Executive summary on EURO PADnet

by Prof. B. Grimbacher, UCL:

EURO PADnet has set out to better understand primary (inborn) deficiencies of antibody production (Primary Antibody Deficiencies; PAD). We documented the exact phenotype of more than 4000 patients into a European web-based database and offered patients participation in approved research protocols. Genetic causes for PADs were sought and more than four novel monogenetic defects have been identified. Moreover, genetic risk factors for becoming antibody-deficient have been identified and better described. We set up *in vitro* experiments and murine models of the diseases to better understand their pathophysiology. First successful steps towards the genetic correction of the first antibody deficiency called Bruton's disease - which actually was the first primary immune deficiency to be described back in 1952 - have been conducted. Not only the role of immunoglobulin G (IgG), but also the role of IgA and IgM and their memory cells has been studied and their importance in the host defence has been highlighted. The consortium has initiated and accompanied investigator initiated observational trials and the results of these have impacted local, national and international policy making for the management and the understanding of antibody deficiencies (for examples please see www.chest-ct-group.eu or www.springerlink.com/content/l4065729w12r1114/).

During the first three years after the start of this collaborative EU project, we have published in Journals such as *The Lancet* and *Nature Immunology* and a total of more than 356 IMPACT FACOR points have been collected.

Most importantly, the consortium runs three websites and has progressed two diagnostic tests into the clinical setting: The project website www.europadnet.eu contains general information about the project and can also be accessed by the partners via a secure login to allow them to exchange information on a confidential level. We also have implemented a teaching website www.ipidnet.org for linking the clinical and cellular phenotyping, and a clinical support website www.chest-ct-group.eu for the analysis of lung complications in antibody deficiencies. Moreover, we have held educational symposia and a Winter School for physicians and researchers in the field.

Within the EURO PADnet consortium, The Binding Site (TBS; www.bindingsite.com) has facilitated the development of both Pneumococcus-specific polysaccaride (PCP) IgM and IgA ELISAs. The assays have been validated and the IgM and IgA responses to Pneumovax have been determined in normal healthy subjects. The development of both PCP IgM and IgA ELISAs has involved the identification, location and preparation of suitable materials. The optimisations of assay conditions and clinical validation have been achieved. Both assays have been initiated as new products and entered into the New Product Development system at The Binding Site (TBS). This process involves full product specification and commercial justification which was established through the EUROPADnet group.

Patients with antibody deficiency often require IgG antibody replacement made from human plasma from healthy donors. This product contains traces of IgA. Some patients with antibody deficiency unfortunately have auto-antibodies against IgA. These often lead to the intolerance of the IgG replacement product and may end up in an anaphylactic reaction. To screen for these in order to assess the risk for possible adverse side effects, an anti-IgA ELISA has been established by EURO PADnet collaborators which is now marketed by www.biovendor.com

Taken together, the EURO PADnet consortium progressed the field of primary antibody deficiency research in Europe in an unparalleled way in just 3 years.