Québec Highlights

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Transcriptional Landscape of APL Identifies Aberrant Podoplanin Expression As a Defining Feature and Missing Link for the Bleeding Disorder of This Disease

Vincent-Philippe Lavallée, M.D.1,2, Miriam Marquis, Ph.D.3*, Marie-Ève Bordeleau, Ph.D.2*, Jalila Chagraoui, Ph.D.4*, Tara MacRae, M.Sc.4*, Isabel Boivin, M.Sc2*, Geneviève Boucher, M.Sc2*, Patrick Gendron, M.Sc2*, Sébastien Lemieux, Ph.D.5,6*, Arnaud Bonnefoy, Ph.D.7,8*, Georges E. Rivard, M.D.7,8, Josée Hébert, M.D.1,2,3,8 and Guy Sauvageau, M.D., Ph.D

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Monday, December 5, 2016: 4:30 PM
Marriott Grand 2-4 (Marriott Marquis San Diego Marina)
Transcriptional Landscape of APL Identifies Aberrant Podoplanin Expression As a Defining Feature and Missing Link for the Bleeding Disorder of This Disease

Vincent-Philippe Lavallée

• Acute promyelocytic leukemia (APL) is a favorable-risk subgroup of AML characterized by the t(15;17) translocation.

• The leading cause of early death in APL is uncontrolled bleeding mostly attributed to aberrant expression of tissue factor (F3) and annexin A2 (ANXA2) on leukemic promyelocytes leading to disseminated intravascular coagulation and hyperfibrinolysis, respectively.

• To prevent or treat such complications, early suspicion of APL and rapid initiation of therapy and supportive measures are critical.

• Podoplanin or PDPN is a surface glycoprotein expressed in most cell types, but not in blood cells.

• CLEC-2, the PDPN receptor, is expressed on normal platelets and was found to be necessary for the separation of blood and lymphatic vessels during embryogenesis.

• PDPN expression (whether endogenous or ectopic) in cell lines induces platelet aggregation, which can be inhibited by chemical tool compounds or by monoclonal antibodies.

• Aims and Methods: Analysis of the transcriptome of 30 APL comprised in the Leucegene 430 AML cohort.
Transcriptional Landscape of APL Identifies Aberrant Podoplanin Expression As a Defining Feature and Missing Link for the Bleeding Disorder of This Disease

Vincent-Philippe Lavallée
Transcriptional Landscape of APL Identifies Aberrant Podoplanin Expression As a Defining Feature and Missing Link for the Bleeding Disorder of This Disease

Vincent-Philippe Lavallée

• Results: Several mutated genes in this cohort, most of which are non-specific and previously identified.

• CEBPE mutations were the only exception and were specific to APL specimens in this cohort (2/30 vs 0/400, p= 0.005).

• Authors identified PDPN as the single most differentially overexpressed gene in APL

• PDPN is not expressed in whole blood, bone marrow and in any sorted cell subpopulations from these normal tissues, including promyelocytes. This indicates that platelets are never exposed to PDPN in the adult vasculature and reveals that this gene is ectopically expressed in APL promyelocytes.

• Hypothesis: aberrant PDPN expression on leukemic promyelocytes contributes to abnormal platelet aggregation in APL patients. High PDPN expression is associated with lower platelet counts at presentation (18 vs 34 x 10^{12}/L, median PDPN expression ≥ 10 vs < 10 RPKM, p = 0.016, Fig C).

• Strong inverse correlation was observed between the number of estimated circulating PDPN* promyelocytes and platelet counts

• By incorporating anti-PDPN antibody in the EuroFlow protocol, PDPN expression test was 90% sensitive and 100% specific for APL (n=48 and 50 APL and non-APL primary AML, respectively). Of note, 5 APL cases considered positive expressed low levels of PDPN.

• Comparing expression of all coagulation and fibrinolysis genes in APL (n=30) to that of non-APL specimens (n=400), PDPN was the most discriminatory transcript. This result stands in sharp contrast with that found with F3 and ANXA2 which largely overlap in these APL versus non-APL human AML.
Chemo-Transcriptomic Analysis of Complex Karyotype AML Reveals Increased Expression of Cell Cycle Components and Exquisite Dependency on Polo-like Kinase 1

Vincent-Philippe Lavallée, M.D.\textsuperscript{1,2}, Clarisse Thiollier, Ph.D.\textsuperscript{2*}, Céline Moison, Ph.D.\textsuperscript{2*}, Marie-Ève Bordeleau, Ph.D.\textsuperscript{2*}, Isabel Boivin, M.Sc\textsuperscript{2*}, Geneviève Boucher, M.Sc\textsuperscript{2*}, Patrick Gendron, M.Sc\textsuperscript{2*}, Sébastien Lemieux, Ph.D.\textsuperscript{3,4*}, Anne Marinier, Ph.D.\textsuperscript{5,6*}, Josée Hébert, M.D.\textsuperscript{1,2,7,8} and Guy Sauvageau, M.D., Ph.D.\textsuperscript{1,6,7,8}

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Monday, December 5, 2016: 10:30 AM
Pacific Ballroom 15-17 (Marriott Marquis San Diego Marina)
The Risk of Major Bleeding with Low-Molecular-Weight-Heparins for Venous Thromboembolism in Dialysis Patients: The Q-VTE Study

Adi J. Kil-Drori, MD1,2, Janie Coulombe, MSc3*, Sharon J. Nessim, MD MSc4,5* and Vicky Tagalakis, MD, MSc6,7

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Saturday, December 3, 2016: 10:30 AM
Room 31 (San Diego Convention Center)
The Risk of Major Bleeding with Low-Molecular-Weight-Heparins for Venous Thromboembolism in Dialysis Patients: The Q-VTE Study

Adi J. Kliil-Drori

- **Background:** Low-molecular weight heparins (LMWH) are not traditionally used to treat venous thromboembolism (VTE) among dialysis patients because their renal clearance may lead to less predictability in the degree of anticoagulation for a given dose.
- The authors determined the risk of major bleeding with LMWH compared with vitamin K antagonist (VKA) use in dialysis patients diagnosed with VTE in a real world setting.
The Risk of Major Bleeding with Low-Molecular-Weight-Heparins for Venous Thromboembolism in Dialysis Patients: The Q-VTE Study

Adi J. Kliil-Drori

- **Results**: In all, 647 dialysis patients with VTE were identified: 467 started VKA, 82 started LMWH, and 96 started both. Initiators of LMWH were 35 dalteparin, 26 tinzaparin, 19 enoxaparin, and 2 nadroparin.

- Median (interquartile range, IQR) daily doses were 12,500 (7,500-17,570) IU dalteparin, 16,080 (13,540-20,000) IU tinzaparin, 100 (70-120) mg enoxaparin, and 15,910 (15,200-16,625) IU nadroparin. Median (IQR) duration of LMWH monotherapy was 37 (22-87) days, and 132 (65-235) for VKA monotherapy.

- More than 90% of LMWH monotherapy was from 2004 and onwards, and 80% of LMWH users had cancer.

- There were 22 major bleeding events (86% gastrointestinal), 20 in VKA and 2 in LMWH users.

- No fatal bleeding occurred.

- Compared with VKA monotherapy, LMWH monotherapy was not associated with major bleeding (adjusted HR, 1.21; 95% CI: 0.20-7.37).
527 Targeting Pre-Leukemic Stem Cells in T-Acute Lymphoblastic Leukemia

Bastien Gerby, PhD1*, Diogo F.T Veiga, PhD1*, Jana Krosl, PhD1*, Julianne Ouellette1*, André Haman1*, Geneviève Lavoie, PhD1*, Iman Fares, MSc1*, Mathieu Tremblay, PhD1*, Véronique Litalien1*, Elizabeth Ottoni1*, Milena Kosic1*, Dominique Geoffrion1*, Joël Ryan1*, Paul Maddox, PhD2*, Jalila Chagraoui, PhD1, Anne Marinier, Ph.D.1*, Josée Hébert, M.D.3, Guy Sauvageau, M.D., Ph.D.1, Benjamin H Kwok, PhD1*, Philippe P Roux, PhD1* and Trang Hoang, PhD1

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Sunday, December 4, 2016: 5:30 PM
Room 10 (San Diego Convention Center)
Targeting Pre-Leukemic Stem Cells in T-Acute Lymphoblastic Leukemia

Bastien Gerby, PhD

• Current chemotherapy of pediatric T cell acute lymphoblastic leukemia (T-ALL) efficiently reduces the tumor mass with, however, undesirable long term consequences and remains ineffective in adolescent and adult T-ALL.

• Furthermore, relapse can be caused by pre-leukemic stem cells (pre-LSCs) that were spared by current protocols and evolved to malignancy.

• A distinctive characteristic of pre-LSCs is their critical dependence on interactions with the microenvironment for survival, which guided our strategy to target pre-LSCs using niche-based screening assays.
527 Targeting Pre-Leukemic Stem Cells in T-Acute Lymphoblastic Leukemia

Bastien Gerby, PhD

• Using transgenic mouse models that closely reproduce the human disease, the authors had showed that the SCL/TAL1 and LMO1 oncogenic transcription factors establish a pre-leukemic state by reprogramming normal pro-T cells into aberrantly self-renewing pre-LSCs (Gerby et al. PloS Genetics, 2014).

• They now provide direct evidence that pre-LSCs are much less chemosensitive than leukemic blasts to current drugs, due to a distinctive lower proliferative state as assessed by real-time imaging in a competitive assay.

• The authors designed a robust protocol for high-throughput screening (HTS) of compounds targeting primary pre-LSCs that are maintained on stromal cells engineered for optimal NOTCH1 activation to mimic the thymic microenvironment.

• Screened 1904 compounds and identified UM0119979 that disrupts both cell autonomous and non-cell autonomous pathways: UM0119979 abrogates pre-LSC viability and self-renewal activity in vivo by specifically inhibiting the translation of MYC, a downstream effector of NOTCH1, and preventing SCL/TAL1 activity.

• In contrast: normal hematopoietic stem/progenitor cells remain functional.

• Moreover, in vivo administration of UM0119979 efficiently reduced the leukemia propagating activity of primary human T-ALL samples in xenografted mice.

• Finally, in addition to SCL-LMO-induced T-ALL, these results reveal a novel possibility of therapeutic intervention in MYC-dependent hematologic malignancies.
527 Targeting Pre-Leukemic Stem Cells in T-Acute Lymphoblastic Leukemia

Bastien Gerby, PhD

• Conclusion:
  • This screening assay, built on the genetic dependencies of pre-LSCs, revealed their vulnerabilities to compounds that inhibit both the primary oncogenes and non-cell autonomous pathways triggered by the microenvironment.
  • The results illustrate how recapitulating tissue-like properties of primary cells in high throughput screening is a promising avenue for innovation in cancer chemotherapy.
75 Endosome-Mitochondria Interface Controls Intracellular Iron Trafficking in Erythroid Cells

Amel Hamdi, PhD1,2, Daniel Garcia-Santos, PhD4*, Tariq Roshan, MD3*, Alex Sheftel, PhD1,5* and Prem Ponka, MD, PhD, FCMA1,2

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Saturday, December 3, 2016: 10:00 AM
Room 3 (San Diego Convention Center)
In erythroid cells, more than 90% of transferrin-derived iron enters mitochondria where ferrochelatase inserts Fe\(^{2+}\) into protoporphyrin IX. However, the path of iron from endosomes to mitochondrial ferrochelatase remains elusive.

The prevailing opinion is that, after its export from endosomes, the redox-active metal spreads into the cytosol and mysteriously finds its way into mitochondria through passive diffusion.

An opposing view is that the highly efficient transport of iron toward ferrochelatase in erythroid cells requires a direct interaction between transferrin-endosomes and mitochondria ("kiss-and-run" hypothesis; Ponka Blood 89:1, 1997).

Using 3D live confocal imaging of reticulocytes following their incubation with MitoTracker Deep Red (MTDR) and Alexa Green Transferrin (AGTf), the authors have demonstrated transient endosome-mitochondria interactions.

They have thusly identified a population of particles labeled with both fluorescent markers, representing endosomes interacting with mitochondria. FACS followed by 2D confocal microscopy confirmed the association of both organelles in the double-labeled population.
75 Endosome-Mitochondria Interface Controls Intracellular Iron Trafficking in Erythroid Cells

Amel Hamdi

- The authors examined whether reticulocyte mitochondria interact with transferrin (Tf) in a cell-free system. Lysates of reticulocytes previously labeled with MTDR were incubated with AGTf for various time intervals.

- Increase in the number of mitochondria in contact with fluorescent Tf. This can be prevented by the presence of excess, unlabeled Fe₂-Tf, but not by albumin (Fig. 1). Moreover, the addition of unlabeled Fe₂-Tf to reticulocyte lysates removed AGTf from mitochondria, indicating that mitochondria from reticulocyte lysates are associated with TfR that can reversibly bind Tf.
Endosome-Mitochondria Interface Controls Intracellular Iron Trafficking in Erythroid Cells

Amel Hamdi

- Endosomes containing mutated recombinant holotransferrin, which cannot release iron, remain associated with mitochondria, while endosomes containing mutated recombinant apotransferrin, which cannot bind iron, are not associated with mitochondria. These findings indicate that endosomes containing holo-Tf promote their attachment to, and drive the detachment of apo-Tf-endosomes from, mitochondria, respectively.

- By co-immunoprecipitation assay (from murine erythroleukemia [MEL] cells and reticulocytes lysates), the authors purified the voltage-dependent anion channel 2 (VDAC2), which is located at the outer membrane of the mitochondrion with DMT1. They confirmed the colocalization of VDAC2 and DMT1 in MEL cells and reticulocytes by both immunofluorescence and confocal microscopy. Moreover, they found a significant decrease in the number of mitochondria in contact with Tf-endosomes after depletion of VDAC2 in MEL cells or after treatment of reticulocyte lysates with the mitochondrial uncoupler CCCP, further supporting the concept of a physical interaction between endosomes and mitochondria.

- Depleted MEL cells of VDAC2 or inhibited VADC2 using erastin (a specific VDAC2 inhibitor that alters its gating) and measured $^{59}$Fe incorporation from $^{59}$Fe-Tf into heme. They found decreased $^{59}$Fe incorporation into heme of MEL cells with silenced or inhibited VDAC2 supports the idea that this outer-membrane mitochondrial protein is involved in the interaction of endosomes with mitochondria.
2306 Bortezomib Consolidation after Nonmyeloablative Allogeneic Stem Cell Transplantation Leads to a High Incidence of Immunophenotypic Complete Response in Young and/or High-Risk Multiple Myeloma Patients

Richard LeBlanc, MD1, Imran Ahmad, MD2, Rafik Terra, PhD3*, Séverine Landais, PhD2*, Michael Sebag, MD, PhD4, Emilie Lemieux-Blanchard, MD5, Nadia M. Bambace, MD2, Lea Bernard, MD2, Sandra Cohen, MD1, Jean-Sebastien Delisle, MD, PhD6, Thomas Kiss, MD2, Silvy Lachance, MD6, Denis-Claude Roy, MD2, Guy Sauvageau, MD, PhD7 and Jean Roy, MD8

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Saturday, December 3, 2016, 5:30 PM-7:30 PM
Hall GH (San Diego Convention Center)
2306 Bortezomib Consolidation after Nonmyeloablative Allogeneic Stem Cell Transplantation Leads to a High Incidence of Immunophenotypic Complete Response in Young and/or High-Risk Multiple Myeloma Patients

Richard LeBlanc

- Allogeneic stem cell transplantation (alloSCT) is the only curative modality for newly diagnosed multiple myeloma (NDMM) patients (pts).
- The authors have previously shown in a large cohort of 92 pts that relapse remains common (49%) and the incidence/severity of chronic GVHD is significant (79%) after tandem auto-allo SCT in NDMM pts (Ahmad et al. BMT 2016;51:529).
- They hypothesized that a tandem auto-nonmyeloablative (NMA) alloSCT followed by bortezomib (btz) consolidation might be safe, while decreasing both the severity/incidence of chronic GVHD and the risk of relapse in young and/or high-risk NDMM pts.
- In addition, they hypothesized that bortezomib might further increase depth of responses after alloSCT.
2306 Bortezomib Consolidation after Nonmyeloablative Allogeneic Stem Cell Transplantation Leads to a High Incidence of Immunophenotypic Complete Response in Young and/or High-Risk Multiple Myeloma Patients

Richard LeBlanc

- **Methods:** NDMM pts with either ISS stage III, plasma cell leukemia, abnormal cytogenetics defined as t(4;14) with ISS II or III, t(14;16), t(14;20), 17p-, 1p-, or 1q+ in ≥ 10% of purified plasma cells or age ≤ 50 years with a 6/6 sibling or 8/8 unrelated donor were prospectively enrolled in this phase II trial.

- After a btz-based induction with ≥ partial response and autologous (A) SCT, outpatient NMA alloSCT was performed with either a conditioning of fludarabine 30 mg/m² x 5 days and cyclophosphamide 300 mg/m² x 5 days (sibling donor) or fludarabine 30 mg/m² x 3 days and TBI 2Gy (unrelated donor), followed by G-CSF mobilized stem cells infusion.

- Acute GVHD prophylaxis consisted of tacrolimus and mycophenolate mofetil. Btz 1.3 mg/m² SC every 2 weeks was started on day +120 after alloSCT for 1 year.

- Bone marrow aspirates before alloSCT, before starting btz and every 3 months thereafter were prospectively collected for 2 years in order to assess the impact of btz on minimal residual disease (MRD) by a highly sensitive (≥10⁻⁵) multiparametric flow cytometry using the 8-color Euroflow protocol evaluating ≥ 10 x 10⁶ cells/specimen.

- MRD negativity was defined as the detection of < 30 clonal aberrant plasma cells. Response evaluation is based on IMWG criteria including immunophenotypic complete response (iCR) defined as a stringent CR (sCR) plus a negative MRD. Immunophenotypic remission (iR) is defined as MRD negativity regardless of other disease status.
2306 Bortezomib Consolidation after Nonmyeloablative Allogeneic Stem Cell Transplantation Leads to a High Incidence of Immunophenotypic Complete Response in Young and/or High-Risk Multiple Myeloma Patients

Richard LeBlanc

Table 1. Response rates after treatment phases

<table>
<thead>
<tr>
<th>n = 15</th>
<th>Induction (%)</th>
<th>ASCT (%)</th>
<th>Allo SCT (%)</th>
<th>Bortezomib (%)</th>
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<tr>
<td>iR</td>
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<td>13</td>
<td>13</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>PD</td>
<td>-</td>
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</table>

ASCT: autologous stem cell transplantation; Allo SCT: allogeneic stem cell transplantation; iR: immunophenotypic remission; iCR: immunophenotypic complete response; sCR: stringent complete response; CR: complete response; VGPR: very good partial response; PR: partial response; SD: stable disease; PD: progressive disease
4677 Tandem Autologous Followed By Nonmyeloablative Allogeneic Transplantation in Relapsed High Risk Follicular Lymphoma Leads to Excellent Long Term Progression-Free Survival after 8 Years of Follow-up
Clinical Allogeneic Transplantation: Results
Poster Abstracts
Session: 732. Clinical Allogeneic Transplantation: Results: Poster III

Magalie Tardif, MSc, MD Student1*, Imran Ahmad, MD2, Nadia M. Bambace, MD2, Lea Bernard, MD2, Lambert Busque, MD2, Jean-Sebastien Delisle, MD, PhD3, Thomas Kiss, MD2, Isabelle Fleury, MD2, Silvy Lachance, MD3, Luigina Mollica, MD, PhD4, Céline Nkoué, MD2*, Denis-Claude Roy, MD2, Jean Roy, MD2 and Sandra Cohen, MD5

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4677 Tandem Autologous Followed By Nonmyeloablative Allogeneic Transplantation in Relapsed High Risk Follicular Lymphoma Leads to Excellent Long Term Progression-Free Survival after 8 Years of Follow-up

Magalie Tardif, MSc, MD Student

Prospective protocol initiated in April 2003 for pts with high risk relapsed FL as defined by chemorefractory disease, early 1st relapse, >1st relapse or transformation into aggressive histology.

At least one therapy was attempted to document chemosensitivity prior to ASCT.

Regardless of disease status prior to transplant, pts underwent ASCT followed 3 months later by an outpatient NMT from an HLA-identical sibling.

NMT comprised 5 days of fludarabine 30 mg/m²/day and cyclophosphamide 300mg/m²/day followed by an infusion of >2x10⁶CD34⁺ cells/kg.

GVHD prophylaxis: tacrolimus starting on day (D) – 8 to achieve levels of 8–12 nmol/L then tapered off by D+100 or D+180 depending on disease risk and of

Report on 40 pts with a median f/u of 8 yrs.
4677 Tandem Autologous Followed By Nonmyeloablative Allogeneic Transplantation in Relapsed High Risk Follicular Lymphoma Leads to Excellent Long Term Progression-Free Survival after 8 Years of Follow-up

Magalie Tardif, MSc, MD Student

• Up until July 2015, 40 pts were enrolled with a median age of 50 yrs (34-65).

• Pts had previously been treated with a median of 3 lines of therapy (2-6).

• Median time from diagnosis to ASCT was 33 months. Disease status at ASCT was: 14 CR, 16 PR and 10 refractory.

• Conditioning for ASCT included BEAM/BEAC (n=39), and Cy-TBI (n=1).

• 4 pts received radiotherapy after ASCT to sites of previously bulky disease.

• Median time between ASCT and NMT was 138 days (75-238).

• Pre NMT disease status was: 25 CR, 12 PR and 3 refractory.

• Engraftment was prompt in all pts after ASCT and median neutrophil and platelet recovery were respectively 13 days (0-19) and 0 day (0-18) post NMT.
4677 Tandem Autologous Followed By Nonmyeloablative Allogeneic Transplantation in Relapsed High Risk Follicular Lymphoma Leads to Excellent Long Term Progression-Free Survival after 8 Years of Follow-up

Magalie Tardif, MSc, MD Student
1535 Modeling of Pediatric Acute Megakaryoblastic Leukemia Using Cord Blood Stem/Progenitor Cells

Oncogenes and Tumor Suppressors
Program: Poster Abstracts
Session: 603. Oncogenes and Tumor Suppressors: Poster I

Saturday, December 3, 2016, 5:30 PM-7:30 PM
Hall GH (San Diego Convention Center)

Sophie Cardin, PhD*, Louise Laramee**, Tara MacRae, M.Sc.*, Jalila Chagraoui, PhD*, Guy Sauvageau, MD, PhD®, R. Keith Humphries, MD, PhD®, Josée Hébert, M.D.*, Brian T. Wilhelm, PhD® and Sonia Cellot, MD, PhD®

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9University of Montreal, Montreal, QC, CAN
Modeling of Pediatric Acute Megakaryoblastic Leukemia Using Cord Blood Stem/Progenitor Cells

Sophie Cardin, PhD

• Pediatric acute megakaryoblastic leukemia (AMKL) accounts for 10% of childhood acute myeloid leukemia (AML) cases and remains a high fatality cancer. CBFA2T3-GLIS2, NUP98-KDM5A, RBM15-MKL1 and MLL gene rearrangements are recurrent aberrations that are mutually exclusive and found at similar frequencies in half the cases of pediatric AMKL.

• The recently identified CBFA2T3-GLIS2 and NUP98-KDM5A chimeric oncogenes are associated with inferior outcomes (overall survival, OS: ~30%) compared to patients harboring the RBM15-MKL1 gene fusion (OS ~70%).

• To investigate NUP98-KDM5A driven leukemogenesis, human cell lines and mouse models were engineered using overexpression of the chimeric oncogene in CD34+cord blood (CB) stem/progenitor cells.
cDNA of the NUP98-KDM5A fusion: nuclear pore protein nucleoporin 98 (NUP98) gene fused to the histone lysine demethylase 5A (KDM5A) gene, was cloned into a MNDU lentiviral vector carrying a GFP reporter gene.

Using optimized culture conditions, 10,000 freshly isolated CB-CD34+ (day 0) cells were seeded in multiple wells in vitro and transduced with either NUP98-KDM5A or control (CTL) vectors.

Xenotransplantation of 75% of day 7 cells in immunodeficient mice resulted in the development of overt AMKL in 1 of 3 mice after 32 weeks. Recipient mouse bones were white and brittle, and the marrow cavity infiltrated by 30% hCD45loCD61+GFP+ leukemic blasts, with typical megakaryoblastic morphology.

The leukemic blasts were also detected in blood (5%), and in enlarged spleen (0.2%). Secondary transplantation of isolated AMKL cells (from bone marrow and spleen) was performed, along with expression profiling by RNA sequencing.
2372 Burden of Relapse Following Allogeneic Hematopoietic Stem Cell Transplantation on Health Care Resource Utilization in the Management of Acute Leukemia and Myelodysplastic Syndrome

Health Services Research—Malignant Conditions
Program: Oral and Poster Abstracts
Session: 902. Health Services Research—Malignant Conditions: Poster I

Saturday, December 3, 2016, 5:30 PM-7:30 PM
Hall GH (San Diego Convention Center)

Silvy Lachance, MD¹, Joelle Bibeau²* and Jean Lachaine³*
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²Peripharm Inc, Montreal, QC, Canada
³Faculty of pharmacy, Universite de Montréal, Montreal, QC, Canada
2372 Burden of Relapse Following Allogeneic Hematopoietic Stem Cell Transplantation on Health Care Resource Utilization in the Management of Acute Leukemia and Myelodysplastic Syndrome

Silvy Lachance

Table 1. Patients' characteristics at relapse

<table>
<thead>
<tr>
<th></th>
<th>Complete record (n=25)</th>
<th>All patients (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (SD)</td>
<td>46.5 (10.0)</td>
<td>46.5 (11.2)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>16 (64.0)</td>
<td>20 (55.6)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AL (%)</td>
<td>21 (84.0)</td>
<td>32 (88.9)</td>
</tr>
<tr>
<td>MDS (%)</td>
<td>4 (16.0)</td>
<td>4 (11.1)</td>
</tr>
<tr>
<td>Conditioning regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloid (%)</td>
<td>23 (92.0)</td>
<td>32 (88.9)</td>
</tr>
<tr>
<td>Nonmyeloid (%)</td>
<td>2 (8.0)</td>
<td>4 (11.1)</td>
</tr>
<tr>
<td>Source of Stem cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral blood (%)</td>
<td>22 (88.0)</td>
<td>31 (86.1)</td>
</tr>
<tr>
<td>Bone marrow (%)</td>
<td>3 (12.0)</td>
<td>5 (13.9)</td>
</tr>
<tr>
<td>Type of transplant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Related (%)</td>
<td>17 (68.0)</td>
<td>25 (69.4)</td>
</tr>
<tr>
<td>Post AH SCT Graft versus host disease (GvHD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute GVHD (%)</td>
<td>15 (60.0)</td>
<td>24 (66.7)</td>
</tr>
<tr>
<td>Chronic GVHD (%)</td>
<td>12 (48.0)</td>
<td>17 (47.2)</td>
</tr>
<tr>
<td>Months between AH SCT and relapse (SD)</td>
<td>8.2 (10.1)</td>
<td>7.2 (8.6)</td>
</tr>
<tr>
<td>Mean survival in months (SD)</td>
<td>19.4 (14.3)</td>
<td>16.6 (13.2)</td>
</tr>
<tr>
<td>Follow-up time in months (SD)</td>
<td>10.4 (14.3)</td>
<td>7.5 (9.7)</td>
</tr>
</tbody>
</table>

Table 2. Mean health care resource utilization per patient

<table>
<thead>
<tr>
<th></th>
<th>Complete record (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse-related hospitalizations (SD)</td>
<td>2.2 (2.6)</td>
</tr>
<tr>
<td>Duration (SD)</td>
<td>40.4 (54.5)</td>
</tr>
<tr>
<td>Emergency visits (SD)</td>
<td>1.8 (2.2)</td>
</tr>
<tr>
<td>Outpatient consultations</td>
<td></td>
</tr>
<tr>
<td>Hematologist (SD)</td>
<td>32.4 (37.3)</td>
</tr>
<tr>
<td>Ophthalmologist (SD)</td>
<td>1.2 (2.6)</td>
</tr>
<tr>
<td>Medical Microbiology (SD)</td>
<td>0.8 (2.5)</td>
</tr>
<tr>
<td>Pneumologist (SD)</td>
<td>0.4 (1.2)</td>
</tr>
<tr>
<td>Other specialists (SD)</td>
<td>1.44 (3.1)</td>
</tr>
<tr>
<td>Procedures</td>
<td></td>
</tr>
<tr>
<td>Imaging (SD)</td>
<td>18.0 (17.5)</td>
</tr>
<tr>
<td>Biopsy (SD)</td>
<td>3.2 (3.7)</td>
</tr>
<tr>
<td>Other procedures (SD)</td>
<td>6.7 (11.4)</td>
</tr>
<tr>
<td>Blood tests (SD)</td>
<td>172.2 (206.8)</td>
</tr>
<tr>
<td>Blood products (SD)</td>
<td>32.2 (39.9)</td>
</tr>
</tbody>
</table>
2372 Burden of Relapse Following Allogeneic Hematopoietic Stem Cell Transplantation on Health Care Resource Utilization in the Management of Acute Leukemia and Myelodysplastic Syndrome

Silvy Lachance

<table>
<thead>
<tr>
<th>Table 3. Survival by treatment choice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relapse treatment</strong></td>
</tr>
<tr>
<td>Supportive care (SD)</td>
</tr>
<tr>
<td>Chemotherapy (CT) (SD)</td>
</tr>
<tr>
<td>Donor lymphocyte infusion (DLI) (SD)</td>
</tr>
<tr>
<td>2nd transplant (SD)</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitor (TKI) (SD)</td>
</tr>
<tr>
<td>DLI + TKI (SD)</td>
</tr>
<tr>
<td>CT + TKI (SD)</td>
</tr>
</tbody>
</table>

* One patient receiving a second transplant and both patients receiving DLI, were still alive at the time of analysis
Donor Lymphocytes Depleted of Alloreactive T-Cells (ATIR101) Improve Event-Free Survival (GRFS) and Overall Survival in a T-Cell Depleted Haploidentical HSCT: Phase 2 Trial in Patients with AML and ALL

Denis-Claude Roy, MD1, Silvy Lachance, MD2, Jean Roy, MD3, Irwin Walker, MBBS4, Johan Maertens, MD, PhD5*, Jean-Sebastien Delisle, MD, PhD2, Stephen Ronan Foley, MD6, Philippe Lewalle, MD-PhD7*, Eduardo Olavarria8*, Dominik Selleslag, MD9, Manfred Rüdiger, PhD10*, Jurjen Velthuis, PhD10*, Lisya Gerez10*, Jeroen Rovers, MD PhD10*, Halvard Bonig, MD, MA11 and Stephan Mielke, MD12

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2Division of Hematology and Medical Oncology, Stem Cell Transplant Program, Department of Medicine, University of Montreal, Maisonneuve-Rosemont Hospital CIUSSS East Montreal, Montreal, QC, Canada
3Division of Hematology and Medical Oncology, University of Montreal, Maisonneuve-Rosemont Hospital CIUSSS East Montreal, Montreal, QC, Canada
4Juravinski Hospital and Cancer Centre, McMaster University, Hamilton, ON, Canada
5Department of Hematology, University Hospital Gasthuisberg, Dept. of Hematology, Leuven, Belgium
6McMaster University, Department of Medicine, Juravinski Hospital and Cancer Centre, Hamilton, ON, Canada
7Laboratory of Experimental Hematology, Jules Bordet Institut, Bruxelles, BEL
8Centre for Haematology, Imperial College London at Hammersmith Hospital, London, United Kingdom
9AZ St-Jan Brugge AV, Brugge, Belgium
10Kiadis Pharma, Amsterdam-Duivendrecht, Netherlands
11German Red Cross Blood Centre and Institute for Transfusion Medicine and Immunohematology, Johann-Wolfgang-Goethe University, Hematopoietic Cell Research Group, Frankfurt, Germany
12Division of Hematology and Oncology, Department of Internal Medicine II, Würzburg University Medical Center, Würzburg, Germany

Monday, December 5, 2016: 6:30 PM
Room 30 (San Diego Convention Center)
Challenge in Haploidentical Donor Transplantation
### ATIR101 manufacturing

**Effects ATIR101 procedure**

- Selective removal of GVHD-causing T-cells
- Preservation of the immune repertoire
  - Key immune cells are retained to protect against infections
  - T-cells directed against leukaemic antigens are retained

**Potential benefits**
- 5 day manufacturing process
- Release data
- Performed in advance of HSCT procedure
- Cells cryopreserved until infusion

<table>
<thead>
<tr>
<th>Step</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Immune cells collected and mixed ex vivo</td>
</tr>
<tr>
<td>2.</td>
<td>Activation of donor T-cells</td>
</tr>
<tr>
<td>3.</td>
<td>TH9402 addition</td>
</tr>
<tr>
<td>4.</td>
<td>Exposure to light</td>
</tr>
<tr>
<td>5.</td>
<td>ATIR infusion</td>
</tr>
</tbody>
</table>

**Diagram**

- Patient
- Donor

**Schedule**

- Day 1 - 4
- Day 5
• **Phase II clinical trial**

- Aim is to develop an **immunosuppressant-free** transplant regimen for haploidentical donor transplantation
- Based on T-cell depletion: CD34⁺-mega dose approach (Perugia)
- Pre-emptive post-HSCT administration of **donor lymphocytes (ATIR101) depleted of alloreactive T-cells**
  - Avoid GVHD
  - Reduce infections/TRM/relapse

---

Diagram:
- **Conditioning**: Myeloablative conditioning
- **Haplo HSCT**: T-cell depleted stem cell graft from family member
- **Isolation**: No prophylactic immunosuppression
- **ATIR101 infusion**: Donor lymphocyte infusion 28 – 32 days post-HSCT

**Selective photodepletion to eliminate GVHD-causing T-cells**

**CD34⁺ PBMC graft**
**Patient & Donor characteristics**

**Patient & Donor**
- N=23 patients (HSCT + ATIR101)
- Median patient age (range): 41 years (21 – 64)
- Gender: 13 female, 10 male
- Median donor age (range): 33 years (21 - 61 )
- HLA matching (HLA-A, B, DR)
  - 3/6 match: 16
  - 4/6 match: 6
  - 5/6 match: 1 (7/10 match)
- Donors:
  - Father/mother 4 (17%)
  - Sibling 9 (39%)
  - Son/daughter 9 (39%)
  - Other 1 (4%)

**Diagnosis**
- Acute myeloid leukemia – N=16 (70%)
  - 11 in CR1
  - 5 in CR2
- Acute lymphoblastic leukemia – N=7 (30%)
  - 4 in CR1
  - 3 in CR2
- Cytogenetic risk profile¹:
  - Favorable 0
  - Intermediate 9 (39 %)
  - Adverse 14 (61 %)
- Disease-risk index²:
  - Low risk index 0
  - Intermediate risk index 10 (43 %)
  - High risk index 13 (57 %)

¹ Mrozek K, et al. JCO 2012, 30 (36):4515-4523
• Transplantation characteristics (n=23 patients)

Conditioning
• TBI (1200 cGy; n=11) or melphalan (120mg/m²; n=12)
• Thiotepa (10 mg/kg), fludarabine (30 mg/m² x 5d) and ATG (2.5mg/kg x 4d)

HSCT
• CliniMACS® CD34 isolation system (Miltenyi Biotec)
• Target: 8-11x10⁶ CD34+ cells/kg, with max. of 3x10⁴ CD3+ cells/kg

Prophylaxis
• No GVHD prophylaxis
• CMV/EBV monitoring
• Prophylactic use of gancidovir / foscarnet (CMV + recipient/donor)

HSCT

<table>
<thead>
<tr>
<th>Graft</th>
<th>Median (cells/kg)</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD34⁺</td>
<td>10.9 x 10⁶</td>
<td>3.2 – 24.4 x 10⁶</td>
</tr>
<tr>
<td>CD3⁺</td>
<td>0.28 x 10⁴</td>
<td>0 – 1.8 x 10⁴</td>
</tr>
</tbody>
</table>

Engraftment

<table>
<thead>
<tr>
<th>Neutrophils</th>
<th>Median (days)</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>8 – 34</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Platelets</th>
<th>Median (days)</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>9 – 35</td>
<td></td>
</tr>
</tbody>
</table>

GVHD
• No Grade III-IV GVHD
• Grade II acute GVHD in 3 patients
• Chronic GVHD: 1 patient

ASH 2016, Session 711, Oral presentation on Monday December 5, 18h30
Donor Lymphocytes Depleted of Alloreactive T-Cells (ATIR101) Improve Event-Free Survival (GRFS) and Overall Survival in a T-Cell Depleted Haploidentical HSCT: Phase 2 Trial in Patients with AML and ALL

*Denis-Claude Roy*

**Figure 1**

**Table 1**

<table>
<thead>
<tr>
<th>Kaplan-Meier Estimates of:</th>
<th>6 months after HSCT</th>
<th>12 months after HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haplo+ATIR101</td>
<td>83%</td>
<td>61%</td>
</tr>
<tr>
<td>Haplo alone</td>
<td>63%</td>
<td>20%</td>
</tr>
<tr>
<td>GRFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haplo+ATIR101</td>
<td>78%</td>
<td>57%</td>
</tr>
<tr>
<td>Haplo alone</td>
<td>57%</td>
<td>20%</td>
</tr>
<tr>
<td>MUD (8/8-10/10)</td>
<td>63%</td>
<td>41%</td>
</tr>
</tbody>
</table>
Invitation to meetings:

Cell & Gene Therapy Revolution
Montreal: March 9-10, 2017

- Québec City: 27 janvier 2017
- Montréal: 7 avril 2017