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Keynotes

[Monday 16 September 2002, 09.00–09.30]
Receptor revision is a common mechanism of antibody diversification in human B cells
Patrick Wilson and J. Donald Capra
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Our laboratory has published methods of separating human tonsilar B cells that take advantage of the cell surface markers CD38 and IgD. Using this general scheme, we first demonstrated that somatic hypermutation begins in germinal center (Bm3) cells. Later we showed that Bm5 cells were memory cells. In the course of these studies we have studied an unusual subset of tonsilar B cells, which we call IgD positive GC cells. These cells have undergone an unusual class switch event in which Cmu is lost, but Cdelta is retained thus producing an IgD-only lineage that is incapable of further class switch. These cells display an unusually high frequency of somatic mutations and predominantly utilize lambda light chains. We documented that another new mechanism of diversity was manifest in this subset: receptor revision – that is – the substitution of a new/hybrid VH gene for a heavily mutated one during the course of normal B cell differentiation. We subsequently showed that this was a common pathway for diversity generation. Very recently, in unpublished work, we have documented that selection of the VH repertoire used by various human B cells, particularly in regards to self-reactive specificities, is more dependent on ISOTYPE than on B cell differentiation during an immune response as they mature through a GC reaction.

[Monday 16 September 2002, 13.45–14.15]
The infectious origin of APS. Molecular mimicry between microbial pathogens and β2-GPI: The induction of experimental APS (**Keynote lecture**)
Yehuda Shoenfeld
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The anti-phospholipid syndrome (APS) is characterized by a wide variety of hemocytopenic and vaso-occlusive manifestations and is associated with autoantibodies directed against negatively charged phospholipids

The pathogenicity of anti-β2GPI Abs has been demonstrated in naive mice and rabbits.

The factor(s) causing production of aPL-β2GPI in APS remain unidentified. Several indirect arguments support the idea that microbial agents might influence the course of APS and an association between APS and several microbial pathogens was documented.

Employing peptide phage display library, we identified three hexapeptides that react specifically with the anti-β2GPI mAbs. Using the Swiss Protein database revealed high homology between the hexapeptides with different bacteria and viruses. Naive mice were immunized with a panel of pathogen particles. All the immunized mice developed antiphospholipid Abs. However, the most significant levels of mouse anti-β2GPI were detected in the mice immunized with Haemophilus influenzae or with Neisseria gonorrhoeae and bound β2GPI. Affinity purified specific immunoglobulins were infused i.v. into BALB/c mice and the development of APS clinical manifestations was studied. Only the mice which were infused with mouse antibodies derived from mice immunized with Haemophilus influenzae or with Neisseria gonorrhoeae, directed to the peptide TRLVYK, had the potential to induce clinical manifestations which resemble experimental APS. We hypothesize, in the current case, that the mechanism of pathogenic anic anti-(2GPI generations is induced by epitope mimicry.

Ref: Blank M., Shoenfeld Y., Cabilly S., Heldman Y., Fridkin M., Kachalski-katzir E.: Prevention of experimental antiphospholipid syndrome and endothelial cell activation by synthetic peptides. Proc. Natl. Acad Sci. USA 96:5164–5168,1999.

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[Monday 16 September 2002, 17.25–18.05]
If we can make any antibody we want then how come we don't have it?
James Larrick
Planet Biotechnology, San Diego, USA

Keynote not received

[Tuesday 17 September 2002, 08.30–09.00]
Stealth antibodies
Herman Waldmann, Mark Frewin and Luis Graca
Sir William Dunn School of Pathology, University of Oxford, Oxford OX1 3 RE, UK

The immunogenicity of therapeutic antibodies remains a concern for their long-term application. Humanisation and related approaches have partly resolved the problem. A potential solution may be found in the classical observations of Chiller and Weigle who demonstrated that foreign immunoglobulins were obligate tolerogens once deaggregated. We will show that therapeutic antibodies which are prevented from binding to cells and exerting any biological effector function for a short period after systemic administration, are in that period, able to act as tolerogens. This means that when, in time, cell-binding is regained the antibodies are no longer capable of immunizing the host.

The application of stealth technology has enabled us to completely eliminate the immunogenicity of hman antibodies targeted to mouse lymphocytes. We infer that this would do the same for rodent antibodies targeted to human cells.

The combination of stealth technology with humanization, and its related approaches, should result in the generation of completely 'immunologically-silent' antibodies.

[Wednesday 18 September 2002, 09.00–09.30]
Status of human monoclonal antibody therapy against gram-negative pathogens
A. Lang
BernaBiotech, Berne, Switzerland

Keynote not received