Molecular structure of the best-studied human cancer T cell antigen revealed

The ability to see how biomolecules look is of paramount importance to modern medicine and drug design. These molecules are far too small to see in detail even with the most advanced light microscopes. One of the best techniques to produce images of such molecules at the atomic level involves looking at them in solid crystalline form using X-rays, and 'X-ray crystallography' has become primary method for determining the molecular conformation of biological molecules like proteins and DNA.

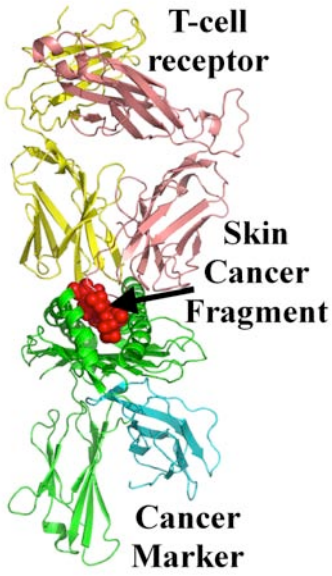

Figure 1. How the immune system sees skin cancer

Cardiff University recently identified the need for X-ray crystallography and has made considerable investment in this area. This investment included the appointment of Nobel Laureate Robert Huber and the recruitment of Matthias Bochtler to the School of Chemistry. Cardiff University School of Medicine also invested in this area with the appointment of Dr. Pierre Rizkallah, a scientist that used to run the central protein X-ray beams at the Daresbury Synchrotron. The University's investment in X-ray crystallography is now beginning to show returns.

Professor Sewell of the School of Medicine has led a team that used X-ray crystallography to determine the structure of the best ever studied human cancer antigen in complex with a human T-cell receptor (Figure 1). This 'antigen' molecule is upregulated on the surface of human melanoma cells and enables killer T-cells to identify and eliminate these cancerous cells using their T-cell receptor (Figure 2). Professor Sewell said "We anticipate wide interest in this structure as it is only the second human cancer/T-cell receptor complex ever solved. Our T-cells are really designed to eliminate 'foreign' molecules and they are crucial for the elimination of pathogens. T-cells perform less well at eliminating cancer as cancer cells are derived from our own tissue and pose the immune system a greater challenge."

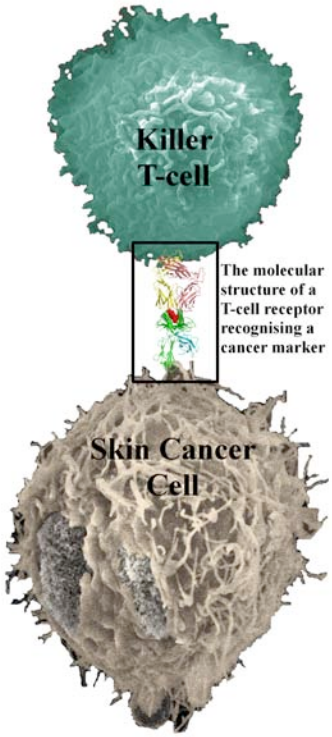

Figure 2. Killer T-cells can use their T-cell receptor to recognise and kill human cancer cells

Professor B. Paul Morgan, the new Head of the School of Medicine was instrumental in establishing X-ray crystallography in the school while Head of the Department of Infection, Immunity and Biochemistry. "The solving of this structure vindicates the investment that the School made in appointing an expert in protein crystallography. We expect that Dr. Rizkallah will solve many more important structures in the near future."

Dr. David Cole, the study's first author, said, "this structure has important implications for cancer vaccine design. Now we can visualize these interactions we can begin to improve them. We have already improved the affinity this particular interaction by over 20 million fold as part of our unpublished research. This structure has been essential for allowing us to see what is happening at the atomic level. I am thrilled to get this result first as we knew that we were in a race with several other groups around the world. "

The research was partially funded by the Cardiff University Link Chair scheme and was published on-line last week in the *Journal of Biochemistry* [link]

RELATED LINKS

Cardiff School of Medicine (http://www.cardiff.ac.uk/medic/)

Nobel Laureate Robert Huber appointed to Cardiff
http://www.nature.com/naturejobs/2006/061123/full/nj7118-516a.html

Engineered T-cell receptors beat HIV
http://www.cardiff.ac.uk/news/articles/hivs-disguises-no-match-for-engineered-cells.html

Cardiff T-cell Research (www.tcells.org)