VII MEETING OF ESID, GOTEBORG, JUNE 6-9, 1996. SUMMARY AND MEETING REPORT.

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Since we last met in Sitges south of Barcelona, our understanding of the genetic background of the primary immunodeficiency syndromes have rapidly increased. Much new insight have come from results in gene-targeted mice and studies on T and B cell ontogeny and activation. Appropriately, the main themes of this year's ESID meeting was targeted deletions of the immune system and genetic diseases. But important clinical problems such as stem cell transplantation, gene therapy and gammaglobulin therapy were also covered. The proceeding of the meeting will by published by Elsevier Science late this year

As for the last ESID meetings, the patient´s organization, IPOPI, and the international nursing group, INGID had their meetings parallel to ESID. Part of the program was common to all three organizations. Before the meeting officially started, informal discussions between patients, parents, nurses and doctors took place. These discussion dealt with important mutual problems such as patient compliance, what the patients should know and safety of blood derived products. The impression was that all participants found them very fruitful and saw the talks as a basis for further discussions at coming meetings of ESID, INGID and IPOPI.

The official program started with a keynote address by professor *L. A. Hanson*, who elegantly summarized the latest development about IgA deficiency.

Tak Mak reviewed what we have learned about T cell ontogeny from mice with knock outs for different membrane proteins and intracellular signaling components. Neither CD4 nor CD8β are absolutely necessary for development and function of T_H cells, while CD8α knock outs have a complete lack of cytotoxic T cells. CD30 of the TNF family is involved in negative selection and in CD30 -/- mice very few T cells undergo apoptosis during development in thymus. Also CTLA4 is an important negative regulator. In knock outs for CTLA4 all immune parameters are increased and the animals have large spleens and lymph nodes. Their immunoglobulin levels are increased up to 10.000 times. IL-2 -/- mice were found to be quite normal as IL-15 can substitute for the missing IL-2.

Fred Alt discussed V(D)J recombination mechanisms and defects. *Klaus Schwartz* later in the program followed up with presentation of human V(DJ) recombination defects. RAG1 and RAG2 introduces the breaks in the DNA and both mice and humans lacking RAG do not develop any T or B cells. At least two genes are necessary to bring the two DNA ends together. One product is the KU protein, a heteromer encoded at the human chromosome 22, which binds covalently to free double strand-DNA ends. A second DNA-dependent protein kinase, the activation of wich requires KU binding, is involved in the next step. No human defect is so far known in this second step.

Alexander Tharakhovsky continued by analyzing the antigen receptor-mediated signaling in B lymphocytes and especially PKC activation and its dependence on calcium and interaction with btk. *Edvard Smith* reviewed btk, the kinase defect in X-linked agammaglobulinemia. More than 130 mutations of the btk gene are known today. The CD40/CD40 ligand axis and the associations with its intracellular part was critically discussed by *Raif Geha*.

Bloom´s syndrome is an interesting rare autosomal recessive disorder, in which the genetic background recently has been clarified. The patients are short with a thin face and a large nose. They are prone to infections and malignancies. *James German III* has devoted life-long research to this syndrome. His group has localized the gene, blm, to 15q21. Its product is a helicase with homology to helicases in *E. coli* and *S. cerevisiae*, and

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lack of blm gives chromosome inestability with breakages and a high frequency of sister chromatide exchanges.

SCID in its varying forms was discussed by several speakers. *Luigi Notarangelo* pointed to the importance of JAK1 and 3 in cell activation. Phosphorylation brings the two JAKs together and provides docking sites for kinases and further signal transduction. Patients with JAK-3 deficiency have an autosomal recessive form of SCID with T-, B+. *Geneviève de Saint Basile* reviewed X-linked SCID with defect in the common receptor chain of IL-2R, IL-4R, IL-7R, IL-9R and IL-15R. It is the loss of IL-7 function which explains the defect. She presented several interesting aberrant patients with for example a reverse mutation in CD8+ cells. ZAP-70/Syk deficiency results in a SCID variant with normal number of B cells, non functional CD4+ cells and a complete lack of CD8+ cells. This disorder was presented by *Arthur Weiss*, who suggested that ZAP70´s association with CD3ζ requires lck or fyn kinase, as in lck -/-, fyn -/- mice thymopoiesis is severely affected.

Walter Reith took advantage of the MHC class II deficiency syndrome to describe the regulation of MHC gene activation. Five different complementary groups of this heterogeneous syndrome are presently known. Group C and D are defects in the RFX protein which together with other proteins binds the regulator sequences for the MHC genes. It has two known subunits, and defects are known for the p75 subunit (group C), while p36 subunit mutations are not yet known (group D). It was speculated that group B is a defect in a postulated third subunit of RFX. Complementary group A is a defect in another protein, CIITA, which influences the function of the MHC regulator genes.The protein has no homology to any other known protein.

Hans Ochs brought us up to-date with Wiskott-Aldrich syndrome and the WASP gene. The product is 502 amino acids long and is constitutively expressed in all stem-cell-derived cells. The protein interacts with the SH3 domain of p47 ^{nck} and the GTPase Cdc42 ^{rac}. Its function is still unclear but much points that WASP is connected with the cytoskeleton. Today monoclonal antibodies are available to the protein as was commented from the auditorium (Nelson D, J Clin Invest, June, 1996).

Three round-table discussions focused on important clinical issues. *Alain Fischer* chaired the discussion around stem cell transplantation. Clinical results from EBMT were reviewed. More than 700 immunodeficiency patients in Europe are so far transplanted, of those about half are SCIDs and 80 WAS. The survival for SCID T+, B- patients are better than for SCID T-, B-. As T- B-SCIDs have NK cells, while the others lack NK cells, it was speculated that NK cells reject the donated marrow. *Peter Hoogerbrügge* had brought together the gene therapy round table. Here must be mentioned the introduction by *Jaak Vossen*. He gave from his background as a pioneer of BMT and chairman of the Dutch gene therapy group, a very thorough review of the prerequisites for gene therapy under the motto *"gene therapy is not therapy until it will be therapeutic"*. In the round-table on gammaglobulin therapy chaired by *Helen Chapel* and *Lennart Hammarström,* much attention was focussed on safety. The outcome for the patients infected during the latest accident with hepatitis C transmission from intravenous gammaglobulin and treated with high dose interferon early after diagnosis, gave some hope.

Finally, *Maria Kanariou*, greeted us all welcome to the 1998 ESID meeting in Greece. The meeting will take place on Rhodes in early October.