Satellite Symposium:

“ATIR: DLI depleted of alloreactive T-cells post-haploidentical SCT”

Chairs:

K. Rezvani (London, United Kingdom) and H. Messner (Toronto, Canada)
Kiadis Pharma signs license agreement with Hospira to commercialize ATIR™ in Europe and Asia - Partnership would advance innovative stem cell transplant product.
Two years ago at the European Blood and Marrow Transplantation meeting in Göteborg, Kiadis Pharma organized its first Symposium to enlighten you on selective alloe depletion in order to improve the outcomes of matched and mismatched transplants. This year we follow-up with a Symposium entitled: “ATIR™: Donor Lymphocyte Infusions depleted of alloreactive T-cells post-haploidentical hematopoietic stem cell transplantation (HSCT)”. Earlier this year, Kiadis Pharma entered into a licensing deal for ATIR™ with Hospira, a much respected global pharmaceutical company. We are extremely pleased with their support and today we are looking forward to sharing exciting medical news on the development of ATIR™ with you.

The main purpose of ATIR™ is the possibility of using 50% mismatch (haploidentical) family donor stem cells in patients with a hematologic cancer for whom another form of treatment is not possible anymore. We all know that after searching for a related matched donor (availability ± 25%) or a matched unrelated donor in the unrelated worldwide donor bank (availability ± 40%), there are still some 30 – 35% of all patients in need of an allogeneic stem cell transplantation (SCT) for whom a donor is lacking. For many of these patients a haploidentical HSCT might be the last opportunity. In order to minimize the development of Graft-versus-Host Disease (GvHD), one of the big drawbacks in haploidentical SCT, the donor graft can be depleted of its T-cells by using CD34+ selected peripheral stem cells. Although minimizing the chances of developing GvHD, T-cell depletion provides a worse engraftment and a poor immune reconstitution post SCT. Subsequently many of the patients transplanted will die of infectious-related complications. With ATIR™, a high number of T-cells - photodepleted of the alloreactive T-cells - can be infused in the post-transplant period in order to improve immune reconstitution and thus minimizing Transplant-Related-Mortality. Today, experts in the field of haploidentical transplantation and alloe depletion will provide scientific background on our current pivotal trial entitled: “An open-label, uncontrolled, multinational, multinational study on the efficacy and safety of administration of donor lymphocytes depleted of alloreactive T-cells (ATIR™), through the use of TH9402 and light treatment in an ex vivo process, in patients receiving a CD34+ selected peripheral blood stem cell graft from a related, haploidentical donor”. We hope you will be as enthusiastic as our Principal Investigators on this study and we hope to see you all at the Symposium on Sunday April the 3rd at 13:30.

With kind regards,

R. Maarten Egeler,
MD, PhD
CMO Kiadis Pharma

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**programme**

**13:30 – 13:55**  
Haploidentical SCT in adults: where do we stand anno 2011?  
*Dr. A. Velardi (Perugia, Italy)*

**13:55 – 14:20**  
Selective alloe depletion as a platform to improved allogeneic stem cell transplantation  
*Dr. S. Mielke (Würzburg, Germany)*

**14:20 – 14:45**  
Haploidentical SCT plus DLI depleted of alloreactive T-cells (ATIR™). Results of the Phase I/II study and preliminary results of current Registration trial  
*Dr. D.C. Roy (Montreal, Canada)*

**14:45 – 15:00**  
General Discussion
Dr. Katy Rezvani, MD, PhD, is a Clinical Senior Lecturer and consultant hematologist in the Department of Hematology, Hammersmith Hospital, Imperial College, London. She is the clinical lead in allogeneic stem cell transplantation and clinical director of the JACIE accredited GMP cellular facility. Dr. Rezvani has an active laboratory based program. Her main research interest is in translational tumor and transplant immunology. Her research projects include strategies to enhance post-transplant immune reconstitution, with a strong focus on the role of T, B and Natural Killer (NK) cells in Graft-versus-Host Disease (GvHD) and Graft-versus-Leukemia (GVL) effects.

Dr. Rezvani has also set up a translational program in immunotherapy and has developed novel protocols for the manufacturing of GMP grade cellular products to improve patient outcome following allogeneic stem cell transplantation. Her laboratory studies in immune responses to leukemia have led to the initiation of a number of clinical trials of vaccination against tumor antigens including PR1 and WT1 in patients with myeloid malignancies.

Dr. Hans Messner is a graduate of the Medical School University Freiburg (Germany) and obtained his MD degree from the University of Ulm (Germany). He completed a PhD degree at the University of Toronto and joined the Medical and Research Staff of the Princess Margaret Hospital (PMH), Toronto. Since 1970 he is a member of the allogeneic Blood and Marrow Transplant Program at PMH with a particular clinical focus on the treatment of patients with leukemia. He has a longstanding research interest in the detection and regulation of normal and abnormal hematopoietic progenitors and their role in transplantation. Work in his laboratory resulted in the description of the first assay for human pluripotent hematopoietic progenitors. He was the founding president of the Canadian Blood and Marrow Transplant Group (CBMTG). As part of an Expert Working Group he was involved in the drafting of the “Canadian Standard of Transplantation of Cells, Tissues and Organs and reproductive Technology” and remains the chair of the Technical Subcommittee on Lymphohematopoietic Cells.
Dr. Andrea Velardi has established a research team and developed projects investigating immune reconstitution after allogeneic hematopoietic transplantation and anti-tumor T cell and NK cell immunity. In 1993 the Perugia BMT Center pioneered the haploidentical hematopoietic stem cell transplant for patients with acute leukemia and, within that setting, he discovered that Natural Killer (NK) cell alloreactivity exerts striking control of leukemia relapse. This seminal breakthrough set the standard for donor selection in haploidentical transplantation and has generated international enthusiasm for, and interest in, NK cell alloreactivity as a form of tumor immunotherapy. The impact of this discovery was recognized by the EBMT with the Van Bekkum Award at the 2002 Annual Meeting, and by the American-Italian Cancer Research Foundation’s Annual Prize for Scientific Excellence in Medicine. Dr. Velardi authored more than 120 publications in peer-reviewed international journals, including Journal of Immunology, Blood, the New England Journal of Medicine, Journal of Experimental Medicine and Science. He is a member of the Editorial Board of Blood and served as reviewer for Journal of Immunology, Journal of Clinical Investigation, Immunity, Cancer Research, Leukaemia, Nature Medicine, the New England Journal of Medicine. He was nominated as reviewer for the ASH and EBMT annual conferences. He is a member of the scientific advisory board of the American-Italian Cancer Research Foundation and acted as reviewer of NIH grant applications. Since April 2008 he is Chairman of the Immunobiology Working Party of the European Group for Blood and Marrow Transplantation (EBMT).

Haploidentical SCT in adults: where do we stand anno 2011?

Dr. A. Velardi (Perugia, Italy)

One of the main barriers to the widespread application and success of allogeneic transplantation has been the recognition by the immune system of foreign non-self histocompatibility antigens leading to an alloimmune response. Hematopoietic stem cell transplantation (HSCT) involves the transfer of immunocompetent cells from the donor and the alloresponse can occur in both directions leading to Host-versus-Graft (rejection) and Graft-versus-Host (GvH) responses. Such responses generally have been considered to be mediated by T cells and, in an attempt to minimize such responses, high degrees of donor recipient MHC matching has been sought. However recognition that NK cells are capable of allore cognition and the pioneering work of the Perugia group in haploidentical HSCT has lead to renewed interest exploiting the NK alloresponse as an immunotherapy tool for the treatment of leukemias. Full HLA haplotype-mismatched (“haploidentical”) transplants are necessary because many leukemia patients, who might benefit from an allogeneic HSCT, fail to find a matched related or unrelated graft. >>
In this setting, donor versus recipient NK cell alloreactivity is effected by donor NK cells which express inhibitory Killer Cell Immunoglobulin-like Receptor(s) (KIR) for self class I ligand(s) (“KIR ligands”). Across KIR ligand mismatches, they sense missing expression of self (donor) KIR ligand(s) in the recipient and mediate alloreactions. Milestones along the way towards this breakthrough discovery were observations that: 1) extensive ex-vivo T cell depletion of the graft prevented Graft-versus-Host Disease (GvHD) in haploidentical transplants for patients with severe combined immunodeficiency (Reisner et al, Blood 1983); 2) a “megadose” of T cell-depleted stem cells ensured engraftment across MHC barriers in mice (Bachar-Lustig et al, Nat Med 1995), and across HLA barriers in clinical transplantation (Aversa et al., Blood 1994; NEJM 1998); 3) human NK cells exerted alloreactivity (Colonna et al., Science 1993); and 4) transplantation from haploidentical donors that were able to mount donor versus recipient NK cell alloreactions eradicated acute myeloid leukemia, favored engraftment, protected from GvHD and greatly improved survival, as demonstrated by integrating clinical and pre-clinical data (Ruggeri et al Blood 1999; Science 2002; Blood 2007).
In Germany, Kiadis Pharma collaborates with Dr. Stephan Mielke from the Allogeneic Stem Cell Transplant Center at the Julius-Maximilians University of Würzburg.

Dr. Mielke is an expert in the field of translational immunology with a particular research interest in selective depletion strategies in allotransplantation including enhancement of Graft-versus-Leukemia effects and control of Graft-versus-Host Disease. Clinically he focuses on mismatched alternative donor transplantations and individualized cancer therapy.

Supported by a postdoctoral grant from the “Dr.-Mildred-Scheel Stiftung für Krebshilfe” in Germany he worked in the Allotransplantation Section of the Hematology Branch at the National Institutes of Health, USA, where he initiated a clinical trial on TH9402-based selective Allodepletion as the Principal Investigator. After writing his professorial thesis in 2009 he received his habilitation (venia legendi) from the Faculty of Internal Medicine and was conferred the title of a Privatdozent for Internal Medicine by the Julius Maximilian University of Würzburg in 2010. Dr. Mielke chairs the international multicenter trial with ATIR™ in haploidentical transplants for Europe as the coordinating investigator. He has published more than 40 peer-reviewed papers with a cumulative impact factor of more than 200. Dr. Mielke is member of the American Society of Hematology (ASH), the European Group for Blood and Marrow Transplantation (EBMT) and the German Society of Hematology and Oncology (DGHO).

He has joined the Immunobiology working party of EBMT and the editorial boards of Bone Marrow Transplantation and Pharmacogenomics and Personalised Medicine.

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Selective alloreduction as a platform to improved allogeneic stem cell transplantation

Dr. Stephan Mielke (Würzburg, Germany)

Despite the overall success of allogeneic hematopoietic stem cell transplantation (HSCT), persistently high relapse rates for advanced risk malignancies, high rates of transplantation related mortalities (TRM) in the mismatched setting and unavailability of donors for every patient in need remain as the challenges to optimal allotransplantation in today’s world. Selective depletion (SD) is an ex vivo strategy to eliminate host-reactive donor T-cells from allografts to prevent Graft-versus-Host Disease (GvHD) while conserving useful donor immunity (Mielke et al., Cytoterapy, 2005).

To overcome fluctuations in activation-based surface marker expression and achieve a more consistent and effective alloreduction, we developed a GMP-based, semi-closed photodepletion (PD) process (Mielke et al., Blood 2007 and 2008). This method of alloreduction targets activation-based changes in p-glycoprotein resulting in an altered efflux of TH9402 (Kiadis Pharma, The Netherlands), a rhodamine-based photosensitizer.
The feasibility of SD HSCT depends on sufficient T cell depletion strategies to avoid severe GvHD in the first place. The additional add back of selectively depleted lymphocytes in the absence of immune suppression is applied to provide immunity against infections and the underlying malignant disease. Although PD is at a relatively early stage of clinical development first clinical results look promising. In a Phase I trial selectively photodepleted donor lymphocytes have shown their ability to reduce post-transplant infectious complications in the absence of clinically significant GvHD after haploidentical transplantations (Roy et al., ASH abstract 2009) and reduced the risk of severe GvHD and relapse in matched transplants (Mielke et al. ASH abstract 2009). Based on these promising results an international multi-center trial using selectively photodepleted mismatched donor lymphocytes (ATIR™, Kiadis Pharma, The Netherlands) to reduce TRM after haploidentical HSCT has been initiated.
Dr. Denis-Claude Roy, MD, Professor of Medicine at the University of Montreal, Canada is our leading academic partner for the development of our blood cancer products. Dr. Roy significantly contributed to the development of all our blood cancer products, ATIR™, Reviroc™ and Rhitol™. He is the principal investigator for the Kiadis Pharma ATIR™ clinical trial in North America. His research interests focus on the immunobiology of stem cell transplantation, and particularly the treatment of stem cell grafts to specifically eliminate T cell subsets mediating Graft-versus-Host Disease. He has published some 100 original articles and book chapters in prestigious journals such as Cell, PLoS Medicine, Nature Medicine and Blood. He has trained more than 55 students, M.Sc., Ph.D. and post-docs. He has been on numerous scientific review panels, including the Fonds de la Recherche en Santé du Québec (president), Cancer Research Society, Leukemia and Lymphoma Society, and is currently sitting on the Canadian Institutes for Health Research scientific review panel. Dr. Roy is Director of the Clinical Applications Arm of the Canadian Stem Cell Network, and former board member of the Canadian Blood and Marrow Transplant Group and Executive Committee of the National Cancer Institute of Canada-CTG-Hematology. He is currently Director of the Hôpital Maisonneuve-Rosemont Research Center and Director of the Center of Excellence in Cellular Therapy.

Haploidentical SCT plus DLI depleted of alloreactive T-cells (ATIR™).

Results of the Phase I/II study and preliminary results of current Registration trial

Dr. D.C. Roy (Montreal, Canada)

Photodepletion (PD) is a particularly versatile approach that can be incorporated into several treatment options in order to address the most important clinical problems in stem cell transplantation: Graft-versus-Host Disease (GvHD), delayed immune reconstitution and disease relapse. Indeed, we and others have shown that the photosensitizer dibromorhodamine can be used to eliminate alloreactive T cells in order to prevent GvHD after transplantation of patients with major histocompatibility complex (MHC) incompatible donors. This uniquely potent photosensitizer accumulates in activated T cells, but not in resting T cells, and leads to the elimination of the former cell population upon visible light exposure (514 nM). Such a mechanism offers a particularly appealing opportunity to eliminate cells responsible for GvHD, while preserving resting T cells for reactivity against infectious agents and malignant cells.

The Perugia group has shown that stem cell transplantation can be performed successfully using MHC-mismatched haplo-identical donors. When using such a strategy, the extensive T cell depletion that is required to prevent the development of acute GvHD leaves patients with...
impaired T cell immunity for extended periods of time and at high risk for opportunistic infections. Following ex vivo exposure of donor lymphocytes to host cells, T cells with reactivity toward MHC-incompatible host antigens can be eradicated using dibromorhodamine-mediated photodepletion. Residual donor cells can recognize non-self antigens and be used in the form of donor lymphocyte infusions to promote immune reconstitution (ATIR™). This strategy has now been evaluated in a Phase I clinical trial of haplotype-matched stem cell transplantations. One month post-transplantation, patients were administered increasing doses of T cells treated with the ATIR™ process. All patients engrafted but no severe (grade III-IV) GvHD was observed. In addition, infectious complications decreased with increasing doses of T cells. These exciting results confirmed the clinical potential of this novel immunotherapeutic strategy and prompted the development of a Pivotal clinical trial that is now in progress in Europe and North America to evaluate ATIR™ in a large number of patients.

Patients undergoing a HLA-matched stem cell transplantation could also benefit from the depletion of T cells recognizing minor histocompatibility antigens in order to prevent the development of GvHD. Here the ability to specifically activate donor cells against minor histocompatibility antigens in vitro represents a significant hurdle. Strategies to achieve this goal have been investigated by Drs. S. Mielke and J. Barrett. In addition, immunoreactive T cells could be eliminated from the blood circulation of patients with GvHD by using photopheresis. This therapeutic option is particularly appealing for the treatment of patients with chronic GvHD and is currently undergoing clinical evaluation (Rhitol™). Moreover, PD treatment also has the ability to induce several logs of elimination of malignant cells. This represents an interesting opportunity to infuse tumor-free stem cell grafts in the context of autologous stem cell transplantations (Reviroc™). In conclusion, dibromorhodamine forms the basis of several PD strategies that harbor most favorable features with a potential to improving significantly the outcome of transplanted patients.