RAAF Captures Flying Saucer On Ranch in Roswell Region

No Details of Incident Given

Roswellians Have Differing Opinions

House Passes Tax Slash by Margin

Morrison & Kane Win All-Star Game
Types of Transplants

- **Syngeneic**
  - Identical twin

- **Allogeneic**
  - From another person
    - family member (sibling, parent, other relative)
    - unrelated donor

- **Autologous**
  - Self
RPCI BMT Program:

- Autologous up to age 75
- Allogeneic
  - Myeloablative up to age 60
  - Reduced Intensity up to age 75
- Goal: Increasing patient access with decreasing mortality and improved outcome
  - Reduce the toxicity of chemotherapy and radiation therapy
  - Reduce the toxicity of Graft-versus-Host Disease (GvHD) and preserve the Graft-versus-Tumor (GvT) effect
Hematopoietic Stem Cell Transplantation - Classification -

- Allogeneic
  - HLA-identical Other Unrelated sibling relative
- Syngeneic
- Autologous

Donor

Conditioning Regimen Intensity

Graft Source

Graft manipulation

Non-myeloablative

Reduced Intensity

Myeloablative

Bone Marrow

Peripheral Blood

Peripheral Blood

Bone Marrow

Umbilical cord blood

Ex vivo expansion

In vivo selection

Negative or positive selection

Courtesy M Pasquini, CIBMTR
Autologous BMT

High dose Chemo +/- XRT

Blood or Marrow Collection

Patient

Freezer
Allogeneic BMT

High dose Chemo +/- XRT

Donor

Recipient
HLA (Human Leukocyte Antigens) Inheritance Simplified

Father

A2
B7
DR 01

A11
B15
DR 11

A23
B51
DR 04

A30
B35
DR 13

Mother

A2
B7
DR 01

A 2
B 7
DR 01

A30
B35
DR 13

A23
B51
DR 04

A11
B15
DR 11

A30
B35
DR 13

A23
B51
DR 04

A11
B15
DR 11
Location of Centers participating in the CIBMTR 2011
Transplant Activity in the U.S.
1980-2010
Transplant activity worldwide 1980-2009

- Autologous
- Allogeneic
Allogeneic Stem Cell Sources by Recipient Age 2000-2009

Transplants, %

- Bone Marrow (BM)
- Peripheral Blood (PB)
- Cord Blood (CB)

Age ≤ 20 yrs

2000-2004: Bone Marrow (BM) 60%, Peripheral Blood (PB) 20%, Cord Blood (CB) 20%
2005-2009: Bone Marrow (BM) 50%, Peripheral Blood (PB) 30%, Cord Blood (CB) 20%

Age > 20 yrs

2000-2004: Bone Marrow (BM) 40%, Peripheral Blood (PB) 40%, Cord Blood (CB) 20%
2005-2009: Bone Marrow (BM) 30%, Peripheral Blood (PB) 70%, Cord Blood (CB) 10%
Autologous Stem Cell Sources by Recipient Age 2000-2009

Transplants, %

- Bone Marrow (BM)
- Peripheral Blood (PB)
- BM + PB

<table>
<thead>
<tr>
<th>Year</th>
<th>Age ≤ 20 yrs</th>
<th>Age &gt; 20 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000-2004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005-2009</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CIBMTR
Trends in Transplants by Type and Recipient Age*
2000-2009

* Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma

Transplants, %

<table>
<thead>
<tr>
<th>Allogeneic Transplants</th>
<th>Autologous Transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=20 yrs</td>
<td>&lt;=20 yrs</td>
</tr>
<tr>
<td>21-40 yrs</td>
<td>21-40 yrs</td>
</tr>
<tr>
<td>41-50 yrs</td>
<td>41-50 yrs</td>
</tr>
<tr>
<td>51-60 yrs</td>
<td>51-60 yrs</td>
</tr>
<tr>
<td>&gt;60 yrs</td>
<td>&gt;60 yrs</td>
</tr>
</tbody>
</table>

CIBMTR

Slide 6
He had choose between LIFE or LOVE and DEATH...

JOHN TRAVOLTA

THE BOY IN THE PLASTIC BUBBLE

FROM THE DIRECTOR OF "GREASE"
Bubble Boy (2001)
Graft-versus-Host Disease (GvHD) and Graft-versus-Tumor (GvT)

- Graft-versus-Host Disease (GvHD) is caused by the immune activation of donor cells recognizing recipient cells as foreign.
- Acute GvHD occurs ~ 100 days after BMT and affects Skin, GI tract and Liver.
- Chronic GvHD occurs after acute GvHD; up to 3 years following BMT.
- GvHD is the most frequent cause of mortality after allogeneic BMT.
- However, GvHD is accompanied by a Graft-versus-Tumor (GvT) effect that can result in eradication of the underlying cancer.
Scylla (GvHD) and Charybdis (Tumor)

MECHANISM OF GVHD

Afferent phase

- Ag presentation
- Cell activation
- Clonal proliferation & differentiation

Efferent phase

- Lymphokine dysregulation
- Target cell Death

Courtesy of Mohamed Soliman
RPCI Flow Cytometry
Probability of Relapse After 2,254 HLA-identical Sibling Transplants for Early Leukemia
Probability of Survival after HLA-identical Sibling Donor Transplants for AML

Early (N=6,317)
Intermediate (N=1,675)
Advanced (N=2,645)

P < 0.0001
Transplant regimens

Immunosuppression

- Flu-Cy
- Flu-Cy-ATG
- Flu-low dose
- TBI
- Flu ATG

- Flu-Mel
- Flu-Bu
- Flu-Mel-TBI

- Cy-TBI
- Bu-Cy

Regimen Related Toxicity

Later Graft-versus Disease Effect

- Allo
  - Nonmyeloablative
- Allo
  - Reduced Intensity

Auto and Allo Myeloablative

Earlier Anti-Disease Effect

Relapse

Myelosuppression
Non-Myeloablative BMT

Immunosuppression with Chemo +/- XRT

Donor → Recipient → Recipient → Recipient
NMDP Report Card 2012

- There are 156 Allogeneic BMT Centers reporting to the NMDP.
- There are 14/156 (9%) Allogeneic BMT Centers with survival outcomes that are statistically superior to their expected outcomes.
- RPCI is one of these 14 Allogeneic BMT centers.
- Data Source: [http://marrow.org/Patient/Transplant_Plan/Choosing_a_Transplant_Center/U_S_Transplant_Centers.aspx](http://marrow.org/Patient/Transplant_Plan/Choosing_a_Transplant_Center/U_S_Transplant_Centers.aspx)
RPCI BMT Program

• N=132 patients
• Actual 1-year survival rate = 68%
• Predicted 1-year survival rate = 58%
• 95% CI predicted 1-yr survival rate = 50%-66%
• Result: RPCI actual 1-year survival is statistically significantly higher than predicted
Risk Categories range from 0 (lowest risk) to 5 (highest risk). Data prepared by the National Marrow Donor Program for patients who received a related (2011 -2012) or unrelated donor BMT. Data from 2012 represent patients transplanted from 2007 to 2009.
Chimera

Etruscan bronze sculpture from Arezzo, Italy
5th–4th century BC. In the Archeological Museum, Florence. Height 80 cm.
“Around the time he disappeared from his bookstore, Steven was treated for aplastic anemia at UVA,” I said. “I’ve talked with his hematologist. Steven received total lymphoid irradiation, chemotherapy (sic). Gordon’s marrow was infused into Steven, and Steven then spent time in a laminar flow room…”
No improvements in outcomes for older AML pts treated on ECOG protocols 1973-1997

AML pts $\leq$ 55 yo (n=2000)  AML pts $>$ 55 yo (n=1000)


Slide Courtesy of E Wang
Long-Term Prognosis of Acute Myeloid Leukemia According to the New Genetic Risk Classification of the European LeukemiaNet Recommendations: Evaluation of the Proposed Reporting System

Table 1. Standardized Reporting for Correlation of Cytogenetic and Molecular Genetic Data in Acute Myeloid Leukemia With Clinical Data According to the ELN Guideline

<table>
<thead>
<tr>
<th>ELN Genetic Risk Group</th>
<th>Subsets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>t(8;21)(q22;q22); RUNX1-RUNX1T1 inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); CBFβ-MYH11 Mutated NPM1 without FLT3-ITD (normal karyotype) Mutated CEBPα (normal karyotype)</td>
</tr>
<tr>
<td>Intermediate-I</td>
<td>Mutated NPM1 and FLT3-ITD (normal karyotype) Wild-type NPM1 and FLT3-ITD (normal karyotype) Wild-type NPM1 without FLT3-ITD (normal karyotype)</td>
</tr>
<tr>
<td>Intermediate-II</td>
<td>t(9;11)(p22;q23); MLLT3-MLL Cytogenetic abnormalities not classified as favorable or adverse</td>
</tr>
<tr>
<td>Adverse</td>
<td>inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1 t(6;9)(p23;q34); DEK-NUP214 t(v;11)(v;q23); MLL rearranged −5 or del(5q); −7; abnl(17p); complex karyotype</td>
</tr>
</tbody>
</table>

Abbreviation: ELN, European LeukemiaNet.
Long-Term Prognosis of Acute Myeloid Leukemia According to the New Genetic Risk Classification of the European LeukemiaNet Recommendations: Evaluation of the Proposed Reporting System

Rollig et al JCO 2011, E 18 to 60 years; F > 60 years
Prognostic Utility of the European LeukemiaNet (ELN) Genetic-Risk Classification in Adults with De Novo Acute Myeloid Leukemia (AML): A Study of 1,550 Patients. Mrozek et al Abstract 414
### Molecular Mutations associated with AML Outcome

<table>
<thead>
<tr>
<th>Cytogenetic Risk Group</th>
<th>Subset</th>
<th>N (%)</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>CBF AML, NPM1 mutation or biallelic CEBPA mutation without any other molecular marker and no favorable or adverse cytogenetics</td>
<td>354 (35)</td>
<td>62.2</td>
</tr>
<tr>
<td>Intermediate I</td>
<td>FLT3-ITD ratio &lt;0.5 (without RUNX1 or MLL-PTD) and no favorable or adverse cytogenetics</td>
<td>157 (15.5)</td>
<td>24.3</td>
</tr>
<tr>
<td>Intermediate II</td>
<td>FLT3-ITD ratio ≥0.5 and/or RUNX1 mutation and/or MLL-PTD+</td>
<td>298 (29.5)</td>
<td>12.4</td>
</tr>
<tr>
<td>Adverse</td>
<td>inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1 t(6;9) (p23;q34); DEK-NUP214 t(v;11)(v;q23); MLL rearranged, -5 or del(5q); -7; abnl(17p); complex karyotype</td>
<td>201 (19.9)</td>
<td>8.7</td>
</tr>
</tbody>
</table>

**CBF Core Binding Factor; CEBPA CCAAT/enhancer-binding protein alpha; DEK, nuclear phosphoprotein; EVI1, ecotropic virus integration-1 ITD, Internal Tandem Deletion; MLL, Mixed Lineage Leukemia (Histone-lysine N-methyltransferase HRX), NPM1, Nucleophosmin; PTD, NUP, Nucleoporin; Partial Tandem Duplication; RPN1 Ribophorin; Runt-related transcription factor 1 (RUNX1) aka (AML1) or CBFA2);**

**Alpermann et al Evaluation of the New Genetic Risk Classification of the European LeukemiaNet Recommendations in 1,110 Patients with De Novo AML and Proposal of a Refined Version Abstract 413**
GENE MUTATIONS AS PREDICTIVE MARKERS FOR POSTREMISSION THERAPY IN YOUNGER ADULTS WITH NORMAL KARYOTYPE AML

- Individual Patient Data (IPD) meta-analysis of 872 younger adults (16-60 yrs) with normal karyotype AML entered on four AMLSG treatment trials between 1993 and 2004 - consistent features:
  - Double induction (ICE)
  - First consolidation (HiDAC)
  - Second consolidation (genetic allocation)
    - Family donor: allogeneic SCT (85%)
    - No family donor: HiDAC or autologous SCT
- Analysis of gene mutations in 509-577 patients:
  - NPM1, FLT3 ITD/TKD, CEBPA, NRAS, MLL

*Courtesy of Schlenk R et al, NEJM 2008*
Genetic Subgroup Analysis: RFS

NPM1+/FLT3 ITD-

Relapse-free Survival (%)

0 12 24 36 48 60 72 84 96

p=0.71

donor n=35

no donor n=92

Others

Relapse-free Survival (%)

0 12 24 36 48 60 72 84 96

p=0.02

donor n=45

no donor n=125

Courtesy of Schlenk R et al, NEJM 2008
MUD Transplantation in Relapsed Patients with Unfavorable Genotype

![Survival curve graph]

- **MUD n=37**
- **Other strategy n=67**

Survival after relapse (%)

- 0%
- 100%

Time (months)

- 0
- 24
- 48
- 60

Survival after relapse (%)

- 0
- 20
- 40
- 60
- 80
- 100

p<0.0001
Mouse Models of Hematopoietic Stem Cell Transplantation

Dr. Michael Nemeth
Ben Povinelli
Dr. J Thompson
Dr. K Lee

Dr. Xuefang Cao
Dr. Elizabeth Repasky
Maegan Capitano
Tara Wilkerson

Dr. Andrei Gudkov
Dr. Alexander Shakhov
Major Histocompatibility (MHC) Mismatch Model

- Examination of:
  - Graft-versus-Host Disease modulation
    - Robust immune response
    - Faster disease progression
    - Easily reproducible
  - Graft-versus-Leukemia
    - Transgenic mice are in C57BL/6
    - Tumor lines in different H-2 backgrounds
**Preparation of Donor Cells**

- **Femur**
- **Spleen**

**Anti-thy-1.2 mAB & Guinea pig C’ for 45 mins @ 37°C**

**Plastic Petri dish coated with goat α mouse Ab for 1 hr @ 4°C**

**T cell-depleted BM**

**Non-adherent (T cell-enriched) cells**

*Adapted from a slide, courtesy of M Capitano*
Murine Transplant Simplified

Less or No GvHD
Fewer T cells

More or Severe GvHD
More T Cells

800-1300 cGy

TCD Bone Marrow (1-2 x 10^6 cells) + increasing T cell doses (1-5 x 10^5)
Can we reduce the toxicities of make BMT?

• Can we identify patients at high risk for poor outcome prospectively and
  – modify BMT treatment?
  – intervene earlier in the course of BMT?
Pathways Investigated in Relation to Toxicity

• Metabolic
  – CYP2B6
  – CYP2C19
  – CYP3A4
  – CYP3A5
  – MTHFR
  – ABCB1

• Detoxification/ROS
  – GSTM1, T1, P1, A1
  – CAT
  – SOD
  – GPX
  – NQO1, NQO2
  – NOS
Pathways Investigated in Relation to Toxicity

• DNA Repair
  – XRCC1
  – XRCC2
  – XRCC3
  – XPD

• Immunomodulatory
  – IL1α, IL1β, IL1RN
  – IL2, IL4, IL6, IL10
  – TNFa, LTA
  – NR3C1
  – CARD15
  – CTLA4
  – PADI4
  – VDR
A deletion polymorphism in glutathione-S-Transferase Mu (GSTM1) and/or Theta (GSTT1) is associated with an increased risk of toxicity after autologous blood and marrow transplantation

Theresa Hahn, PhD
Evgenia Zhelnova, MD, PhD
Philip McCarthy, MD
Christine Ambrosone, PhD
Lara Sucheston, PhD
Irina Demidova, MD
Valeri Savchenko, MD
Minoo Battiwalla, MD
Shannon Smiley, MD

Funded by American Cancer Society
Roswell Park Alliance Foundation
Collaboration with the National Hematology Research Center in Moscow (not Idaho)
Study Population

• Selected from 699 consecutive first autologous and allogeneic BMT patients treated at
  – RPCI from 1/1996 to 12/2002 (N=496)
  – NRCH (Moscow) from 1/1996 to 12/2006 (N=203)

• 356 (51%) had procured bone marrow or peripheral blood samples available
• 321 (90%) yielded amplifiable DNA

# Rate of Grade 2-4 RRT by Organ Site

*RRT defined by Bearman et al JCO, 1988*

<table>
<thead>
<tr>
<th>Organ Site</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall RRT 2-4</strong></td>
<td><strong>56%</strong></td>
</tr>
<tr>
<td>Stomatitis RRT 2-4</td>
<td>46%</td>
</tr>
<tr>
<td>Renal RRT 2-4</td>
<td>13%</td>
</tr>
<tr>
<td>Cardiac RRT 2-4</td>
<td>7%</td>
</tr>
<tr>
<td>GI RRT 2-4</td>
<td>5%</td>
</tr>
<tr>
<td>Pulmonary RRT 2-4</td>
<td>5%</td>
</tr>
<tr>
<td>CNS RRT 2-4</td>
<td>4%</td>
</tr>
<tr>
<td>Hepatic RRT 2-4</td>
<td>4%</td>
</tr>
<tr>
<td>Bladder RRT 2-4</td>
<td>3%</td>
</tr>
</tbody>
</table>

*N=321*  

<table>
<thead>
<tr>
<th>Genotype</th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autologous BMT patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSTM1 Present</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Null</td>
<td>1.59</td>
<td>0.91 - 2.77</td>
<td></td>
</tr>
<tr>
<td>GSTT1 Present</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Null</td>
<td>1.25</td>
<td>0.63 – 2.48</td>
<td></td>
</tr>
<tr>
<td>GSTM1+/-GSTT1 Both Present</td>
<td>1.0</td>
<td></td>
<td>0.035</td>
</tr>
<tr>
<td>Either/Both Null</td>
<td>1.87</td>
<td>1.05 – 3.33</td>
<td></td>
</tr>
<tr>
<td><strong>Allogeneic BMT patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSTM1 Present</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Null</td>
<td>1.36</td>
<td>0.64 – 2.89</td>
<td></td>
</tr>
<tr>
<td>GSTT1 Present</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Null</td>
<td>0.72</td>
<td>0.31 – 1.70</td>
<td></td>
</tr>
<tr>
<td>GSTM1+/-GSTT1 Both Present</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Either/Both Null</td>
<td>1.26</td>
<td>0.57 – 2.75</td>
<td></td>
</tr>
</tbody>
</table>

What’s next?

• GSTM1 and GSTT1 SNP analysis while useful is limited as it does not account for other genetic influences.
• Can a candidate gene approach be useful for examining complications such as accelerated bone loss after BMT?
Genetic susceptibility to Bone Mineral Density (BMD) loss after Auto & Allo BMT

Song Yao, PhD
Theresa Hahn, PhD
Lara Sucheston, PhD
Philip McCarthy, MD
Shannon Smiley, MD
Minoo Battiwalla, MD
Kathy West, PharmD
Dominick Lamonica, MD

Funded by CALGB Young Investigator Award
A delicate balance between bone formation & resorption

Bone loss and risk of fracture

Modified from Khosla & Melton. NEJM 2007;356:2293-2300
Study population

• Prospective cohort study
• Jan 2006 - Jan 2009
• 206 adult (≥18 yrs) first consecutive auto and allo BMT patients
• Dual-energy x-ray absorptiometry (DXA or bone density scan), 25OH-D, Ca, PTH levels
  – Within 30 days pre-BMT
  – At ~ 100 days post-BMT
• No routine vitamin D or calcium supplementation

Yao, et al, BBMT 2010
Table 2. BMD Change between Baseline and Post-HCT DXA Scans by Autologous and Allogeneic Transplantation*

<table>
<thead>
<tr>
<th>BMD Measures</th>
<th>Autologous HCT</th>
<th>Allogeneic HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spine, Median (IQR)</td>
<td>Femur, Median (IQR)</td>
</tr>
<tr>
<td>BMD loss, adjusted to 100 days (g/cm²)</td>
<td>0.03 (0-0.05)</td>
<td>0.05 (0.04-0.08)</td>
</tr>
<tr>
<td>Annualized rate of BMD loss (%)</td>
<td>7 (0-14)</td>
<td>9 (0-19)</td>
</tr>
<tr>
<td>Ratio of observed/expected annual BMD loss rate (fold)‡</td>
<td>37 (3-112)</td>
<td>27 (12-46)</td>
</tr>
<tr>
<td>Years aged by the BMD loss within ~4 months after transplant</td>
<td>10 (1-31)</td>
<td>7 (3-13)</td>
</tr>
</tbody>
</table>

% annual decrease in BMD

![Graph showing expected and observed annual decrease in BMD]

Yao, et al., *BBMT* 2010
Osteoblasts/stromal cells

- **PTH/PTHrP**
- **VitD3**
- **Ca\(^{2+}\)**
- **RANKL**
- **OPG**
- **Wnt / Lrp5**
- **Collagen type I, osteocalcin, alkaline phosphatase, etc**
- **Calcineurin/NFAT**
- **M-CSF, G-CSF**
- **PGE\(_2\)**
- **COX2**
- **CYP19**
- **CYP27A1/B1**
- **CYP24**
- **Diet**
- **DBP**

Osteoclasts

- **RANK**
- **Ca\(^{2+}\)**
- **Bone resorption**

OC precursors

- **Differentiation, formation**
- **IL-1, IL-6, TNF-α**
- **TGF-β, IGF-1**

Estrogen

- **VDR**
- **PTHR**

Precursors

- **EP**
- **ER-α**

Mg\(^{2+}\)

Calcitonin

Absorption
Genes and SNPs selected

46 genes and 170 SNPs classified into 6 groups:

- 1. Cytokines and receptors
- 2. Bone matrix proteins and regulators
- 3. Vitamin D receptor / metabolism enzymes
- 4. Estrogen receptor / metabolism enzymes
- 5. PTH & GC
- 6. Miscellaneous

S Yao et al PLOS One 2011
<table>
<thead>
<tr>
<th>Pathway</th>
<th>Auto BMT, Spine</th>
<th>Auto BMT, Femur</th>
<th>Allo BMT, Spine</th>
<th>Allo BMT, Femur</th>
</tr>
</thead>
<tbody>
<tr>
<td>RANKL-RANK-OPG and regulating cytokines/receptors</td>
<td>None</td>
<td>IL1RN</td>
<td>RANKL *</td>
<td>RANKL *</td>
</tr>
<tr>
<td>Bone matrix proteins and regulating factors</td>
<td>BGLAP</td>
<td>MTHFR, ALOX12</td>
<td>None</td>
<td>COL1A1 *</td>
</tr>
<tr>
<td>Vitamin D receptor and metabolism enzymes</td>
<td>GC, CYP24A1</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Steroid hormones/receptors</td>
<td>None</td>
<td>ESR1 *</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
Proportion of variance in BMD loss attributed to clinical factors, SNPs and other risk factors

**Auto HCT, Spine BMD**
- Clinical Factors: 16%
- SNPs: 10%
- Other Factors: 35%

**Auto HCT, Femur BMD**
- Clinical Factors: 12%
- SNPs: 35%
- Other Factors: 12%

**Allo HCT, Spine BMD**
- Clinical Factors: 5%
- SNPs: 30%
- Other Factors: 5%

**Allo HCT, Femur BMD**
- Clinical Factors: 14%
- SNPs: 29%
- Other Factors: 29%
Future Directions

- Preventing BMD loss after BMT is important to prevent risk of fractures and other bone related complications
- >80% of pre-BMT patients are vitamin D insufficient/deficient
- Bisphosphonates require sufficient vitamin D levels and also affect cytokine levels
Genetic susceptibility to unrelated donor hematopoietic cell transplantation-related mortality

NIH (NHLBI) R01 HL107213-01A1
7/5/10-6/30/14

Multiple-PI:
Theresa Hahn, PhD
Dept of Medicine

Lara Sucheston, PhD
Dept of Cancer Prevention & Control
6 Institutions, 12 Investigators

Institutions:
- RPCI
- CIBMTR (Center for International BMT Research)
- NMDP (National Marrow Donor Program)
- Univ. Buffalo
- Univ. Chicago
- Univ. Southern California

Co-Investigators:
- Philip McCarthy, MD
- David Tritchler, DSc
- Marcelo Pasquini, MD
- Stephen Spellman, MBS
- Song Liu, PhD
- Tom Furlani, PhD
- Ken Onel, MD, PhD
- Chris Haiman, DSc
- Gary Chen, PhD
- David Van Den Berg, PhD
Opportunities for Improving Unrelated Donor (URD) BMT Outcome

– 5000 URD BMT occurred between 01/08 to 01/09
  • These 5000 are 21% of all URD BMT in the USA in past 21 yrs

– One year Mortality for matched URD
  • Treatment Related Mortality is 36%
    – Including GvHD, Infection, Multiorgan Failure
  • Death due to Leukemia Relapse is 12%

– 2 out of 3 eligible allogeneic BMT candidates do not have a suitable sibling donor and need a URD
Study population

• 2,800 recipients and their matched donors of 10/10 high-resolution HLA-matched unrelated donor allogeneic BMT from 2000-2008 reported to CIBMTR
• 1,000 recipient/donor pairs from 2009-2011
• Genome Wide Association Study (GWAS) of >1 million SNPs and CNVs
Genetic susceptibility to unrelated donor stem cell transplant-related mortality

- To determine the host and donor genetic contribution to survival (TRM, PFS, OS) after matched unrelated donor BMT
- To determine if the genetic contribution to survival varies by a) conditioning regimen intensity, b) myeloablative conditioning regimen (CyTBI vs BuCy)
- To replicate the top genetic associations in an independent cohort
Multiple Myeloma

• Induction therapy followed by autologous SCT alone will cytoreduce but not cure most Multiple Myeloma (MM) patients

• Can maintenance therapy:
  – prevent or delay disease progression?
  – convert partial responses to complete responses?
  – improve overall survival?
Which level of response should be measured?

Depth of response is related to TTP

Depth of response:
- Treatment initiation
- MR
- PR
- VGPR/ nCR
- CR
- sCR
- Molecular/Flow CR

Progression

TTP

Courtesy Dr. J San Miguel

MRD investigation in MM: molecular & Immunophenotypic tools
A rational combination therapy approach

Lonial et al
CCR 2011
Stage 1-3 <70 years
Therapy at least 2 cycles
Stable Disease or better
≤1 year from Rx initiation
2 x 10^6 CD34 cells/kg

Registration

Mel 200
ASCT

Restaging
Days 90–100

CR
PR
SD

Placebo

Lenalidomide
(CC-5013)
10 mg with ↑↓
(5–15 mg)

Stratification based on Diagnostic B2M and IMiD Use during Induction
ITT Analysis with a Median Follow-up from transplant of 28 months. P < 0.001 Estimated HR=0.38 (95% CI = 0.27 to 0.55),

CALGB 100104, IMW 2011 follow up to 04/17/2011
Median follow-up of 28 months

P = 0.018

CALGB 100104, follow up to 04/17/2011, IMW 2011

23 deaths in the lenalidomide arm and 39 deaths in the placebo arm
BMT CTN 0702 StaMINA (Stem Cell Transplant for MM incorporating Novel Agents): SCHEMA

Register and Randomize → MEL 200mg/m² → Lenalidomide Maintenance**

- VRD x 4*
- MEL 200mg/m² → Lenalidomide Maintenance**

* Bortezomib 1.3mg /m² days 1, 4, 8, 11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg days 1, 8, 15

**Lenalidomide 10 mg daily x 3mo then 15 mg daily. Total duration of maintenance 3 years

Courtesy M Pasquini
Arrows indicate time points for disease assessment for immunophenotyping BM samples for the PRIMeR Study.
People and Services who make the clinical BMT program possible

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There is always a patient involved in a BMT.
Thank you very much.