Clinical Trials of Gene Therapy for ADA-Deficient SCID

Donald B. Kohn, M.D.
University of California, Los Angeles (UCLA)
A Long Time Ago, In a Galaxy Far Away.....
A Long Time Ago, In a Galaxy Far Away…..

Three newborns with ADA-deficient SCID treated in 1993 under an amendment to the original NIH ADA gene therapy trial that had targeted T cells.

U.S. FDA required future subjects to be treated under new specific protocol.

CHLA and NIH Clinical Trial of Gene Therapy of ADA-SCID (1999-2012)

MND-ADA
Kohn - CHLA

GCsap-M-ADA
Candotti - NIH
**CHLA and NIH Clinical Trial of Gene Therapy of ADA-SCID (1999-2012)**

Developed Clinical Trial To Be Performed At Two U.S. Sites

MND-ADA
Kohn - CHLA

GCsap-M-ADA
Candotti - NIH
UCLA / NHGRI Clinical Trials

Challenges of Multi-Site Trials

Harmonize and oversee both sites:
- Cell processing, product and end-point testing.
- Clinical trial management and medical care
- Data management
- AE and other regulatory reporting

Funding - Staff, cell processing materials, lab testing, clinical costs

Staffing: Clinical coordinator, research nurse, clinicians
- data manager, regulatory,
- Stem cell processing lab staff.
- Research sample processing and analysis
When I get to the bottom, I go back to the top of the slide, where I stop and I turn and I go for a ride, ‘till I get to the bottom and I see you again.

(Yeah, yeah, yeah.)
U.S. Trials of Gene Therapy for ADA-SCID Using CD34+ Cells from Bone Marrow

**Phase I**
- **2001**
  - no Busulfan
  - + PEG-ADA
  - compare 2 retroviral vectors
  - 4 subjects treated 2001-2002

**Phase II**
- **2005**
  - + Busulfan (4 mg/kg)
  - no PEG-ADA
  - compare 2 retroviral vectors
  - 6 subjects treated 2005-2009
- **2009**
  - + Busulfan (4 mg/kg)
  - no PEG-ADA
  - one retroviral vector
  - 8 subjects treated 2009-2011

**Subjects**
- Subject #200s
- Subject #300s
- Subject #400s
PBMC ADA Enzyme Activity and Absolute Lymphocyte Counts (ALC)

5A
No Busulfan, On ADA ERT

6A
Candotti et al Blood e-pub 2012
PBMC ADA Enzyme Activity and Absolute Lymphocyte Counts (ALC)

No Busulfan, On ADA ERT

Busulfan, ADA ERT Stopped

Candotti et al Blood e-pub 2012
UCLA / NHGRI Trial of Gene Therapy for ADA-Deficient SCID - Phase II Trial

Type of Vector: murine γ -RV (GALV): MND-ADA
Conditioning: busulfan 90 mg/m2 (~4 mg/kg).
Inclusion: no matched sibling donor.
Exclusion: Poor organ function. Active infection. PB cytogenetic abnormalities.
End-points: 1° -safety.
2° -gene marking, immune reconstitution
ClinicalTrials.Gov # NCT00794508
ADA Gene Therapy - Funding

Phase I - 2001-2008

CHLA Clinical Research Award 1999-2000
$65,000 Vector production, 0.5 FTE

Doris Duke Charitable Foundation DCSA 2000-2005 (7)
~$200,000/yr 2.0 FTE

NHLBI SCOR on HSC 2000-2005
~$75,000/yr, 0.5 FTE

NCRR, NIH: General Clinical Research Center 2000-2009
~$150,000/ yr 1.0 FTE Plus ALL Clinical Costs

Phase II – 2009-2012

FDA/NIH Orphan Product Development Award 2005-2009 (12)
~$300,000/yr for Phase II Trial

3rd party payers (insurance) covered auto-BMT clinical costs
ADA cDNA Retroviral and Lentiviral Vectors

**γ-Retroviral Vector:**

\[
\text{MND} \quad \psi \quad \text{Hu ADA} \quad \psi \quad \text{MND}
\]

**Lentiviral Vectors**

\[
\text{MND} \quad \psi \quad \text{Hu ADA}
\]

\[
\text{PGK} \quad \psi \quad \text{Hu ADA} \quad \text{WPRE}
\]

\[
\text{EFS} \quad \psi \quad (\text{coop})\text{Hu ADA} \quad \text{WPRE}
\]
Transduction of Human CB CD34+ Cells by ADA Vectors
The EFS-ADA Lentiviral Vector

Made by Thrasher/Gaspar (UCL)

pCCLc, EFS promoter, codon-optimized huADAcDNA, WPRE (orf-)

High titer (10e7 TU/ml raw, 3-10x10e9 TU/ml concentrated).

Transduces huBM CD34+ cells efficiently in 2 day culture.

Expresses ADA enzyme/VC similar to MND-ADA RV and MND-ADA LV.

Expresses 1-3x endogenous in human CD34→ My in vitro, T in NSG.

IVIM – no colonies from EFS-ADA vs. SFFV-GFP (p< 0.05).
The Slow Road To EFS-ADA Lentiviral Vector Trial

<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></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIH RAC Review: (December 2009)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Protocol, IC, Appendix M)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiate NHBLI GTRP Application</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(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>NHLBI GTRP Approval (March 2011)</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 in vitro and in vivo tox studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UCLA IRB (Approved pending modifications)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UCLA IBC (Approved pending modifications)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submit NIAID U01 app for UCLA clinical costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIH IRB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIH IBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perform in vitro 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>Qualify clinical reagents, vector</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Submit IND</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>
Clinical Grade EFS-ADA lentiviral vector 20 L batch made at Indiana University Vector Production Facility.

Titer 3 x10e9 TU/ml.

Works great!
In Vitro Insertional Mutagenesis Assay
EFS-ADA

Replating Frequency

Replating Frequency/VCN

Mock  R5F91.GFP  MND.ADA  EFS-ADA

Ratio Positive/Negative Assays

0:4  5:3  10:2  0:13

0:4  5:3  10:2  0:13

Ratio Positive/Negative Assays

p<0.05
p<0.01

* p<0.05
** p<0.01
Perform independent parallel trials in UK and US.

Try to harmonize as many elements as possible of clinical trial design, cell processing, end-point assays.

Use same vector lot, share production costs.

Cross report vector-related SAE (if any).
Perform independent trials in UK and US.

Try to harmonize as many elements as possible of clinical trial design, cell processing, end-point assays.

Use same vector lot, share production costs.

Cross report vector-related SAE (if any).
Transatlantic Gene Therapy Consortium

- Children’s Hospital Boston (Boston)
- Great Ormond Street (London)
- Hannover Medical School (Hannover)
- Cincinnati Children’s Hospital (Cincinnati)
- German Cancer Institute (Heidelberg)
- Mattel Children’s Hospital (Los Angeles)
- Georg-Speyer-Haus (Frankfurt, Germany)
- Genethon (Paris)
- CIEMAT (Madrid)
Gene Transfer for SCID-X1 Using a Self-Inactivating (SIN) Gammaretroviral Vector

Vector SIN RV using EFS-gammaC Christopher Baum
Pre-clinical POC – Thrasher, Fisher
Pre-clinical toxicology – Williams et al CCHMC, Baum Hannover
Clinical PIs – Thrasher, Cavazzana-Calvo, Williams

Trial- France, London, USA

Plan: enrolling 20 boys with X-linked SCID:
11 from Europe (London-UCL/GOSH, Paris- Hôpital Necker)
3 from each of 3 US sites (Boston, Cincinnati, LA)
NGVB – RCL testing, U Penn (Bushman) - VISA
Many of these recommended changes conflicted with recommended changes made during previous reviews!

Particularly difficult was the insistence on mouse studies that were predictably uninformative for safety demonstration. Unfunded and time consuming.
Challenges of Multi-Center/Multi-National Trials

Difficult to maintain uniformity of approach with separate regulatory oversight.

Difficult to combine funding streams for common reagents.

Differences in health care insurance across states and countries; research harm financial obligations related small biotech/‘academic reagents’ (IRB, NIH)

It’s better to collaborate with friends than to compete!
ADA SCID Clinical Trials:
Fabio Candotti
Rob Sokolic
Elizabeth Garabedian
Linda Muul
Bobby Gaspar UCL/GOSH
Ken Cornetta IUPUI

Sickle Cell Disease Team:
UCLA - Gay Crooks
CHLA - Tom Coates
USC - Herb Meiselman
CHRCO - Mark Walters
UCSF - E.J. Read
IUPUI - Ken Cornetta

Sangamo Biosciences
Philip Gregory
Michael Holmes
Andreas Reik
Fyodor Urnov

Funding:
FDA OPD
NHLBI
NIAID
DDCF
NCI
NGVB
Los Angeles