

Allogeneic Hematopoietic Stem Cell Transplantation for Primary Immune Deficiency Diseases: Feasibility and Immune Reconstitution

Co-Sponsored by NIAID and the Office of Rare Diseases, NIH

Bethesda, MD, Monday-Tuesday, May 12-13, 2008

Workshop Agenda

This will be a full day and one-half meeting. Day 1 will begin at 8:00 am with presentation of the current data for allogeneic HCT for PIDD for the US and Canada (“Section A” below). The afternoon will continue with presentations from the individual working groups (“Section B” below), with discussion. Day 2 will begin at 8:00 am with presentation of the final considerations and recommendations from each of the individual working groups. The proceedings will be submitted to a peer reviewed journal for publication.

A. Review status of current data for allogeneic HCT for PIDD for the US and Canada.

Speakers	Aims; Comments
<p>Duke SCID BMT data – Rebecca Buckley (Duke)</p> <p>MSKCC SCID BMT data – Richard O’Reilly (MSKCC)</p> <p>Toronto SCID BMT data – Chaim Roifman (Toronto)</p> <p>PBMTC SCID BMT data (especially challenges of a multi-center clinical trial) – Naynesh Kamani (Children’s National Medical Center, Washington, DC)</p> <p>CIBMTR, an overview / analysis of North American data for PIDD – Mary Eapen (CIBMTR)</p> <p>European data, allogeneic HCT for PIDD, a summary (SCID and Non-SCID)- Luigi Notarangelo (Harvard)</p> <p>Allogeneic HCT for non-SCID, an overview – Alexandra (Lisa) Filipovich (Cincinnati)</p> <p>Life without transplant for Non-SCID PIDD (especially Wiskott-Aldrich syndrome) – Kathleen Sullivan (CHOP / Penn)</p>	<p><u>Aims:</u> The steering committee will develop a common list of questions to be addressed by each of the speakers.</p> <p><u>Comments:</u> We will assemble this data as best we are able prior to the workshop and provide in advance to all participants for their consideration prior to arrival at the spring workshop.</p> <p>The focus of these presentations will be the North American data.</p>

B. Working groups.

1) SCID (including SCID with residual T cell function, and other “leaky SCID”)

- a. Case-control retrospective study – design**
- b. Prospective study - design**
- c. Immunologic mechanistic ancillary studies (see note)**

Note: a representative of the SCID group will participate in the Laboratory Studies group

Investigators	Aims; Comments / questions to consider
<p>Jennifer Puck (UCSF; group chair; liaison with Group #3 Core Labs; ad hoc liaison with Group #5 Databases)</p> <p>Mort Cowan (UCSF; group co-chair)</p> <p>Rebecca Buckley (Duke; ad hoc liaison with Group #5 Databases)</p> <p>Neena Kapoor (CHLA/USC)</p> <p>Luigi Notarangelo (Harvard)</p> <p>Richard O’Reilly / Trudy Small (MSKCC)</p> <p>Chaim Roifman (Toronto, CANADA)</p> <p>Donald Kohn (CHLA/USC; gene therapy representative)</p>	<p><u>Aims:</u></p> <ol style="list-style-type: none"> 1. Design an observational (cross sectional retrospective) study for allogeneic HCT for SCID. 2. Design a prospective study for allogeneic HCT for SCID. 3. Propose immunologic mechanistic / ancillary assessments for the above clinical trials, working in collaboration with Group #3 Core Labs 4. Identify long-term outcomes, QAL, 2nd effects of particular importance for SCID, and communicate this summary to Group #4 Long-Term Outcomes. <p><u>Comments / questions to consider:</u></p> <p>Subgroup to present a first draft suggestion in February for a retrospective study for SCID.</p> <p>Subgroup to present a first draft suggestion in February for a prospective study for SCID.</p> <p>Depending on the type of SCID diagnosis, a chemotherapy preparative regimen for HCT may / may not be an option considered.</p>

2) Non-SCID

a. Case-control retrospective study – design

b. Prospective study - design

c. Immunologic mechanistic ancillary studies (see note)

Note: a representative of the non-SCID group will participate in the Laboratory Studies group

Investigators	Aims; Comments / questions to consider
<p>Alexandra (Lisa) Filipovich (Cincinnati; group chair)</p> <p>Joanne Kurtzberg (Duke; group co-chair)</p> <p>Hans Ochs (Univ. Washington; liaison with Group #3 Core Labs)</p> <p>Raif Geha (Harvard)</p> <p>Steve Holland (NIAID, Clinical Center, NIH)</p> <p>Elizabeth Kang (NIAID, Clinical Center, NIH)</p> <p>Harry Malech (NIAID, Clinical Center, NIH; gene therapy representative)</p> <p>Fabio Candotti (NHGRI; gene therapy representative)</p>	<p><u>Aims:</u></p> <ol style="list-style-type: none"> 1. Design an observational (cross sectional retrospective) study for allogeneic HCT for non-SCID. 2. Design a prospective study (or studies) for allogeneic HCT for non-SCID. 3. Propose immunologic mechanistic / ancillary assessments for the above clinical trials, working in collaboration with Group #3 Core Labs 4. Identify long-term outcomes, QAL, 2nd effects of particular importance for non-SCID, and communicate this summary to Group #4 Long-Term Outcomes. <p><u>Comments / questions to consider:</u></p> <p>Common feature for all of these diagnoses – they all need the same type of conditioning. You must use chemo preparative regimen for HCT for these patients.</p> <p>A viable research question would be to look at myeloablative vs. NST, enroll all of these disease diagnoses, and then stratify based on the disease diagnosis.</p> <p>The type /extent of chimerism attained that is needed for CGD may / may not be different from hyper IgM.</p> <p>Given increased risks of BMT for non-SCID, as compared to SCID, need to weigh BMT vs. no BMT, so natural history studies are critical.</p> <p>Risk factors for morbidity/mortality (null mutation genotype, older age, infectious complications, autoimmunity, etc) need to be defined so approach to BMT, gene therapy risk benefit can be understood.</p>

3) Laboratory ancillary evaluations / studies core, including immune reconstitution and response criteria (see note)

Note: this group will work together with a representative of the SCID group and a representative of the non-SCID group to consider testing that could be merged into a core facility.

Investigators	Aims; Comments / questions to consider
<p>Thomas Fleisher (Division of Laboratory Medicine, Clinical Center, NIH; group chair)</p> <p>Robertson Parkman (CHLA; co-chair)</p> <p>Jacob (Jack) Bleesing (Cincinnati)</p> <p>Mary Ellen Conley (St. Jude)</p> <p>Naynesh Kamani (Children’s National Medical Center, Washington, DC)</p> <p>Trudy Small (MSKCC)</p> <p>Jennifer Puck (UCSF; liaison from Group #1 SCID)</p> <p>Hans Ochs (Univ. Washington; liaison from Group #2 non-SCID)</p> <p>Fran Hakim (NCI; ad hoc consult immune reconstitution after HCT)</p> <p>Linda Griffith (NIAID; ad hoc)</p>	<p><u>Aims:</u></p> <ol style="list-style-type: none"> 1. Specify diagnostic criteria and diagnostic tests for disease. 2. Specify immune reconstitution criteria and tests. 3. Relative merits central core labs vs. local institutional labs. <p><u>Comments / questions to consider:</u></p> <p>What is the baseline testing needed to make the diagnosis and determine optimal treatment; what is the appropriate follow-up testing for all patients; for specific diagnoses.</p> <p>Which tests can / should be merged into a core facility. Work with the Groups #1 and #2 to develop / discuss which tests could be merged into testing at a core facility.</p> <p>What would be needed to standardize a particular test over multiple test sites.</p> <p>Discuss relative merits / use of commercial labs.</p>

4) Long-term outcomes, QOL, 2nd effects

Investigators	Aims; Comments / questions to consider
<p>William Shearer (Texas Children’s Hospital / Baylor, Houston, TX; group chair)</p> <p>Kirk Schultz (Vancouver, CANADA; group co-chair)</p> <p>Scott Baker (Univ. Minnesota)</p> <p>Rebecca Buckley (Duke)</p> <p>Jean Sanders (FHCRC)</p> <p>Kathleen (Kate) Sullivan (CHOP / Penn)</p> <p>Wendy Packman (Pacific Grad. Sch. of Psychology, Redwood City, CA)</p>	<p><u>Aims:</u></p> <ol style="list-style-type: none"> 1. Propose a plan for long term follow-up that will be applicable / common to all allogeneic HCT for PID studies. 2. Propose a plan for long term follow-up to address issues specific to individual PID diagnoses. 3. Identify issues in long term follow-up that may complicate / challenge full compliance with the protocol.

5) CIBMTR / USIDNET - data harmonization / communication, specifics of each database

Investigators	Aims; Comments / questions to consider
<p>Luigi Notarangelo (Harvard; summarize problems encountered in European database; group chair)</p> <p>Hans Ochs (Univ. Washington)</p> <p>Mary Eapen (CIBMTR Associate Medical Director for Immune Deficiencies / Inborn Errors Working Group / Medical College of Wisconsin)</p> <p>Mary Horowitz (CIBMTR Chief Scientific Director / Medical College of Wisconsin)</p> <p>Rebecca Buckley (Duke; ad hoc)</p> <p>Alexandra (Lisa) Filipovich (Cincinnati; ad hoc)</p> <p>Jennifer Puck (UCSF; ad hoc)</p> <p>TBA (USIDNET / Immune Deficiency Foundation, Towson, MD) (John Boyle is coordinator of data fields and languages and will serve as an interim resource if needed) (Michael Blaese is an administrator and will serve as an interim resource if needed) (Charlotte Cunningham-Rundles, Mount Sinai is an interim resource if needed)</p> <p>Linda Griffith (ad hoc; NIAID PO CIBMTR)</p> <p>Josiah Wedgwood (ad hoc; NIAID PO USIDNET)</p>	<p><u>Aims:</u></p> <p>1. Develop a proposal as to how USIDNET and the CIBMTR will coordinate database activities regarding non-transplanted and transplanted patients. Build on the successful experience with the European SCETIDE Registry for HSCT in PIDs, and compare with the CIBMTR Registry and the provisional disease-specific USIDNET sub-registries, in order to come with a single Registry that can be applied to all forms of PID treatable by HSCT.</p> <p>2. For the retrospective studies - develop realistic estimates of how many patients exist / are available for study. (Suggest the database folks will need to work with groups #1 and #2 very closely to try to calculate early estimates to present at the February meeting).</p> <p>3. For the prospective studies - develop realistic estimates of how many new PIDD patients are diagnosed per year. Specifically, how many new SCID, WAS, and CGD patients are diagnosed each year in the US? How many of the WAS and CGD don't get transplanted? (Suggest the database folks will need to work with groups 1 and 2 very closely to try to calculate early estimates to present at the February meeting).</p> <p><u>Comments / questions to consider:</u></p> <p>The immunologists will be following the non-transplanted patients. This group is important as a comparison to the transplanted group (USIDNET database).</p> <p>Some events are specific to patients who are transplanted (CIBMTR database).</p> <p>Consider issues of data / forms harmonization for CIBMTR and USIDNET.</p> <p>Group #4 and Group #5 will need to communicate – LTFU will need to be captured in the allogeneic HCT (CIBMTR) and non-transplant (USIDNET) databases.</p> <p>The statistical expertise resides within the CIBMTR, so the analyses from the databases (CIBMTR and USIDNET databases, when data is</p>

	<p>used from both databases) should be performed by CIBMTR.</p> <p>Consider issue of required vs. voluntary reporting.</p> <p>Consider issues of access / “ownership” and collaboration.</p>
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