



Curative cellular therapies for autoimmune diseases
2nd European Symposium

Executive Summary

May 2005

The 2nd CELLAID symposium on curative cellular therapies was held in Brussels on April the 3rd and 4th 2006. The purpose of the meeting was to serve as a discussion platform for rheumatologists, haematologists and immunologists as well as industry partners and European Commission representatives and focused on the translation of cell-based therapies into clinical applications next to defining strategies, recommendations and future activities of the CELLAID initiative.

The sessions:

1 - Competence fields in Europe - state of the art

In this session, *Andrew Cope* (The Kennedy Institute of Rheumatology Division, Faculty of Medicine, Imperial College, London, UK), *Ken Smith* (Cambridge Institute for Medical Research and the Department of Medicine, University of Cambridge, UK), *Steffen Gay* (WHO Collaborating Center for Molecular Biology and Novel Therapeutic Strategies for Rheumatic Diseases, Department of Rheumatology, University Hospital Zurich, Switzerland), *Wlodzimierz Maslinski* (Institute of Rheumatology, Dept. of Pathophysiology and Immunology, Warsaw, Poland) and *Tom Huizinga* (Leiden University Medical Center, Leiden, The Netherlands) provided insights into the current understanding of the regulation and perpetuation of chronic inflammation by both, lymphoid and non-lymphoid cells as well as the role of proinflammatory cytokines in rheumatoid arthritis, a major focus of current research expanding from TNF and IL-1 blockade. Finally, new genetic analyses tools were presented, which allow a better understanding of the nature of arthritis and are crucial for a reliable understanding of genetic data in relation to disease expression.

2 - Presentation of industry partners: Technology transfer, product development, cooperation with large, small and medium companies

In the following session, different industry sectors were introduced by *Johannes Irsch* (Miltenyi Biotec GmbH, Bergisch Gladbach, Germany), *Sönke Brunswick* (CellGenix Technologie Transfer GmbH, Freiburg, Germany), and *Noel Warner* (Becton, Dickinson and Company, NJ, USA), offering solutions for the transfer of biomedical research and cell-based therapies into the clinics.

3 - Translation of cell therapies & reset of tolerance

This session encompassed 4 presentations from *Stefan Rose-John* (University of Kiel, Institute of Biochemistry, Kiel, Germany), *Mario Assenmacher* (Miltenyi Biotec GmbH, Bergisch Gladbach, Germany), *Falk Hiepe* (Charité University Hospital, Medical Clinic for Rheumatology and Clinical Immunology, Berlin, Germany), and *Alan Tyndall* (University of Basel, Dept. of Rheumatology, Basel, Switzerland) on new strategies to either inhibit inflammatory cascades or to reset tolerance to autoantigens in human disease.

In mouse models for rheumatoid arthritis, a fusion protein consisting of a soluble form of the cytokine receptor gp130 and the Fc portion of human IgG1 (sgp130Fc) proved to be effective in blocking autoimmune reactions via trans-signalling, revealing sgp130Fc as a potential drug for human autoimmune disease. Switching from designer biologicals to studies combining immunoablation with autologous stem cell transplantation, the technological aspects of obtaining highly pure populations of antigen-specific and regulatory T cells for clinical usage were presented first followed by clinical studies on this form of therapy. It became clear that further research is needed aiming at understanding the rebound of protective and auto immune responses. Finally, the immune modulatory potential of Mesenchymal stem cells (MSC) was reviewed. MSCs reduce proliferation of T and B cells in respect to both antigen-receptor ligation and cytokines. Allogeneic ex vivo expanded MSCs have been given to 30 patients as treatment of Graft versus Host Disease (GvHD) with promising results and two EBMT coordinated trials protocols have been finalised: acute GvHD treatment and GvHD prevention/graft enhancement.

4 - Potentials of cellular therapies in autoimmune diseases

The second day started with a session on the potential of cellular therapies in autoimmune diseases. *Andreas Radbruch* (chairman of the CELLAID initiative, German Rheumatism Research Centre, Berlin, Germany), *Rikard Holmdahl* (Medical Inflammation Research, Lund University, Lund, Sweden), and *Iain McInnes* (University of Glasgow, Glasgow Royal Infirmary, Glasgow, UK) discussed the concepts and the European potential of cellular therapies in autoimmune diseases.

Accordingly, therapies should move from symptomatic up to curative and regenerative. Steps to improve treatment include means to better suppress inflammation, abrogate particular destruction, separate inflammation from destruction pathways. At the same time, tolerance of the treatment has to be improved and cost reduced. These requirements place an increased demand on the biomedical research community and will be best met by the creation of an integrated pre-clinical, and early clinical trial network across Europe to capitalise on the requisite expertise contained therein and the enormous resource in terms of patient pathology that is available if coordinated.

5 - Measures for translation

In the following session, *Berent Prakken* (Department of Pediatric Immunology, University Medical Center Utrecht, The Netherlands), *Riccardo Saccardi* (Policlinico di Careggi, Department of Haematology, Firenze, Italy), and *Michael McDermott* (Leeds Institute of Molecular Medicine, St. James University Hospital, Leeds, UK) presented data on the European experience and transplantation technology for autoimmune diseases. During the past 10 years altogether 720 registrations were reported to the EBMT, mostly on autologous peripheral blood hematopoietic stem cell transplantations. Various technologies have been developed to induce a better immunosuppression such as new conditioning regimens, in vivo T cell depletion methods (serotherapy) as well as ex vivo T cell depletion strategies by different selection procedures.

Finally, the issue which patients ethically to select for targeted therapies on a European level was discussed by addressing the patient consent required for testing of targeted therapies, the ethics of recruiting patients with active inflammatory processes and the role of placebo arms in a double blind randomized phase III trial as well as the disparity between Eastern European centres for low-cost clinical trials and Western centres.

6 - The European perspective

The last session of the meeting was opened by the current president of EULAR (European League Against Rheumatism), *Tore Kvien*. The goal of EULAR, an umbrella organisation of 43 national scientific societies across Europe and of 30

social leagues, is to foster research and also education that will be translated into improved treatment and care. EULAR in collaboration with several MEPs (Members of the European Parliament) has initiated Written Declaration 41/2005 on rheumatic diseases, which calls on the Commission and Council to ensure that the EU's 7th Research Framework Programme makes rheumatic diseases one of its explicit priorities and also to ensure that the EU's new health strategy makes arthritis (musculoskeletal disorders) one of its priorities. This declaration also calls for strengthening legislation to outlaw disability discrimination through a specific Disability Directive and encourages Member States to take measures to ensure better access to the full range of treatments in all EU countries.

Stéphane Hogan (Head of Unit – Biotechnology & Applied Genomics, Health Directorate, DG Research, European Commission) continued the session with data on the EU's 7th Framework programme. The main improvements of FP7 compared to FP6 include the gradual increase of annual budget, collaborative research, continuity in themes and instruments, longer duration, funding levels (50%) to be raised in specific cases (+25%), simplification of procedures (flat rates; collective responsibility), and new ideas from European Research Council and Joint Technology Initiatives.

The last speaker of the symposium, *Andreas Radbruch* (chairman of the CELLAID initiative, German Rheumatism Research Centre, Berlin, Germany), summarised the activities related to the CELLAID program so far. The European research area can maintain excellence and scientific, technological and economic competitiveness with innovative medicines for autoimmune diseases through networking. Such networking of European research institutions and clinics will enhance standardisation of clinical interventions and quality assessment e.g. immune monitoring. Patient cohorts will be adding up even for rare autoimmune diseases. Translation of concepts into clinics will involve extensive industry cooperation: joint efforts will increase the competitiveness of small, medium and large biotech and pharmaceutical companies in Europe. Cooperation with European scientific societies and regulatory bodies (European League Against Rheumatism, EULAR; The European Group for Blood and Marrow Transplantation, EBMT; European Medicines

Agency, EMEA, etc.) will help to overcome bottlenecks and accelerate the progress of translation.

Conclusions and perspectives:

There is a clear need for networking between European research institutions and clinics. This will enhance standardisation of not only clinical interventions and quality assessment but also of regulatory requirements, which will help patients across Europe to receive the benefits of this.

Cooperation with European scientific societies and regulatory bodies (EULAR, EBMT, EMEA etc.) will help to overcome bottlenecks and accelerate the progress of translation.