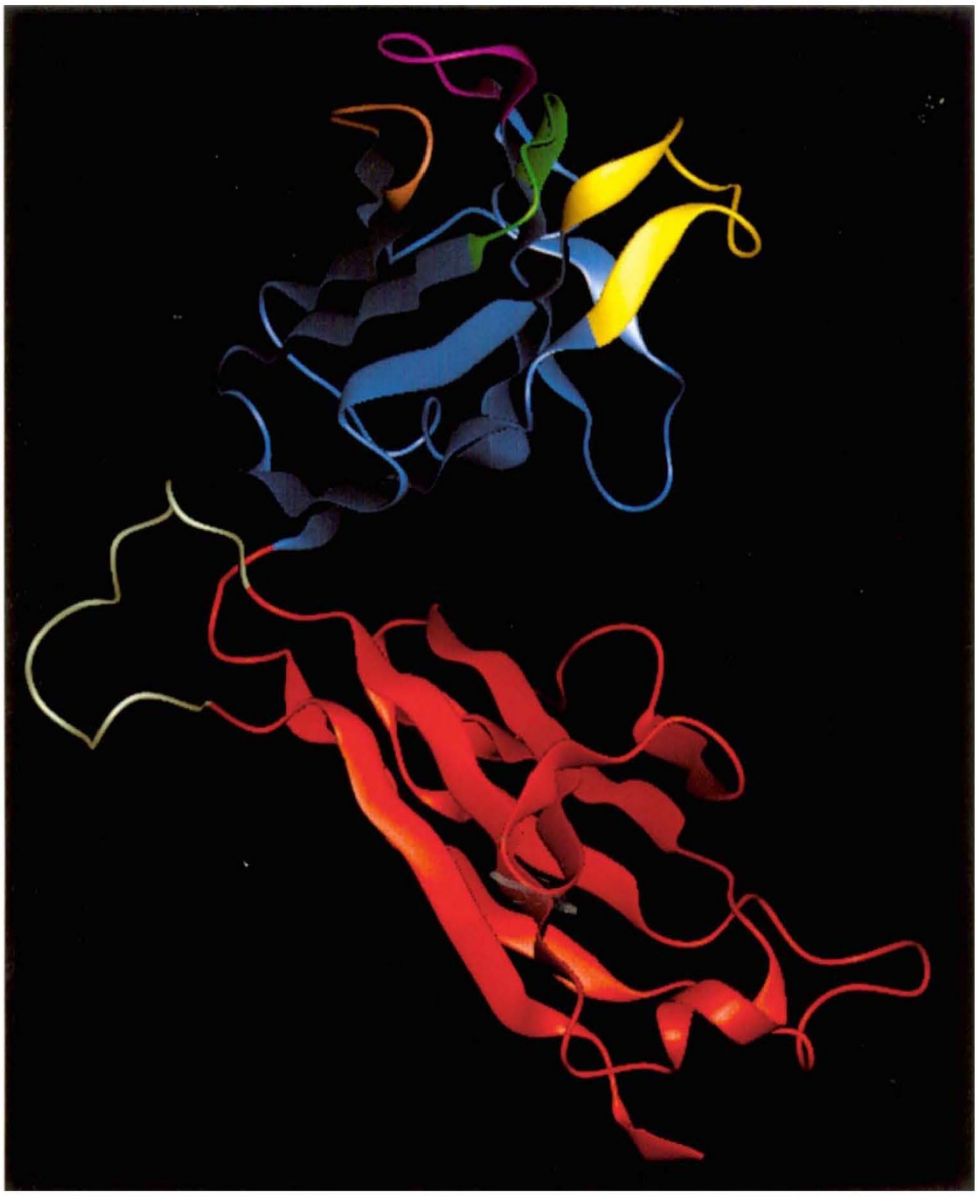
Giving TCR the elbow

An important arm of the cell-mediated immune system is provided by cytotoxic T cells and T helper cells: although the two different cell types have different functions in the immune system they both recognize either the infected host cell (in the case of the cytotoxic T cell) or antigen presenting cells (T helper cells) through the T-cell receptor (TCR). The determination of the high resolution structure of the extracellular portion of the β-chain of the TCR (Bentley, G.A., Boulot, G., Karjalainen, K. & Mariuzza, R.A. *Science* **267**, 1984-1987; 1995) confirms the prediction that the TCR bears more than a passing resemblance to the immunoglobulins.



The TCR is a transmembrane molecule, consisting of two disulphide-linked polypeptide chains: α and β (or γ and δ). The β-chain (shown left) consists of two β-sheet domains: a variable (V_β; shown in blue) and a constant (C_β; red) domain, structurally homologous to the V and C domains found in antibodies.

The structure of the TCR V_β domain is more similar to the immunoglobulin light chain V domain than the heavy chain V domain. There are four loops which protrude into the solvent at the free end of V_β (top) and three of these are homologous to the complementarity-determining regions (CDRs) found at the end of the V regions in antibodies (CDR1, 2 and 3; green, violet and yellow). These CDRs are most likely the regions that interact with the peptide-bound MHC molecules on the target cells. The last loop is known as the fourth hypervariable region (HV4; orange)—implicated in the binding of superantigens. The proximity of the HV4 loop to the CDRs supports the possibility that HV4 is also involved in peptide-MHC recognition and that CDR1 and 2 may modulate the interaction with superantigens. A model of the TCR αβ heterodimer has a very similar structure to an antibody Fab fragment, with an elbow angle of 154°.

The C_β domain shows a number of important differences with the C domains from immunoglobulins; perhaps the most obvious being a solvent-exposed 'bulge' (grey-green) at the junction, or elbow, between V_β and C_β. Indeed, there are extensive interactions between the V_β and C_β domains resulting in a buried surface area of 822 Å^2, compared to that of 200–350 Å^2 between V_H and C_H1 regions in antibodies. Bentley and colleagues suggest that this will result in a relatively rigid elbow which, in turn, may be important for transmitting structural changes on binding ligand and thus mediating signal transduction. The C_β bulge may have an important role in contacting associated CD3 molecules in the TCR-CD3 complex. **GR**