

# 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)







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

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Dr. Irwin Walker

Dr. Walker is Professor of Medicine at McMaster University, Hamilton. He graduated from Melbourne University in 1965, Internal Medicine 1970 (Australia) and Hematology 1973 (Canada). He has been involved in Bone Marrow Transplantation, as physician since 1981, as Head of the Hamilton Health Sciences BMT Program since 1994, as Chair of the CBMTG Strategic Planning Committee in 1998 and as President of CBMTG 2002-4. Currently he is the Principal Investigator for the CBMTG0801 clinical trial for prevention of chronic GVHD and is a member of the NIH Design of Clinical Trials Working Group. Other positions have included Chief of Medicine at McMaster University Medical Centre, and Chair of the Medical Scientific Advisory Committee to the Canadian Hemophilia Society.

# Challenges of alternative donor transplantation

Dr. I. Walker (Hamilton, Canada)

Alternative donor transplantation presents challenges but also opportunities to solve generic problems in transplantation. For example, alternative donor transplantation may close the gap in supply of matched donors. This gap will not be completely overcome by increasing the size of registries. A second generic problem is the regrettable complication rate for transplantation, even when donors are fully matched.

The term "alternative donor" has been applied variously since the early 1980s, to mismatched related, matched unrelated and mismatched unrelated donors, but this term now increasingly applied just to cord blood and haplomatched donors. The choice of the best donor is often difficult. Donor sources beyond matched siblings do not fall into a hierarchy of choices because an increasing number of other variables are now taken into account. For example, is a male recipient better served by a matched sibling donor, who is female, or by a matched unrelated donor who is male, and if so, would there be an unreasonable delay in a particular case before an unrelated donor is secured, thereby making an "alternative donor" the best choice?

Cord blood transplantation is now well established in pediatric practice. Cord blood grafts are more quickly available than grafts from volunteer donor registries, graft versus host disease is less, and the risk of leukemic relapse may be less. The ability to tolerate a greater degree of mismatch offsets the limited supply. Drawbacks to cord blood include cost, variable quality, limited suitability for adult recipients, and slow engraftment. Experimental approaches to solving slow engraftment include ex-vivo expansion and facilitation of homing. A different approach to delayed engraftment is that of infusing haplo-identical donor grafts along with unrelated cord blood. Engraftment is rapid and is sustained even after the haplo-identical graft atrophies.

Haplo-identical family donors are available to almost all recipients and are the source most rapidly available.

As well, engraftment is usually more rapid than with cord blood grafts. The challenge to performing such transplants is in preventing fatal GVHD due to the wide HLA disparity between donor and recipient. This field is very much in evolution, there being a number of different

approaches which are broadly based on T-cell deplete and T-cell replete approaches. A key observation is that anti-host T-cell reactivity may be separable from the T-cell reactivity that provides immunity and graft-versus-tumour effect. Approaches to suppressing or removing anti-host reactivity have included ex-vivo column separation and functional MLR systems, while in-vivo methods include post transplant cyclophosphamide or infusion of regulatory T-cells. Some centres attempt to overcome HLA disparity by increasing immunosuppression.

Alternate donor grafts can be made available for all recipients, thereby overcoming graft shortage. Establishing such grafts as routine involves confronting head on generic problems of GVHD, immune reconstitution and graft failure. Alternative donor transplantation requires extra measures compared with conventional transplantation to prevent these complications, but the advances made so far suggest that in establishing these platforms the long-standing generic complications may be more likely solved than in the setting of conventional grafting.

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Dr. Stephan Mielke

Dr. Mielke graduated in 1999 from Georg-August University Medical School in Göttingen, Germany. After completion of his scientific thesis at the Department of Obstetrics and Gynecology he received his doctoral degree from Georg-August University. He started his residency and fellowship program at the Albert Ludwig University of Freiburg in Germany, Department of Internal Medicine, Division of Hematology and Oncology. In 2003 he was awarded a postdoctoral grant from the Dr.-Mildred-Scheel-Stiftung in Germany. From May 2004 to August 2007 Dr Mielke worked in the Allotransplantation Section of the Hematology Branch at the National Institutes of Health, Bethesda, MD, USA. Afterwards he joined the Department of Internal Medicine II at the Julius-Maximilian University of Würzburg in Germany where he carries responsibilities as attending internist since 2008. As a specialist for Hematology and Oncology he clinically focuses on allogeneic hematopoietic stem cell transplantation from matched and mismatched donors. He wrote a professorial thesis about selective T cell depletion strategies in allogeneic stem cell transplantation and received his habilitation in 2009. In 2011 he became director of the Adult Allogeneic Stem Cell Transplant Program and headed the successful JACIE-based accreditation process in 2013. In 2014 Dr. Mielke was announced professor at the Medical Faculty of the University of Würzburg.

Dr. Mielke has published 50 peer-reviewed articles with a cumulative impact factor of 250 and has procured 1,2 million Euros of extramural and competitive funding. He is member of the American Society of Hematology (ASH), the European Group for Blood and Marrow Transplantation (EBMT), the International Society of Cellular Therapy (ISCT) and the German Society of Hematology and Oncology (DGHO). He has been elected into the office of the European Treasurer at the ISCT for the period of 2011 to 2014 and has joined the editorial boards of "Bone Marrow Transplantation" and "American Journal of Blood Research".

# Selective depletion to overcome challenges in allogeneic transplants

Dr. S. Mielke (Würzburg, Germany)

Allogeneic hematopoietic stem cell transplantation has become a standard of care curative option for a variety of patients with lymphomas and leukemias. For those patients having matched related or unrelated donors available transplant-related mortality has reached a four-decade minimum leaving fewer patients than ever with high-grade acute GvHD and severe infectious complications

behind. This however highlights more and more the control of the malignant disease as the real challenge in these cases. Selective *in vivo* or *ex vivo* depletion of hostreactive T cells causing GvHD may serve as a strategy to enhance graft-versus-leukemia effects in the presence of less or no immunosuppression thereby offering a curative option also to patients with high-risk leukemias and lymphomas.

However, in cases where a matched donor is unavailable the use of alternative stem cell sources such as haploidentical familiy donors harbors significant risks for the patients as the feasibility of haploidentical allogeneic stem cell transplantation largely depends on sufficient *in vivo* and *ex vivo* T cell depletion strategies to ensure engraftment and avoid severe GvHD. Consequently infectious complications are increased limiting the overall success of this approach.

Therefore novel strategies aim to improve immune reconstitution after haploidentical stem cell transplantation to reduce infectious complications. In this context *ex vivo* and *in vivo* selective depletion of alloreactive T cells using immunotoxins, suicide genes and photodynamic procedures have become the focus of today's translational transplant approaches aiming to improve the outcome of both matched and mismatched transplants.

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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.

# 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.

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.

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Dr. Robert Preti

Dr. Preti is PCT's co-founder and the visionary behind its successful growth and development strategy over the last two decades. Dr. Preti built PCT to meet a recognized need for high quality manufacturing and development services in an emerging industry. His leadership has been instrumental in creating PCT's Client-focused model that helps bridge the gap between discovery and patient care through efficient transfer of cell-based therapies from laboratory into clinical practice. Dr. Preti's vision for PCT includes expansion of its manufacturing capacity in the U.S. and Europe, as well as the development of new technological and engineering innovations that will help streamline and automate cell processing techniques, leading to faster scale up, lower cost of goods, and improved robustness for the industry.

Dr. Preti acts in a leadership capacity for many professional organizations, including as treasurer and founding member of ISCT (International Society for Cellular Therapy). He recently completed a five year term as a director for AABB, and is currently an Executive Committee member for the Alliance for Regenerative Medicine (ARM), where, among other activities, he co-chairs the Standards and Technology Committee. Dr. Preti has published and presented extensively on a variety of topics relating to cellular therapies.

Dr. Preti also serves as Chief Scientific Officer of NeoStem, Inc., PCT's parent company, where he is involved in directing the development and expansion of NeoStem's cell therapy pipeline, and setting NeoStem's strategic direction.

Dr. Preti earned his Ph.D (with distinction) from New York University.

# Change control during process development: How the application of Quality by Design (QbD) resulted in stable and robust ATIR™ manufacturing

Dr. R. Preti, (Allendale, NJ, USA)

No cell therapy presentation seems to be complete without reference to the unique challenges associated with navigating their successful path towards commercial reality. At yet it is clear that as the field matures, the solutions are forming along the lines of the challenges pursuant to the complexities and novelty of the therapeutics we are developing. Rational, and perhaps more importantly, successful clinical development

strategies include the concept of "keeping commercialization in mind" throughout the development cycle. And for some time now we have focused on strong product characterization to provide a spine around which product development – change – can occur. However, while this inside-out approach is certainly foundational, what does this mean in the context of a reality-based program to bring therapeutics to market?

the need for adherence to a basic developmental philosophy that results in a manufacturing process that can consistently yield high product quality, at a reasonable cost of goods, that meet demand – an issue of scalability – over the commercial life of the therapeutic – an issue of sustainability. Specifically, from the perspective of the CMC development and manufacturing environment, we have defined what tools we require and how best to apply them to both define the end – the desired state - and work in a methodical way towards achieving it. We have based this approach on a Quality by Design (QbD) platform that defines discrete unit operations

and how the successful execution of each, i.e. produces acceptable critical quality attributes (CQA's), contributes to achieving final product quality in a consistent and robust manner. In this report, we will review the basic principles of QbD and how they were applied to the development program of ATIR, a promising cellular therapy in oncology. This exciting case study highlights the importance of this approach – as well as the perils of falling short - and demonstrates the power it has to assist the developer address the unique challenges associated with the successful development of cellular therapies.

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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 graftversus-leukemia to design immunotherapy for hematological malignancies.

## 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?

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.

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