Transplant and gene therapy for inborn errors of immunity

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Oncology Nursing Brown Bag Lunch, Center for Cancer Research, NCI

Disclosures

I have no conflict of interests to disclose

I will discuss off-label use of a variety of medications used in pediatric transplantation, and off-label use of the CliniMACS device of Miltenyi Biotec
Overview

- Background on inborn errors of immunity and treatment with cellular therapy
- Overview of current trials in ID-CTP
- Transplant for SCID → CSIDE trial
- Gene Therapy for inborn errors of immunity
  - X-linked SCID
  - Wiskott-Aldrich syndrome
  - DOCK8 deficiency (in development)

Overview of immune cells and functions

- Neutrophils: Phagocytosis, Produce bactericidal reactive oxygen species
- Macrophages: Phagocytosis, Antigen presentation, Clearance of debris
- Dendritic cells: Antigen presentation, Phagocytosis
- Natural killer (NK) cells: Kill virally infected cells, Kill tumor or foreign cells
- CD3/CD4 T cell: Cellular immunity, Help B cells class switch, Help CD8 T cells kill
- CD3/CD8 T cell: Cellular immunity, Cytolytic activity
- B cells: Make antibody, Antibodies opsonize bacteria, Antigen presentation

BACTERIA/FUNGI contribute to all VIRUSES (esp DNA viruses) VIRUSES PNEUMOCYSTIS FUNGI BACTERIA (esp encapsulated)
The number of defined PIDs, many with genetic causes, is now ≈350 ~450

The vast majority of these are amenable in theory to correction with cellular therapy.

HCT for primary immunodeficiency at Boston Children’s Hospital

PID BMT volume (unique patients) 1991-2019

Fiscal year

56 patients, 5 dx
(1971-2003, 32 years)

Contributed cases for multi-institutional papers
DOCK8, TTC7A, IPEX

Aydin et al JACI 2015
Kammermeier et al Blood 2016
Barzaghi et al JACI 2018

Boston leading
NEMO (2)
Paiz et al JACI 2008
Permaul et al Imm Res 2009
DOCK8 (11)
McDonald et al JACI 2010
Al-Herz, Chu et al JACI 2016
TTC7A (1)
Chen et al JACI 2013
ICOS, OX40L, FASL, DOCK2
(1-2 each)
Chou et al JACI 2015
Chou et al JACI 2015
Sobh et al JACI 2016
Alosaimi et al JACI 2019
TRFC (5)
Whangbo et al JACI In Practice 2021

SCID, Omenn, WAS, DOCK8, IPEX, CGD, LAD

OCD, 10

ICOS, LIMEA, CD40, CR4, CD22, CD80, CD86

ICOS, ORAI1, FASL, DOCK2

TRFC

Other 23

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Survival of different disease types after allo HSCT in Boston

The general goal of cellular therapy is to replace the long-term HSC
Conditioning eliminates HSC and progenitors

After transplant, HSC and all progeny are donor-derived
After transplant, HSC and all progeny are donor-derived

ID-CTP Protocols

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<thead>
<tr>
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<th>PI</th>
<th>Approval date</th>
<th>Accrual to date</th>
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<td>13-C-0132</td>
<td>Allogeneic HSCT for pts with GATA2 or Monomac</td>
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<td>20-C-0070</td>
<td>Allogeneic HSCT for pts with Primary Immune Deficiency</td>
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<td>2020-03-17</td>
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<tr>
<td>15-C-0067</td>
<td>Dose escalation of palifermin after unrelated donor HSCT</td>
<td>Pavletic</td>
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<td>16-C-0060</td>
<td>Alvelestat, an oral neutrophil elastase inhibitor, in bronchiolitis obliterans after allogeneic HSCT</td>
<td>Pavletic</td>
<td>2016-01-13</td>
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<td>16-C-0094</td>
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<td>19-C-0136</td>
<td>KD025 (ROCK inhibitor) in refractory chronic GVHD</td>
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<td>20-C-0058</td>
<td>Front-line ibrutinib for newly diagnosed chronic GVHD</td>
<td>Pavletic</td>
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Transferring/upcoming

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<td>Allogeneic HSCT for pts with DOCK8 deficiency</td>
<td>Shah → Gonzalez</td>
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<tr>
<td>TBA</td>
<td>Allogeneic HSCT for pts with VEXAS</td>
<td>Hickstein</td>
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Overview

- Background on inborn errors of immunity and treatment with cellular therapy
- Overview of current trials in ID-CTP

- Transplant for SCID → CSIDE trial
- Gene Therapy for inborn errors of immunity
  - X-linked SCID
  - Wiskott-Aldrich syndrome
  - DOCK8 deficiency (in development)

Background on severe combined immunodeficiency (SCID)

A congenital disease in which babies are born without T lymphocytes

<table>
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<tr>
<th>Genetic subtypes</th>
<th>B cells present (B+ SCID)</th>
<th>B cells absent (B- SCID)</th>
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<tr>
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<td>Cytokine receptor</td>
<td>CD3 &amp; other</td>
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<td>Recombination defects</td>
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<td></td>
<td></td>
<td>Metabolic defects</td>
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<tr>
<td>IL2RG (X-linked)</td>
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<td>CD3D CD3E CD45</td>
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<tr>
<td>JAK3 IL7R</td>
<td>RAG1 RAG2 DCLRE1C (Artemis)</td>
<td>ADA PNP</td>
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<td>IL7R</td>
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- Death by 1 year of life from opportunistic infection
- B cells if present fail to function without T cells → no antibody production
- Lack of T cells and inability to reject permits allogeneic transplant without stem cell ablation or immunosuppression
SCID is special—HCT can be performed without conditioning

Healthy donor

matched sibling

haplo parent

T cell depletion or post-transplant cyclophosphamide

Cyclophosphamide
Fludarabine
ATG
Campath

Busulfan
Melphalan
Treosulfan

Transplant

Well

T cells

Reconstitution after cellular therapy for SCID with and without conditioning

The strong selective advantage of donor-derived or gene transduced T cells underlies the success of cellular therapy for SCID
Historically “all or nothing” approach
Now we know some SCID patients need conditioning for good outcome

Reconstitution after cellular therapy for SCID with and without conditioning

The Primary Immune Deficiency Treatment Consortium (PIDTC)

NIAID funded consortium (U54-AI082973) with ORDR founded 2009
Recently refunded through 2024
Goal: To analyze outcome of HCT for PIDs such as SCID and determine factors important for survival and immune reconstitution

Natural history studies in SCID, Wiskott-Aldrich syndrome, chronic granulomatous disease, primary immune regulatory disorders
Interventional transplant trial: CSIDE for SCID
What factors are important for survival after HCT for patients with SCID in North America?

Transplantation Outcomes for Severe Combined Immunodeficiency, 2000–2009
Sung-Yun Pai, M.D., Brent R. Logan, Ph.D., Linda M. Griffin, M.D., Ph.D., Rebecca H. Bailey, M.D., Robert B. Larrick, B.S., Christopher C. Duran, M.D., Nenu Kappor, M.D., Ireneza C. Hanson, M.D., Alexandra Filipovich, M.D., Samir Jain, M.D., Kathleen E. Sullivan, M.D., Ph.D., Trudy H. Sigmund, M.D., Laura Barmbrack, M.D., Gaurav Sindhu Srinivas, M.D., Ann E. Hogge, M.D., Audra Grizzle, M.P.H., Michael A. Schipper, M.D., Ka-Wai Chee, M.D., Ramesh L. Fabre, M.D., Da-Haddad, M.D., Ph. D., Brent Lockelt, M.D., Victor M. Aquino, M.D., Alfred Collins, M.D., Jeffrey Davis, M.D., Alan Grunen, M.D., Angela R. Smith, M.D., Theodore E. Moore, M.D., Marlis L. Schneider, M.D., Frederick G. Goldman, M.D., James A. Connelly, M.D., Matthew H. Portas, M.D., Ph.D., Quan Xiong, M.S., William T. Shearer, M.D., Ph. D., Thomas A. Fischer, M.D., Donald R. Kohn, M.D., Jennifer M. Fudk, M.D., Luigi D. Nistazian, M.D., Morton J. Cowan, M.D., and Richard J. O'Reilly, M.D.

Retrospective study of 240 patients with SCID transplanted at 25 PIDTC institutions 2000-2009
(typical SCID only)

NIH/NIAID funded: U54AI082973

Donor, age and infection status impact survival

Haddad et al, Blood 2018
Genotype impacts survival

Survival in 571 patients after HCT (excluding matched sibling donors)

B+ SCID (IL2RG/JAK3, IL7R, CD3)
RAG1/RAG2

ADA
DCLRE1C
unknown

None/IS vs. RIC/MAC mortality

Conditioning and genotype impact immune reconstitution

T cell reconstitution at 2-5y (CD3 >1000, CD4 >500, PHA response)

- Conditioning
  HR 9.77, p<0.001

- Genotype
  IL2RG/JAK3 = IL7R/CD3 = ADA > DCLRE1C, unknown > RAG1/2

B cell function at 2-5y (Independence from Ig substitution)

- Conditioning
  HR 5.39, p<0.001

- Donor type
  Matched relatives and unrelated donors > Haploidentical related donors

- Genotype
  IL7R/CD3 = ADA > IL2RG/JAK3 = RAG1/2 = DCLRE1C > unknown

RAG1/2

<table>
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<tr>
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<th>None/IS</th>
<th>RIC/MAC</th>
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<tbody>
<tr>
<td>6 mos</td>
<td>CD3 &gt;1000 0% 61.5%</td>
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<tr>
<td></td>
<td>CD4 &gt;500 0% 61.5%</td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td>CD3 &gt;1000 0% 55.6%</td>
<td></td>
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<tr>
<td></td>
<td>CD4 &gt;500 0% 66.7%</td>
<td></td>
</tr>
<tr>
<td>2 years</td>
<td>CD3 &gt;1000 0% 88.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD4 &gt;500 0% 88.9%</td>
<td></td>
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<tr>
<td>Off IgG</td>
<td>0% 60%</td>
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IL2RG/JAK3

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<th></th>
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<th>RIC/MAC</th>
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<tr>
<td>6 mos</td>
<td>CD3 &gt;1000 51% 44.1%</td>
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<tr>
<td></td>
<td>CD4 &gt;500 52.5% 55.9%</td>
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<tr>
<td>1 year</td>
<td>CD3 &gt;1000 72% 84.4%</td>
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<tr>
<td></td>
<td>CD4 &gt;500 72.8% 84.4%</td>
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<tr>
<td>2 years</td>
<td>CD3 &gt;1000 80.4% 100%</td>
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<td></td>
<td>CD4 &gt;500 67% 96.2%</td>
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<tr>
<td>Off IgG</td>
<td>16.7% 74.2%</td>
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</table>
IL2RG/JAK3 SCID B cells are intrinsically unresponsive to IL-21 signaling despite T cell help from donor-derived TFH after HSCT

Healthy

IL2RG/JAK3 SCID post-HCT

Conditioning is needed for some types of SCID to improve T cell numbers and B cell function

Conditioning:
- Replaces HSC with donor HSC
- Improves T cell output by providing continuous seeding of thymus with donor cells
- Leads to development of donor-derived B cells

Can we use less conditioning?
Do different genetic forms need different amounts of conditioning?

Dvorak et al J Allergy Clin Immunol 2014
Haddad et al Blood 2018
Heimall et al Blood 2019
Conditioning SCID Infants Diagnosed Early
CSIDE (Protocol chairs: Pai/Pulsipher)

Central questions:
Are lower doses of busulfan (30-60 vs. 90 mg\textsuperscript{h/L}) sufficient to reconstitute both T and B cell function?
Is the dose needed different for different genotypes?

39 sites open
11 sites in progress

15 patients treated
- 7 IL2RG/JAK3
- 8 RAG1/RAG2

8 randomized to Bu 30
7 randomized to Bu 60

6 haplo
9 URD

Overview

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  - X-linked SCID
  - Wiskott-Aldrich syndrome
  - DOCK8 deficiency (in development)
Gene therapy is an alternative to allogeneic transplant

Healthy donor

Matched sibling

Haplo parent

Limitations of allogeneic transplant

- Most patients lack the ideal donor (matched sibling)
- Risk of rejection
- Risk of graft-versus-host disease

Sick

Well

Gene therapy is an alternative to allogeneic transplant

\(\gamma\)RV or LV

Transplant

Advantages:

- Patient is own donor
- No GVHD
- Vector integrates into the DNA of the cell, and passes the gene to all progeny
Gene therapy was first successful in inborn errors of immunity


BMT
- X-linked SCID
- ADA SCID
- XCGD
- WAS
- LAD type 1

cDNAs cloned
- ADA SCID
- X-linked SCID
- Art SCID
- XCGD
- WAS
- LAD type 1

γRV GT trials
- ADA SCID
- X-linked SCID
- XCGD
- WAS
- LAD type 1
- 5/20 T ALL (2-6y)
- 1/20 T lymphoma (15y)
- Most LMO2
- 5/9 T ALL
- 1/9 AML
- 1/9 T ALL & AML
- Most LMO2 or MECOM
- Gene silencing

LV GT trials
- Marketed as Strimvelis 2016
1/16 T-ALL
since EMA approval
(reported Oct 2020)

>120 patients treated
No insertional events reported to date
Why did insertional oncogenesis occur?
Why did insertional oncogenesis occur?

Multi-institutional trial to test the SIN vector: Opened in Boston 2010

- No sibling donor
- No matched unrelated donor OR active treatment-resistant infection at diagnosis
- autologous BM harvest
- CD34+ selection
- SCF IL3 TPO Flt3L
- 3 rounds of transduction in retronectin coated bags
- NO CONDITIONING
- d-4 d-2 d-1 d0

SIN-yc (SRS11.EFS.IL2RG.pre)
How could vector redesign improve safety?

- Initial insertion pattern is unchanged
- Impair transactivation of neighboring genes

---

How could vector redesign improve safety?

- Change the initial insertion pattern
- Avoid transcriptional start sites
Gene therapy for X-linked SCID (SCID-X1)

**SIN-γRV**

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<th>Busulfan</th>
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<th>13/14 none, 1/14 low dose</th>
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<td>Trials</td>
<td>Paris n=10</td>
<td>International (Boston, Paris, Los Angeles, Cincinnati, London)</td>
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<td></td>
<td>London n=10</td>
<td>IND Sponsor: David Williams</td>
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<tr>
<td></td>
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<td>Funding: NIAID</td>
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<tr>
<td>Years</td>
<td>1990s</td>
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<td>T cell reconstitution</td>
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<tr>
<td>B cell function</td>
<td>&lt;50%</td>
<td>1/14 (rec’d low dose busulfan)</td>
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<td>Survival</td>
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<tr>
<td>Insertional oncogenesis</td>
<td>5/20 T cell leukemia (2-6y)</td>
<td>None to date</td>
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<td></td>
<td>1/20 T cell lymphoma (15y)</td>
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<td>Status</td>
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Gene therapy for X-linked SCID (SCID-X1) using self-inactivating γRV

- 14 patients enrolled (9 reported), 13/14 alive
- 11/13 patients have T cell reconstitution (1 repeat GT)
- No opportunistic infections
- Reduced insertion sites near LMO2 and similar genes
- No insertional oncogenesis to date (median 8.9y)

Hacein-Bey-Abina, Pai et al NEJM 2014 and unpublished
Lack of conditioning leads to suboptimal immune outcome

Lack of gene marking in neutrophils (surrogate HSC)  
Lack of gene marking in B cells  
All patients remain on IgG replacement  
Decline of CD4/CD8 ratio below normal over time

Low dose conditioning \(\rightarrow\) multilineage engraftment & B cell function

Older patients with SCID-X1 have multilineage gene marking after 6 mg/kg busulfan and lentiviral GT

De Ravin et al Sci Transl Med 2016

Patient 14  
2 days of busulfan targeted to 30 mg*h/L

- Sustained gene marking  
- Off IgG  
- Vaccine response

Hacein-Bey-Abina, Pai et al NEJM 2014 and unpublished
Gene therapy for X-linked SCID (SCID-X1)

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<td>None to date</td>
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Gene therapy for X-linked SCID (SCID-X1)

CL20-i4-EFlα-hyc-OPT vector (Sorrentino, St. Jude)
Lentiviral vector, EFS promoter, codon optimized transgene, insulator element
With low dose busulfan

2y to 40y
PI: Suk See De Ravin
NIAID

Post-transplant with poor immune reconstitution eligible

NCT01306019

Infants up to 24 months
Pis: Gottschalk, Mamcarz (St. Jude)
Cowan (UCSF)
Petrovic (Seattle)

8 patients reported
• 1 repeat GT
• 1 patient autoimmune hemolytic anemia

De Ravin et al Sci Transl Med 2016

Mamcarz et al NEJM 2019
Phase I/II trial of Lentiviral Gene Transfer for SCID-X1 with Low Dose Targeted Busulfan Conditioning

**U.S.A.**

- **Boston Children’s Hospital**
  - David A. Williams (IND Sponsor)
  - Jennifer Whangbo
- **UCLA Mattel Children’s Hospital**
  - Donald B. Kohn, Satiro De Oliveira
- **Children’s Healthcare of Atlanta**
  - Shanmuganathan Chandrakasan, Suhag Parikh
- **Cincinnati Children’s Hospital Medical Center**
  - Sharat Chandra
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  - Jennifer Heimall, Nancy Bunin

**U.K.**

- **Great Ormond Street Hospital**
  - Claire Booth, Adrian Thrasher

**Overall PI**

Sung-Yun Pai
National Cancer Institute

NCT03311503
Funding: NIH/NIAID AI125051
(Pai → Williams)

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Gene therapy for X-linked SCID (SCID-X1)

- 8 patients enrolled and 7 treated
  - 6 mobilized peripheral blood, 1 bone marrow
  - 2 without enhancers (VCN 0.6-0.7)
  - 5 with enhancers (VCN 0.76-1.2)
  - All alive and well
  - f/u 8m – 3y

- **T cell**
  - Both patients > 2 years post-GT
    - Off IgG replacement
    - Vaccine response

- **CD3+ T cell**

- **CD4/CD8 ratio**

- **B cell**

- **Neutrophil**

- **Open and enrolling**
  - NCT03311503
Gene therapy for Wiskott-Aldrich syndrome

**Conditioning**
- Busulfan 6.4-9.6 mg/kg
- Fludarabine 60 mg/m2
- Anti-CD20 mAb

**Trials**
- Milan n=17 (16/17)
- London n=7 (6/7)
- Paris n=5 (4/5)
- Boston n=5 (5/5)

**Survival**
- 1 death neurologic
- 1 death London post-splenectomy sepsis
- 1 death Paris infection

**Immune reconstitution**
- Yes

**Platelet reconstitution**
- Variable

**Safety**
- No events to date

**Status**
- Closed
- Licensed to Orchard Therapeutics

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Sustained multilineage gene marking and WAS protein expression

**T cells (CD3+) gene marking**

**B cells (CD19+) gene marking**

**NK cells (CD56+) gene marking**

**PMN (CD15+) gene marking**

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**T cells (CD3+) WASp expression**

**B cells (CD19+) WASp expression**

**NK cells (CD56+) WASp expression**

Labrosse, Chu, Armant, Pai, Notarangelo, Williams manuscript in preparation
Correction of platelet count is variable and related to transduction efficiency

**Improvements to implement:**
1. Enhance transduction efficiency
2. Vector design/codon optimization
3. Nontoxic conditioning
4. Gene editing

![Graph showing infection score and eczema score](Image)

![Graph showing Platelets over months post GT](Image)

![Graph showing VCN in CFU](Image)

Ferrua et al Lancet Haem 2019

Hacein-Bey-Abina et al JAMA 2015

Investigation of biology of immunodeficiency diseases
Tailoring cellular therapy to PID biology

**Pai lab**
- CSIDE trial biology studies
- X-linked SCID GT biology studies
- Preclinical development of GT for DOCK8 deficiency
- Collaborations for next generation GT trial for Wiskott-Aldrich syndrome

**Upcoming protocols**
- HSCT for VEXAS (Hickstein)
- Nontoxic conditioning (JSP191) for good risk GATA2 deficiency
- Disease specific HSCT

**Growing the ID-CTP**
- Staffing to fill current needs
- Recruitment of faculty (gene editing, novel conditioning)
- Expansion of pediatrics
o Ubiquitous expression may not be tolerated by HSC
o Redesign vectors to be cell type specific (WAS promoter?)
 o Test in Dock8-deficient mice

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MND promoter leads to efficient Dock8 expression at lower VCN

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