

President's Column

Peter Nickerson, MD, FRCPC, ASHI President-elect,
for Dr. Charles Orosz, ASHI President

On behalf of ASHI, and in fulfilment of one of ASHI's primary goals, namely to further develop our relationship with our sister societies, it is a pleasure, at the beginning of 2005, to open up the president's column to Dr. Erik Thorsby, immediate past-president of EFI. Indeed, in his article, first published as his last address as president of EFI in the EFI Newsletter No. 43, 2004, Dr. Thorsby provides all of us in the field of histocompatibility and immunogenetics with a broad view of where we have been and what the future might hold. His insights should serve us all well as we stand at the beginning of a new age in molecular diagnostics.

Immunogenetics: Past, Present and Future

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Until quite recently, the main pillars of clinical immunogenetics were blood group serology and histocompatibility testing. Now we are seeing dramatic changes and expansions in our field, which represent challenges we have to meet. These are briefly outlined in these reflections.

It can be safely said that immunogenetics was born in 1901, by Karl Landsteiner's discovery of the ABO blood groups.¹ The term was, however, first used by Robert Irwin in 1936², to describe a new discipline that would combine immunology and genetics. In the same year the first glimpse of the H-2 complex was seen, by Peter Gorer's description of erythrocyte antigen II in mice.³ In 1948 he joined George Snell, and together they reported that antigen II was also a major histocompatibility antigen,⁴ leading to the full birth of the H-2 complex. The "Big Bang" of human immunogenetics came, however, with the discovery of the HLA complex, initiated by Jean Dausset's description in 1958 of leucocyte antigen MAC,⁵ later to become HLA-A2. When it was established that the HLA complex is also the major histocompatibility complex in man, as H-2 is in mice, histocompatibility testing and matching became a new major clinical service function in immunogenetics (in addition to blood grouping and matching). Mainly as a result of the vision of another HLA pioneer, Jon van Rood, this was also the main driving force behind the establishment of EFI in 1985. The main aim of EFI, as well as ASHI and other immunogenetics societies, was originally to secure the necessary high quality of histocompatibility testing, and promote research to nourish further developments in this field.

Today, HLA testing and matching are cornerstones in clinical organ and haematopoietic stem cell transplantation. We should be proud that our international federations and societies of immunogenetics and histocompatibility have contributed so much to the advancement of these important clinical fields. Optimal or acceptable HLA matching have saved innumerable transplanted organs and prolonged the life, and increased its

quality, of countless patients. And yet, it is a widespread misconception among surgeons that HLA matching mostly has become superfluous. While it is generally accepted that hyperacute rejection can usually be avoided by appropriate cross-matching and that highly sensitized patients may be transplanted by application of acceptable HLA mismatch programs,⁶ many surgeons argue that severe acute rejections to a large extent may be avoided by the use of modern immunosuppressive drugs like cyclosporine etc. Recent data both from large multicentre⁷ and single centre⁸ studies clearly demonstrate, however, that optimal HLA matching still has a lot to offer, also to patients treated with cyclosporine etc. Not only do HLA matched kidneys enjoy significantly longer graft survival, one also sees a reduction in the frequency and strength of acute rejections.⁸ HLA matching also plays an important role in chronic rejection.⁹ Hence, optimal HLA matching may render it possible to avoid high doses of immunosuppressive drugs and their accompanying side effects. Further, the weaker the histocompatibility barrier, the easier it is to achieve donor specific tolerance,¹⁰ the "Holy Grail" of all transplanters. It is encouraging that these recent facts have led to signs of conversion in some previously unconvinced surgeons. It is important that we continue to ask our clinical colleagues the question: "Why not take the benefits of both modalities, both optimal HLA matching and modern immunosuppression?" What we need still to aim for is making the selection process as quick and simple as possible, to avoid cumbersome and time-consuming procedures which may delay transplantation and upset the surgeons. In haematopoietic stem cell transplantation, the need for optimal HLA matching is far more accepted,¹¹ as is also witnessed by the continual growth of registries of HLA typed volunteer donors.

Histocompatibility is, however, more than HLA. Previous studies have demonstrated the importance of certain minor histocompatibility antigens¹² and cytokine genes¹³ in haematopoietic stem cell transplantation. Very recently, a polymorphism in the promoter region of the IL-10 gene was found to be a marker of a favourable outcome after haematopoietic stem cell transplantation.¹⁴ Further, the receptors of NK cells and their ligands have created great interest. Not only may the lack of appropriate NK cell receptor-ligand interactions be associated with NK cell mediated rejection, but also anti-leukaemia effects,¹⁵ which is exactly what we want to obtain. Thus, in stem cell transplantation we should hunt both for given optimal matches and mismatches. The bottom line is that we, as histocompatibility typers, now have to walk outside the HLA complex to achieve our goals.

And HLA is more than histocompatibility. We now know that the histocompatibility function of the HLA class I and II molecules is just a side effect of their immunobiological function: To inform T cells of foreign intruders. This was first established through the work of Rolf Zinkernagel and Peter Doherty in 1974^{16,17} and then beautifully visualized by Pamela Björkman and her associates in 1987.¹⁸ The extensive polymorphism of HLA class I and II genes is there to secure that there are a sufficient number of different HLA molecules to select from, so that any

foreign intruder may be dealt with by T cells, at least by some members of the population. As a consequence, the HLA molecules of an individual determine his or her immune response repertoire. The first glimpse of this was seen already in 1969. Based on pioneering work by Baruch Benacerraf and others, Hugh McDavitt and Allen Chinitz made the seminal observation that some antibody responses are controlled by genes in the H-2 complex.¹⁹

The implications of this for clinical immunology are many. When vaccinating, the antigenic complexes must match the HLA molecules of the individual. In many cases the antigenic complexes used for vaccination (attenuated viruses etc.) are processed into so many immunogenic peptides that some will always bind with sufficient avidity to the HLA molecules of the recipient. For some viruses (HIV etc.), and more importantly selected tumour antigens, the repertoire of potential immunogenic peptides may, however, be more limited and the HLA profile of the recipient more critical. Thus, it may be increasingly important to select the right immunogenic peptides for given individuals, dependent on his or her HLA types.

The immunobiological function of HLA molecules also explains why we see HLA-associated protection against some infectious diseases, caused by HIV,²⁰ Hepatitis C virus²¹ etc. Further, certain HLA class I and II molecules are the strongest predisposing factors for most autoimmune diseases,²² as HLA-B27 is for ankylosing spondylitis. In both cases preferential binding by the involved HLA molecules of peptides from the foreign intruder or potential autoantigens, respectively, may be a likely mechanism.²³ Thus, the responsible part of the corresponding genes is the protein-coding region.

But also the immunogenetics of diseases is more than the classical HLA genes. In excess of 130 genes have been identified in the HLA complex, and many more than those encoding the HLA class I and II molecules have immune functions. Several of these additional genes contribute as disease-predisposing genes, as have recently been shown in several studies and confirmed by the Disease Component of the 13. International Histocompatibility Workshop.²⁴ Further, there are many other disease-predisposing genes elsewhere in the genome. Interestingly, several of these additional genes, both in the HLA complex and elsewhere, seem to predispose more to autoimmunity in general. Additionally, in these cases the strongest predisposition may be to the non-protein coding region of the gene, as seems to be the case for CTLA-4,²⁵ suggesting an influence of alternative splicing, expression etc.

There are good reasons to assume that many SNPs in the regulatory or protein-coding regions of genes involved in the immune response may influence their function. This would be a result of natural selection. *Immunogenetics may thus tentatively be described as studies of polymorphic genes and their products involved in the immune response.* Functional immunogenetics focuses more on how these polymorphisms influence the immune response, in health and disease. It follows that our field, immunogenetics, has become very large, and a major part of immunology in general.

Here lies our challenge. Given the importance of immunology for diseases, both in protecting us from infectious diseases, causing diseases (autoimmune, host-versus-graft and graft-versus-host diseases) or influencing the course of diseases,

immunogenetics will play an increasing role. In parallel with a more precise identification of the genes involved in the immune response and their mode of action, we will become in a better position to interact and interfere; i.e. to increase protection, reduce or abolish susceptibility and influence the course of diseases.

Immunogenetics thus is, and will in the future, become an even more important tool in personalised medicine. Selection of optimally matched (and mismatched) donor-recipient combinations in allotransplantation is a very good example of this. I have already mentioned the need for a "personal touch" in many vaccinations. Further, we can now identify individuals at high risk to develop given autoimmune diseases. This in itself is of little use and may cause anxiety. Given better knowledge of the function of the involved genes, however, we may soon be able to interfere before or at an early stage of the disease, preventing it from fully developing in individuals at high risk; i.e. *predict* and *prevent*. And there is good reason to believe that many genes involved in the immune response may also interfere with the metabolism and action of pharmaceuticals; i.e. immunogenetics may also become an important tool in pharmacogenomics.

Since 1901, six immunogeneticists have received the Nobel Prize in physiology or medicine: Karl Landsteiner in 1930; Baruch Benacerraf, Jean Dausset and Georg Snell in 1980, and Peter Doherty and Rolf Zinkernagel in 1996. Unfortunately, Peter Gorer died too early (at an age of only 54 years in 1961) to receive it. Several more, some of whom are mentioned above, would also have been good candidates. These Nobel Prizes are not only tributes to the pioneers in our field, they also show its importance. How this heritage is managed and further developed depends on us, immunogeneticists. As we now widen the scope of our activities in accordance with the developments in our field, international societies of immunogenetics, like EFI and ASHI, should in the future become even stronger players not only in histocompatibility and immunogenetics at large, but in *molecular medicine*.

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