IMPLICATION OF GENE THERAPY IN PEDIATRICS: LEUKODYSTROPHIES

Cellicon Valley

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May 6, 2021

Children's Hospital of Philadelphia℠
Leukodystrophy Center of Excellence

DISCLOSURES

- Grant funding:
  - NIH
  - National Multiple Sclerosis Society
  - American Brain Foundation
  - United Leukodystrophy Foundation
- Investigator-initiated funding:
  - Ionis Pharmaceuticals
- Clinical study sites:
  - Retrophin
  - bluebird bio
- Philanthropy:
  - Elise's Corner
  - Grayson's Ladder
  - Brooks Coleman White Foundation
  - The Calliope Joy Foundation
  - Hunter's Hope
  - Families and private donors
- Consultant/Honoraria
  - UpToDate
  - Optum Inc

OBJECTIVES

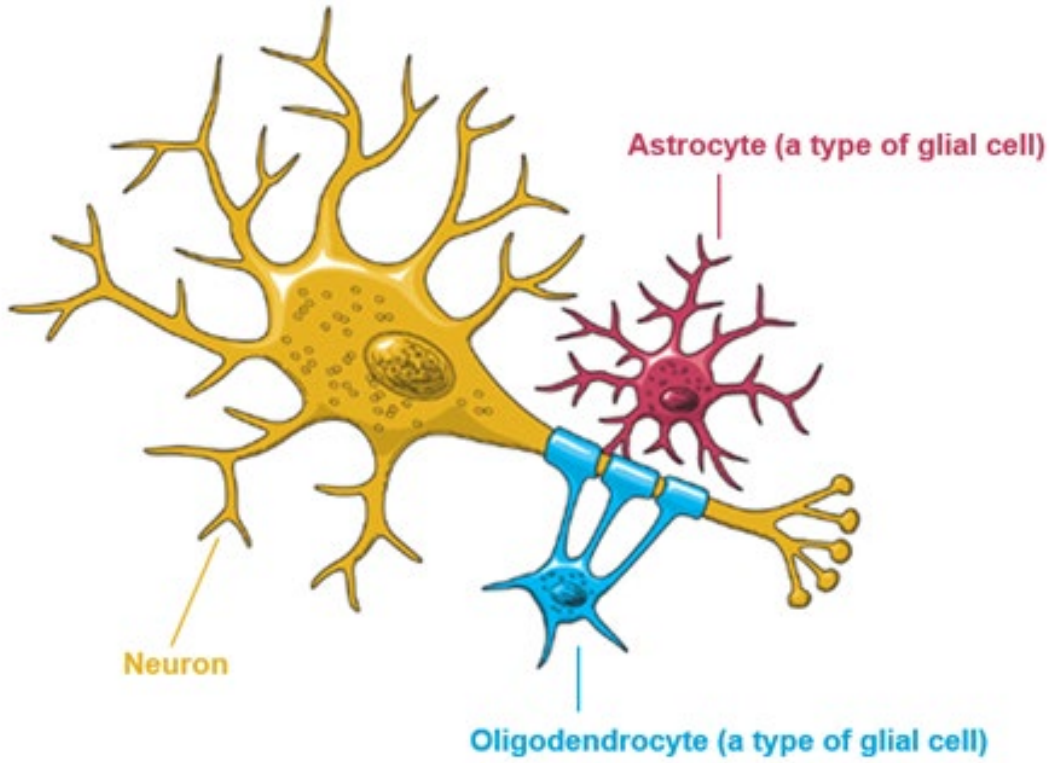
1. To review disease mechanisms
2. To present data from leukodystrophy gene therapy trials
3. To discuss additional challenges in neurologic gene therapy trials

DEFINING LEUKODYSTROPHIES

- Leukodystrophies are *heritable* disorders affecting the *white matter* of the central nervous system with or without peripheral nervous system involvement

>30 distinct disorders whose primary pathology includes glial cell or myelin sheath abnormalities (such as *oligodendrocytes*, *astrocytes*)

- Significant axonal pathology
- Excludes neuronal disorders and gray matter disease
- Excludes inborn errors of metabolism, which are categorized as genetic leukoencephalopathies (>90 disorders)



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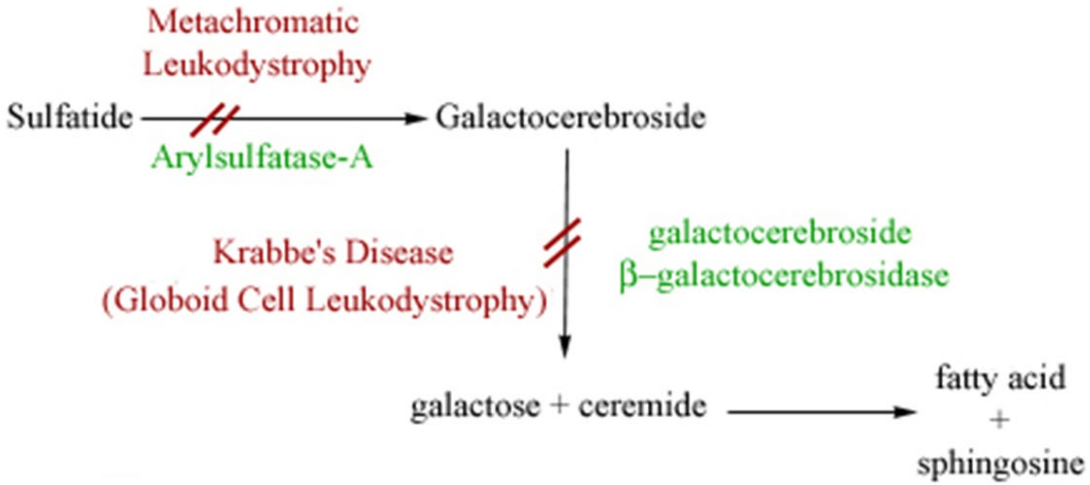
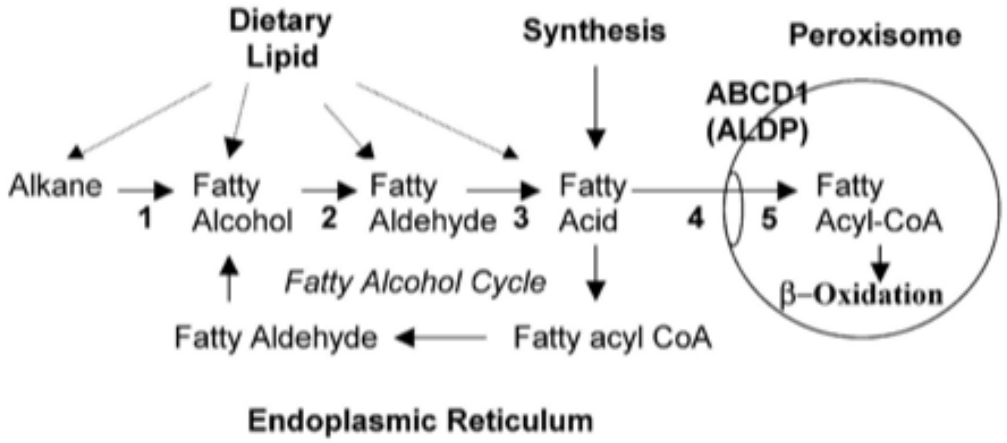
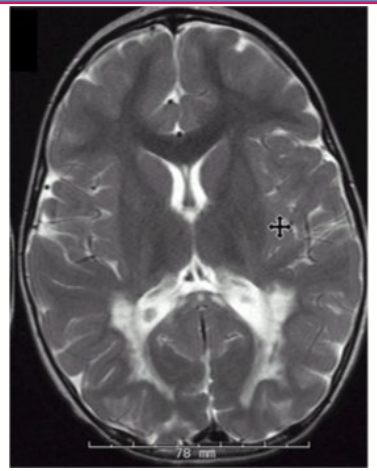
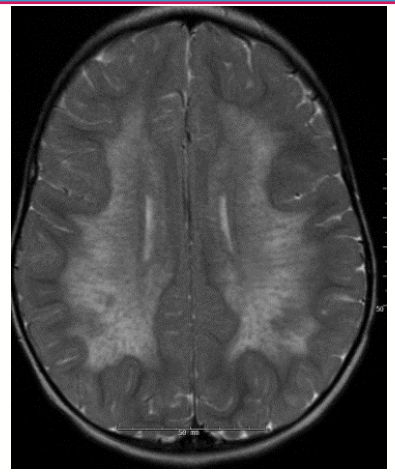
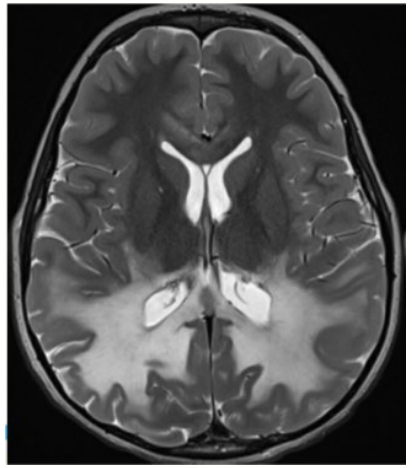
Vanderver A, et al. Molecular Genetics and Metabolism 2015 114:494
Image: http://www.qthera.com/live/getattachment/Technology/Overview/q-thera-simplified-neuron-and-glia.png.aspx

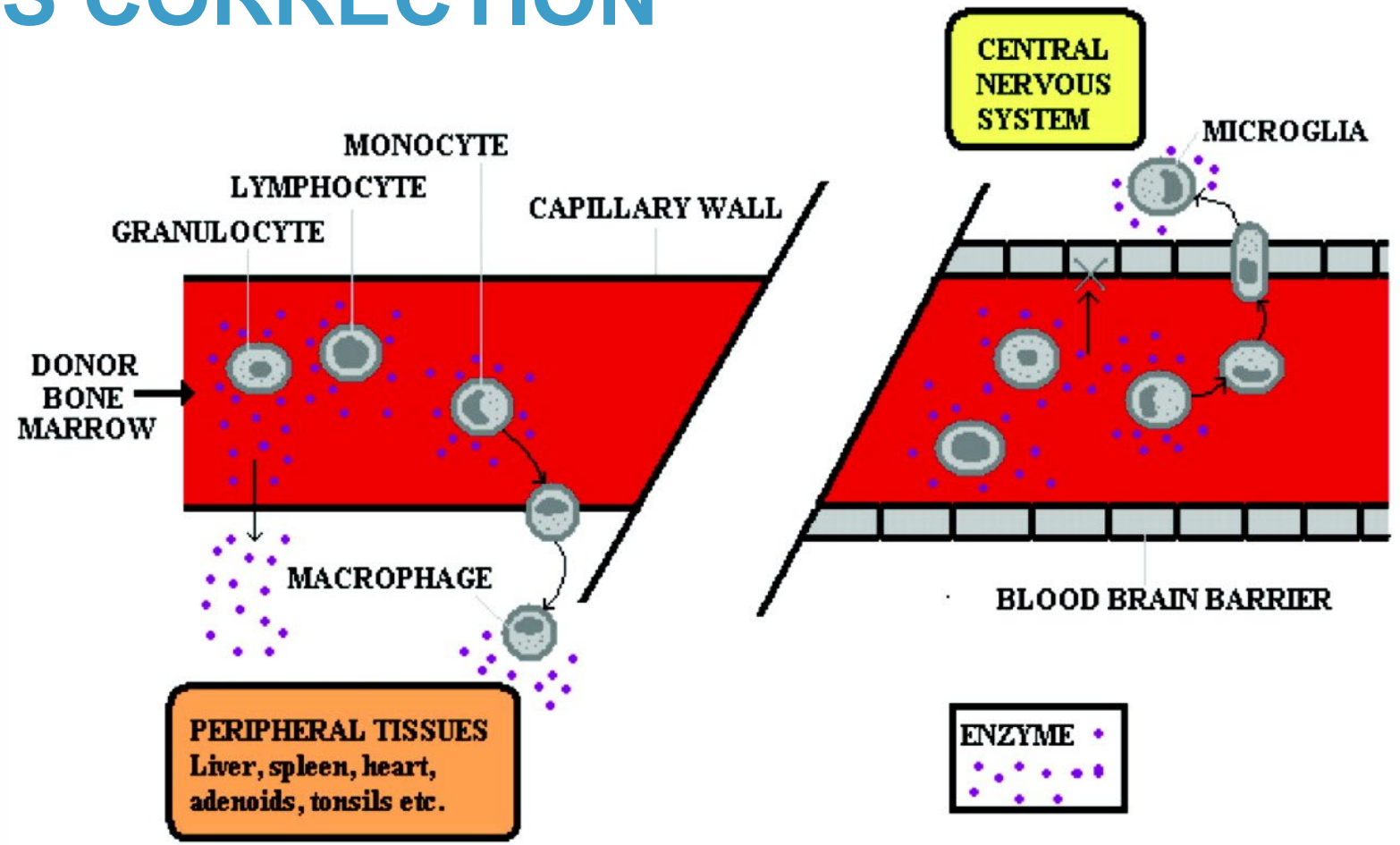
GENE THERAPY FOR LEUKODYSTROPHIES

Organelle	Leukodystrophy	Pathology	Vector
Lysosome	Globoid cell leukodystrophy (Krabbe)		AAVhu68
	Metachromatic leukodystrophy (MLD)		Lentiviral + HSCT
Peroxisome	Adrenoleukodystrophy (X-ALD)		Lentiviral + HSCT

GENE THERAPY FOR LEUKODYSTROPHIES

Organelle	Leukodystrophy	Regional differences	Vector
Lysosome	Globoid cell leukodystrophy (Krabbe)	 Krabbe	AAVhu68
	Metachromatic leukodystrophy (MLD)	 MLD	Lentiviral + HSCT
Peroxisome	Adrenoleukodystrophy (X-ALD)		Lentiviral + HSCT

HEMATOPOIETIC STEM CELL TRANSPLANT: CROSS CORRECTION



Wynn R *Hematology* 2011;2011:285-291

HEMATOPOIETIC STEM CELL TRANSPLANT

ANNALS of Clinical and Translational Neurology
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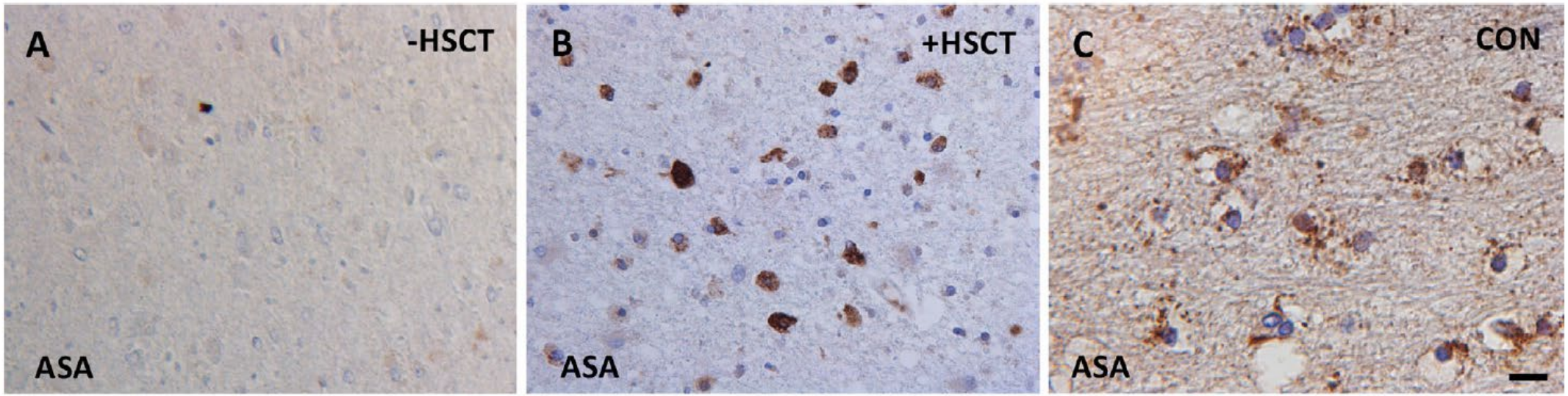
RESEARCH ARTICLE

Metachromatic leukodystrophy and transplantation: remyelination, no cross-correction

Nicole I. Wolf[1], Marjolein Breur[1,2], Bonnie Plug[1,2], Shanice Beerepoot[1,3], Aimee S. R. Westerveld[1,2], Diane F. van Rappard[1], Sharon I. de Vries[4], Maarten H. P. Kole[4,5], Adeline Vanderver[6,7], Marjo S. van der Knaap[1,8], Caroline A. Lindemans[9,10], Peter M. van Hasselt[11], Jaap J. Boelens[9], Ulrich Matzner[12], Volkmar Gieselmann[12] & Marianna Bugiani[1,2]

NO EVIDENCE OF CROSS CORRECTION IN MLD

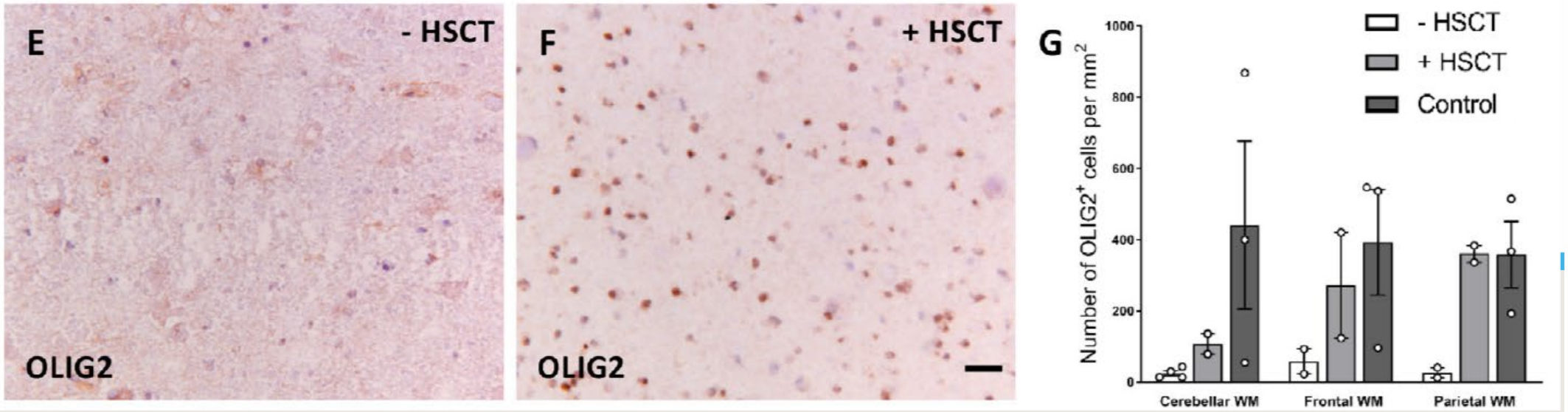
- Design: Autopsy brain tissue
  - MLD: N=8 (2 transplanted and 6 non-transplanted)
  - Age matched controls: N=2
- 2 transplanted patients
  - Donor macrophages were found throughout the white matter
  - Unable to detect arylsulfatase (ASA) in oligodendrocytes or astrocytes, suggesting that true cross-correction to these cell types did not occur



Wolf N et al. *Annals of Clinical and Translational Neurology* 2020; 7(2): 169–180.

REMYELINATION IN MLD

- 2 transplanted patients
  - Higher numbers of oligodendrocyte precursors and mature myelin-forming oligodendrocytes were present in brains of transplanted patients
  - Ultrastructural evidence of remyelination
  - HSCT supports survival, proliferation, and differentiation of oligodendrocytes, which in turn are capable of restoring myelin



Wolf N et al. *Annals of Clinical and Translational Neurology* 2020; 7(2): 169–180.

METACHROMATIC LEUKODYSTROPHY

- Central and peripheral nervous system demyelination
- Various disease phenotypes
  - Late-infantile
  - Juvenile
  - Adult
- Late-infantile MLD
  - HSCT is rarely indicated due to rapid disease progression
- Supportive care

EX VIVO GENE THERAPY IN MLD

- Non-randomized, open-label, single-arm phase 1/2 trial of pre-symptomatic early infantile or early symptomatic juvenile MLD
  - Comparison group: historical controls and sibling pairs
- Autologous stem cell transplant with ex vivo lentiviral gene transfer
- Conditioning regimen: Busulfan
- Enrollment
  - 20 patients (Milan, Italy)

RESEARCH ARTICLE SUMMARY

Lentiviral Hematopoietic Stem Cell Gene Therapy Benefits Metachromatic Leukodystrophy

Alessandra Biffi,* Eugenio Montini, Laura Lorioli, Martina Cesani, Francesca Fumagalli, Tiziana Plati, Cristina Baldoli, Sabata Martino, Andrea Calabria, Sabrina Canale, Fabrizio Benedicenti, Giuliana Vallanti, Luca Biasco, Simone Leo, Nabil Kabbara, Gianluigi Zanetti, William B. Rizzo, Nalini A. L. Mehta, Maria Pia Cicalese, Miriam Casiraghi, Jaap J. Boelens, Ubaldo Del Carro, David J. Dow, Manfred Schmidt, Andrea Assanelli, Victor Neduva, Clelia Di Serio, Elia Stupka, Jason Gardner, Christof von Kalle, Claudio Bordignon, Fabio Ciceri, Attilio Rovelli, Maria Grazia Roncarolo, Alessandro Aiuti, Maria Sessa, Luigi Naldini*

READ THE FULL ARTICLE ONLINE
http://dx.doi.org/10.1126/science.1233158

Cite this article as A. Biffi *et al.*, *Science* **341**, 1233158 (2013).
DOI: 10.1126/science.1233158

FIGURES IN THE FULL ARTICLE

Fig. 1. Gene marking in patients after HSC-GT.

Fig. 2. ARSA expression in patients after HSC-GT.

Fig. 3. Clinical follow up of MLD patients after HSC-GT.

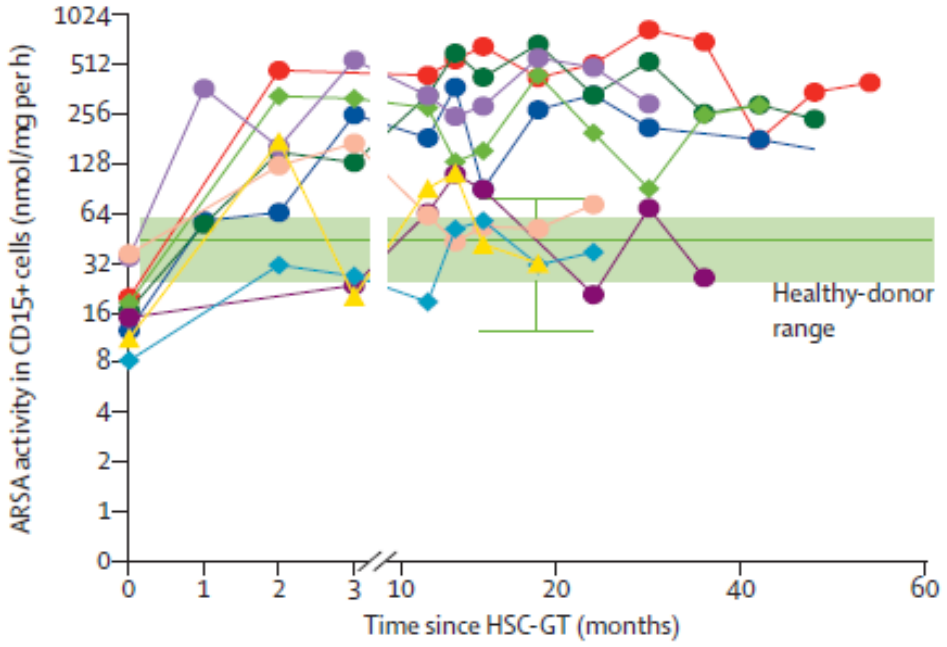
Articles

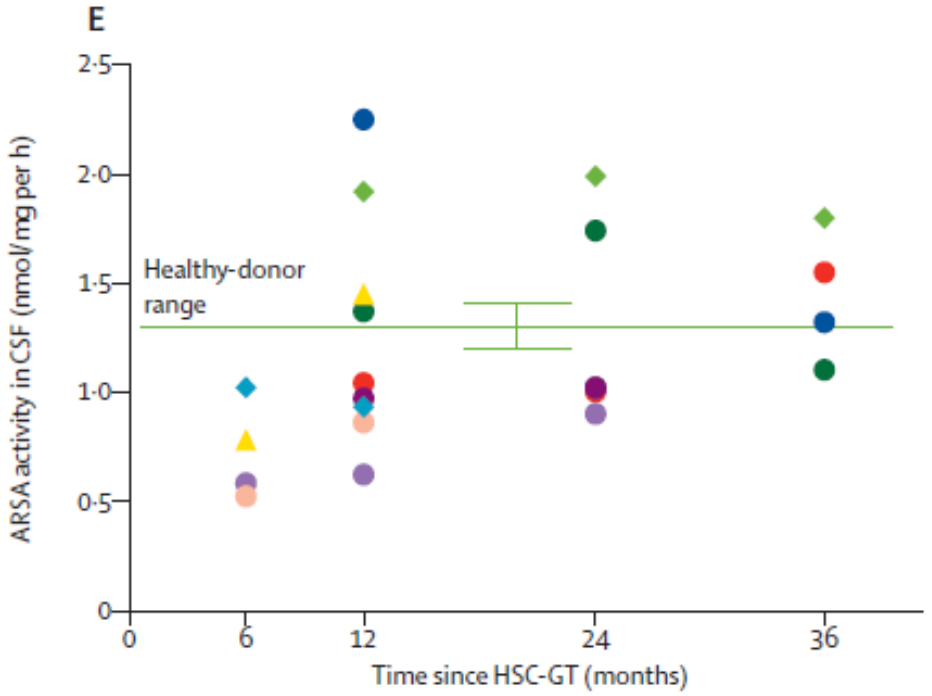
Lentiviral haemopoietic stem-cell gene therapy in early-onset metachromatic leukodystrophy: an ad-hoc analysis of a non-randomised, open-label, phase 1/2 trial

Maria Sessa, Laura Lorioli*, Francesca Fumagalli, Serena Acquati, Daniela Redaelli, Cristina Baldoli, Sabrina Canale, Ignazio D Lopez, Francesco Morena, Andrea Calabria, Rossana Fiori, Paolo Silvani, Paola M V Rancoita, Michela Gabaldo, Fabrizio Benedicenti, Gigliola Antonioli, Andrea Assanelli, Maria Pia Cicalese, Ubaldo del Carro, Maria Grazia Natali Sora, Sabata Martino, Angelo Quattrini, Eugenio Montini, Clelia Di Serio, Fabio Ciceri, Maria Grazia Roncarolo, Alessandro Aiuti, Luigi Naldini, Alessandra Biffi*

OUTCOMES

- Transduction
  - Targeted ≥2 vector copy number per genome
  - Vector copy number: median 2.5 (1.7 – 4.4, efficiency 92.8%)
- Engraftment
  - Begins at 1 month
  - 45-80% of the colonies harbored the lentivirus genome
- ARSA activity
  - Supra-normal levels of ARSA activity
  - ARSA protein isolated from hematopoietic cells as early as 1 month
  - Protein also detectable in cerebrospinal fluid at 1-2 years





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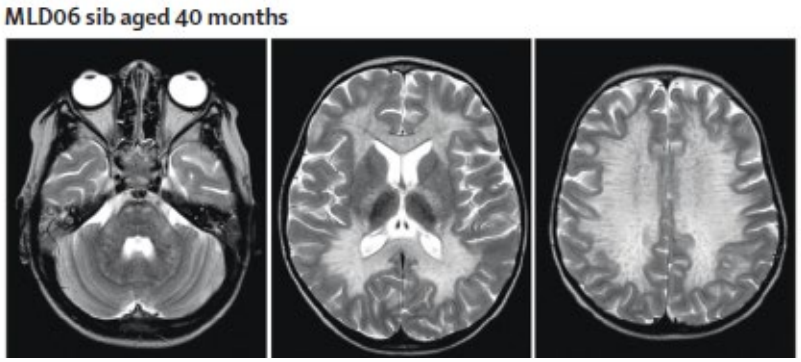
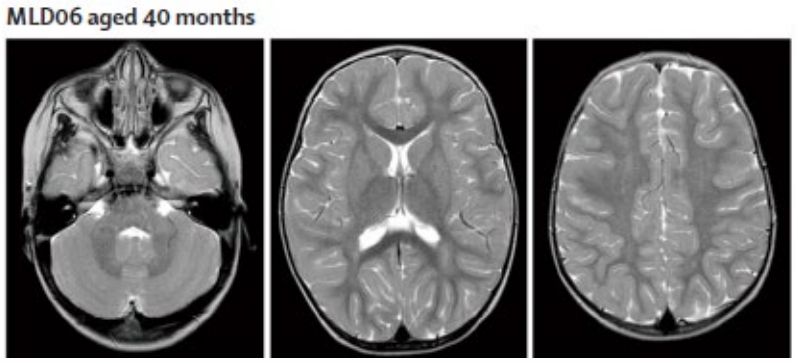
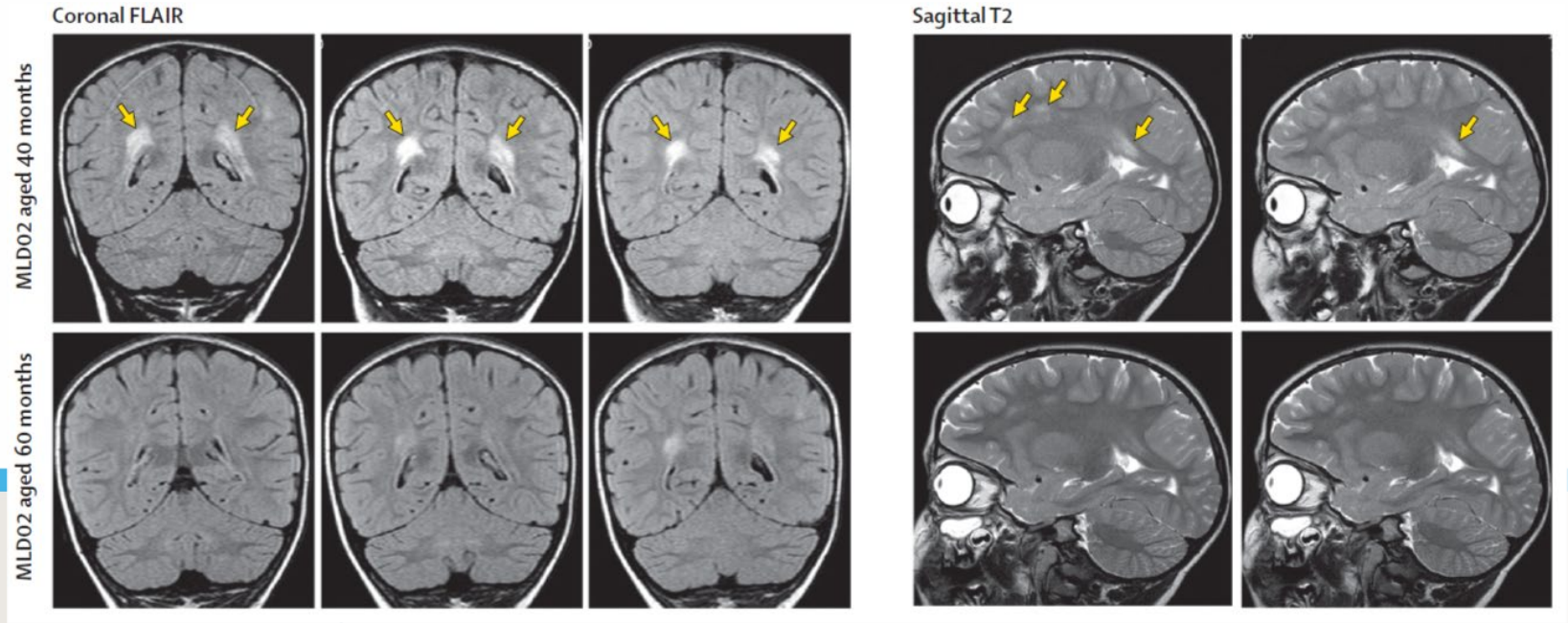
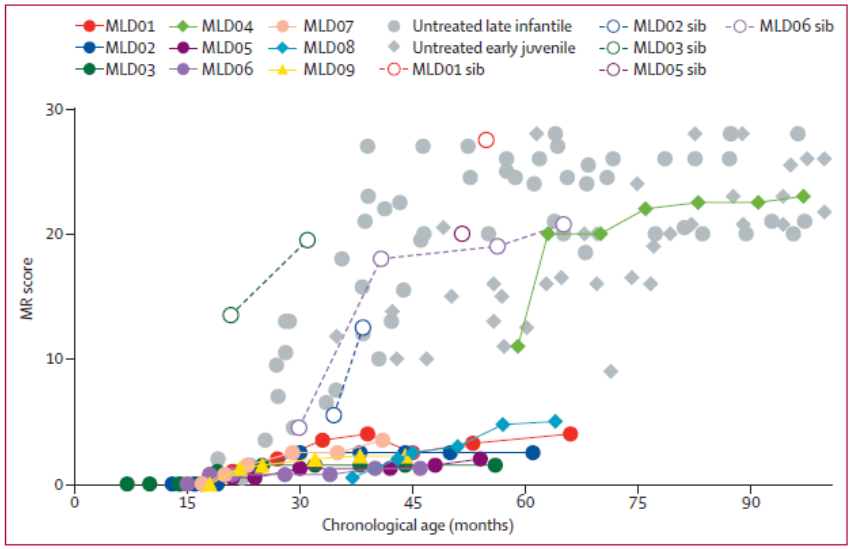
Biffi A, et al. *Science* 2013;341:1233158
Sessa M, et al. *The Lancet* 2016;388(10043):476-487

REMYELINATION ON MRI IN TREATED PATIENTS









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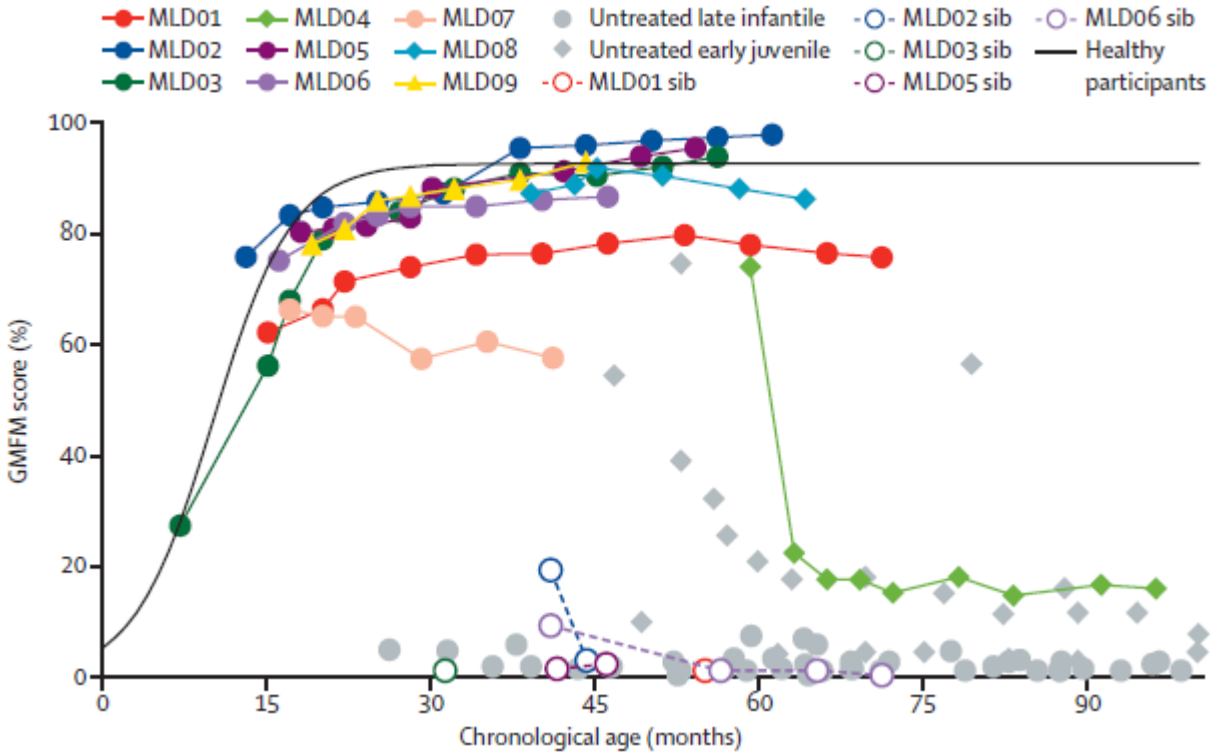
OUTCOMES

- Safety
  - *"At the time of analysis*, all had survived"
    - Median follow-up 36 months, range 18-54 months
  - "No serious adverse events *related to the medicinal product were reported*"
- Efficacy
  - 8 patients: prevention of disease onset or halted disease progression
    - 7 received treatment while pre-symptomatic
  - 6 patients: gross motor scores similar to normally developing children



9 patients:

6 late-infantile (circle)

2 early-symptomatic, early-juvenile (diamond)

1 early-onset disease (unclassified) (triangle)

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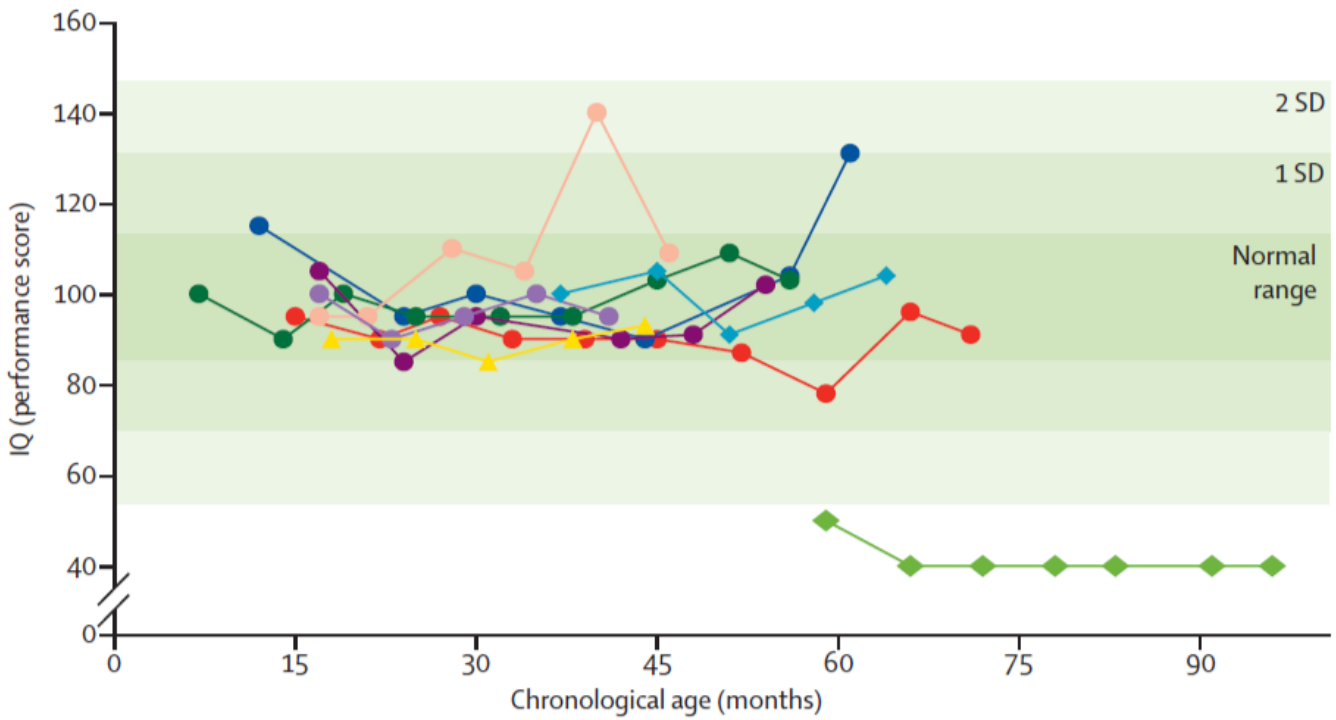
Biffi A, et al. *Science* 2013;341:1233158

Sessa M, et al. *The Lancet* 2016;388(10043):476-487

NEUROLOGIC OUTCOMES POST-TREATMENT

- Gross and fine motor difficulties
  - Contractures
  - Handwriting
- Cognitive decline
  - Reading
  - Spelling
  - Math
- Pain
  - Spasticity
  - Peripheral neuropathy



LIBMELDY: AUTOLOGOUS CD34+ CELLS ENCODING *ARSA* GENE

- Orchard Therapeutics
- EMA authorization 12/17/20
- Not yet FDA approved
- Future directions: MLD newborn screening initiatives

Genetics inMedicine

www.nature.com/gim

Check for updates

ARTICLE

Toward newborn screening of metachromatic leukodystrophy: results from analysis of over 27,000 newborn dried blood spots

Xinying Hong, PhD[1,7,8], Jessica Daiker, BS[1,7,8], Martin Sadilek, PhD[1], Nicole Ruiz-Schultz, PhD[2], Arun Babu Kumar, PhD[1], Stevie Norcross, PhD[2], Warunee Dansithong, PhD[2], Teryn Suhr, RN[3], Maria L. Escolar, MD[4], C. Ronald Scott, MD[5], Andreas Rohrwasser, PhD[2] and Michael H. Gelb, PhD[1,6]

X-LINKED ADRENOLEUKODYSTROPHY

- Peroxisomal disorder
- Various disease phenotypes
  - Childhood cerebral ALD
  - Addison's disease
  - Adrenomyeloneuropathy
- Newborn screening
- HSCT is indicated in EARLY cerebral disease
- Supportive care in those with elevated MRI score, neurologic and cognitive impairments

BLUEBIRD BIO: STARBEAM STUDY

- Multicenter, single group, open-label, phase 2–3 study
- Autologous stem cell transplant with ex vivo lentiviral gene transfer
  - Conditioning regimen: Busulfan and cyclophosphamide
- Eligibility:
  - Eligible for allogeneic hematopoietic stem cell transplant (HCT) but with *no* matched sibling donor
  - Confirmed early-stage, active CCALD
    - Gadolinium enhancement on MRI
    - Loes score between 0.5 – 9.0
    - Neurologic Function Scale ≤1
- Enrollment: 17 patients as of March, 2016

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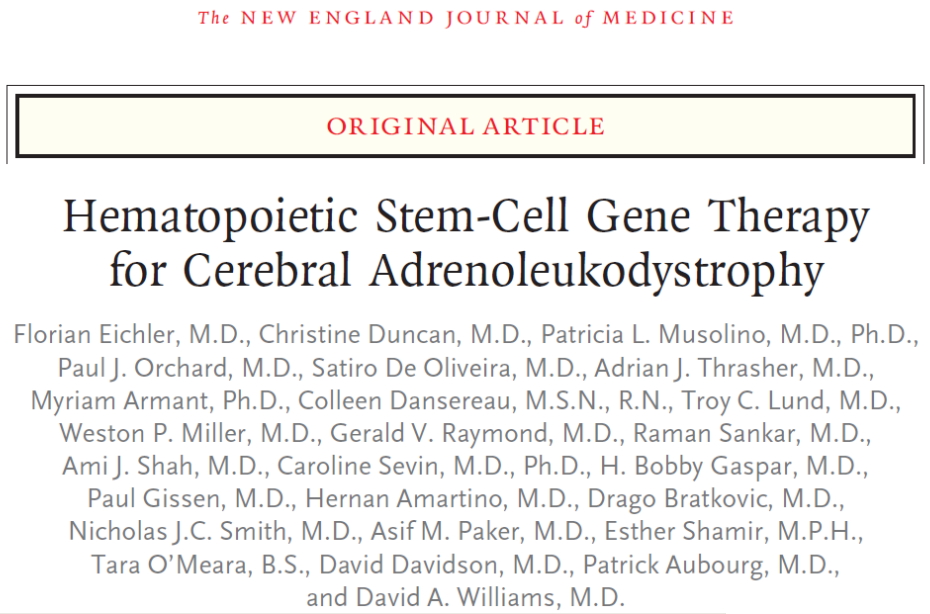
Eichler F, et al. *NEJM* 2017;377:1630-8.



BLUEBIRD BIO: STARBEAM STUDY

- Endpoints:
  - Alive
  - No major functional disabilities at 2 years

Table 10-1 Neurologic Function Score (NFS) for CALD

Symptom / Neuroexam	Score
Hearing / auditory processing problems	1
Aphasia / apraxia	1
Loss of communication *	3
Vision impairment /field cut	1
Cortical blindness *	2
Swallowing / other CNS dysfunctions	2
Tube feeding *	2
Running difficulties / hyperreflexia	1
Walking difficulties / spasticity / spastic gait (no assistance)	1
Spastic gait (needs assistance)	2
Wheelchair dependence *	2
Complete loss of voluntary movement *	3
Episodes of incontinence	1
Total incontinence *	2
Nonfebrile seizures	1

* These disabilities will be considered "MFDs" for data analysis of the primary efficacy endpoint in this study.

Eichler F, et al. *NEJM* 2017;377:1630-8.

BLUEBIRD BIO: STARBEAM STUDY

- Initial enrollment N=18
  - 1 deemed not eligible
- 15 /17 patients (88%) were alive and free of major functional disabilities
  - 2 died
    - Allogeneic transplant
    - Rhabdomyolysis, acute kidney and liver failure
- Safety: “consistent with myeloablative conditioning”
  - “One possibly drug-related serious adverse event”
    - Grade 3 BK-mediated viral cystitis
  - “One possibly drug-related adverse event”
    - Grade 1 tachycardia

Eichler F, et al. *NEJM* 2017;377:1630-8.

www.bluebirdbio.com

OUTCOMES

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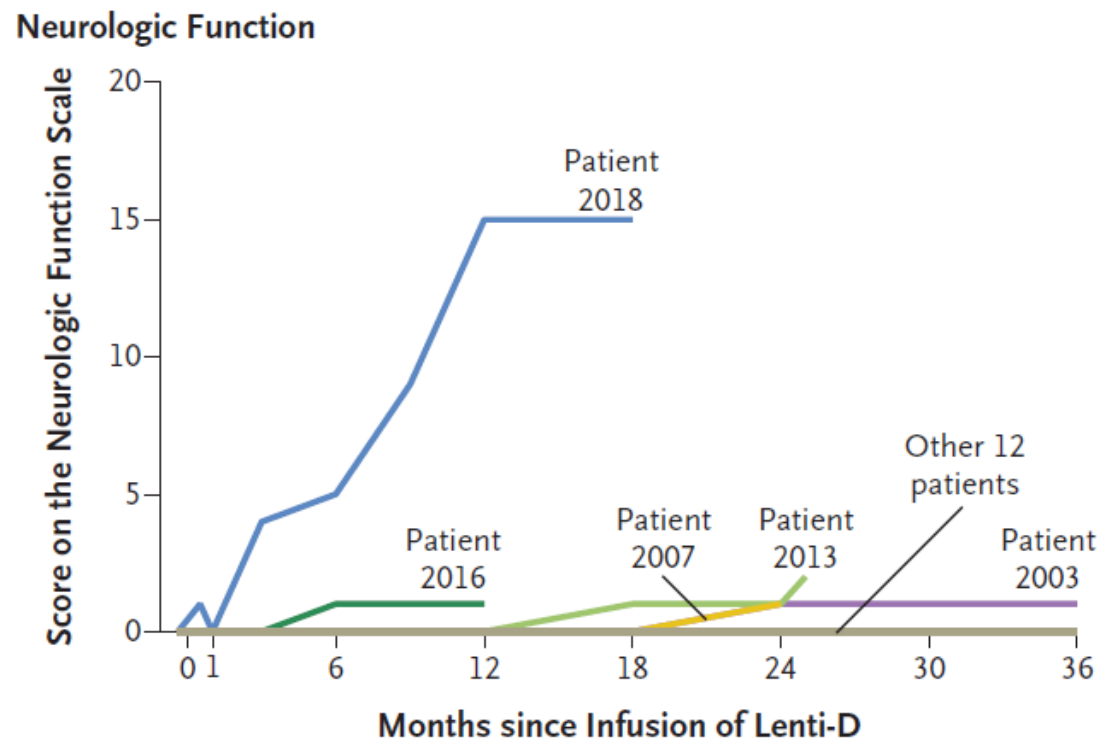
Neurologic Function Scale



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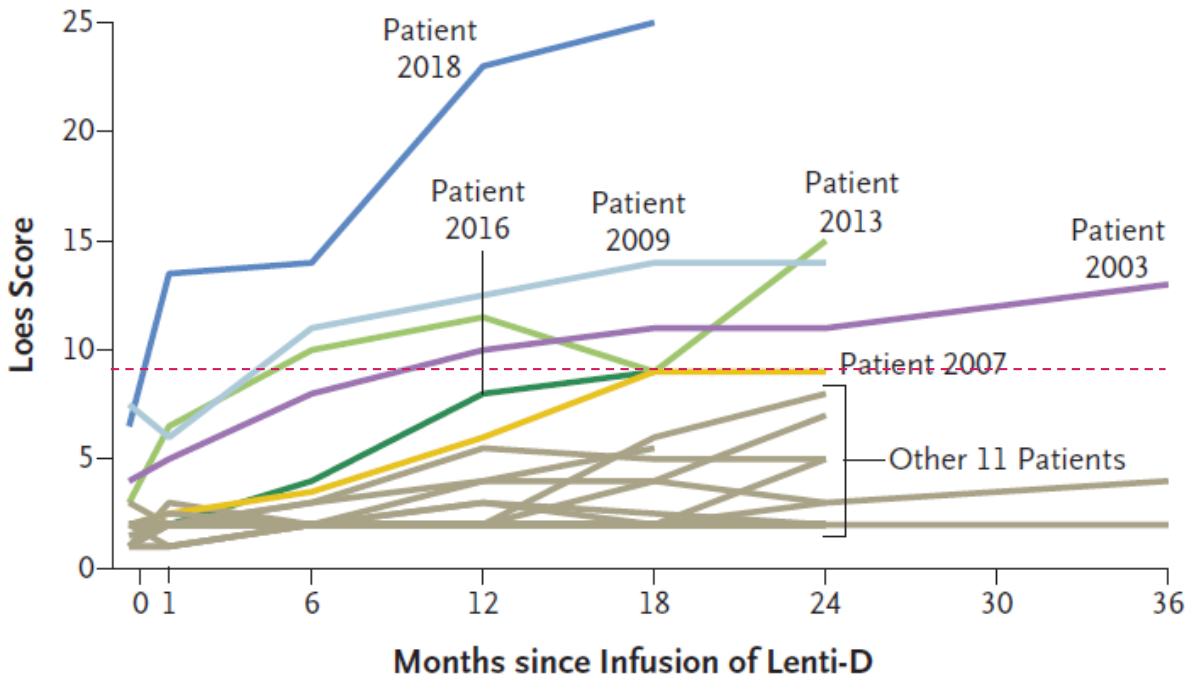
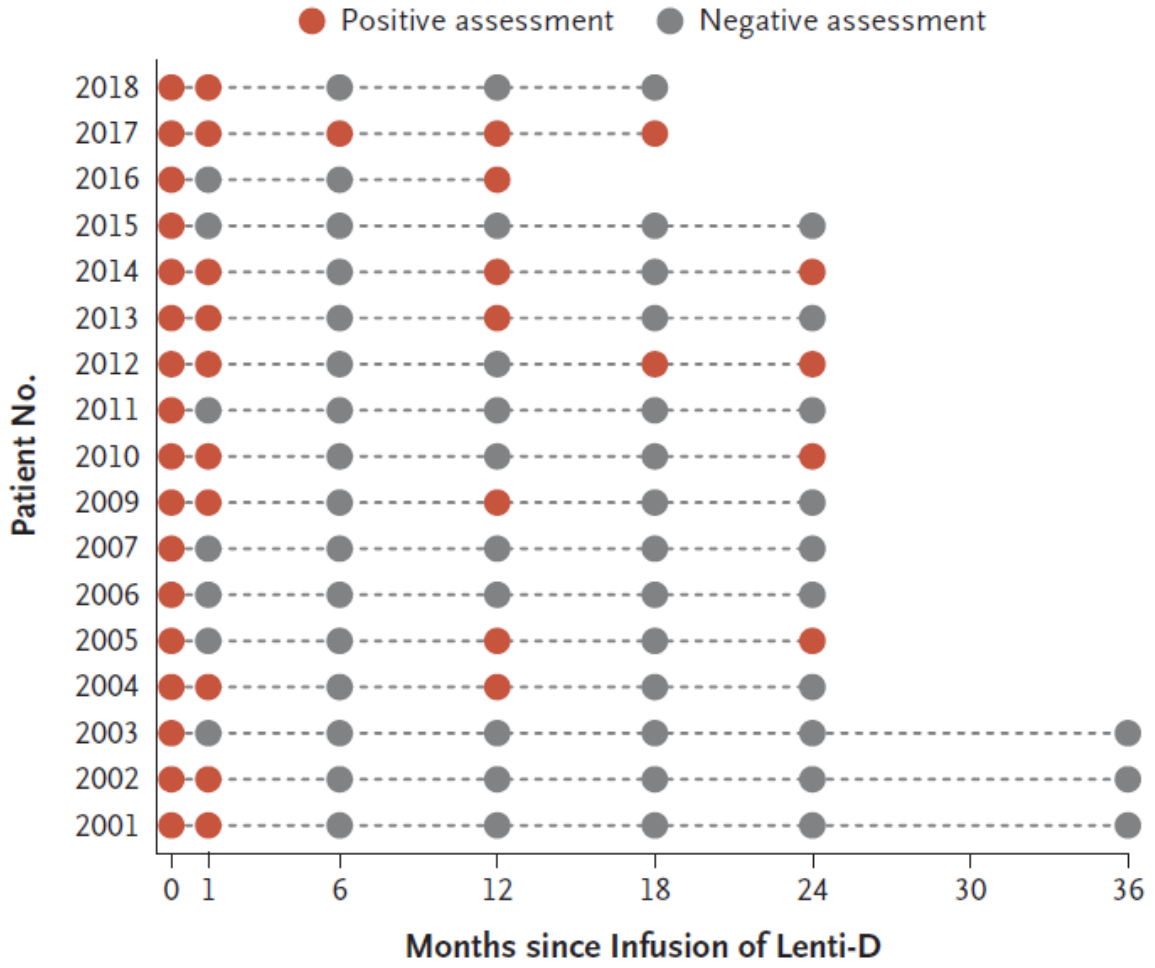
Eichler F, et al. *NEJM* 2017;377:1630-8.

DISEASE PROGRESSION AND INFLAMMATION ON MRI POST TREATMENT



Gadolinium Enhancement on MRI



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Eichler F, et al. *NEJM* 2017;377:1630-8.

CNS DELIVERY, CHALLENGES, AND TOXICITY

- Access to regional brain structures
- Need for improved outcome measures
- Ex vivo gene therapy and HSCT
  - Neurotoxicity of the conditioning regimen
- In vivo gene therapy
  - Dose limiting toxicities (1 x 10^{14} GC/kg) of systemic AAV
  - ICM: Dorsal root ganglion toxicity

SPECIAL SECTION ON NEUROMUSCULAR DISEASE GENE THERAPY

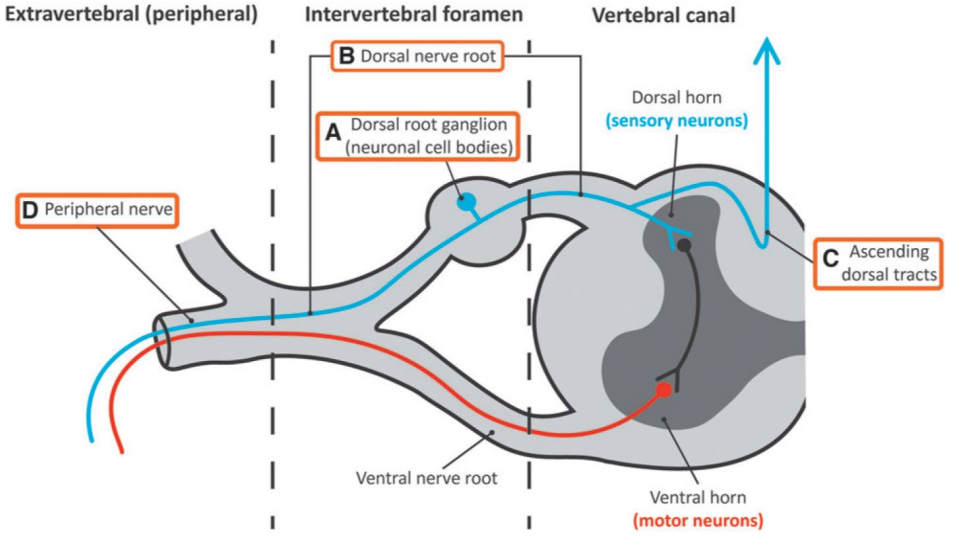
Guest Editor, Dongsheng Duan, PhD

HGT

Adeno-Associated Virus-Induced Dorsal Root Ganglion Pathology

Juliette Hordeaux,† Elizabeth L. Buza,† Cecilia Dyer, Tamara Goode, Thomas W. Mitchell, Laura Richman, Nathan Denton, Christian Hinderer, Nathan Katz, Ralf Schmid, Rod Miller, Gourav R. Choudhury, Makoto Horiuchi, Kalyani Nambiar, Hanying Yan, Mingyao Li, and James M. Wilson*

Gene Therapy Program, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.
†These authors contributed equally to this work.



LEUKODYSTROPHY GENE THERAPY TRIALS

- MLD data challenge the theory of cross-correction
- Pre-symptomatic or early symptomatic intervention is critical
  - Identified through families with other affected siblings
  - Newborn screening initiatives
- Disease progression
  - Clinical symptoms in MLD
  - MRI disease progression in X-ALD
- Efficacy trials require rigorous designs that account for brain development
- Improve treatment-related toxicities

ACKNOWLEDGEMENTS

Patients and their families!

the calliope joy foundation

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United Leukodystrophy Foundation

GRAYSON'S LADDER CLIMBING TO A CURE

The Brooks Coleman White Foundation

HUNTER'S HOPE

NIH National Institute of Neurological Disorders and Stroke

Reducing the burden of neurological disease...