



## Satellite Symposium:

“ATIR™ as immunotherapy following haploidentical HSCT:

No need for prophylactic immunosuppressants due to  
low risk of GvHD”

## Chair:

Dr. Armand Keating (Toronto, Canada)



## programme

<b>16:00-16:10</b>	Welcome and general introduction	Dr. Armand Keating, Toronto, Canada
<b>16:10-16:25</b>	Challenges of alternative donor transplantation	Dr. Irwin Walker, Hamilton, Canada
<b>16:25-16:40</b>	Selective depletion to overcome challenges in allogeneic transplants	Dr. Stephan Mielke, Würzburg, Germany
<b>16:40-17:05</b>	Excellent OS and low GvHD following ATIR™ treatment in patients with hematological malignancies	Dr. Denis-Claude Roy, Montreal, Canada
<b>17:05-17:30</b>	Change control during process development: How the application of Quality by Design (QbD) resulted in stable and robust ATIR™ manufacturing	Dr. Robert Preti, Allendale, NJ, USA
<b>17:30-17:55</b>	What transplant strategies compete with ATIR™?	Dr. John Barrett, Bethesda, MD, USA
<b>17:55-18:00</b>	Closing remarks	Dr. Armand Keating, Toronto, Canada



## Kiadis Pharma company profile

Kiadis Pharma B.V. is a private, clinical stage biopharmaceutical company focused on the development of innovative and potentially life-saving therapies for patients with late stage blood cancers and related disorders, an area of significant unmet medical need.

Kiadis Pharma's lead product is ATIR™, a cell based product designed to enable stem cell transplantations from partially mismatched (haploidentical) family donors. Kiadis Pharma is collaborating with internationally renowned centers in Europe and North America for the successful development and manufacturing of ATIR™.



**Dr. Armand Keating**

Dr. Keating, MD, FRCP(C) is Professor of Medicine and also a Professor in the Institute of Biomaterials and Biomedical Engineering, at the University of Toronto, Toronto, Canada. For the past 19 years he was Director, Division of Hematology and Epstein Chair in Cell Therapy and Transplantation at the University of Toronto. He is Director of the Cell Therapy Program and the Orsino Cell Therapy Translational Research Laboratory at Princess Margaret Cancer Centre and a Senior Scientist in Experimental Therapeutics at the Toronto General Research Institute. He obtained the MD degree from the University of Ottawa, completed residencies in internal medicine and hematology at the University of Toronto and a research fellowship at the University of Washington and the Fred Hutchinson Cancer Research Center in Seattle, Washington. He was a Cancer Research Scientist of the National Cancer Institute of Canada for 10 years and upon his return to Toronto established the largest stem cell transplant program in Canada. He was Chief of Medical Services and Head, Department of Medical Oncology and Hematology at Princess Margaret Hospital/Ontario Cancer Institute in Toronto for a decade. He is listed in Best Doctors in Canada and the US. He has mentored over 80 postdoctoral research fellows, clinical fellows and graduate students. Over the past 8 years he established the largest and most active cell therapy program in Canada involving local, national and international collaborators and is the recipient of a multimillion dollar Canada Foundation for Innovation Award for a regional Center for Cell and Vector Production in Toronto. Dr. Keating has been active in the American Society of Hematology (ASH) and was President of ASH in 2012. He is a past president of the American Society for Blood and Marrow Transplantation and was Chair of the Steering Committee for Cell-Based Therapy of the National Heart, Lung, and Blood Institute, US National Institutes of Health. He was also Chair of the Medical and Scientific Committee of The Leukemia & Lymphoma Society and a member of its Board of Directors for 8 years. He heads the Clinical Translation Committee of the International Society for Stem Cell Research (ISSCR). He is a member of the Canadian Stem Cell Network and is on the advisory boards of the Ontario Stem Cell Initiative, Centre for Commercialization of Regenerative Medicine, the Argentine Stem Cell Consortium and the Andalusian Advanced Therapies Program. He is on numerous editorial boards of scholarly journals, and is a Co-Editor of Bone Marrow Transplantation and Associate Editor of Biology of Blood and Marrow Transplantation. Dr. Keating's clinical and research interests focus on cell-based tissue regeneration, anti-cancer cell therapy, blood and marrow transplantation, and leukemia and lymphoma. He has conducted laboratory, translational and clinical research in all these areas, particularly on the biology and clinical application of mesenchymal stromal cells. He has authored over 375 publications.











**Dr. Denis-Claude Roy**

Dr. Roy received his M.D. degree in 1982 from the University of Montreal. After completing an Internal Medicine residency and training in Hematology at the University of Montreal, Dr. Roy did a research fellowship at Harvard University, in the Division of Tumor Immunology, Dana-Farber Cancer Institute, Boston. In 1990, Dr. Roy joined the Division of Hematology and Bone Marrow Transplantation at the Maisonneuve-Rosemont Hospital, University of Montreal, as Director of the Cell Therapy Laboratory and Autologous Transplantation Program. Dr. Roy was a member of the Hematology Training Program at the University of Montreal, served on the Royal College Examination Board-Hematology for numerous years. He is currently a Full Professor of Medicine at the U of M and an Adjunct professor at McGill University. His research interests focus on the immunobiology of stem cell transplantation, and particularly at the treatment of cell grafts to foster immunotolerance and develop post-transplant immune therapies. 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 Therapeutics Arm of the Canadian Stem Cell Network, Co-Director of the ThéCell FRSQ 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 Hopital Maisonneuve-Rosemont Research Center and Director of its Center of Excellence in Cellular Therapy.

➤➤ 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 haploidentical stem cell transplantation. 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 were 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 Phase II clinical trial that is now in progress in Europe and North America to evaluate ATIR in a larger number of patients. Early results from this Phase II clinical trial will be presented.

**Notes**

## Excellent OS and low GvHD following ATIR™ treatment in patients with hematological malignancies

**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 graft-versus-host disease, while preserving resting T cells for reactivity against infectious agents and malignant cells. ➤➤







Dr. John Barrett

Dr. Barrett trained at St. Bartholomew's Hospital in London and specialized in Hematology studying in London and Paris. Between 1978 and 1988, he was Head of Department of Hematology at Charing Cross and Westminster Medical School, London. He was appointed Professor of Hematology in 1982. Between 1988 and 1993, he was Professor of Hematological Medicine at the Hammersmith Hospital London. In 1993, he became Chief of the National Heart, Lung and Blood Institute's Bone Marrow Stem Cell Allotransplantation Section of the Hematology Branch, National Heart, Lung and Blood Institute, National Institutes of Health. His contributions to hematology center around his work in stem cell transplantation, which includes the early development of transplants for inborn errors, and translational research to reduce GVHD while conserving GVL effects using a procedure termed "selective allodepletion". The major theme of his work is the role of the immune system in controlling and eradicating malignant disease. This has involved studies of graft-versus-host disease graft-versus-leukemia and graft versus tumor immunity and designing improved ways to reconstitute the immune system. Major achievements of his group include the introduction of immunosuppressive therapy for myelodysplastic syndrome, discovery of PR1, the first defined vaccine for myeloid leukemias, and the graft-versus-tumor effect of allogeneic stem cell transplantation for renal cell carcinoma. Currently he is developing new ways to boost graft versus leukemia effects through vaccines and adoptive T cell therapy and applying what has been learned from graft-versus-leukemia to design immunotherapy for hematological malignancies.

➤➤ Data from early clinical studies suggest that the ex-vivo allodepletion of donor T cells in ATIR results in immune reconstitution which is at least as favorable as competing haplo-id strategies. Furthermore, the toxicity profile of ATIR post T deplete haplo-id seems very favorable: the incidence of GVHD is very low even though none of the treated patients received prophylactic immunosuppression. Lastly, TRM rates and relapse rates with ATIR seem to be low. While these results are promising it is too early to determine whether the ex-vivo depletion approach leads to better clinical results than the in-vivo depletion of T cells caused by high dose cyclophosphamide or the use of UCB. Many questions remain about the generalizability of ex vivo selective T cell depletion to other transplant settings. At least in matched sibling SCT there is little capacity of the technique to reduce the much

weaker alloresponse, and trials of selective depletion in HLA matched sibling SCT have not shown any obvious advantages over either T depleted or T replete SCT. While ATIR could find a place in MUD transplants it cannot be easily applied to UCB SCT without strategies to miniaturize the process to the single small cord blood donation needed for engraftment. This is a period of rapid development for many competing mismatched SCT approaches. Is it possible that haplo-id SCT with its ease of availability within the family and its potential for powerful graft-versus-leukemia effects could outcompete UCB SCT and partially matched unrelated donors? Within the next 10 years that winners and losers will be better defined, but if haplo SCT remain as popular as they are currently we will have an opportunity to make reliable comparisons of ATIR against competing haplo-id SCT technologies.

Notes

## What transplant strategies compete with ATIR™?

Dr. J. Barrett (Bethesda, MD, USA)

When no HLA identical sibling donor is available for stem cell transplantation (SCT) there are three options for alternative donors – matched unrelated SCT (MUD), variably matched umbilical cord blood (UCB) transplants and haploidentical (haplo-id) family members. Haplo-id SCT have a long history, but until recently were infrequently used because of poor post-transplant survivals related to graft versus host disease (GVHD), rejection and high transplant related mortality (TRM) reflecting the type of patient selected and the intensive conditioning regimens used. However in the last decade haplo-id SCT have become popular because a number of strategies have been developed to resolve the specific issues associated with the HLA disparity between the donor and patient. Earlier attempts to prevent GVHD in haplo-id SCT by

profound T cell depletion led to a high treatment failure rate from opportunistic infection. However the judicious infusion of regulatory T cells in the T-depleted setting (pioneered by the Perugia group) have greatly improved outcomes. Inspired by promising results from T cell replete approaches, involving G-CSF stimulated marrow transplants with extensive post-transplant immunosuppression, several European studies have reported similar outcomes. More recently the Johns Hopkins group in Baltimore introduced post-transplant cyclophosphamide as a means to selectively deplete alloreacting cells in vivo and report very low TRM albeit with a continuing relatively high relapse probability in the older patients selected for this type of transplant. How does the ATIR technology compare with these existing developments? ➤➤





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