NAS Forum on Regenerative Medicine
Hematology and Immunology Session II
Transplant and Gene Therapy for Monogenic Diseases

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Allogeneic Hematopoietic Stem Cell Transplant for Monogenic Diseases

Has become or is becoming the standard of care as curative therapy for:

- Hemoglobinopathies and inherited bone marrow failure syndromes
- Primary immune deficiencies
- Lysosomal storage diseases, some metabolic enzyme deficiencies and leukodystrophies
Successful transplant requires:

• A suitably HLA matched donor

• An adequate and safe conditioning regimen to achieve permanent engraftment

• A preventative regimen to reduce or prevent graft versus host disease

• Prevention, detection and effective treatment of virus, bacterial and fungal infections
Allogeneic Hematopoietic Stem Cell Transplant for Monogenic Diseases

Current commonly used transplant regimens:

- **Donor:** HLA matched sibling or matched unrelated donor found through National Marrow Donor Program

- **Conditioning regimen:** Deplete lymphocytes with chemotherapy/radiation/serotherapy; Deplete hematopoietic stem cells with chemotherapy/radiation.

- **Prevent GVHD:** Immune suppressors or tolerance inducing agents

- **Infection:** Early virus detection PCR – antivirus agents; Improved bacterial/fungus detection – New antibiotics.
Allogeneic Hematopoietic Stem Cell Transplant for Monogenic Diseases

Transformative emerging technologies/approaches:

- **Donor**: Expanding the donor pool through approaches allowing use of haploidentical related donors.

- **Conditioning regimen**: Serotherapy to replace radiation or alkylating agents to target hematopoietic stem cells.

- **Prevent GVHD**: Eliminating alloreactive T cells.

- **Infection**: Retaining anti-viral T cells; Treatment with virus specific donor or third party T cells.
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Expanding the donor pool: Haploidentical related donors.


NIH Haplo Donor Conditioning Regimen

-7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8

- 200cGy graft

Fludarabine 30mg/m2
Cyclophosphamide 14.5mg/kg
Busulfan 3.2mg/kg
Cyclophosphamide 50mg/kg
Sirolimus
Outcome to date 2014-2016 of a haplo donor protocol: Chronic Granulomatous Disease (group of disorders with mutations in subunits of the neutrophil microbicidal oxidase, leading to recurrent life-threatening infections and autoinflammation)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Donor</th>
<th>GvHD</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 - Gp91</td>
<td>Father</td>
<td>Grade 1 gut, resolved with steroids</td>
<td>2 years post, doing well</td>
</tr>
<tr>
<td>#2 - Gp91</td>
<td>Father</td>
<td>Grade 1 gut, resolved with steroids</td>
<td>1 year post, doing well, still with PLE*</td>
</tr>
<tr>
<td>#3 - P47</td>
<td>Brother</td>
<td>Grade 2 gut and skin including eyes, resolving</td>
<td>100 days post, GvHD resolving with steroids and tacrolimus</td>
</tr>
<tr>
<td>#4 - P67</td>
<td>Mother</td>
<td>Grade 1 gut, resolved</td>
<td>100 days post, doing well</td>
</tr>
<tr>
<td>#5 - Gp91</td>
<td>Father</td>
<td>Grade 1 gut, resolved with steroids</td>
<td>60 days post, doing well</td>
</tr>
</tbody>
</table>
Allogeneic Hematopoietic Stem Cell Transplant for Monogenic Diseases

Replacing alkylating agents/radiation for marrow stem cell clearance conditioning: Serotherapy.

- Anti-c-Kit monoclonal antibodies to deplete HSCs from bone marrow niches with enhancement of the Fc-mediated antibody effector activity through simultaneous blockade of CD47, a myeloid-specific immune checkpoint, extends anti-c-Kit conditioning to fully immunocompetent mice. Such a targeted conditioning regimen that uses only biologic agents has the potential to transform the practice of HSC transplantation and enable its use in a wider spectrum of patients. Chhabra A, Ring AM, Weiskopf K, Schnorr PJ, Gordon S, Le AC, Kwon HS, Ring NG, Volkmer J, Ho PY, Tseng S, Weissman IL, Shizuru JA. Hematopoietic stem cell transplantation in immunocompetent hosts without radiation or chemotherapy. Sci Transl Med. 2016 Aug 10;8(351):351ra105.

- Further development of the concept such as use of toxin conjugated antibodies or development of anti-cKit CAR T-cells might improve the efficacy of this approach, though off-target effects must be considered.
Adding to the already known agents that induce tolerance and prevent GVHD (rapamycin, cyclosporine A, tacrolimus, mycophenolate mofetil, methotrexate); There is a pressing need for development of new targets to prevent GVHD:

Highly effective measures to prevent GVHD may be associated with increased risk of virus infection in the early post transplant period: Virus specific T cell therapies

Serious viral infections are a common cause of morbidity and mortality after allogeneic stem cell transplantation, particularly with enhanced approaches to prevent GVHD despite improvements in early detection by digital drop pcr and improved antivirus drugs. Virus specific donor or third party T cells are increasingly being used to reduce mortality and provide a bridge to the re-acquisition of T cell immunity in post-transplant patients. Leen AM1, Heslop HE, Brenner MK. Antiviral T-cell therapy. Immunol Rev. 2014 Mar;258(1):12-29.
Integrating Vector Transduced Autologous Hematopoietic Stem Cell Transplant Gene Therapy for Monogenic Diseases

In the last 15 years there have been an accelerating number of published reports of clinical trials demonstrating significant unequivocal long-lasting clinical benefit from integrating vector autologous HSC gene therapy (See: Malech HL, Ochs HD. An emerging era of clinical benefit from gene therapy. JAMA. 2015 313:1522) and many current trials for these and related monogenic disorders that are in progress:

- **Hemoglobinopathies**
- **Primary immune deficiencies**
- **Leukodystrophies**
Clinical trial reports demonstrating significant unequivocal long-lasting clinical benefit:


Clinical trial reports demonstrating significant unequivocal long-lasting clinical benefit:


Integrating Vector Transduced Autologous Hematopoietic Stem Cell Transplant Gene Therapy for Monogenic Diseases

Clinical trial reports demonstrating significant unequivocal long-lasting clinical benefit:


Clinical trial reports demonstrating **significant unequivocal long-lasting clinical benefit**:


Restoration of immunoglobulin production in older X-SCID patients treated with lentivector transduced autologous HSC with prior busulfan conditioning.

P1, P2 & P3: Serum IgG and IgM (from De Ravin SS, et al. Sci Translat Med 2016 8:335ra57)

Subjects 1 & 2 became supplemental IgG independent and responded with protective titers to tetanus, diphtheria, menigococcus & influenza immunization. Significant restoration of humoral immunity was also seen in the Wiskott-Aldrich studies using busulfan conditioning and lentivector transduction.
Self-inactivating lentivirus vectors appear to be the current lead agent, but related integrating vectors need to be explored and there is a need for transformative emerging technologies/approaches in the following areas:

- **Enhancing receptivity of HSC to transduction.**
- **Less toxic marrow HSC conditioning regimens.**
- **Can lentivector or related integrating vectors (foamy virus vectors for example) be developed that can be delivered and targeted to HSC in vivo (i.e. “drugable” versions of integrating vectors)?