

Rational vaccine designs against cancer

The BioPark Hertfordshire, Welwyn Garden City, AL7 3AX

16 October 2007

- 9:00 – 9:45 **Registration**
- 9:45 – 10:00 **Introduction by the Chair:** Professor Freda Stevenson, University of Southampton, UK
- 10:00 – 10:30 **Developing DNA fusion vaccines to induce specific cytotoxic T lymphocyte responses against tumour antigens**
Dr Jason Rice, University of Southampton, UK
 The majority of known human tumour-associated antigens derive from non-mutated self-proteins. T-cell tolerance, essential to prevent autoimmunity, must therefore be cautiously overcome to generate CTL responses against these targets. We have explored DNA fusion vaccines as a strategy to induce CTL responses to a model tumour-associated antigen (TAA). The DNA construct contained foreign sequences from tetanus toxin to induce a non-tolerant CD4 T-cell helper response, and an MHC Class I-binding tumour peptide sequence derived from the TAA. This simple strategy can engage anti-microbial T-cell help to activate polyclonal lower avidity tumour-reactive CTL from a tolerized repertoire, with no evident autoimmunity.
- 10:30 – 11:00 **Synthetic viral nucleic acids as adjuvants for cancer immunotherapy**
Dr Sandra Diebold, Guy's Hospital, London, UK
 Viral nucleic acids have been identified as potent immune stimulators triggering a variety of innate pattern recognition receptors. There are three classes of viral nucleic acids, all of which are recognised by specific Toll-like receptors upon uptake into a specialised endosomal compartment and by ubiquitously expressed cytoplasmic pattern recognition receptors inside virus infected cells. Toll-like receptor-mediated activation plays an important role in linking innate immune responses with the induction of suitable adaptive immune responses. Because of their potent adjuvant activity, synthetic mimics of viral nucleic acids are promising candidates to improve the efficacy of current protocols for tumour immunotherapy.
- 11:00 – 11:10 **Group photo**
- 11:10 – 11:30 **Mid-morning break and Poster Viewing**
- 11:30 – 12:00 **CD8 T cell programming by members of the TNF receptor superfamily**
Dr. Aymen Al-Shamkhani, University of Southampton, UK
- 12:00 – 12:30 **Intradermal delivery of DNA vaccines: from mouse to clinical application**
Dr John Haanen, NKI-AVL, Amsterdam
 Two years ago we developed a novel intradermal DNA vaccine delivery strategy. This was based on in vivo antigen expression measurements using the luciferase reporter. The strategy makes use of a permanent make-up or tattoo device and is robust in terms of induction of cellular vaccine-specific immunity. The strategy that was developed in a mouse model has been successfully validated in a non-human primate model and will be tested in end-stage melanoma patients in 2007. Furthermore, models are being developed to unravel the mechanism of action of DNA tattooing using intravital imaging and a ex vivo human skin model is now available for optimizing the strategy for human skin.
- 12:30 – 12:50 **Tour of the BioPark**
- 12:50 – 13:50 **Lunch and Poster Viewing**

- 13:50- 14:20 **Prime-boost with alternating DNA vaccines designed to engage different antigen-presentation pathways**
Dr Stephen Thirdborough, Southampton University, UK
The route for presentation of antigen to CD8 or CD4 T cells following DNA vaccination is critical for determining outcome, but the pathways involved are unclear. We have generated two DNA vaccine designs aimed to elicit CD8 T-cell responses against a specific peptide-epitope either by direct- or cross-presentation. These vaccines can be combined in an alternating prime-boost regime, in either order, to generate substantially expanded memory CD8 T cells, with potent effector function. Our findings demonstrate that vaccination protocols involving different modes of antigen presentation at prime and boost can significantly improve the effectiveness of immunization
- 14:20 – 14:50 **T cell immunity to Cancer-Testis Antigens in patients with multiple myeloma**
Professor Paul Moss, University of Birmingham, UK
Cancer testis antigens are expressed in the testis and exist in an immunologically privileged site where they are not thought to induce T cell tolerance. However, expression of proteins within the CTA_g family is detected in many malignant cells where they can induce cellular and humoral immunity. Within the last few years expression of several CTA_g proteins has been described in malignant plasma cells isolated from patients with multiple myeloma. We have studied the CD8 and CD4 T cell immune response to CTA_g in these patients and demonstrate a fluctuating pattern of immunity with disease progression. The relevance of this to immunotherapeutic approaches will be discussed
- 14:50 - 15:20 **The polycomb group proteins, BMI-1 and EZH2, are tumour-associated antigens**
Dr Jane Steele, Birmingham University, UK
We applied SEREX technology to patients with primary hepatocellular carcinoma and identified the polycomb group (PcG) protein BMI-1 which is over-expressed in a range of different tumours. Further studies identified T cell responses to both BMI-1 and another PcG protein, EZH2, in cancer patients and at relatively lower levels in some normal donors. EZH2-derived peptides can stimulate the in vitro expansion of specific T cells from peripheral blood lymphocytes, and this is enhanced when the CD25 T cell population is depleted. EZH2-specific CTL clones recognize endogenously processed EZH2 in both HLA-matched fibroblasts and tumour cell lines.
- 15:20 – 15:45 **Afternoon Tea/Coffee and Last Poster Viewing**
- 15:45 – 16:15 **The individuality of the anti-tumor T cell repertoire in patients supports the need to individualize monitoring and therapeutic approaches**
Dr Thomas Wolfel, Johannes Gutenberg University, Mainz, Germany
- 16:15 – 16:45 **Taking DNA vaccination into the clinic**
Dr Christian Ottensmeier, University of Southampton, UK
DNA vaccines are a promising strategy for inducing specific immune responses in patients. In an early phase clinical trials programme we assess whether DNA vaccines building on our preclinical work can successfully induce specific immune responses. We are using sequences from tetanus toxin, to induce strong linked T cell help for the tumour antigen of interest and to break tolerance. Early clinical trials data support that such responses can safely be induced in patients
- 16:40 – 17:00 **Chairman's summing up**