

A large version of the CELL AID logo, featuring the word 'CELL' in a light blue outline font and 'AID' in a solid dark blue font, with four small squares (light blue, light blue, orange, dark blue) between them.

1st European Symposium

Curative cell therapies for autoimmune diseases

20.-21. June 2005

Berlin, Germany

Summary of the 1st Symposium



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The potential and perspectives of 'Curative cell therapies for autoimmune diseases' were presented and discussed at the meeting on June 20th and 21st 2005. It was a successful start for a pan-european network: around 30 talks and discussion with 140 European experts filled two summer days in Berlin.

New and innovative Therapies for inflammatory rheumatic and other autoimmune diseases are autologous stem cell transplantation and concepts for the modification of regulatory T cells. Currently practised and partially successful are steroids, cyclophosphamides and biologics such as monoclonal antibodies specific to targets of T or B cells. All of these therapies basically suppress the autoimmune reaction. They may be able to stop the inflammation but they do not achieve remission. They are also accompanied with systemic side effects or long term therapies may lead to decreased protective immunity or incompatibility with the biologic.

New and innovative therapies will have to target more specifically the components of the inflammation and/or will have to eliminate the cause of the chronic autoimmune reaction. Cure will be possible if effector cells (producing mediators for the inflammation or secreting pathogenic antibodies) of the autoimmune reaction can be identified, modified or eliminated. The subsequent aim is to rebuild tolerance or to re-establish balance between autoaggressive and protective immunity.

These aspects were the basis of the detailed presentations on the components and pathology of autoimmune reactions, cellular basis of protective and pathogenic immune reactions and genetic background of autoimmunity. Innovative therapies were discussed, studies on stem cell transplantations were presented.

All presentations were of high scientific value and offered many discussion points and ideas for future concepts of cell based therapies. The chairmen of the session summarized their session (and some comments on the meeting as such) and they contributed implications for the next meeting.

The following summaries of sessions were provided by the chairmen (in italic).

Cellular Concepts I: T cells and antigen-presenting cells in autoimmunity

Chair *Steffen Jung, Alexander Scheffold*

Antonio Coutinho of the Gulbenkian Institute, Portugal, appropriately opened the Symposium with a historic overview covering immunological paradigm changes over the last 3 decades. Dr. Coutinho is one of the early defenders of a holistic view of the immune system that includes the existence of regulatory circuits, such as idiotypic antibody networks and regulatory T cells (Treg). With their recent molecular definition as FoxP3-expressing cells, in particular the latter regained recent attention by the immunological community and Treg's remained after their introduction by Dr. Coutinho a main theme of the symposium.



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Bernd Arnold of the German Cancer Research Center presented his work on the developing neonatal immune system. His group recently reported the lymphopenia-driven proliferation (LIP) of CD8 T cell grafts in neonates. He now addressed why such potentially self-destructive expansion is limited to a small T cell subset, while most T cells seem to be subjected to a unique neonatal tolerance mechanism. Interestingly, this neonatal LIP control is Treg independent (as it occurs in Rag-deficient mice) and seems to be established by parenchyma rather than dendritic cells.

Stefan Rose-John from the University of Kiel gave an exciting presentation on the in vivo consequences of IL-6 transsignalling. Studies conducted in several inflammatory disease models, incl. Inflammatory Bowel Disease (IBD) and Rheumatoid Arthritis (RA) revealed that blockade of the IL-6/IL6R axes reduced disease severity by suppressing mononuclear leukocyte infiltration. Clearly there remains a lot to be understood about the pleiotropic pro- and anti-inflammatory effects of IL6. However, manipulation of IL6 transsignalling through the soluble gp130 can be expected to become a valuable therapeutic tool.

Sergio Romagnani from the University of Florence extended his work on the role of Th1/Th2 cells in human diseases, which they initially discovered in the human system. His group has identified a new splice variant of the chemokine receptor CXCR3 (CXCR3-B) which acts as functional receptor for CXCL4, whereas the classic variant (CXCR3-A) mainly interacts with CXCL9, CXCL10, and CXCL11. Based on the interactions of CXCL10 and CXCL4 with CXCR3-A or CXCR3-B these chemokines differentially modulate Th1/Th2 cytokine expression by T cells. This newly discovered regulatory pathway for Th1/Th2 polarization may play an important role in the amplification and/or control of chronic inflammatory processes, including autoimmune and allergic disorders.

Frederica Sallusto presented her recent work on Toll-like receptors (TLRs) and the role of NK cells in lymph node (LN) T cell responses. The finding of the Bellinzona group that TLR agonist combinations synergistically trigger a TH1-polarizing program in dendritic cells (DC) adds another layer of complexity to our understanding of the development of adaptive immune responses. Cooperation of TLR-driven signaling cascades is likely to help DC to decipher and react to specific pathogen challenge. In the second part of her talk Frederica Sallusto showed the impact of rapid NK cell recruitment on LN T cell responses. According to her findings NK cells act primary source of IFN γ and thereby provide the reason for the early TH1 bias of lymph node T cell responses.

Cellular Concepts II: B cells and plasma cells in autoimmunity

Chair: *René van Lier*, Reinholdt Schmidt

Part of the sessions of the CELLAID symposium dealt with strategies to deplete B cells in human auto-immune disease (AID). The case for depleting B cells and/or reducing pathogenic antibody levels in AID has grown much stronger in recent years. First, as illustrated by Scofield (Oklahoma, USA) autoantibodies can be used as predictors for the development of AID. This group made elegantly use of the US army cohort to find antibodies that predict development of SLE. Analogous the detection anti-CCP antibodies prior to the emergence of clinical manifest rheumatoid arthritis, anti-DNA antibodies can be found on



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average 3 yrs before SLE diagnosis. The number of different antibody specificities in individual patients increases over time but remains stable in established disease. Interestingly 10 individuals have been identified that start with a single anti-RO antibody. These antibodies cross-react with a peptide from the EBV protein EBNA-1. This together with the observation that all SLE patients (n=300) in the cohort were EBV carriers (vs 92% of the controls) suggests that EBV infection may elicit SLE in genetically predisposed individuals.

Second, Smith (Cambridge, UK) discussed polymorphisms in Fc γ R11b related to a strongly increased risk for developing SLE. Fc γ R11b is a ITIM containing, inhibitory receptor for IgG. A polymorphism found in the TM region inhibits the ability of Fc γ R11b to associate with Fc γ RI thereby blocking its function. The observation that not all individuals homozygous for this polymorphism suffer from disease suggests that other molecules modulate clinical penetration of SLE.

Third the effects of rituximab (a humanized CD20 monoclonal antibody that gives a strong and long-lasting depletion of B cells) were discussed on a variety of human AID, including rheumatoid arthritis, SLE and vasculitis. Concerning vasculitis (Smith, Cambridge, UK) rituximab induced B cell depletion gave a prolonged drop in disease activity in patients that were maintained on prednisolon. Interestingly, relapse only occurred after the return of B cells and ANCA levels dropped after improvement of clinical symptoms. These combined findings suggest that B cells rather than the antibodies they produce may be the main factor in pathogenesis.

Unresolved B cell/antibody questions that can be answered in collaborative European studies

- Is negative selection of autoreactive B cells disturbed in major human AID?
- Which AID benefit from B cell depletion?
- Which mechanism(s) underlie the beneficial effects of B-cell depletion on AID. Specifically, are we treating immunostimulatory/regulatory B cells or pathogenic antibodies?
- If antibodies are at play, which pathogenetic mechanisms are being used?
- Are there options to inhibit the formation of plasmablasts and plasmacells (both lack CD20) that produce autoantibodies?

Genomic dimension of cellular therapies

Chair: G. Kollias, L. Rogge

The topic (of the CELLAID meeting):

There is no doubt that curative cell therapy for autoimmune disease is a very important research objective for the future and represents an area which should be of interest to the EC.

One of the fascinating aspects of this meeting was to bring together people that share a common interest in autoimmune diseases but use completely different approaches. As a matter of fact, I cannot remember to have attended a meeting that covered so many different aspects of clinical and fundamental research in autoimmunity with concise, yet in-depth presentations. The meeting highlighted some of the breakthroughs in the clinics (for example treatment of RA and SLE with anti-CD20 of RA) and pointed also to some of the more complicated issues (for example autologous hematopoietic stem cell transplantation in SLE and RA). Given the current hype of regulatory T cells, many speakers eluded to the



opportunities that these cells might offer for future treatment strategies. In this context, it was fascinating for me to hear initial observations from a clinical trial using Tr1 cells to prevent GvDH.

The session: Genomic dimension of cell based therapies

R. Holmdahl discussed his approach to identify genes outside the major histocompatibility complex that regulate autoimmune diseases. The identification of genes underlying quantitative-trait loci for complex diseases such as RA has been notoriously difficult. The Holmdahl laboratory has been the first to identify a gene (*Ncf1*) that regulates arthritis severity in rats and mice by positional cloning. This work demonstrates the power and importance of the genetic analysis of autoimmune diseases. R. Holmdahl is certainly one of the leading figures in this field.

P. Peterson presented new data relating to the biochemical function of the autoimmune regulator AIRE. AIRE is mutated in patients with the rare hereditary autoimmune disease APECED, the only known autoimmune disorder characterized by a defect of a single gene. Although AIRE has been implicated in the expression of self-antigens in medullary thymic epithelial cells (mTECs), the mechanism by which AIRE achieves this effect has remained elusive. Biochemical studies presented by P. Peterson in this session demonstrate an interaction of the AIRE protein with the histone acetyltransferase CBP. He also demonstrated that the AIRE protein localizes to specific nuclear bodies in mTECs and that a colocalization with CBP was found only in the minority of cells. Although much work remains to be done to elucidate the mechanism by which AIRE regulates expression of self-proteins in mTECs, this is certainly an important and "hot" field.

The last talk in the session was given by U. Baron (instead of S. Olek) on the analysis of DNA methylation. Alterations in DNA methylation are associated with changes in gene expression. U. Baron presented a technique related to bisulfite genomic sequencing that is able to generate fingerprints of DNA methylation characteristic for specific cell types. Although the analysis of DNA methylation and of other epigenetic markers is of great interest, it was not immediately apparent whether the approach described by U. Baron was particularly well-suited for the analysis of cells and tissues in autoimmunity.

Concerning how the speakers contributed to the topic of the session, one could argue that only R. Holmdahl presented a "genomic" approach (a genome-wide analysis using animal models of autoimmune diseases). P. Peterson used a more biochemical approach to understand the function of AIRE (which is of course important!) and U. Baron's attempts to analyze DNA methylation were not on a genomic scale. Possibly a talk on gene expression profiling of cells or tissues in autoimmune diseases could have rendered this session more "genomic".

Technological basis of cellular therapies

Chair: F. Emmrich

Willem van Eden (Utrecht University, The Netherlands) opened the session by presenting data on the immunoregulatory qualities of heat-shock proteins. He demonstrated the suppression of clinical symptoms in his proteoglycan-induced arthritis model by HSP70 pre-immunization and furthermore showed that vaccination of cattle with HSP70 could interrupt the transmission of *Mycobacterium paratuberculosis* infections.



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Georg Schett (Medical University of Vienna, Austria) focussed in his presentation on bone erosion in chronic arthritis and the mechanisms of joint repair. He pointed out that therapeutic interventions aiming at joint repair have to restore a balanced bone metabolism by effectively blocking resorption as well as fostering bone formation. Blockage of osteoclast formation by inhibition of RANKL is considered to be a promising therapeutic tool for bone protection. Other repair mechanisms like the frequent formation of osteophytes in spondylarthropathies but not in rheumatoid arthritis and still not fully understood.

Steffen Gay (University of Zurich, Switzerland) first pointed out that although a major breakthrough has been achieved with the development of novel biologics current treatment of RA has not achieved an ACR 70 above 60%. Synovial fibroblasts derived from RA patients (RA-SF) maintain their activated phenotype even in the absence of stimulating macrophages or T and B cells by expressing receptors for the TNF superfamily member LIGHT. Activation of LT β R and HVEM results in inflammation and blockage of apoptosis.

Special lectures

Chair: S. Gay, G.R. Burmester

George Kollias (Biomedical Sciences Research Center "Al. Fleming", Vari-Athens, Greece) opened the session by discussing the function of TNF and TNFR in physiology and disease. Recent evidence supports a dualistic role – pro-inflammatory as well as immune-suppressive - for TNF in many autoimmune diseases. G. Kollias showed the heterogeneity of TNF receptor usage in murine disease models and put forward a rationale for a predictably beneficial effect of anti-TNFR instead of anti-TNF treatment in chronic inflammatory and autoimmune conditions. He further presented data on FDC-specific gene-targeting experiments where he showed that triggering of p55TNFR on FDCs is sufficient to support development of FDC networks and GCs, independent of FDC-specific IKK2. In contrast the generation of an efficient humoral immune response depends on IKK2.

Benoit Salomon (Hôpital de la Pitié-Salpêtrière, Paris, France) presented data on the role of endogenous Treg in the pathophysiology of type 1 diabetes. Only in young NOD mice these cells exert potent regulation of the disease, resulting in only weak inflammation of pancreatic islets. He showed that Treg specific for pancreatic islet antigens, but not polyclonal Treg, efficiently suppress type 1 diabetes even at a late stage of the autoimmune process. He further demonstrated that Treg as a successful cellular therapy for uveitis can be injected either systemically or at the site of infection. A therapeutic utilisation for polyclonal Treg could be envisaged in autoimmune diseases with a global deficit of Treg like RA, MS or GvHD.

The last talk of the session addressing the role of T regulatory type 1 (Tr1) cells in tolerance after allogeneic haematopoietic stem cell transplantation (HSCT) was given by Maria G. Roncarolo (San Raffaele Telethon Institute for Gene Therapy, Milan, Italy). IL-10 inducible Tr1 cells exert their CD4⁺ suppressive function via IL-10 and TGF- β either directly or indirect and can regulate immune responses in a number of different Th1- and Th2-mediated pathologies. She presented data on both, the in vivo generation of murine Tr1 in a model of pancreatic islets transplantation by repeated administration of rapamycin and IL-10, and the generation of human Tr1 by activation of CD4⁺ with allogeneic monocytes in the presence of exogenous IL-10.



Targeting the autoimmune memory

Chair: *P. Miossec*, HH Peter

The session entitled targeting the autoimmune memory was the first one of the second day of the meeting. It was chaired by Prof. H.H. Peter, Freiburg, Germany and Prof. P. Miossec, Lyon, France. Four talks were presented, which were all connected.

Maria Leandro gave the first presentation on the targeting of B cells in autoimmunity. The London group has been instrumental in the demonstration of the efficacy of anti-CD20 targeting starting with rheumatoid arthritis later extended to lupus. She focused on the important relationship between a prolonged depletion of circulating B cells and the clinical response to rituximab. She discussed in details the possible mode of action of anti-CD20 in these diseases.

Switching from B cells to T cells, Hendrik Schulze-Koops, Erlangen, Germany, discussed the role of T cell derived cytokines in the control of inflammation as in the context of rheumatoid arthritis. He focused on the defects in IL-4 production and function with a link between these abnormalities and chronic inflammation. This observation is based on previous demonstration of the anti-inflammatory properties of IL-4 in association with the low if not undetectable levels of IL-4 in RA. He provided results on the genetic aspects by showing results on the role of one IL-4 gene polymorphism.

Lars Klareskog, Stockholm, Sweden, discussed the current and future means of the control of chronic inflammation. He focused on the need to develop better markers of severity and of response to treatment. Most of the results were based on the study of TNF inhibitors developed in Sweden.

Ian McInnes gave the final talk on cytokines of the innate immune response as potential therapeutic targets in rheumatoid arthritis. This group of cytokines is involved in the initiation and amplification of the immune response. This list includes IL-12, IL-18, IL-15 among others. These cytokines have in common the effect on the amplification of the immune response in particular through an activation of the Th1 pathway. Some of these concepts have already been tested in the clinic in particular through the use of an anti-IL-15 antibody in rheumatoid patients.

This session provided a nice overview of the different targets and means able to target chronic inflammation and autoimmunity. Moreover, it provided a clear demonstration of the ability of research centres all located in Europe to provide new concepts with clinical applications.

Into the clinics I – current status

Chair: *J. Kalden*

Session: Into the clinics I – current status on autologous stem cell transplantation in systemic lupus erythematosus (SLE), scleroderma and RA.

New developments and new modifications of autologous stem cell transplantation for treating SLE patients, patients suffering from systemic sclerosis and patients with a severe course of rheumatoid arthritis were discussed within this section.



Although for SLE patients, available medications have considerably improved the life expectancy, still not all patients respond to the treatment principles, including new biologic and new immunosuppressive agents. Moreover, chronic treatment with steroids and immunosuppressive drugs can cause a variety of adverse side effects and might increase morbidity and mortality. Applying a new modification of autologous stem cell transplantation by combining immunoablation with autologous stem cell transplantation, a possible curative effect might be expected, as reported by Dr. Hiepe, for scientists from the Charité and the German Research Center for Rheumatic Diseases in Berlin. By the development of a technology allowing a complete immunoablation including the elimination of antibodies secreting long-lived plasma cells the base has been provided for creating a new immune system by the transplantation of autologous stem cells. Data presented indicate that the thymus in SLE patients undergoing this treatment principle remains activated for up to four years as demonstrated by the presence of naïve CD31+ T-lymphocytes in the blood. Likewise naïve CD27 low and IgD+ B-lymphocytes reappeared in circulation. In terms of frequency and absolute numbers of naïve lymphocytes the newly generated immune system resembles a juvenile immune system giving the possibility that central and peripheral tolerance can be re-established in response to this treatment. This new modification of autologous stem cell transplantation might be in the future a potential medication for SLE patients who do not respond sufficiently to available treatment principles or in which available medications had to be stopped because of severe side effects. If this combination of immunoablation and autologous stem cell transplantation can really reprogram an autoreactive immune system, has to be shown by further investigations. The advantage of this treatment approach is based on the selective ablation of the pathogenic part of the patient's immune system, not majorly affecting the protective immunological memory.

Dr. Tyndall reported on behalf of the EBMT and the EULAR autoimmune disease stem cell working party on the present status of using hematopoietic stem cell transplantation in patients with systemic sclerosis. In a first analysis of 65 out of 88 patients registered in the EBMT/EULAR data base, nearly 70 % had an improvement of more than 25 % in the modified Rodnan skin score, however, in 12.5 % treatment related mortality was observed. A second, later analysis showed a curable improvement in about two thirds of patients with a treatment mortality of 9 %. Co-morbidity still plays a major role in relation to the treatment related mortality. Particularly patients with a known or unsuspected cardiac involvement due to the potential Cy toxicity of the conditioning medication as well as elevated mean pulmonary artery pressure are specifically on risk.

Two important prospective randomised trials have evolved, one running in Europe and one in the US. It will be of utmost interest, what the outcome of these two prospective randomised studies will be. That in both terms, in the improvement of clinical appearance of patients with systemic sclerosis as well as regarding treatment related mortality. In summary, as based on available data, the application of autologous stem cell transplantation in systemic sclerosis has improved significantly, at least for a subgroup of patients with this disease, a treatment possibility resulting in a retardation or hold of disease progression

Finally, Dr. Tyndall discussed the possibility of mesenchymal stem cells which have been applied successfully in experimental animal models such as collagen induced arthritis and EAE. However, one has to wait if this form of autologous stem cell transplantation will be of benefit for patients of different autoimmune diseases.



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With regard to rheumatoid arthritis, new treatment principles including the combination of TNF-blockers and methotrexate have considerably improved our treatment armament for this disease. However, about 30 % of patients will not respond, not even to the new biologics. Therefore also in RA, new approaches for new treatment principles are necessary. Dr. Snowden summarized studies ongoing in Australia, US and Europe, indicating the feasibility to use hematopoietic stem cell transplantation for RA patients. Overall, a significant initial response was observed in most of the patients. However, most of the patients had to come back to a medication with DMARDs. There was an interesting phenomenon, that patients being refractory to certain DMARDs renewed their sensitivity to the salvage DMARD medication. Patients who are negative for a rheumatoid factor appeared to develop a better response than those which are seropositive. No data on any other autoantibodies such as anti-CCP antibodies are available. However, as based on the data presented, further studies are definitely necessary to really define the place of hematopoietic stem cell transplantation in the management of severe and resisting rheumatoid arthritis.

In summary, this session gave an excellent and critical survey with regard to the present situation of hematopoietic stem cell transplantation as a treatment principle in autoimmune diseases. However, more work has to be done, more trials have to be designed as in the case of SLE to really demonstrate that this approach for treating autoimmune diseases being refractory to common therapeutic immunomodulatory regimes might be of clinical benefit with an acceptable adverse side effect.

Into the clinics II – perspectives

Chair: *J. van Laar, R. Arnold*

The session 'Into the Clinics II-perspectives' focussed on clinical applications of cellular therapy in autoimmune diseases.

M. Assenmacher (Miltenyi Biotec, Bergisch Gladbach, Germany) gave an overview of cell processing techniques to enrich or deplete specific cellular subsets from peripheral blood using immunomagnetic beads and cell separation columns. This technology enables the user to obtain on a clinical-scale target cells, such as CD34⁺ and CD133⁺ hematopoietic stem cells, CD304⁺ or CD1c⁺ blood dendritic cells, CD4⁺CD25⁺ regulatory cells and CMV-specific T cells, or deplete unwanted cells, such as CD3⁺ T cells and CD19⁺ B cells. It is anticipated that the availability of such cell separation techniques will greatly expand the possibilities to develop tailor-made therapies for patients with autoimmune diseases.

R. Burt (Northwestern University, Chicago, USA) summarized the largest-single center experience with immunoablative therapy and autologous stem cell transplantation in patients with severe autoimmune diseases, with a focus on systemic lupus erythematosus (SLE). The results showed impressive improvements of disease-activity scores (SLEDAI), as well as of laboratory abnormalities with a regimen of high dose cyclophosphamide, antithymocyte globulin, followed by reinfusion of CD34⁺-selected hematopoietic stem cells. Longterm remissions were observed in the majority of patients (5 years or more). Treatment-related mortality of transplanted patients was remarkably low (1.5%), which underscores the importance of patient selection and transplant experience.



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B. Prakken (University Medical Center Utrecht, The Netherlands) highlighted the role of regulatory T cells in children with juvenile idiopathic arthritis, treated with immunoablative therapy and autologous stem cell transplantation. Following successful treatment, a preferential expansion of CD4⁺CD25^{br} T cells expressing foxp3 was observed, which correlated with clinical outcome. This was associated with a switch in the hsp60 specific T cell repertoire from a Th1-bias towards a more regulatory phenotype. Such tolerogenic immune responses to specific hsp60 T-cell epitopes could open the way to new vaccination strategies using hsp60 in juvenile idiopathic arthritis.

F. Dazzi (Imperial College London, UK) presented data on the immunosuppressive effects of mesenchymal stem cells (MSC) in an in vitro murine model in which T cells were generated against the male HY minor histocompatibility antigen. Striking irreversible inhibition of T proliferation was observed in the presence of MSC by induction of cell cycle arrest through cell-cell contact. B cell proliferation and differentiation of dendritic cells was also impaired. Although MSC constitute a minor fraction of bone marrow cells, they seem to be more abundant in rheumatoid synovium, and may thus contribute to the hypoproliferative phenotype of synovial T cells from patients with rheumatoid arthritis.

P. Lamprecht (University of Lübeck, Germany) demonstrated that immunoablative therapy and autologous stem cell transplantation may be a valuable salvage treatment in patients with systemic vasculitis, refractory to conventional immunosuppressive medication, such as Wegener's disease. A small number of cases has been published so far, but a EBMT registry analysis of 24 transplanted patients with primary vasculitis is in progress.

The presentations illustrated that cellular therapies have entered the arena of clinical medicine, albeit still at an experimental stage, and stressed that future studies should target well-defined disease categories, and include a comprehensive analysis of immunological events following therapeutic intervention.

European Perspectives

Chair: *W. Maslinski, A. Radbruch*

Recent development in our understanding of the role of different cell types not only in the initiation and perpetuation of chronic inflammation, but also as potential active participants in suspending of these often harmful processes, lead Prof. Andreas Radbruch, the coordinator of the CELAID Symposium, to prepare the proposal to the European Commission to support pan-european meetings for the evaluation of cell based therapies.

The Symposium held last June in Berlin was the first of two that was funded by European Commission. The design of the Symposium well supported its aims. The organizers invited more than 30 leading European researchers and few American colleagues to present short summary of their field and most recent data and to discuss different aspects of cell based therapies with European researchers (about 100 attended) involved in the field. The speakers presented many key directions of research, among them: cellular concepts of the role of T and B cells in autoimmunity, regulatory T cells and their potential to control autoimmunity, newly identified genetic components, other cells (like synovial fibroblasts) and mechanisms contributing to joint and bone destruction, cellular attempts of tissue regeneration and contribution of cytokines to perpetuation or resolution of autoimmune diseases. We have also learned about the current status of clinical applications targeting



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cells (with promising therapy eliminating B-cells in autoimmunity) or cell transplantation with either haematopoietic and mesenchymal stem cells.

In the last session entitled "European Integration of research in clinical transfer of cell based therapies in autoimmune diseases" Dr. Riccardo Saccardi, a Chairman of Autoimmune Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT) presented experimental data and early phase I/II studies that support the hypothesis that autologous haematopoietic stem cell transplantation can alter diseases progression in severe autoimmune diseases.

The next speaker, Prof. Josef Smolen (previous President of EULAR) gave an important presentation in which he presented solid and very convincing arguments that European Commission should secure more funding for research in rheumatology in the next Framework Programme. He pointed out the key role of European researchers in the introduction of biological therapies (especially anti-TNF therapy), a real break through in our understanding and treatment of rheumatic diseases. Importantly, he presented data of total costs of consequences of rheumatic disease for European Societies that exceed any other group of diseases. Although most of the researchers present in the audience were well aware of these facts, he appealed for further activities in all European countries to convince politicians that increased funding for research in the field of rheumatic diseases is actually a good investment for the future. This appeal was especially sound at the end of the very successful Symposium that provided solid data that cell based therapies present real future for better understanding the pathogenesis of rheumatic disease and treatment of patients with these diseases.

The last speaker, Christian Wimmer from Directorate General Research, Major diseases, presented European Commission view of present and future directions for funding research in Europe. In his opinion it will be rather difficult to change the priorities, or even add rheumatic diseases to the list of diseases that should get more attention in the prepared 7th Framework Programme. However, it seems that the audience, as several discussants pointed out was in favor of further activities directed toward getting better funding in rheumatology research.

Overall the Symposium was a great success. The subject was well chosen - and given presented results, it is likely that cell based therapies will expand from current applications to more often used and with better results. The size of the Symposium was very good (around 120 participants) and long coffee breaks (30 min), allowed interesting discussions. We are looking forward for the next Symposium that should be at least as good as this one. For the future Symposium, may be more researchers from new European Union member states should be invited. This could expand so needed integration between old and new EU members.

