10 April.**

**Mitchell's single-minded purpose was to understand the mechanistic relationships between the metabolism of cells and the transport of solutes across cellular membranes. Clearly they were related, but how? Metabolism could drive transport, and transport was essential for metabolism, but the links were not known. Metabolism, 1950s style, was bag-of-enzymes stuff, isotropic and reconstitutable in a test tube. Transport, or certainly its effect, was anisotropic. Mitchell reasoned that because ends could not be more anisotropic than their means, the membrane enzymes involved in both metabolism and transport would themselves need to be anisotropic, catalysing a reaction that is vectorial rather than scalar. Because such enzymes would be effecting both chemical transformations and solute translocation, he coined the word 'chemiosmotic' to describe the process that they facilitated.**

**The idea of chemiosmotic processes might have remained a curiosity in the literature but for Mitchell's dramatic exemplification of the concept. He proposed a richly predictive and highly successful mechanism for the manner in which the series of oxidoreductions within membranes, effected by mitochondrial respiratory chains or the photosynthetic apparatus of chloroplasts, could drive the otherwise thermodynamically unfavourable formation of ATP from ADP and phosphate. This idea cut through the impasse caused by abortive searches for the (non-existent) chemical intermediates that were then favoured.**

**The whole theory and its ramifications were set out in two privately published monographs, the unique 'grey books' of 1966 and 1968. They described the solution of a jigsaw, one where some of the parts had to be invented, and where the final picture was revealed only on its completion. Some of the pieces were already well known — the impermeability of membranes to most solutes, anions and cations; the need for specific proteins to provide specific diffusion pathways; the general distribution and, emergingly, the anisotropy of enzymes in membranes; the concept of membrane ATPases as cation pumps. The new pieces were the intrinsic proton-translocating activity of respiratory or photosynthetic oxidoreductions, the postulate of a reversible proton-translocating ATPase and, to complete the picture, reversible coupling of oxidoreductions and ATPase by a flow of protons. To all this was added postulated mechanisms for proton translocation driven by oxidoreductions and ATPases, experimental tests and analysis of the thermodynamic requirements and predictions of the theory.**

**It was an amazing performance, set against a background of poor health, changes in career and marriage, and the need to act as his own architect, works manager and farmhand for at least two years (1963–1965) while he created his own laboratory and home at Glynn, a dilapidated country house in Cornwall. The support of his family was crucial for**



Peter Mitchell — passion for science.

**the success of these endeavours. Some notable exceptions apart, he received little support from grant-giving bodies or the major investigators in the field of oxidative phosphorylation. But he was essentially right. The chemiosmotic theory was tested, accepted and built upon.**

**Mitchell added further valuable ideas, notably for the functioning of ubiquinone, for coupling of ion movements to drive mechanical movements of flagellae, as the field at large moved to closer examination of the molecular mechanisms of chemiosmotic systems. So we arrive at the present, with crystallography, electron diffraction, recombinant DNA, site-directed mutagenesis — the tools available to the modern membranologist are of immense power, but the agenda is distinctly mitchellian.**

**He received numerous honours, yet remained modest, approachable and humorous. In *Who's Who*, his recreations are listed as "enjoyment of family life, home building and creation of wealth and amenity, restoration of buildings of architectural and historical interest, music, thinking, understanding, inventing, making, sailing". One begins to understand how his Cambridge PhD took seven years, what sustained his passion for science, what drove him on.**

Peter Garland

*Peter Garland is at the Institute of Cancer Research, Chester Beatty Laboratories, 237 Fulham Road, London SW3 6JB, UK.*