A Data Resource for Analyzing Blood and Marrow Transplants

Reissuance of RFA for U24 renewal
Center for International Blood & Marrow Transplant Research (CIBMTR)
Hematopoietic Stem Cell Transplantation (HSCT)

- Indications for HSCT: multiple myeloma, Non-Hodgkin lymphoma, Hodgkin disease, AML, ALL, MDS (92%) as well as aplastic anemia, sickle cell disease, etc. (8%)

- Donor types: Autologous and Allogeneic

- Sources: Bone marrow, Peripheral blood stem cells and Umbilical cord

- Increase in rate of utilization: 60,000 HSCT world wide in 2015 (doubled in 10 years mainly due to an increase in allogeneic HSCT from unrelated donors)

- Major challenges:
  - GVHD, infection, relapse and secondary malignancy
  - 1-year mortality rate among allogeneic HSCT recipients remains 30–40%
### NIH programs to improve outcomes of HSCT

#### BMT CTN (U01)
- Conduct large multi-institutional clinical Phase II and III trials
- Over 9000 patients accrued in 38 trials across 20 centers since 2003
- Patients followed only to primary and some secondary endpoints
- Co-funded by NHLBI & NCI (NHLBI 1º)
- RFA renewal released August 2016

#### CIBMTR (U24)
- Collects baseline data (donor/recipient) and post-transplant (outcomes) data and conducts observational research studies
- Clinical database of 425,000 patients, collected from more than 500 centers, ideal for population-based study
- Long-term follow up of transplant patients
- Co-funded by NCI/NHLBI/NIAID (NCI 1º)
- U24 renewal in 2018: requested for 5 years
CIBMTR registry is growing and extensively used

- CIBMTR is the ONLY data resource for BMT in the U.S.
  - 425K cases registered (baseline + long term follow up)
  - ~20K new cases each year (100% of allogenic and 80% of autologous transplants in the US)

- Data sharing
  - Standard annual reports (US Patient Survival Report, Current uses and outcomes of HSCT etc.)
  - Information request forms: 469 requests in 2015 (aiding the larger community with transplant related questions)
  - Research study proposals: 193 in 2015
CIBMTR: Observational Research

- Determine transplant outcomes for smaller subpopulations in common cancer, rare cancers, and underserved population
- Identify factors affecting transplant outcomes, such as age, stage of disease and conditioning regimens
- Determine efficacy of various donor types and graft sources
- Assess long-term quality of life and late complications after transplantation
- Define clinical trials priorities, trial design and likely accrual time frame (in BMT CTN)
Working Committees oversee observational research

- 15 working committees: Acute Leukemia, Chronic Leukemia, GVHD, etc.

- Highly productive process

<table>
<thead>
<tr>
<th>Research Proposal submission (193)</th>
<th>Working Committee triage</th>
<th>Proposal presentation at Working Committee (91)</th>
<th>Final approval and biostatistician assignment (38)</th>
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<tr>
<th>Peer-reviewed publications</th>
<th>2013</th>
<th>2014</th>
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<th>2016 (till Aug.)</th>
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<tbody>
<tr>
<td></td>
<td>40</td>
<td>48</td>
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Patients with FLT3 mutated AML have a poor prognosis and their recommendation for early HSCT was a controversial strategy.

CIBMTR analysis revealed that although FLT3 mutated AML patients have a higher risk of relapse after HSCT, there is no difference in Overall Survival.
Long-term follow up study: Is bone marrow or peripheral blood better for unrelated donor HSCT?

BMT CTN 0201: Peripheral Blood Stem Cells versus Bone Marrow from unrelated Donors

Finding - overall survival similar, cGVHD is higher after PB (Anasetti C et al, NEJM 2012, 367,1487-1496)

CIBMTR Long-term follow up for late effects: Patients receiving bone marrow had significantly less cGVHD, better MHI psychological well-being scores and more likely to be working at a job

Important finding toward recommending BM instead of PB for unrelated donor transplantation
CIBMTR using multiple sources to facilitate research

- Biorepository
  - 48,000 unrelated adult donor/cord - recipient pairs
    - National Marrow Donor Program (Department of Defense)
  - 5,000 related donor-recipient pairs
    - Health Resources and service Administration

- CIBMTR data
  - Clinical baseline data on specimens (NIH U24)
  - Clinical outcome data on specimens (NIH U24)

- Immunologic data
  - High resolution HLA data for 17,500 unrelated donor/cord recipients (Department of Defense)
  - KIR typing data for 10,000 unrelated donor/cord recipients (Department of Defense)

- In 2015, CIBMTR consolidated biospecimens under one management system and incorporated their information into the Integrated Data Warehouse (collaboration funded by different sources)

- Going forward, the repository will be increasingly useful to study genomics linked to clinical data in patients with heme malignancies to understand outcomes, toxicities, and survivorship issues
<table>
<thead>
<tr>
<th>Publications</th>
<th>Reference</th>
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<tbody>
<tr>
<td>High HLA-DP expression and graft-versus-host disease</td>
<td>Petersdorf EW et al., NEJM 2015: 373 (7): 599-609</td>
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<tr>
<td>Donor KIR B genotype improves progression-free survival of NHL patients receiving unrelated donor transplantation</td>
<td>Bachanova V et al., Biol. Blood Marrow Transplant 2016; 22 (9), 1602-1607</td>
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<td>Genome-wide study of cause-specific transplant-related mortality after HLA-matched unrelated donor allogeneic BMT for acute leukemia or MDS demonstrates unique, non-overlapping genetic associations (DISCOVeRY-BMT)</td>
<td>Hahn T et al., Biol. Blood Marrow Transplant 2016; 22 (3), S74-S75 (BMT Tandem meeting abstract)</td>
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<tr>
<td>Minimum information for reporting next generation sequence genotyping (MIRING): guidelines for reporting HLA and KIR genotyping via next generation sequencing</td>
<td>Mack SL et al., Human Immunology: 2015; 76 (12), 954-62</td>
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Biorepository research impact: Associating risk of acute GVHD with genetic makeup

_Biorepository (DoD), Clinical annotation of biospecimen (NIH U24), experimentation (NCI R01)_

With HLA-DPB1 mismatched HSCT (80%), certain recipients have high risk of GVHD

- rs9277534 allele regulates HLA-DPB1 expression
- rs9277534G genotype leads to high expression of the mismatched DPB1 allele and associated with higher GVHD risk as compared to rs9277534A

- Mismatching for G-linked HLA-DPB1-rs9277534 allele should be avoided in unrelated donor HSCT

Summary

- CIBMTR, observational database of HSCT outcomes, is supported by U24 (through 2/28/18), jointly by NCI, NHLBI and NIAID (NCI primary)

- Increase in use of transplant as a curative modality for heme malignances; CIBMTR has played substantial role in this progress

- External review panel strongly recommended continuation of support

**Enhanced emphasis in new grant period:**

- Linking long term outcomes for specifically defined patient subsets with genomic information

- Capture long term outcomes from clinical trials comparing transplant vs. non-transplant treatments
## Proposed Budget (total dollars, millions)

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<td><strong>3.9</strong></td>
<td><strong>4.0</strong></td>
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<td><strong>4.2</strong></td>
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* Increasing follow up burden; ** tentative: IC program directors are requesting

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<td>Reimbursement for data collection</td>
<td>1.77</td>
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<td>PI and co-investigators</td>
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<td>Biostatisticians (6)/Data Mgt. (3)/administrative (1.5) personnel</td>
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<td>Other (travel, supplies, publications etc.)</td>
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<td>Indirect cost</td>
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