s8a.m9.p7 **The crystal structure of a murine TCR bound to an allogeneic MHC molecule.** J.B. Reiser[#], C. Darnault[#], A. Guimezanes[§], C. Grégoire[§], T. Mosser[§], A-M. Schmitt-Verhultz[§], J.C. Fontecilla-Camps[#], B. Malissen[§], D. Housset[#] and G. Mazza[§]. [#] *LCCP, Institut de Biologie Structurale J.P. Ebel, CEA-CNRS-UJF, 41, rue Jules Horowitz, F-38027 Grenoble cedex 1.* [§] *Centre d'Immunologie de Marseille-Luminy, INSERM-CNRS, case 906, F-13288 Marseille cedex 9 e-mail: reiser@lccp.ibs.fr or housset@lccp.ibs.fr*
Keywords: viruses, immunology.

The T lymphocytes (or T cells) are the main actors of the cellular immune response and protect the organism against pathogens such as viruses and intracellular bacteria, and some kind of cancer. To achieve this goal, the T lymphocytes are able to recognize peptide fragments derived from foreign proteins and presented at the surface of infected cells by a Major Histocompatibility Complex (MHC) coded protein, the MHC molecule. For the recognition of a peptide antigen by a T cell, three main partners have been identified : for the antigen presenting cell, the membrane anchored MHC molecule and its bound foreign peptide (pMHC), and for the T lymphocyte, a specific membrane bound Ig like receptor (TCR for T-Cell Receptor). One hundred TCR engaged in complexes with foreign peptides bound to self-MHC molecules, is enough to induce a cascade of signals which eventually activates the specific T cell clone, leading to its proliferation and the death of infected cells.

During the 90s, several crystallographic studies of MHC molecules, TCR and TCR/peptide/self-MHC complexes performed by different groups all over the world allowed to define a general mode of TCR-pMHC interaction[1,2,3]. However, due to the intrisic variability of the TCR, the structural basis for its specificity remains to be elucidated.

The aim of our project is to establish the structural basis of TCR cross-reactivity for several peptides and MHC molecules. On the one hand, the TCR binding degeneracy is essential to insure that at least one T-cell clone, among the large but finite repertoire, reacts with anyone of the millions of putative foreign peptides. On the other hand, TCRs can productively bind intraspecies allelic variant of self-MHC molecules, and consequently govern graft rejection and graft-versus-host disease.

We will present the crystal structure of a complex involving the murine BM3.3 TCR and a naturally processed octapeptide (pBM1) bound to the H-2K^b allogeneic MHC molecule. This structure shows that the TCR/p-alloMHC complex shares the same general binding mode of the TCR/p-selfMHC complexes. However, the peptide "read-out" as well as the details of the MHC footprint differ markedly from the previously determined TCR/pMHC complexes[1,2,3].

[1]. Garcia, K.C., Degano, M., Pease, L.R., Huang, M., Peterson,P.A., Teyton, L. and Wilson, I.A. (1998). Structural basis of plasticity in T cell receptor recognition of a self peptide-MHC antigen. *Science*, **279**, 1166-1172.
[2]. Garboczi, D.N., Ghosh, P., Utz, U., Fan, Q.R., Biddison, W.E. and Wiley, D. (1996) Structure of the complex between human T-cell receptor, viral peptide and HLA-A2. *Nature*, **384**, 134-141.
[3]. Ding, Y.H., Smith, K.J., Garboczi, D.N., Utz, U., Biddison, W.E. and Wiley, D.C. (1998). Two human T cell receptors bind in a similar diagonal mode to the HLA-A2/Tax peptide complex using different TCR amino-acid. *Immunity*, **8**, 1-20.

s8a.m9.p8 **Crystal structure of the human transthyretin-retinol-binding protein complex bound to an anti-RBP Fab.** G. Zanotti [a)], V. Calderone[a)], R. Battistutta [a)], F. Gliubich [a)], G. Malpeli [b)], S. K. Nishida [c)], C. Folli [b)] and R. Berni [b)]. *a) Dept. of Organic Chemistry and Biopolymer Research Center, U. of Padova, Italy b) Institute of Biochemical Sciences, University of Parma, Italy c) Nephrology Division, Escola Paulista de Medicina, Sao Paulo, Brazil.*
Keywords: viruses, immunology.

Retinol-binding protein (RBP) and transthyretin (TTR) are two plasma proteins involved in multiple interactions: they bind small ligands (the alcoholic form of vitamin A and the hormone thyroxine, respectively), form a protein-protein complex in the blood and interact with surface receptors of target cells. Consequently, this system appears to be a good model for the *in vitro* study of protein-protein and protein-small ligand interactions at the molecular level. As a result of constraints imposed by these various interactions, as well as by structural requirements, then three-dimensional structures of RBP and TTR were found to be well preserved in vertebrates species distant in evolution. The crystal structures of apo- and holo- forms of both RBP [1,2,3] and TTR [4,5] have been reported, along with that of the heterologous chicken RBP - human TTR complex [6] and, more recently, of the human RBP - TTR complex [7].

We report here the crystal structure of a complex between human TTR, human RBP and a murine anti-RBP Fab. The complex was crystallized by vapor diffusion. Small needle-shaped crystals (space group C222, **a**=159.34 Å, **b**=222.40 Å and **c**=121.27 Å) diffracted to 3.2 Å resolution at the X-ray diffraction beam line of the ELETTRA synchrotron in Trieste. The structure was solved by molecular replacement, using as templates the models of the single components. The asymmetric unit contains one molecule of the complex, made up by one TTR, two RBP and two Fab, for a total of 10 polypeptide chains and a molecular weight of about 200 KDa. Molecules are arranged symmetrically around a two-fold axis, which runs through the channel of the tetrameric TTR molecule.

[1] Cowan, S.W., Newcomer, M.E., and Jones, A.T. (1990) *Protein Struct. Funct. Gen.* **8**, 44-61
[2] Zanotti, G., Berni, R., and Monaco, H.L. (1993) *J. Biol. Chem.* **268**, 10728-10738
[3] Zanotti, G., Malpeli, G., and Berni, R. (1993) *J. Biol. Chem.* **268**, 24873-24879
[4] Blake, C.C.F., Geisow, M.J., Oatley, S.J., Rerat, B., and Rerat, C. (1978) *J. Mol. Biol.* **121**, 339-356
[5] Wojtczak, A., Cody, Y., Luft, J.R., and Pangborn, W. (1996) *Acta Cryst.* **D52**, 758-765
[6] Monaco, H.L., Rizzi, M., and Coda, A. (1995) *Science* **268**, 1039-1041
[7] Naylor, M. N. and Newcomer, M.E. (1999) *Biochemistry*, **38**, 2647-2653