A Data Resource for Analyzing Blood and Marrow Transplants

Reissuance of RFA for U24 renewal
Center for International Blood & Marrow Transplant Research (CIBMTR)

NIH NATIONAL CANCER INSTITUTE

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8th Joint Meeting of BSA and NCAB, December 6th, 2016

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-fund 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-fund by NCI/NHLBI/NIAID (NCI 1º)
- U24 renewal in 2018: requested for 5 years

CIBMTR registry is growing and extensively used

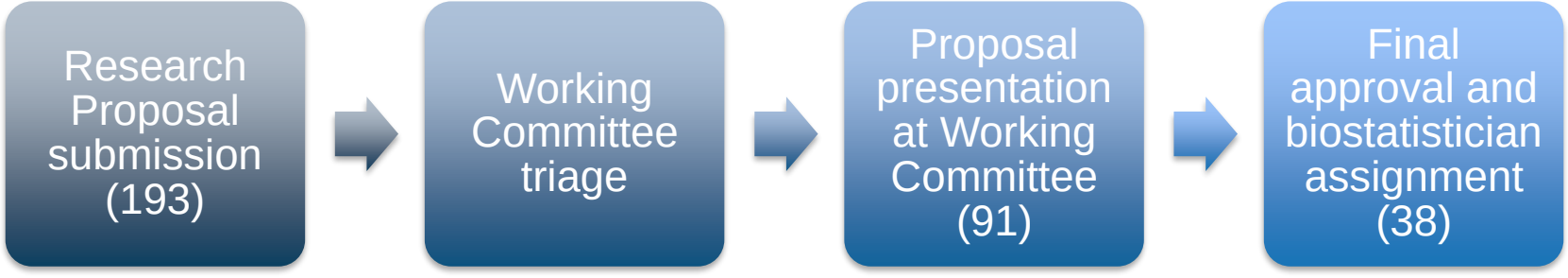
- CIBMTR is the ONLY data resource for BMT in the U.S.
  - 425K cases registered (baseline + long term follow up)
  - ~20K new cases each year (100% of allogenic and 80% of autologous transplants in the US)
- Data sharing
  - Standard annual reports (US Patient Survival Report, Current uses and outcomes 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.

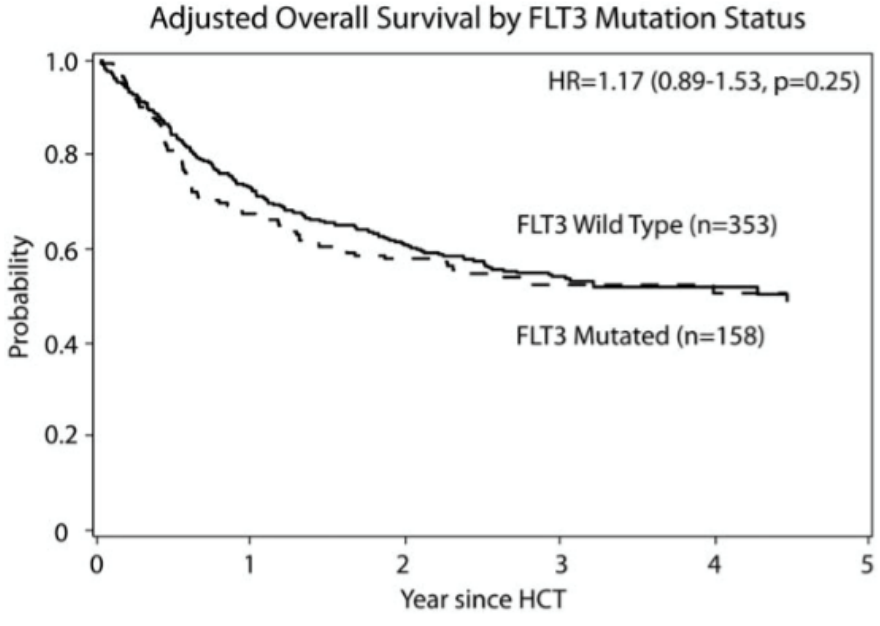


- Highly productive process

	2013	2014	2015	2016 (till Aug.)
Peer-reviewed publications	40	48	38	25

Observational research impact:
Does FLT3 mutation impact survival after HSCT for AML?

Patients with FLT3 mutated AML have a poor prognosis and their recommendation for early HSCT was a controversial strategy.



Deol A. et al, Cancer, 2016: June 17

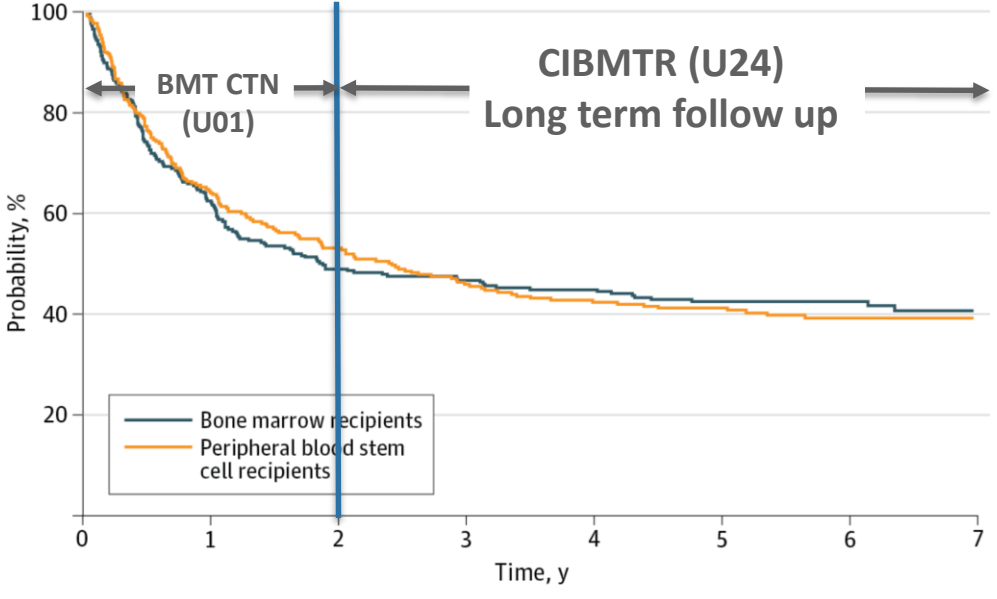
CIBMTR analysis revealed that although FLT3 mutated AML patients have a higher risk of relapse after HSCT, there is no difference in Overall Survival

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*)

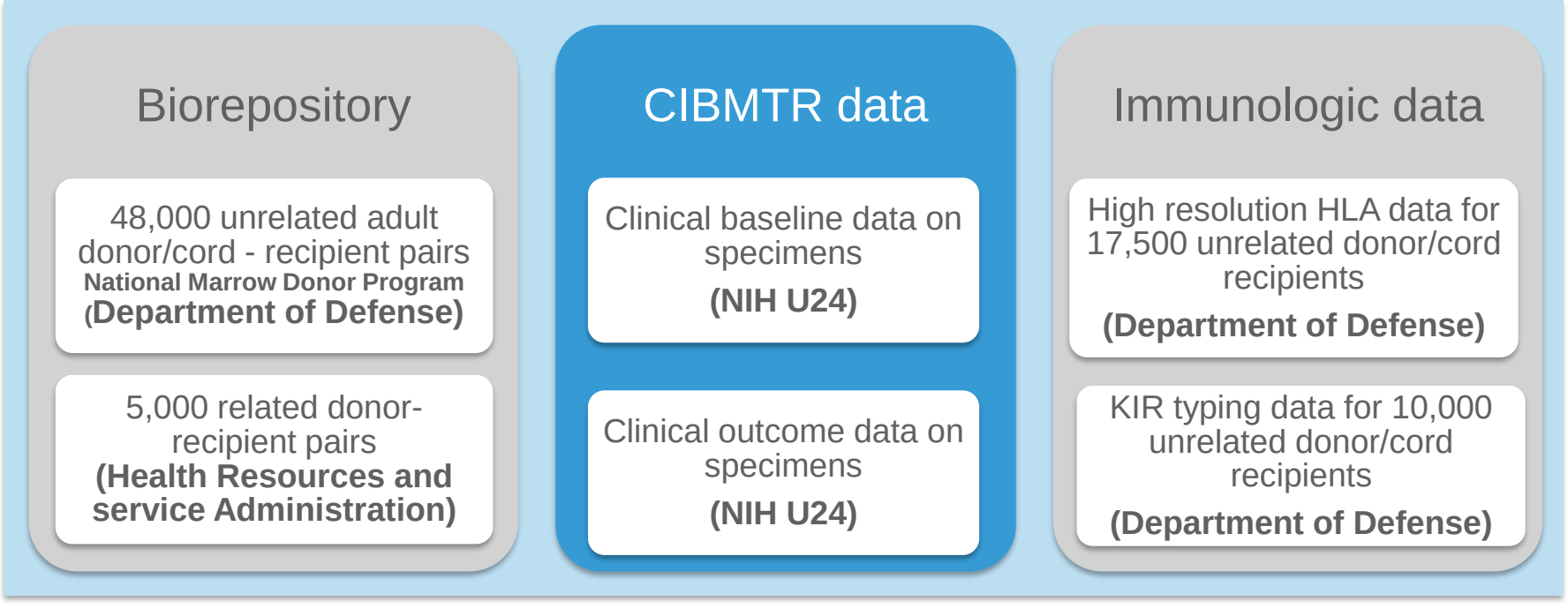
CIBMTR Long-term follow up for late effects: Patients receiving bone marrow had significantly less cGVHD, better MHI psychological well-being scores and more likely to be working at a job



Lee S et al., JAMA Oncology, 2016, Aug. 11

Important finding toward recommending BM instead of PB for unrelated donor transplantation

CIBMTR using multiple sources to facilitate research



- 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

Key publications from collaboration

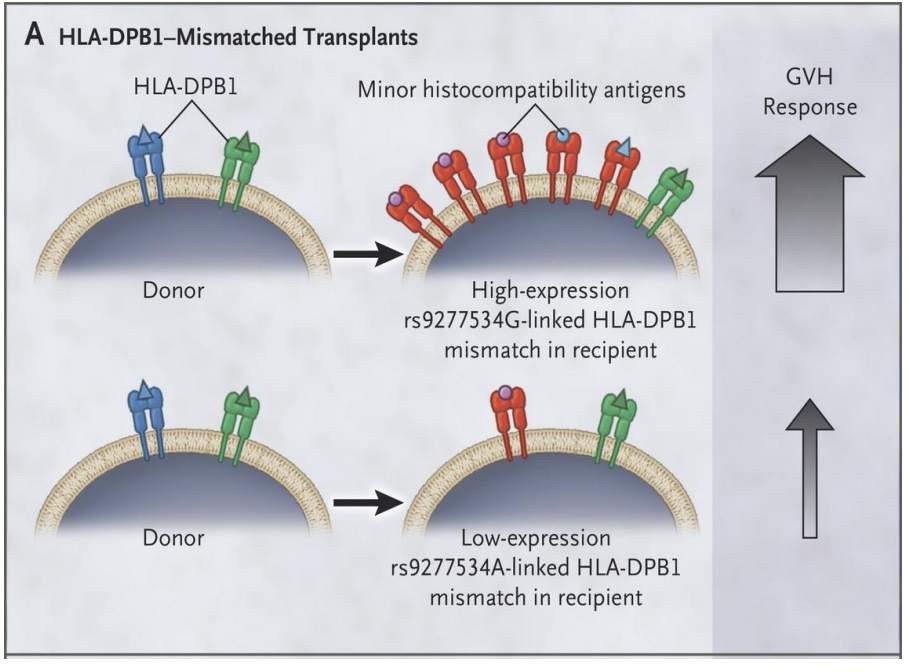
Publications	Reference
High HLA-DP expression and graft-versus-host disease	Petersdorf EW et al., NEJM 2015: 373 (7): 599-609
Donor KIR B genotype improves progression-free survival of NHL patients receiving unrelated donor transplantation	Bachanova V et al., Biol. Blood Marrow Transplant 2016; 22 (9), 1602-1607
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)	Hahn T et al., Biol. Blood Marrow Transplant 2016; 22 (3), S74-S75 (BMT Tandem meeting abstract)
Identification and Utilization of Donor and Recipient Variants to Predict Survival after HCT: Are we ready for Primetime?	Sucheston-Campell LE et al., Current Hematology Rep: 2015; 10(1), 45-59
Minimum information for reporting next generation sequence genotyping (MIRING): guidelines for reporting HLA and KIR genotyping via next generation sequencing	Mack SL et al., Human Immunology: 2015; 76 (12), 954-62

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**



Petersdorf EW et al. N Engl J Med 2015;373:599-609

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

<u>Enhanced emphasis in new grant period:</u>

- 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)

	FY 2013-2017	2018	2019	2020	2021	2022	Total
NCI	2.32	2.5*	2.5	2.5	2.5	2.5	12.5
NHLBI	0.97	1.0**	*1.1*	*1.1*	*1.2*	*1.25*	*5.65*
NIAID	0.30	*0.3*	*0.3*	*0.4***	*0.4*	*0.45*	*1.85*
Total	3.59	*3.8*	*3.9*	*4.0*	*4.1*	*4.2*	*20.0*

* Increasing follow up burden; ** tentative: IC program directors are requesting

	FY 2017
Reimbursement for data collection	1.77
PI and co-investigators	0.18
Biostatisticians (6)/Data Mgt. (3)/administrative (1.5) personnel	0.94
Other (travel, supplies, publications etc.)	0.05
Indirect cost	0.65
Total	3.59

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