Gene Therapy for Adrenoleukodystrophy

Asif M. Paker, MD, MPH
bluebird bio – Who We Are

• Publicly held biotechnology company
• ~90 full-time employees based in Cambridge, MA
• Focused on the industrialization of gene therapy technology to make it broadly available and applicable

Our Vision – Make Hope a Reality

Transforming the Lives of Patients With Severe Genetic and Orphan Diseases
**The Phase II/III ALD-102 Study is our first clinical study of our current Lenti-D viral vector and product candidate.**

**The Phase I/II HGB-205 and HGB-204 Studies are our first clinical studies of our current LentiGlobin viral vector and product candidate.**
ALD Gene defects results in accumulation of VLCFA

http://www.x-ald.nl/biochemistry-genetics/vlcfa/
Clinical Features of CCALD

Onset at ≥3 year of age

Progressive behavioral and cognitive symptoms
Vision impairment/ field cuts
Hearing and speech impairment
Walking and running difficulties
Seizures

MRI abnormality precedes clinical symptoms
MRI Signal Changes Precedes Clinical Manifestations

Brain MRI without Contrast

Brain MRI with Contrast
Transplant is Effective in patients with Early CCALD

Mahmood A et al; Lancet Neurology 2007
Gene Therapy
Gene Therapy Primer: Genes carry our Blueprint
Genes code for Proteins

Genes provide instructions for building proteins
Changes in genes can cause disease

A problem in a gene can lead to a genetic disease

Malfunctioning gene
Blood stem cells
Patient’s Own Stem Cells are Collected with Apheresis

http://www.flickr.com/photos/ec-jpr/4350381831/in/
Vector gene insertion happens outside the body in a lab

Lentiviral vectors transfer a functioning gene
A viral vector carries a functioning gene into a blood stem cell

A functioning gene is inserted into the DNA of the patient’s cells
Lentiviral vectors permanently insert genes into DNA
Lenti-D Drug Product is Administered using Peripheral Line

http://infusionnurse.org/2013/03/06/rns-mixing-iv-medications/
Modified stem cells are returned to the patient.
Monocyte/macrophage lineage differentiates into brain microglia.
Safety Profile of Transplant

- Unrelated donor **75% to 91%** (source: CIBMTR)
- Cord blood **71%** (source: CIBMTR)

- 3-year Transplant Related Mortality:
  - Related Donor 10%
  - Unrelated Donor **18%** *

- Engraftment failure:
  - Related Donor 7%
  - Unrelated Donor **20%** *

Safety Profile of Transplant

- Acute Graft vs. Host Disease
  - Severe (III-IV): 12% *
  - Moderate to Severe (II-IV): 18%

- 13/60 (22%) patients died after transplant**
  - Graft failure (3, 23%)
  - Infection (2, 15%)
  - Acute Graft vs. Host Disease (1, 8%)

Promising Efficacy with Gene Therapy

- Launched autologous gene therapy trial in 2006
- Stabilization of disease observed
- No gene therapy safety issues observed
- No clinical safety issues observed

Patrick Aubourg & Natalie Cartier

StopALD Foundation

European Leukodystrophy Association (ELA)
Promising Clinical Data – CCALD
INSERM Sponsored Study TG04.06.01 (P Aubourg)

Natural Course of Disease

- NFS / Loes currently stable in all patients
- Gad resolved in 3 out of 4 patients
- No gene therapy-related adverse events

ALD #1
After 6 Years
Now 13.5 Years Old

ALD #2
After 5 Years
Now 13 Years Old

ALD #3
After 4 Years
Now 11 Years Old

ALD #4
After 2 Years
Now 6.5 Years Old
Starbeam Study
ALD-102
Starbeam (ALD-102) Study Sites

Don Kohn, Raman Sankar, Ami Shah

Jerry Raymond, Troy Lund, Paul Orchard, Wes Miller

David Williams, Florian Eichler, Christy Duncan

Patrick Aubourg, Andre Baruchel, Jean-Hugues Dalle

Adrian Thrasher, Bobby Gaspar, Paul Gissen, Ashok Vellodi
Making participation easier for study participants

- Patient/Family Travel
  - Passports/Visas
  - Air/rail
  - Accommodation
  - Stipends

- Study Website
  - Disease info
  - Clinical research basics
  - Resources
  - ALD-102 – how to contact a site

- Educational Materials
  - Informed consent pamphlet
  - Gene Therapy 101
  - Physician video
Clinical Study of Lenti-D Gene Therapy for ALD has Initiated

http://www.starbeamstudy.com

clinicaltrials@bluebirdbio.com

patient.advocacy@bluebirdbio.com

http://clinicaltrials.gov (trial identifier: NCT01896102)
LEARN ABOUT THE STARBEAM STUDY

The Starbeam Study, a clinical research study of an investigational gene therapy, is now enrolling up to 15 boys, aged 17 and younger, who have been diagnosed with childhood cerebral adrenoleukodystrophy (CCALD).

The goal of the Starbeam Study is to determine if the one-time investigational treatment can stop the progression of CCALD, and if it is safe and well tolerated. If your family member has CCALD, you may want to learn more about the Starbeam Study.

EXPLORING GENE THERAPY FOR TREATMENT OF CHILDHOOD CEREBRAL ADRENOLEUKODYSTROPHY

Childhood Cerebral Adrenoleukodystrophy (CCALD) is a fatal and rare genetic disorder that affects the nervous system of young boys. CCALD involves a breakdown of the protective sheath of the nerve cells in the brain that are responsible for thinking and muscle control. Symptoms usually occur in early childhood and progress rapidly, if untreated, and can cause a vegetative state, ultimately leading to death.

In the Starbeam Study, gene therapy is being studied as a potential treatment for CCALD. In the study, functioning genes will be used as medicine for the gene that is not working properly. Gene therapy has been studied as a potential treatment for genetic diseases since the 1980s. The goal of gene therapy is to help correct the genetic disease by providing a functioning copy of the gene to make up for the genetic defect.

MORE ABOUT CCALD

CONTACT STUDY SITES
ABOUT THE STUDY SPONSOR

The sponsor of this future study, bluebird bio, is a biotechnology company based in Cambridge, MA. bluebird bio is dedicated to developing next generation products based on the transformative potential of gene therapy to treat patients with severe genetic and orphan diseases. bluebird bio will be working with research centers of excellence to conduct the clinical study. If you would like to learn more about the Starbeam Study:

CONTACT BLUEBIRD BIO