ALD Connect, an all-inclusive consortium to eradicate adrenoleukodystrophy

Breakfast Seminar 4: Patient Powered Research Networks for Rare Diseases
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Financial Disclosures

• PI of ex vivo lentiviral gene therapy trial in adrenoleukodystrophy sponsored by bluebird bio
• PI of L-serine trial in HSAN1 sponsored by FDA Orphan Disease Group

• Consultant to Retrophin on Cerebrotendinous Xanthomatosis
• Consultant to Alexion Pharmaceuticals on MOCD
• Consultant to Third Rock Ventures on rare neurological disorders
History of Adrenoleukodystrophy not unlike that of other rare neurological disorders

Haberfeld and Spieler in 1910:

Exercise for AMN in 2015:

Drama film in 1992:

Schilder’s Disease
Sex-Linked Recessive Transmission
With Specific Adrenal Changes

Herbert H. Schaumburg, MD; Edward P. Richardson, MD; Peter C. Johnson, MD; Richard B. Cohen, MD, James M. Powers, MD, and Cedric S. Raine, MD, Bronx, NY

Spastic Paraplegia Associated with Addison’s Disease:
Adult Variant of Adreno-Leukodystrophy

H. Budka, E. Sluga, and W.-D. Heiss
Neurological Institute and Neurological Clinic, University of Vienna

Received May 13, 1970
The world is changing...

Human beings are more willing to endure risk and suffering for the chance of a benefit.
The world is also changing for rare diseases

Flicker of Hope for Children With Rare and Devastating Disease (RCDP), New York Times, September 2015

The Wall Street Journal Reports On FDA Approval of Cycloextrin Treatment for Niemann Pick Type C, April 2009
The world is also changing for rare diseases


Increase in orphan drug designations (Melnikova, Nature Reviews Drug Discovery 2012)
ALD Connect

• The mission of the consortium is to improve medical care and health outcomes for patients with adrenoleukodystrophy, through advancing scientific knowledge, raising awareness, and improving education.

• Our vision: to revolutionize the practice of medicine by identifying, optimizing, and implementing advances in the care and cure of adrenoleukodystrophy in a multicenter network.

• Our goal is to achieve complete disease eradication through cooperation between patients, patient-advocate groups, clinicians, researchers, industry, and government.
Annual Meeting, Boston 2013

Annual Meeting, Baltimore 2014
Much to Celebrate!

September 25th, 2015

2015 RARE Champion of Hope Honorees

August 27th, 2015: Federal advisory committee for diseases in newborns voted to recommend the addition of ALD to the national newborn screening list.
But also much work ahead

- Approx. 5000 AMN patients, men and women, in U.S. currently have no treatments
- *This year* 40 boys in U.S. will undergo bone marrow transplantation. A third will be too advanced for optimal transplant.
- *This year* another 20 boys in U.S. will not even have any treatment options due to severity of cerebral ALD
Still, misdiagnosis persists in ALD families

FM: Fibromyalgia
MS: Multiple Sclerosis
HSP: Hereditary Spastic Paraplegia
How does ALD Connect work together?

- **Board of Directors**
  - **Work Group 1:** Infrastructure, Governance and Funding
  - **Work Group 2:** Outcome Measures
  - **Work Group 3:** Disease mechanisms
  - **Work Group 4:** Dissemination of ALD-related Disease Information
  - **Biomarkers Summit Organizing Committee**

  - **Drug Algorithm**
    - Website Development
    - Physician Awareness
    - Patient Engagement
    - Patient-Doctor Webinars
How to make progress together?

Board of Directors

- Engage in collaborative discussions
- Mindful of the mission of the consortium
- Strive for consensus, not simply rule by majority
- Have all voices heard, respectful of all
- All inclusive!
Academic Institutions Collaborate

Members and Affiliate Members
NeuroBANK physician portal

Current Number of patients enrolled for “ALD Natural History”

- Total number of patients: 82
- Number of adults (18+): 50
- Number of children (<18): 26
- No demographics data: 6
PATIENT PORTAL
https://nctu.partners.org/ALD/

Who knows the most about Adrenoleukodystrophy?

You do.

Yes, there is much to be known about the genetics and biochemistry. Yes, there are many experts and subspecialists. But no one experiences the burden and pain of the

- Number of patients: 190
- Number of adults: 111
- Number of children: 29
- Did not provide age: 50
MISSION: To eradicate rare disorders of the nervous system by leveraging the power of biological insights towards design and implementation of clinical trials

Building on synergies with the CHGR, the center will establish partnerships that advance treatments for rare diseases. It will do this by

- recognizing and harnessing unmet needs and biological insights of rare diseases
- providing resources to enable investigators fill knowledge gaps and move from bench to bedside
- creating partnerships and collaborations across patient communities, academia and industry
Center for Rare Neurological Diseases (CDRN)

MGH, MEEI and Boston Children’s Hospital
8 departments and 8 companies represented

MGH Rare Disease Think Tank:
Strategic Discussions Across Departments and Industry

CENTER FOR RARE NEUROLOGICAL DISEASES:
Projects and Work Products for Neurological Indications
MGH Rare Disease Think Tank

Endocrinology     Psychiatry    Children’s Hospital        CHGR            Neurology           CHGR        Mass Eye&Ear

Pfizer            Cydan                Third Rock          Pulmonology       Sanofi-Genzyme     Nephrology       Neurology

Genetics          Agilis                Partners Innovation  Retrophin        Oncology          Synageva
CDRN: Working together on Rare Neurological Diseases

Projects to Accelerate Research for Neurological Indications
Example: Ex Vivo Lentiviral Gene Delivery in Boys with Cerebral Adrenoleukodystrophy

Hematopoietic stem cell correction halts the progression of devastating inflammatory demyelination in the brain, prompting first gene therapy trial, now ALD added to RUSP.
With Emerging Therapies Patients Emerge
Early detection and targeted therapies can be transformative.
Steps in Therapy Development for Single Gene Disorders

1. Biological Insights
   – Function of Disease Causing Genes

2. Emerging Therapeutic Identified
   – Ability to correct dysfunction (POC)
   – Reaches CNS

3. Understanding of Disease Course
   – natural history studies
   – outcome measures

Clinical Trial Design becomes possible
Trial Design requires Natural History

- Placebo arm for rare devastating diseases often not acceptable

- Therapeutic window needs to be clear
Emerging Therapies in Mendelian Disorders
(POC studies entering clinical arena)

- ERT Trials
- Ex Vivo Gene Therapy
- In Vivo Gene Therapy
- Cell-based Therapy
- Immunomodulatory Therapy
- ASO Therapy
- Gene Editing

Key Question: Are Disorders Gain of Function or Loss of Function?
CDRN: Identifying Opportunities and Knowledge Gaps

![Diagram showing laboratory models, drug screening, and natural history studies phases with red and green circles indicating availability of specific resources like iPSCs, biomarkers, compounds, and industry partners.](image-url)
Strategic Partnerships for Accelerated Progress in Rare Neurological Diseases

• Understanding common challenges can bring multiple stakeholders together
• Unmet needs and desperate diseases can break down traditional boundaries
• Partnerships across disciplines and institutions possible
• Industry, patient advocacy and academia can complement each other
• Patient engagement and perspective can provide focus: “Move from Engagement Readiness to Trial Readiness!”