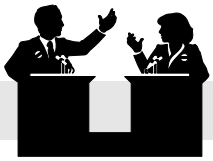

Second Euroconference on Animal Models of Human Diseases

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IMAJ 2002;4:1163–1164

The Second Euroconference on Animal Models of Human Diseases took place in Dublin, Ireland on 24–28 April 2002. Ghyslaine Lebougault (Paris, France) was the meeting coordinator, and the European School of Hematology supported the conference, which was chaired by A. Janin, M. Pla, J.C. Ameisen and M. Giovannini (Paris).

The central issue was the modeling of immune functions in the mouse, from pathogenesis to therapeutic interventions. In the first of two sessions (chaired by C. Babinet, Paris), J. Hoffman (Strasbourg) described the conservation and diversification of insects, especially the *Drosophila* and its antimicrobial defenses. Insects are known to have an innate immune response only and are thus susceptible to microbial infections. Hoffman presented three steps in the immune system of the *Drosophila*. First are the predominant effectors and antimicrobial cationic peptides that react with the negative part of bacteria; second is the control of gene expression and the importance of NFkB-like transcription factor to many important antimicrobial peptides genes in the Drosophilae, like drosomycin (antifungal), diptericin (antibacterial) and others. These activate the toll cascade that reacts against the non-self. The analogue in humans is the toll-like response (TLR) signaling of microbial infection in humans. Third is the recognition of infections and non-self. He concluded with the Imd pathway of *Drosophila* and the tumor necrosis factor-alpha (TNF) receptor in mammals. In *Drosophila* the specific receptor sensing the infection has not yet been identified.

The second session, dealing with an evolutionary perspective on immune defenses, discussed the almost unlimited promise of the mouse genomic engineering model. This possibility derived from the development of isolation methods to screen rare recombination events in mammalian cells, while having the totipotentiality of embryonic stem cells *in vitro*. This lecture described the journey from null mutations, single nucleotide changes and chromosomal rearrangements, to conditional mutagenesis where a given mutation will be expressed in specific types of cells and not in others. J.J. Owen (Birmingham) reviewed the ontogeny of T cells in mice. Transcription factors that are critical are Notch1 (for the generation of T cells) and Delta 1 (for the development of T cells in the thymus and the fetal liver). In the fetal liver, T lymphocytes develop from T minor cells, and B from B minor cells. However, in bone marrow these two populations develop from the same common lymphoid progenitor cell. In the thymus two opposing thymocyte fates (maturation versus death) are directed by signals triggered through the same T cell receptor (TCR). Both involve recognition of self-peptide/major histocompatibility complex (MHC). In this way there is division to the CD4 or CD8 cells. Positive versus negative selection of the developing T cell receptor is directly related to the basis of autoimmunity.

The third session (chaired by J.C. Ameisen, Paris) concerned the control of life and death in the immune system, focusing on the dysregulation of apoptosis and specific signaling in this process. P. Krammer (Heidelberg) described the CD95 signaling in apoptosis. There are two types of signaling: one involves the death-inducing signaling complex, which activates the caspase 8->caspase 3-> and induces cell death. The other involves BCL2->caspase 9,8,3 and amplification of apoptotic signaling via the mitochondria. Stimulation of CD95 was found to induce PLECTIN (a cell skeleton protein) degeneration by caspase 8. Reduction of stroke damage by anti-CD95 was found to attenuate stroke damage. Blocking of CD95 has also been used in spinal cord injuries and the results are promising. D. Green (La Jolla, California), discussing molecular mechanisms of apoptosis, focused on caspase-induced apoptosis, mainly caspase 9. He stressed the importance both of cytochrome C in the mitochondria for inducing the pathway, and of the loss of the mitochondria's outer membrane.

H. de The (Paris) discussed the acute promyelocytic leukemia t(15,17) animal models, whose pathogenesis is known to involve expression of the PML/RARa fusion protein. However, retinoic acid (RA) and arsenic (AR), involving PML/RARa degeneration, have therapeutic importance and the molecular mechanisms of these therapies were discussed in depth. The presentation ended with the recommendation to administer both RA and AR as a first-line therapy so that regression may appear rapidly as well as provide a genetic cure. This is preferable to waiting and using AR as second-line treatment.

The next session dealt with the molecular processes in the discrimination of self and non-self, immune memory and tolerance. O. Lantz (Paris) described these processes in T cell subpopulations, particularly the efficient naïve T cell response, while still maintaining a good recall response. Also discussed was the role of lymphokines (like interleukin-7) and MHC molecules in the survival of naïve and activated CD4+ T cells. Mice transgenic for a TCR against the male antigen restricted by MHC class II are used for studying populations of naïve/activated CD4+ cells. The role of the MHC in the survival of naïve CD4+ T cells has been studied in the same model. Subpopulations (NK T and MAIT cells) develop after a selection process of invariant TCR.

A. Janin (Paris) led the weighty session on Law and Ethics. She discussed the ways of protecting vertebrate animals used for scientific and experimental purposes. W.A. de Leeuw (The Netherlands) reviewed and summarized the ethics committees for animal use in various research institutes. This session was concluded by L.G. Mathiessen (European Commission) who reported the European Union rules regarding research proposals. This was of key interest especially for the young research students who participated in the conference.

The next session on the pathogenesis of immune diseases was opened by the chairman, C. Boitard (Paris), who presented the experimental model for type I diabetes, mainly the NOD model. This model was designed specifically to test ways of preventing this disease, while the DRBB rat model is used for inducing insulinitis and testing treatments; both models involve viral infections (LCMV and Kilham virus respectively). However, while most childhood viral infections protect the child from this disease, the pivotal question is what can induce autoimmunity. It may by viral or it may be a genetic mutation (in *AIRE* or *JM2* genes). A mutation in chromosome nm 21 may harm the genes of these transcription factors, which modulate T cells reactions. The lecturer defined it as a defective cross-talk between B and T cells and immunologic tolerance.

Rheumatoid arthritis is a chronic progressive disease characterized by symmetric joint lesions and bone and cartilage erosions. G. Chocchia (Paris) presented some arthritis animal models, particularly the antigen-induced model, CIA mice (collagen II induced arthritis), as well as the latest models. The etiology is unknown, but it may be infectious, immune, antigen-induced or other, which accounts for the many different ways of inducing arthritis in animal models. In the antigen-induced model, CIA mice, the antigen is type II collagen, and these mice develop T cells and antibodies to type II collagen. The model is induced by injecting the antigen, and antigen-presenting cells secrete interleukin (IL) 12, and via TH1 cells secrete interferon-gamma (IFN). This recruits the macrophages to act and secrete IL-1 and TNF. The mice originate from the transgenic mice strain, I-Aq, which is susceptible to this antigen and develop arthritis after the antigen injection. The aim of most experiments is to intercede in the CIA mouse soon after exposure to the antigen in order to find an effective therapy.

E. Holler (Germany) and K. Cooke (USA) discussed graft versus lymphoma (GVL) and graft versus host disease (GVHD) in leukemia patients. GVHD is a major obstacle in the use of allogeneic bone marrow transplantation in patients with malignant and non-malignant disorders. GVHD can develop within 2 months after bone marrow transplantation, with the donor's lymphocytes attacking the host tissue, possibly inducing the recipient's death. Part of GVHD is needed in order to exert the graft versus lymphoma effect. Bone marrow transplantation treatment and the response of the host are most effective in chronic myelocytic leukemia, as well as in acute myelocytic leukemia and acute lymphocyte leukemia. GVL is the desired response, however the greater the GVL response the greater the unfavorable GVHD response. The balance is very fragile. Major cytokines involving GVHD are IL-12, IL-2, and INF, versus natural killer cells and T cytotoxic cells. These experiments seek ways of isolating these two processes, which are engaged together, by blocking the specific cytokines. The pathophysiology of GVHD is complex and involves donor T cells, cytokines, cytotoxic cells, and endotoxins (endogenous intestinal bacterial flora). Inhibition of the lipopolysaccharide endotoxin was found to inhibit GVHD, but unfortunately it also inhibits the cure for the leukemia. In order to reduce GVHD the mismatches in the HLA complexes should be as few as possible. Susceptibility to develop GVHD includes the following factors: recipient's age over 40, gender mismatch, as well as the recipient's IL-6–174 (GG), INF (3,3), and donor IL-1ra (intron 2). However, when we look at the animal model we encounter a problem – the absence of prophylactic immunosuppression in animal models and the excess amount of stem cells in mice render the models less homologous.

On the subject of regulatory T cells in infectious diseases, K. Milles (Dublin) focused on the effect of infection by *Bordetella pertussis*. The relationship between prion diseases and the immune system was discussed by P. Aucouturier (Paris). Animal models for prion-induced immune diseases are HY DY hamsters (Mink's enchephalopathia), while in mice some species of scrapie develops. Usually there is no mutation identification after infection with the prion, and the incubation times in the different models vary. Ongoing studies on the cellular response against PrP (prion proteins) might pave the way for appropriate vaccine approaches in prion diseases.

For a long time molecular studies at the DNA mRNA or protein level were dedicated to single candidates. However, during the last few years a novel solution has emerged: systems that permit large-scale studies on DNA mRNA or protein, and laser-assisted micro-arrays or microdissection. By using these methods single genes can be rapidly screened for mutations or single nucleotide polymorphisms. Sophisticated mathematical models are required to interpret the results obtained in tissue dissection. Micro-arrays and microdissection arrays were also discussed. R. Simon (Basel) summarized the latest news in the field of tissue arrays. S. Minvielle discussed gene expression profiling of multiple myeloma.

The final session, chaired by K. Shannon, dealt with new advances in experimental therapeutic strategies and the path from vaccine to immunomodulation. He discussed the use of genetically engineered mice for testing novel therapies. He stressed that not only is it not surprising that targeted drugs like the STI 571 are effective, but that they are non-toxic.

The conference ended with a provocative question, posed by M. Pla: Are mice useful for the study of human diseases, which prompted a productive discussion. It was concluded that mouse models are an invaluable gold mine for furthering our knowledge in pathology.

During the conference, young MD, PhD and research students presented short communications on their work with animal models, followed by stimulating discussion. We look forward to next year's conference on animal models for cancer.

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