An ADA-SCID Gene Therapy Update with Dr. Kohn

September 14th, 2022
IDF MISSION
Improving the diagnosis, treatment, and quality of life of people affected by primary immunodeficiency through fostering a community empowered by advocacy, education and research.
HOUSEKEEPING

- Attendees will not have access to their microphone or webcam throughout the event.
- To see the full slides, you can adjust the settings on the speaker view panel on the top of the Zoom screen and select "side-by-side" in the dropdown option.
- Please submit all questions for the presenter via the Q&A box
DISCLAIMER

Immune Deficiency (IDF) education events offer a wide array of educational presentations, including presentations developed by healthcare and life management professionals invited to serve as presenters. The views and opinions expressed by guest speakers do not necessarily reflect the views and opinions of IDF.

The information presented during this event is not medical advice, nor is it intended to be a substitute for medical advice, diagnosis or treatment. Always seek the advice of a physician or other qualified health provider with questions concerning a medical condition. Never disregard professional medical advice, or delay seeking it based on information presented during the event.
- Resources
- Education
- Community
- Support
Where are you in your SCID journey?

Wherever you are on your journey with Severe Combined Immune Deficiency (SCID), use the links below to find the information and support you need.

¿En qué parte del trayecto de la IDCG está?

Dondequiera que esté en el trayecto de la inmunodeficiencia combinada grave (IDCG), use los siguientes enlaces para buscar la información y el apoyo que necesita.
REGISTRATION IS OPEN: www.primaryimmune.org/conference
WELCOME

Donald Kohn, MD
Distinguished Professor
Departments of Microbiology, Immunology & Molecular Genetics;
Pediatric Hematology & Oncology; and Molecular and Medical Pharmacology
University of California, Los Angeles
Update on Gene Therapy for ADA SCID
Donald B. Kohn, M.D.
University of California, Los Angeles
Depts. of Microbiology, Immunology & Molecular Genetics; Pediatrics (Hematology/Oncology); and Molecular & Medical Pharmacology
Broad Stem Cell Research Center
Jonsson Comprehensive Cancer Center
Human Gene and Cell Therapy Program
Conflict of Interest Statement

I am Inventor for the UC Regents on a lentiviral vector for gene therapy of ADA SCID that may produce royalties to me and will be discussed today.

The UC Regents have licensed to ImmunoVec intellectual property on lentiviral vectors on which I am an Inventor.

I am a member of the Scientific Advisory Boards and/or ad hoc paid consultant to Allogene Therapeutics, ImmunoVec, Pluto Immunotherapeutics, MyoGene Bio, Innoskel, TransformaTx, Cimeio Therapeutics,
Hematopoietic Stem Cells (HSC) Produce All of the Blood Cells

HSC come from:
Bone Marrow
Umbilical Cord Blood
or mobilized PBSC
HSC Transplantation Can Cure Genetic Blood Cell Diseases

**HSC come from:**
- Bone Marrow
- Umbilical Cord Blood
- or mobilized PBSC

**Genetic Blood Cell Diseases**

- Chronic Granulomatous Disease
- Leukocyte Adhesion Deficiency
- X-Adrenoleukodystrophy/MLD
- Gaucher and Mucopolysaccharidoses
- Pulmonary Alveolar Proteinosis
- Sickle Cell Disease
- \( \beta \)-Thalassemia (and \( \alpha \)-Thal too)
- Wiskott-Aldrich Syndrome
- Fanconi’s Anemia
- Severe Combined Immune Deficiency
- HLH, XLP, IPEX, X-HIM, WAS
- X-linked Agammaglobulinemia
- Common Variable Immune Deficiency

**Babies**
**Teenagers**
**Adults**
Bone Marrow Transplant
-an example of Stem Cell Therapy

Harvesting bone marrow from the Donor

Processing Stem Cells

Patient is “conditioned” with high dose chemotherapy

Stem cells infused

Intensive medical support until stem cells grow
Collection of PBSC by Leukapheresis

Daily G-CSF

±Plerixafor

PBSC Unit

Infuse Freeze CD34-select Gene Modify Other
The Major Barriers to Allogeneic HSCT are Immunological

a. Normal recipient’s T cells can reject the donor’s cells.

b. Donor’s T cells can “reject” the recipient’s cells (graft versus host disease (GvHD)).
Hypothesis for Gene Therapy Using Hematopoietic Stem Cells:

Gene therapy using autologous HSC that are corrected with the normal gene will have beneficial effects on blood cell production or function, without the immunologic complications of allogeneic HSCT.

Should absolutely eliminate GVHD and reduce need for immune suppression pre- and post-transplant.

Still need to “make space” for HSC engraftment in the bone marrow niche – “conditioning”.
Outcome after HSCT with Full, Partial or No Myeloablative Conditioning

Patient’s Bone Marrow HSC

Donor or Auto/Gtx HSC

Donor Chimerism

Donor Chimerism

Marrow

None

Full Myeloablation

Reduced Intensity Conditioning (RIC)

Minimal

Full

Mixed
Gene Therapy Using Hematopoietic Stem Cells

Normal gene

Add it

Edit

Self-renewal
Commitment

Resting HSC
Activated HSC

Common myeloid progenitor

Common lymphoid progenitor

CFU-GEMM

CFU-E

BFU-E

Thymocyte

CD34+ - The 1%
Ex Vivo Autologous HSC Gene Therapy

1. Collect, Isolate Autologous Stem Cells
2. Gene Addition to Stem Cells with Vector
3. Administer Marrow Conditioning
4. Transplant Gene-Modified Stem Cells

Gene Editing of Stem Cells with Site-Specific Nuclease and Homologous Donor (or other method(s))

γ-Retroviral Lentiviral

Package as Pseudotyped Vector

Your Gene

Kuo and Kohn
In: Clinical Immunology 5th ed., Rich et al, 2017
γ-Retroviral Vector

Entry with Nuclear Membrane Dissolution During Mitosis

Reverse Transcription

Integration into Chromosomal DNA

Expression of Therapeutic mRNA and Protein

Stable Transmission to Progeny Cells

Lentiviral Vector

Entry via Nuclear Pore

Entry, Uncoating
Bone Marrow or Leukapheresis Unit

GMP Lab

RBC/Platelet Deplete

Pre-stim x18-24 hr
Transduce with Lentiviral Vector x18-24 hr

Drug Product

Certify Release

Cryopreserve

CD34 Select

GMP BM/PBSC Stem Cell Processing Schema

DP qualification:
• Viability, cell count
• CD34 flow
• VCN
• Potency
• PCR(+) CFU
• Bacterial culture
• Fungal culture
• Endotoxin
• Mycoplasma

Infuse Stem Cells
Transplant Day
Gene-Corrected Stem Cell Infusion Thru PICC
Development of T Lymphocytes

Adult BM

Hematopoietic Stem Cells (HSC)

Red Blood Cells, Platelets, Neutrophils, Macs, B, NK

Thymus

"The University of T Cells"

SCID

CD4+ CD8-

Mature T Cells

CD8+ CD4-
Human SCID Genotypes

PIDTC 2010-2018 (n=250)

- IL2RG (XSCID) (30.8%)
- RAG1/2 (19.2%)
- Unk. (7.2%)
- ADA (12.8%)

Dvorak et al JACI, 2019
Biochemical Basis for Lymphotoxicity in ADA-Deficient SCID

Absent ADA isozymes observed when typing potential SCID family donors. E. Giblett, 1972.
Adenosine Deaminase (ADA)-Deficient SCID

ADA-deficiency is cause of 10-15% of human SCID. ~10 born/year in U.S. and Canada.

It was the first genetic form of human SCID where the biochemical and genetic causes were determined and the normal gene cloned (ca. 1983).

ADA-deficient SCID patients have profound pan-lymphopenia (T-, B-, NK-) from accumulated toxic adenine metabolites (dATP).

Therapeutic options include:
1. Allogeneic HSCT (MSD, MUD, haplo-identical {parent})
2. Enzyme replacement therapy (ERT) with PEG-ADA
3. Autologous HSCT with gene therapy
Overall Survival after HCT for ADA-deficient SCID.

106 ADA SCID Patients After Allogeneic HSCT from 5 Centers

Hassan et al. Blood 2012;120:3615-3624
Outcomes Following Treatment for ADA-deficient Severe Combined Immunodeficiency: a Report from the PIDTC

Cuvelier et al Blood 2022

• 131 ADA-SCID patients enrolled on PIDTC 6901/6902, diagnosed between 1982-2017, and received first definitive cellular therapy at one of 27 PIDTC centers.

• Patients were divided into one of four groups
  • HCT with no preceding ERT (HCT) (N=56)
  • ERT followed by HCT (ERT-HCT) (N=31)
  • ERT followed by Gene Therapy (ERT-GT) (N=35)
  • ERT Only (N=9)
100% overall survival in adenosine deaminase deficient severe combined immune deficiency patients after gene therapy. Contemporary hematopoietic stem cell transplant approaches after the year 2000 and without an active infection resulted in similar overall survival to gene therapy.
Clinical Trials of Gene Therapy for ADA SCID

# ADA SCID Gene Therapy Subjects/Year

Umbilical Cord Blood IL-3/IL-6/SCF

Improve HSC Processing and Retroviral Vectors

3 yr Clinical Hold

No Conditioning

Phase I

Phase II

Year


MND-ADA Retroviral Vector IND 8665 (cKL/F3L/TPO, SFM, rFBN)

EFS-ADA Lentiviral Vector IND 15440

CHLA UCLA

RIC Busulfan
First and Second Generation Retroviral and Lentiviral Vectors

1st generation retroviral vector

(+) Trans-activate

5’LTR

CELLULAR gene

E/P

Exogenous gene (s)

5’LTR

Vector RNA

ATG

Stop

Therapeutic protein

(+) Trans-activate

3’LTR

CELLULAR gene

2nd generation retroviral/lentiviral vector

(+) Trans-activate

5’LTR

CELLULAR gene

Enhancer deleted

Prom

Exogenous gene (s)

ATG

Stop

Therapeutic protein

(+) Trans-activate

3’LTR

CELLULAR gene

Enhancer deleted

Shaw K and Kohn DB
A Tale of Two SCIDS.
Sci Trans Med, 2011
Clinical Trials Using the EFS-ADA Lentiviral Vector for Gene Therapy of ADA SCID

U.K. Phase I/II Trial: 2012-2015 – (n=10 {+10})
U.K. “Cryo” trial; 2020-2022 (n=10 + 4 CUP)
Bobby Gaspar, Claire Booth, Adrian Thrasher – University College London/GOSH

U.S. Phase I/II Trial: 2013-2016 - (n=20 {+1})
U.S. Cryo Trial: 2016-2018 - (n=10 {+2})
Don Kohn (UCLA) and Fabio Candotti (NHGRI, NIH)
<table>
<thead>
<tr>
<th>TASK</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-clinical studies (under P01 HL073104)</td>
<td>1 2 3</td>
<td>2 3 4</td>
<td>1 2 3</td>
<td>2 4 1</td>
</tr>
<tr>
<td><strong>NIH RAC Review</strong>: (December 2009) (Protocol, IC, Appendix M)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiate NHBLI GTRP Application (GMP vector and GLP toxicology)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDA Pre-IND (September 2010)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NHLBI GTRP Approval</strong>: (March 2011) (Protocol, IC, Appendix M)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tox batch vector made</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Begin <em>in vitro</em> and <em>in vivo</em> tox studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>UCLA IRB</strong>: (Approved pending modifications)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>UCLA IBC</strong>: (Approved pending modifications)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submit <strong>NIAID U01</strong> app for UCLA clinical costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NIH IRB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NIH IBC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perform <em>in vitro</em> insertional mutagenesis assay</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete in vivo tox study primary transplants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete CRFs, SOPs, training</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Define clinical reagents, vector</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Submit IND</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*First patient August 2013*
**Clinical Trial Treatment Schema**

**Consent Screen Admit**
- BM Harvest (PICC)
- Busulfan (4 mg/kg) (pK)

**Day:**
- M -3  
- T -2  
- W -1  
- Th 0  
- Th +30

**Isolate HSC**
**LV Transduction**
**Transplant HSC**

**Immune Reconstitution**

**Clinical Trial Experimental Time**

**EFS-ADA Fresh Trial - NIAID U01 AI100801**

2013-2017 (Linda Griffith)
EFS-ADA Lentiviral Vector Phase I/II Trial – Enrollment Time-Course

IND Open: May 2013
1st subject treated: August 2013
20^{th} subject treated: July 2016
All 2 year follow-up done: July 2018
EFS-ADA Cryo Trial - CIRM CLIN2 09339
2016-2018 Orchard Therapeutics

Consent Screen Admit #1

BM Harvest

0 1 2

~30

LV Transduction

Isolate CD34+ Cells Cryopreserve Certify
**EFS-ADA Cryo Trial**

Enrollment Time-Course 2016-2018

CIRM CLIN2 09339

Orchard Therapeutics

<table>
<thead>
<tr>
<th>UPN</th>
<th>Jan</th>
<th>Feb</th>
<th>Mar</th>
<th>Apr</th>
<th>May</th>
<th>Jun</th>
<th>Jul</th>
<th>Aug</th>
<th>Sept</th>
<th>Oct</th>
<th>Nov</th>
<th>Dec</th>
<th>Jan</th>
<th>Feb</th>
<th>Mar</th>
</tr>
</thead>
<tbody>
<tr>
<td>601</td>
<td>red</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>red</td>
</tr>
<tr>
<td>602</td>
<td>red</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>red</td>
</tr>
<tr>
<td>603</td>
<td>red</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>red</td>
</tr>
<tr>
<td>604</td>
<td>red</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>red</td>
</tr>
<tr>
<td>605</td>
<td>red</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>red</td>
</tr>
<tr>
<td>606</td>
<td>red</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>red</td>
</tr>
<tr>
<td>607</td>
<td>red</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>red</td>
</tr>
<tr>
<td>608</td>
<td>red</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>red</td>
</tr>
<tr>
<td>609</td>
<td>red</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>red</td>
</tr>
<tr>
<td>610</td>
<td>red</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>red</td>
</tr>
<tr>
<td>701</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>green</td>
<td></td>
<td></td>
</tr>
<tr>
<td>702</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>green</td>
<td></td>
<td>red</td>
</tr>
</tbody>
</table>

- **IND amendment accepted** Dec. 2016
- **1st subject treated** February 2017
- **10th subject treated** October 2017
- **2 treated under EAP** Jan/Mar, 2018
Origin of ADA SCID Patients in UCLA EFS-ADA LV Clinical Trials
Report of 50 ADA SCID patients treated with gene therapy in parallel U.S and UK clinical trials under common protocols

CD34+ HSPC transduced with the EFA-ADA lentiviral vector

Reduced intensity conditioning with low dose busulfan

Kohn, Booth et al, NEJM, 2021
Kaplan–Meier Curves for Event-free Survival Over 24 Months (US Studies) and 36 Months (EU Study) in Gene Therapy-treated Subjects.

Kohn, Booth et al, NEJM, 2021
Median Absolute CD3+ T Cell Counts Over 24 Months (US Studies) and 36 Months (EU Study) in Gene Therapy-treated Subjects

Kohn, Booth et al, NEJM, 2021
Serum IgA and IgM Levels Over 24 Months (US Studies) and 36 Months (EU Study) and IgG levels following IgRT cessation.

Kohn, Booth et al, NEJM, 2021
Severe Infection Rate by Time Period

Kohn, Booth et al, NEJM, 2021
Comparison of the US Studies - Fresh vs. Cryopreserved BM VCN in Granulocytes and PBMCs, CD3+ T Cell Counts, and ADA Activity

Granulocyte VCN

PBMC VCN

CD3+ T Cells

RBC ADA

Kohn, Booth et al. NEJM 2021

CIRM CLIN2-09339
Status of EFS ADA LV Gene Therapy

Developed at UCL/GOSH and UCLA.
--Pre-clinical studies (2009-2012) (NHLBI PO1)

  100% OS and 96% EFS (2/50 needed second therapy with ERT or HCT)

Engraftment of genetically modified HSPCs persisted in 29 of 30 patients in the U.S. studies and in 19 of 20 patients in the U.K. study over 2 and 3 years, resp.

Has Orphan Drug, Breakthrough Therapy and Rare Pediatric Disorder Designations

Needs commercial development to BLA for marketing authorization

Licensed from UCL and UCLA to Orchard Therapeutics 2016
Timeline for Development of ADA SCID Gene Therapy

- **1980**: Human ADA cDNAs Cloned
- **1985**: ADA-deficiency as a cause of Human SCID (Giblett - 1972)
- **1990**: NIH PBL Trial
- **1995**: γ-Retroviral Vectors in CD34+ Cells, Italy, U.K., U.S.
- **2000**: Lentiviral Vector in CD34+ Cells, U.K. and U.S.
- **2005**: Strimvelis EMA Approved
- **2010**: You Are Here

You Are Here

Lentiviral Vector in CD34+ Cells, U.K. and U.S.
The Return of EFS-ADA!!

5/21 - Orchard announced intent to cancel the License with UCL and UCLA.

UCLA began to develop new clinical trial for compassionate treatment of patients under CIRM funding.

10/21 Clinical protocol developed and approved by UCLA IRB, IBC.

Phase I/II clinical trial of EFS-ADA gene therapy for ADA SCID (IND #15440) “Efficacy and Safety of Cryopreserved Autologous Mobilized Peripheral Blood CD34+ Hematopoietic Stem and Progenitor Cells Transduced Ex Vivo with the EFS-ADA Lentiviral Vector in Patients with Severe Combined Immune Deficiency Due to Adenosine Deaminase Deficiency”

--Use a batch of clinical grade EFS-ADA LV (IUVPF) from Orchard Therapeutics.

--Plan to use mobilized blood stem cells instead of bone marrow as more abundant stem cell source.

--Improve cell processing to need less vector – treat more patients.
The Return of EFS-ADA!!

January 2022 –

**IND** #15440 returned to UCLA with 1 lot GMP EFS-ADA made at IUVPF.

CIRM transferred CLIN2-09339 grant back to UCLA
-- to cover clinical trial and GMP start-up costs, and treat 3-6 patients.

Need IND amendment submitted to FDA for clinical and GMP plan.
FDA meeting requested to discuss compassionate treatment trial.

3/22- Briefing package sent to FDA, including UCLA IRB-approved clinical protocol, UCLA HGCTF cell manufacturing plan.

4/22- FDA Type B meeting scheduled
The Return of EFS-ADA!!

4/28/22- Type B meeting - FDA requested changes needed:

Clinical Protocol
- Change Objectives and End-point
- Make Overall Survival the primary end-point
- Record the numbers and types of infections
- Perform neurodevelopmental testing

Drug Product manufacture and release testing
- More data on use of mPB, vector batch, new processing
- Develop new release test for vector copy/transduced cell

Q3/22 Submit modified protocol and manufacturing plans back to FDA for review and then submit modified protocol to UCLA IRB/DSMB.

Adds 3-6 more months → current first enrollment target January 2023.
Primary Study Objective:
The Primary Objective is to determine overall survival at two years after administration of the Gene Therapy Medicinal Product (GTMP). Overall survival (OS) is defined as the proportion of subjects alive.

Secondary Study Objectives
The Secondary Objectives are to assess safety and efficacy.

1. Safety. Evaluate safety of the treatment by recording clinical adverse events (AE), and evaluating incidence of development of replication competent lentivirus (RCL) and vector-related clonal expansion.

2. Event-Free Survival (EvFS). Event-free survival is defined as the proportion of subjects alive with no “event”, an “event” being death or treatment failure and the resumption of PEG-ADA ERT or the need for a rescue allogeneic HSCT.


5. Cessation of Immunoglobulin Replacement Therapy (IgRT). Record time post-gene therapy IgRT was stopped based on defined criteria for absolute CD4 and absolute B cell counts, serum IgA or IgM levels, and gene marking detectable in B cells.
Exploratory Objectives:

The Exploratory Study Objectives are to measure biological correlates of efficacy:

1. Gene marking in peripheral blood leukocytes by vector copy number (VCN)
2. Quantification of clonal diversity of vector integrants.
3. ADA enzyme activity in erythrocytes.
4. Total deoxyadenosine nucleotides in erythrocytes.
5. Immune reconstitution. – T, B, NK. QuIgs. Response to vaccine.
6. Performance Status
7. Quality of Life
### Cell Product Manufacture

<table>
<thead>
<tr>
<th>Event</th>
<th>Timeframes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent &amp; Screening</td>
<td>~2-6 weeks</td>
</tr>
<tr>
<td>Admit #1 Mobilize and Leukapheresis</td>
<td>~7 days</td>
</tr>
<tr>
<td>Isolate mPB CD34+ HSPC</td>
<td>~2 days</td>
</tr>
<tr>
<td>EFS-ADA LV Transduction</td>
<td>~5-6 weeks</td>
</tr>
<tr>
<td>Cryopreservation</td>
<td></td>
</tr>
<tr>
<td>GMP Release Testing</td>
<td></td>
</tr>
<tr>
<td>Issue COA and Release Product</td>
<td></td>
</tr>
</tbody>
</table>

### Conditioning, Infusion, Follow-up

<table>
<thead>
<tr>
<th>Event</th>
<th>Timeframes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admit #2 CVC Placement</td>
<td>1-2 Days</td>
</tr>
<tr>
<td>Busulfan Dose 1</td>
<td>Day -4</td>
</tr>
<tr>
<td>Bu pK</td>
<td>Day -3</td>
</tr>
<tr>
<td>Busulfan Dose 2</td>
<td>Day -2</td>
</tr>
<tr>
<td>Bu pK</td>
<td>Day -1</td>
</tr>
<tr>
<td>Cell Product Infusion</td>
<td>Day -0</td>
</tr>
<tr>
<td>Hematologic Recovery</td>
<td>~3-4 weeks</td>
</tr>
<tr>
<td>Follow-up End-points</td>
<td>~2 Years</td>
</tr>
</tbody>
</table>

**Study Schema**

Cryopreserved Autologous Mobilized Peripheral Blood CD34+ Cells Transduced with the EFS-ADA Lentiviral Vector for ADA SCID
The ADA SCID GT Waiting List:

#1. Sept 2017

- 2017 – 3
- 2018 – 5
- 2019 – 4
- 2020 – 4
- 2021 – 7
- 2022 - 3

Total = 26
Collaborators

NIH: Fabio Candotti, Harry Malech, Elizabeth Garabedian, Elizabeth Kang, Sung Yun Pai
UCL/GOSH: Bobby Gaspar, Adrian Thrasher, Claire Booth; BCH: David A. Williams
Duke University: Michael Hershfield, Rebecca Buckley
IUVPF: Ken Cornetta; U.Penn: Rick Bushman, John Everett
UCSF: Mark Walters, Karin Gaensler, Tippi MacKenzie; UCB: Fyodor Urnov;
UCSD: Stephanie Cherqui; Alberta: Nikki Wright, Luis Murgula Favela

Support and Funding

UCLA - BSCRC/αSCC, JCCC, DGSOM, CDI, Depts of MIMG, Peds, MMP
ADA: DDCF, FDA OOPD, NHLBI, NIAID, CIRM
Sickle Cell: CIRM, DDCF, NHLBI, Hina Patel Foundation
XSCID: NIAID, XCGD: CIRM, NHLBI; LAD-1: Rocket Pharma and CIRM
WAS: Wiskott Aldrich Foundation; J.M.F.; SCID Angeles for Life
Ask IDF

Have more Questions?

primaryimmune.org/ask-idf
800-296-4433
Resources on Gene Therapy

• Clinical Trials: [https://clinicaltrials.gov/](https://clinicaltrials.gov/)

• IDF’s Gene Therapy Overview: [https://primaryimmune.org/gene-therapy-0](https://primaryimmune.org/gene-therapy-0)

• Gene Therapy for SCID: [https://scidcompass.org/gene-therapy-0](https://scidcompass.org/gene-therapy-0)
WE VALUE YOUR FEEDBACK...

Please take a moment to complete our Evaluation Survey after the Program!
NEXT PROGRAM

IDF Lunch & Learn: HLH
With Rebecca Marsh, MD
September 28th, 2022
12:00-1:00 PM ET

IDF Calendar of Events