ASGCT Data Review

IR webcast
May 23, 2023

ASGCT IR Event Agenda

TIME	AGENDA TOPIC	SPEAKERS
8:00 – 8:10 a.m.	**Orchard's HSC Gene Therapy Platform and ASGCT Overview**	Bobby Gaspar CEO
8:10 – 8:30 a.m.	**Clinical Data: OTL-203 (MPS-IH) + OTL-201 (MPS-IIIA)**	Leslie Meltzer CMO
8:30 – 8:40 a.m.	**Preclinical: OTL-204 (GRN-FTD) + OTL-104 (NOD2-CD)**	Bobby Gaspar CEO
8:40 – 9:00 a.m.	**Q&A**	

Orchard therapeutics

Forward-looking Statements

Certain information set forth in this presentation and in statements made orally during this presentation contain “forward-looking statements”. Except for statements of historical fact, information contained herein constitutes forward-looking statements and may include, but is not limited to, expectations of Orchard Therapeutics plc (the “Company” or “Orchard) regarding: (i) the safety and efficacy of Libmeldy and its product candidates; (ii) the Company’s ability to establish the infrastructure necessary to enable the treatment of eligible MLD patients and the adequacy of the Company’s supply chain and ability to commercialize Libmeldy; (iii) the expected development of the Company’s business and product candidates; (iv) the timing of regulatory submissions for approval of its product candidates; (v) the timing of interactions with regulators and regulatory submissions related to ongoing and new clinical trials for its product candidates; (vi) the timing of announcement of preclinical data for its product candidates and the likelihood that such data will be positive and support further development and regulatory approval of these product candidates; (vii) the timing and likelihood of approval of such product candidates by the applicable regulatory authorities; (viii) the adequacy of the Company’s supply chain, manufacturing capacity and plans for future investment and commercialization; (ix) execution of the Company’s vision and growth strategy, including with respect to global growth; (x) the size and value of potential markets for and commercialization of Libmeldy and the Company’s product candidates; and (xi) expected financial performance and financial condition, including its cash runway. The words “may,” “should,” “expects,” “intends,” “plans,” “anticipates,” “believes,” “estimates,” “predicts,” “potential,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Forward-looking statements are provided to allow investors the opportunity to understand management’s beliefs and opinions in respect of the future so that they may use such beliefs and opinions as one factor in evaluating an investment.

These statements are neither promises nor guarantees of future performance. Such forward-looking statements necessarily involve known and unknown risks and uncertainties, many of which are beyond the Company’s control, which could cause actual results to differ materially from those contemplated in these forward-looking statements. In particular, these risks and uncertainties include, without limitation, the risk that Libmeldy will not be successfully commercialized, including the risk that the Company may not secure adequate pricing or reimbursement to support continued development of Libmeldy or its product candidates, if approved; the risk that any one or more of the Company’s product candidates, including OTL-200, will not be approved, successfully developed or commercialized; the risk that prior results, such as signals of safety, activity or durability of effect, observed from preclinical studies or clinical trials of Orchard’s product candidates will not be repeated or continue in ongoing or future studies or trials involving its product candidates; the risk that the market opportunity for Libmeldy or its product candidates may be lower than estimated; the risks from high inflation, macroeconomic conditions and geopolitical instability; and, the severity of the ongoing and evolving impact of the COVID-19 pandemic on Orchard’s business, including on preclinical and clinical development, its supply chain and commercial programs. You are cautioned not to place undue reliance on forward-looking statements. For additional disclosure regarding these and other risks faced by the Company, see the disclosure contained in the Company’s most recent annual or quarterly filed with the U.S. Securities and Exchange Commission (the “SEC”), as well as subsequent filings and reports filed with the SEC. These forward-looking statements speak only as of the date of this presentation. The Company undertakes no obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, except as may be required by law.

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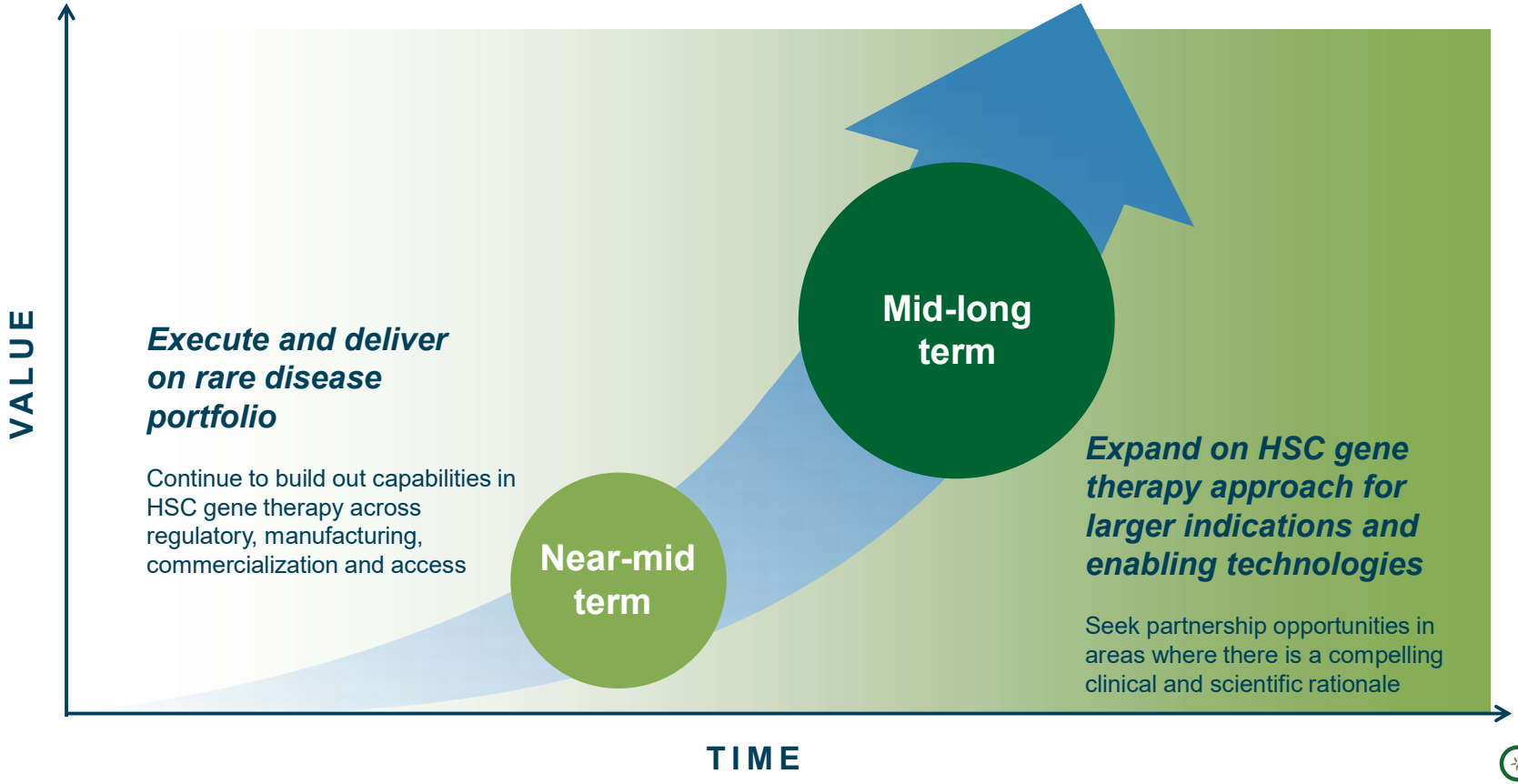
Orchard's Vision to End the Devastation Caused by Severe and other Genetic Diseases



HSC= hematopoietic stem cell

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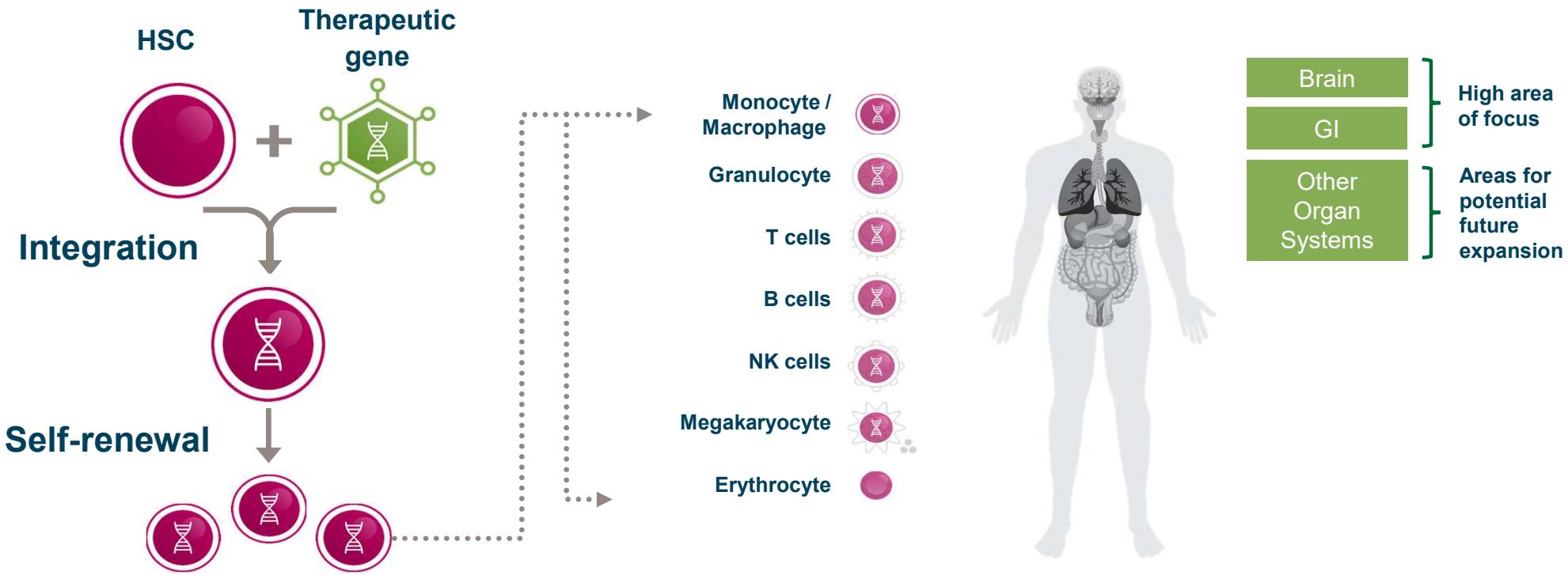
HSC Gene Therapy Offers a Highly Differentiated Approach



Literature references: Alessia Capotondo, Rita Milazzo, Letterio Salvatore Politi, Angelo Quattrini, Alessio Palini, Tiziana Plati, Stefania Merella, Alessandro Nonis, Clelia di Serio, Eugenio Montini, Luigi Naldini, and Alessandra Biffi, PNAS September 11, 2012 109 (37) 15018-15023; https://doi.org/10.1073/pnas.1205858109; Tissue macrophages: heterogeneity and functions, Siamon Gordon and Annette Plüddemann, BMC Biology 2017 15:53, 29 June 2017

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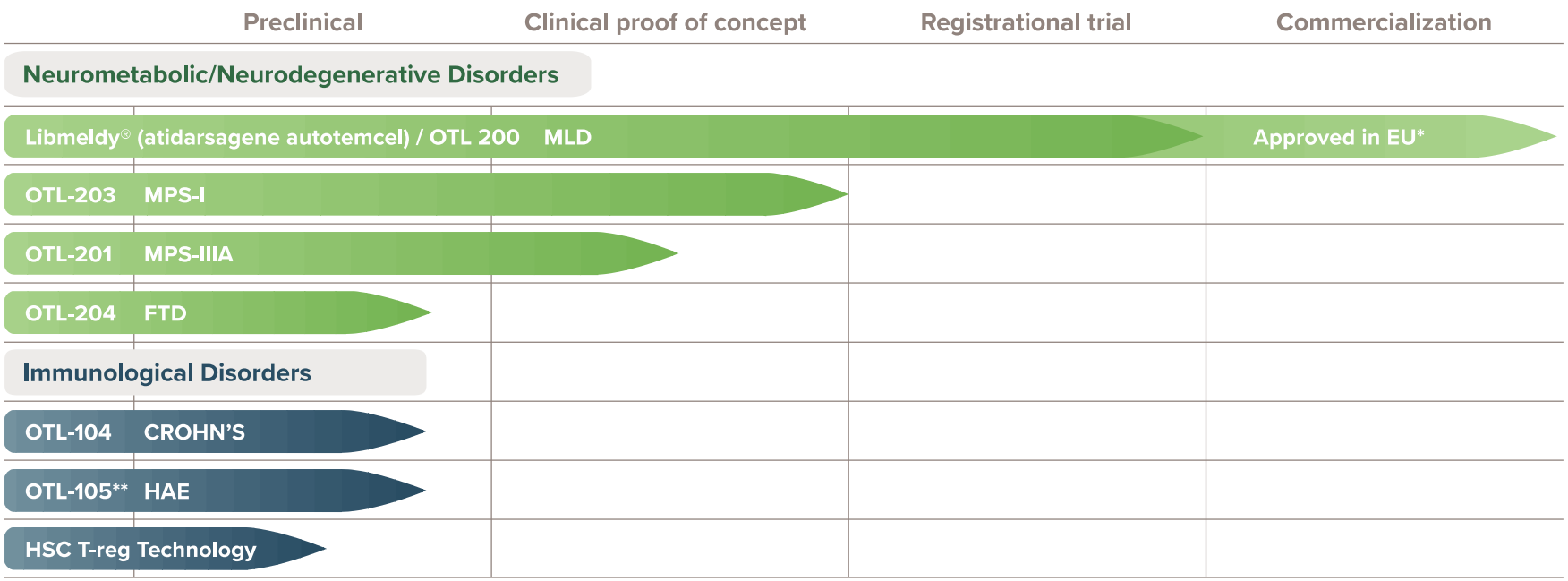
Validated Rare Disease Pipeline with Opportunities for Expansion



Several additional research and preclinical programs under development.

*Libmeldy® is approved in the European Union, UK, Iceland, Liechtenstein and Norway. In the U.S., OTL-200 is an investigational therapy. All other therapies in our pipeline are investigational and have not been approved by any regulatory agency or health authority.

**OTL-105 partnered with Pharming Group N.V.

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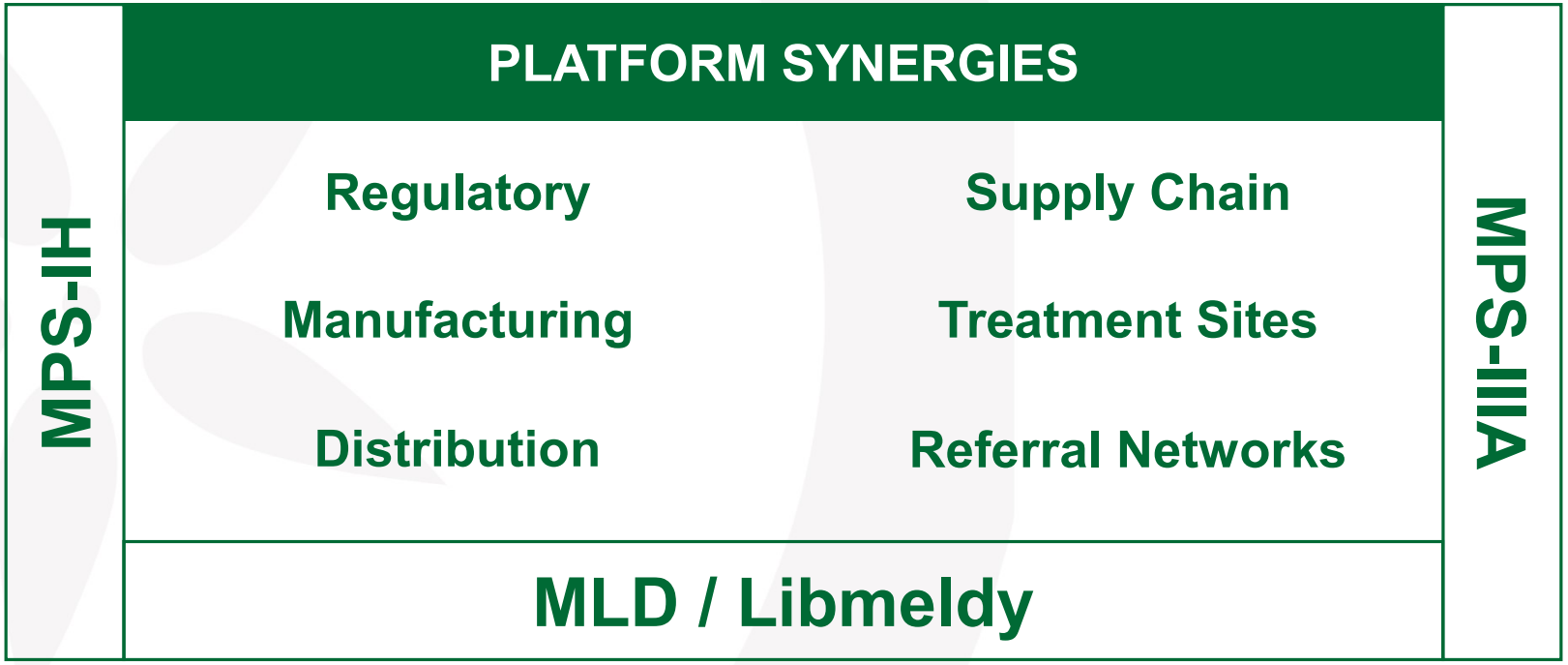
Significant Platform Synergies That Can be Leveraged Across Neurometabolic Pipeline



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ASGCT Snapshot: Six presentations and three oral presentations across five programs

- **OTL-203 for MPS-IH: New PoC data shows extensive metabolic correction in the skeletal system, including normal growth rates, improvement in joint function and progressive acquisition of motor skills**
- **OTL-201 for MPS-IIIA: Updated data from ongoing PoC study show additional favorable neurocognitive outcomes compared to disease natural history with median follow-up out to 2.5 years**
- **OTL-204 for GRN-FTD: First preclinical data highlighting ability of HSC gene therapy to restore microglial function, modulate neuroinflammation, and normalize predictive biomarkers**
- **OTL-104 for NOD2-CD: Preclinical proof-of-concept data show the therapeutic potential in a severe and treatment-refractory form of the disease**

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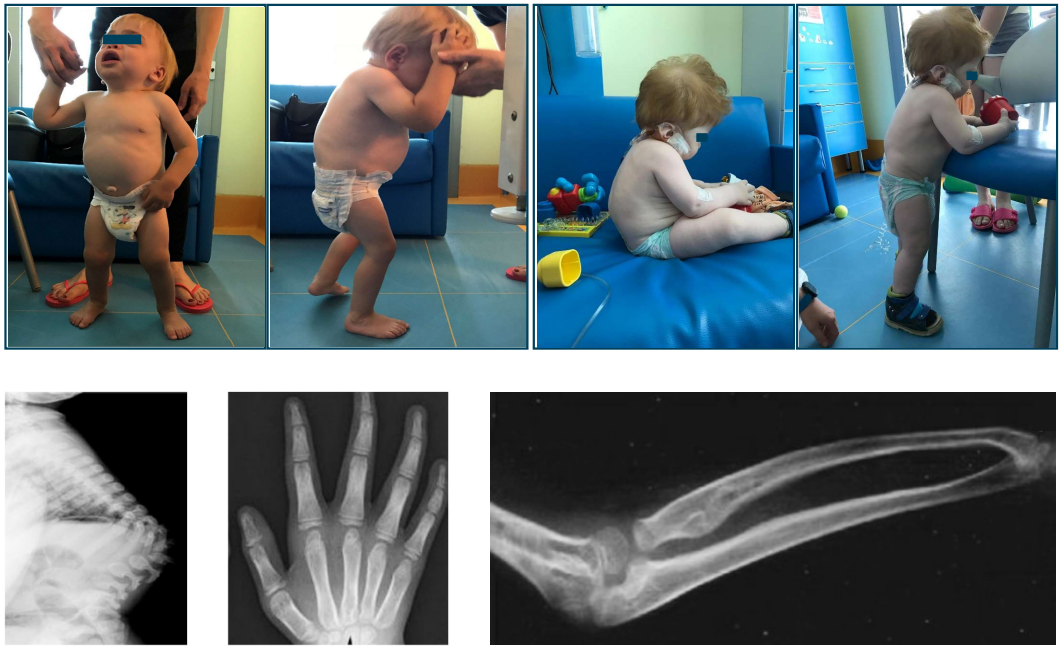
New OTL-203 Data in MPS-IH

MPS-IH is a Highly Debilitating, Multisystemic Condition Impacting Cognitive and Skeletal Function

- Deficiency of **IDUA enzyme** leads to accumulation of heparan and dermatan sulfate
- **Multisystemic** neurometabolic condition affecting cognition, **growth and skeletal** function
- **Current standard of care: HSCT** and/or ERT as a bridging or chronic therapy but with **significant limitations**
- **Incidence:** ~1 in 100,000 live births; Hurler syndrome accounts for 60%[1]
- **NBS established** in some geographies, including[1]
  - National: Netherlands, Taiwan, Austria*
  - Regional/Provincial: Italy, Canada
  - U.S: 33 states screening as of May 2023



MPS Symposium July 2021; Moore 2008; mps1disease.com

* private paid program (Archimed)

Sources:[1]Beck et al. The Natural History of MPS I: Global Perspectives from the MPS I Registry. Genetics in Medicine 2014, 16(10), 759;
[2] https://www.raredisorders.ca/content/uploads/CORD-Submission-on-Newborn-Screening-Program-18Sep2015.pdfhttps://baebies.com/newborn-screening-for-lysosomal-storage-disorders-expands-despite-the-covid-19-pandemic/ , https://pubmed.ncbi.nlm.nih.gov/30409495/, https://pubmed.ncbi.nlm.nih.gov/32235807/, Donati et al. Italian Journal of Pediatrics 2018, 44(Suppl 2):126

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OTL-203 (MPS-IH): Interim Proof-of-Concept (PoC) Study Results Published in NEJM

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 18, 2021 VOL. 385 NO. 21

Hematopoietic Stem- and Progenitor-Cell Gene Therapy for Hurler Syndrome

B. Gentner, F. Tucci, S. Galimberti, F. Fumagalli, M. De Pellegrin, P. Silvani, C. Camesasca, S. Pontesilli, S. Darin, F. Ciotti, M. Sarzana, G. Consiglieri, C. Filisetti, G. Forni, L. Passerini, D. Tomasoni, D. Cesana, A. Calabria, G. Spinozzi, M.-P. Cicalese, V. Calbi, M. Migliavacca, F. Barzaghi, F. Ferrua, V. Gallo, S. Miglietta, E. Zonari, P.S. Cheruku, C. Forni, M. Facchini, A. Corti, M. Gabaldo, S. Zancan, S. Gasperini, A. Rovelli, J.-J. Boelens, S.A. Jones, R. Wynn, C. Baldoli, E. Montini, S. Gregori, F. Ciceri, M.G. Valsecchi, G. la Marca, R. Parini, L. Naldini, A. Aiuti, and M.-E. Bernardo, for the MPSI Study Group*

ABSTRACT

BACKGROUND

Allogeneic hematopoietic stem-cell transplantation is the standard of care for Hurler syndrome (mucopolysaccharidosis type I, Hurler variant [MPSIH]). However, this treatment is only partially curative and is associated with complications.

METHODS

We are conducting an ongoing study involving eight children with MPSIH. At enrollment, the children lacked a suitable allogeneic donor and had a Developmental Quotient or Intelligence Quotient score above 70 (i.e., none had moderate or severe cognitive impairment). The children received autologous hematopoietic stem and progenitor cells (HSPCs) transduced ex vivo with an α-L-iduronidase (IDUA)–encoding lentiviral vector after myeloablative conditioning. Safety and correction of blood IDUA activity up to supraphysiologic levels were the primary end points. Clearance of lysosomal storage material as well as skeletal and neurophysiological development were assessed as secondary and exploratory end points. The planned duration of the study is 5 years.

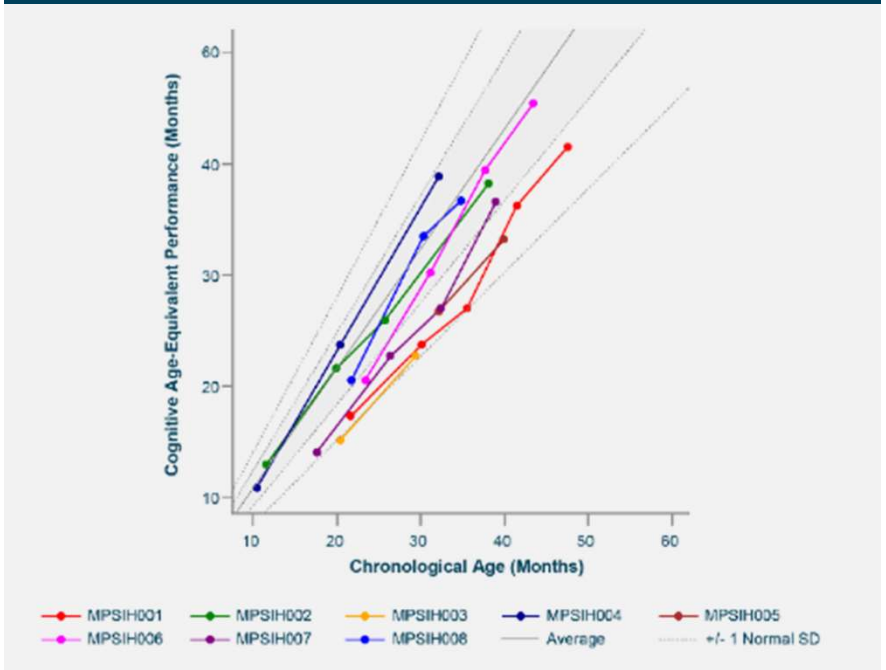
The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Aiuti can be contacted at aiuti.alessandro@hsr.it or at the San Raffaele Telethon Institute for Gene Therapy, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy.

*The members of the MPSI Study Group are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Tucci and Galimberti and Drs. Aiuti and Bernardo contributed equally to this article.

N Engl J Med 2021;385:1929-40.
DOI: 10.1056/NEJMoa2106596

Neuropsychological Tests over Time
Cognitive Age-Equivalent Score (Overall)



SD = Standard Deviation; IQ(C) = Intelligence Quotient (Cognition);
Engl J Med 2021; 385:1929-1940 DOI: 10.1056/NEJMoa2106596

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Early Skeletal Outcome After HSPC-GT for Mucopolysaccharidosis Type I Hurler

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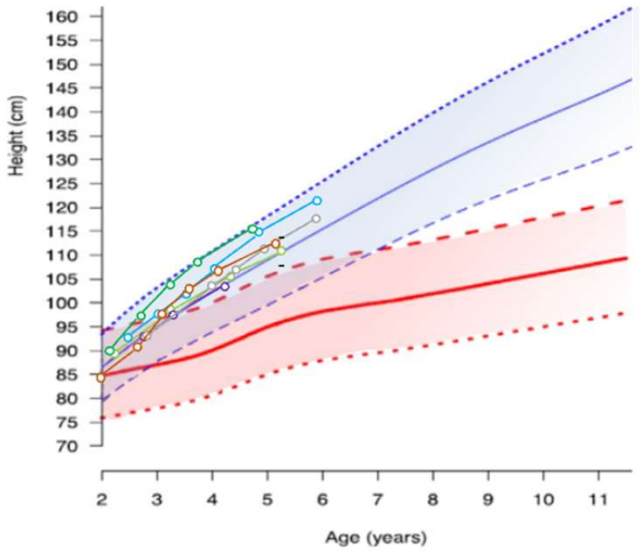
Early Clinical Skeletal Outcome: Auxological Parameters after GT

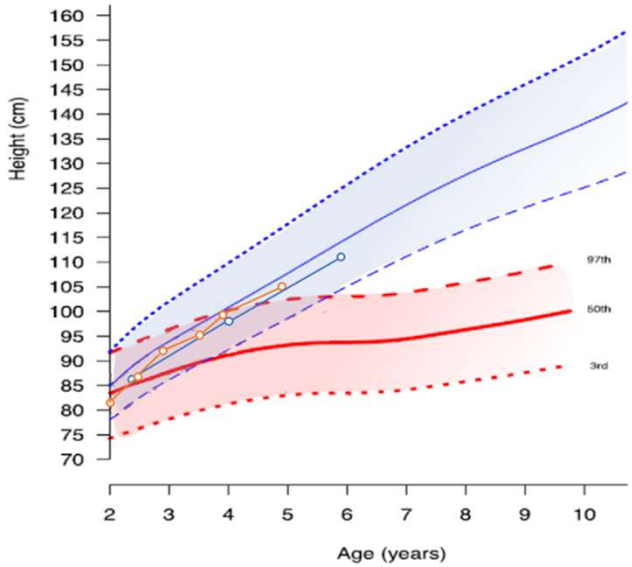
All GT pts. exhibit longitudinal growth within expected reference ranges according to age and gender, with a median height gain greater than the one observed in an external cohort of HSCT patients following a 3-year follow-up. [Short stature defined as height -2 SDS]

Growth charts males



○ MPSIH001 ○ MPSIH002 ○ MPSIH004
○ MPSIH005 ○ MPSIH006 ○ MPSIH007

Growth charts females



○ MPSIH003
○ MPSIH008

Percentiles:
WHO growth charts in blue-shadowed
MPSIH growth charts in red-shadowed

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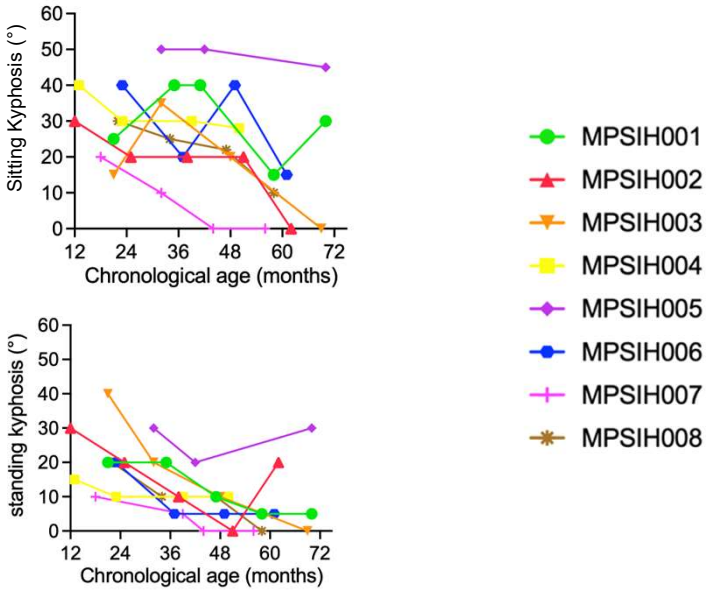
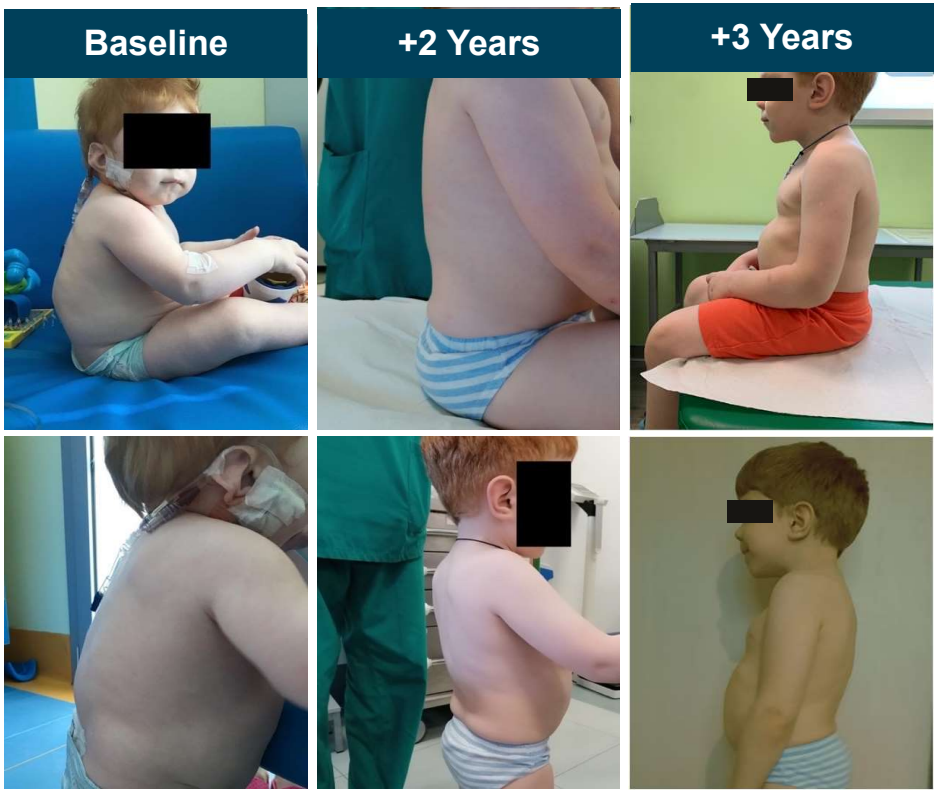
Early Clinical Skeletal Outcome: Standing & Sitting Kyphosis After GT

Clinically measurable reduction in both sitting and standing kyphosis in the majority of the pts.





MPSIH004

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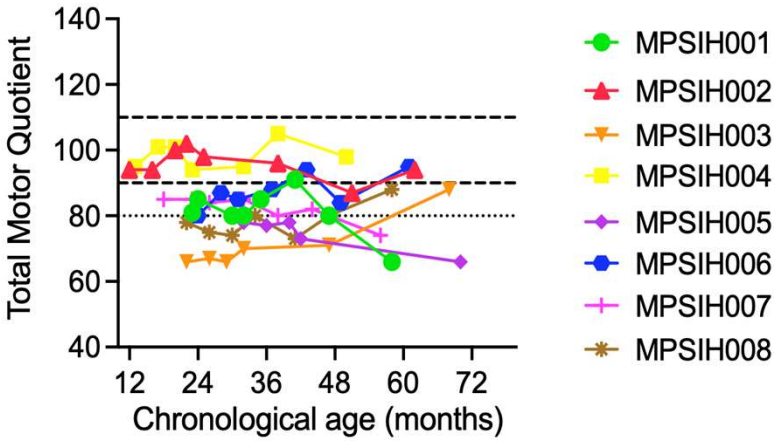
Early Functional Skeletal Outcome: Motor Function & ROM After GT

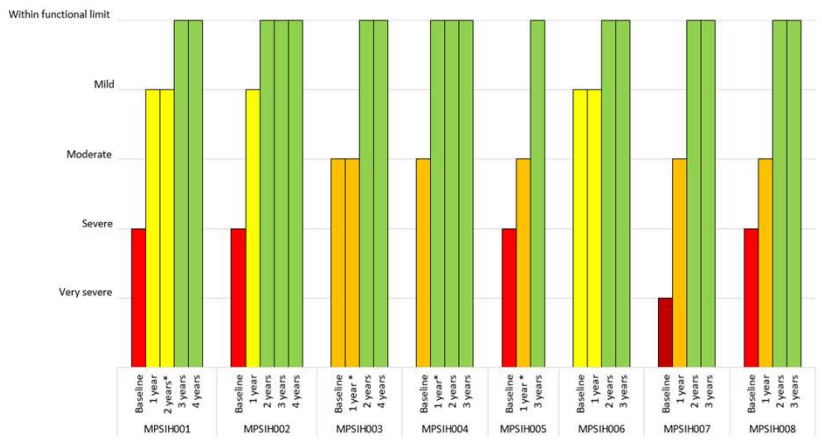
Continuous acquisition of motor skills, fine and gross, as shown by the substantial stability of TMQ (normal/low normal score in 5/8)

Complete and earlier normalization of joint mobility (shoulder abduction and flexion, hip and knee extension ROM) as compared with an external cohort of HSCT pts.

TMQ by Peabody scale



TMQ by Peabody scale



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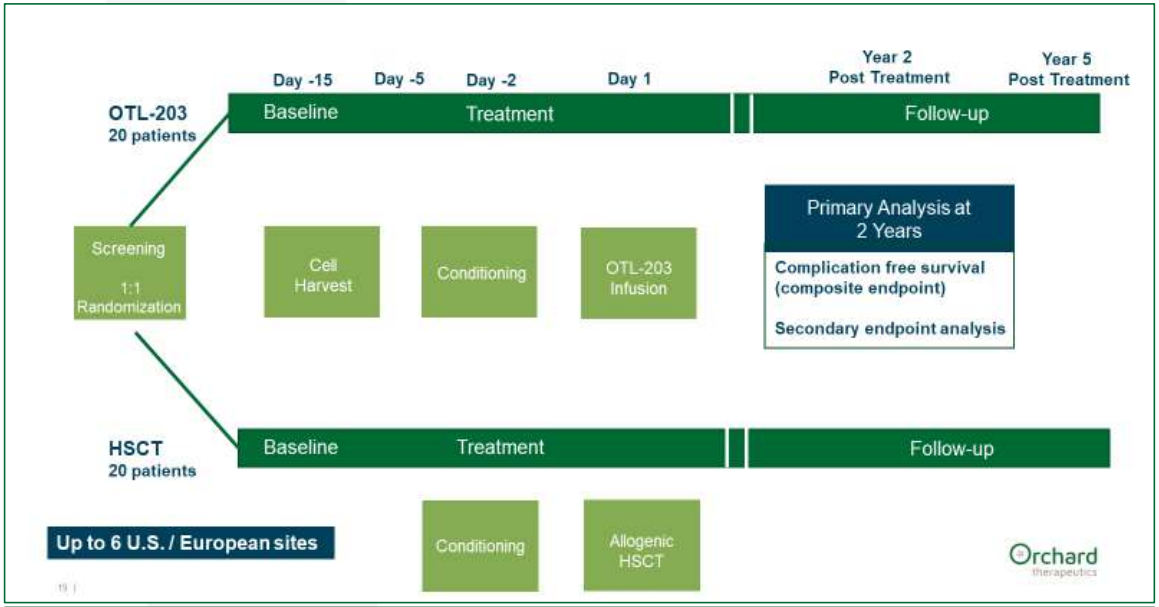
Data Takeaways and Next Steps

OTL-203 (MPS-IH) Moving into a Registrational Trial in 2H 2023

PoC Data Takeaways

New data shows extensive metabolic correction in the skeletal system, including normal growth rates, improvement in joint function and progressive acquisition of motor skills



- Randomized controlled trial vs. HSCT
- 40 patients
- 2-year primary analysis
- Complication free survival composite endpoint

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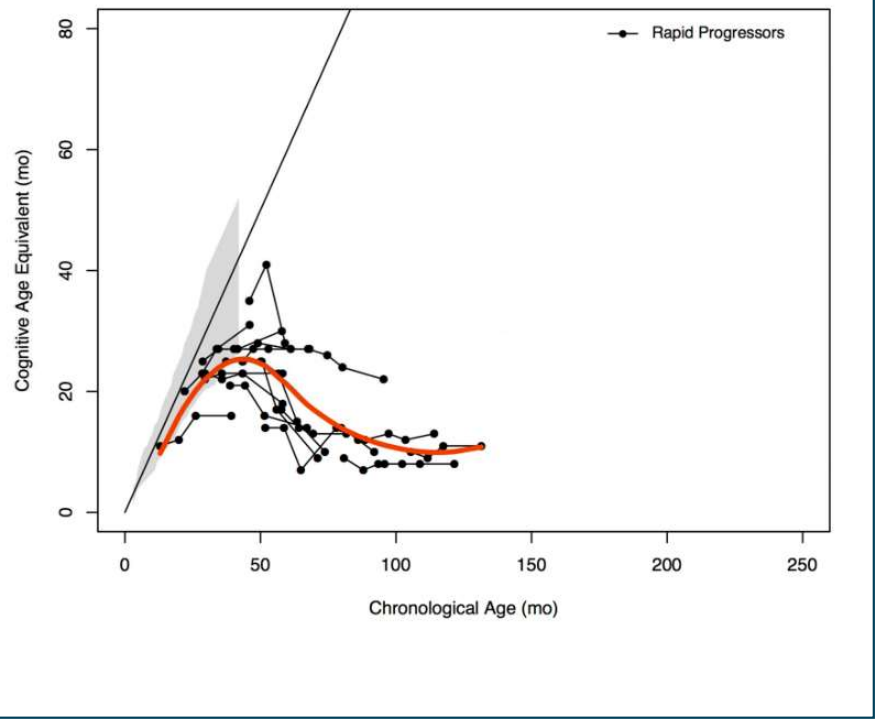
New OTL-201 Data in MPS-IIIA

MPS-IIIA is a Progressive and Devastating Disease

- **Sanfilippo Syndrome type A;** pathogenic variants in ***SGSH* gene**
- Accumulation of **substrate heparan sulfate leading to severe CNS degeneration** w/ somatic manifestations
- **Severe phenotype** – development slows from 3 years of age, followed by cognitive decline, behavioural disturbances, loss of skills and eventual death
- **No successful treatment options**
  - Allogeneic HSCT shows *no modification* of disease phenotype despite wild type donor, full engraftment and early treatment
  - Robust correction of neurocognitive decline and durability of effect *not established* for AAV approaches
- **Incidence: ~1 in 100,000 live births**



SGSH = N-Sulfoglucosamine Sulfohydrolase
Shapiro EG, et al. J Pediatr 2016;170:278-87.
Photos adapted from Natural History of Sanfilippo Syndrome in Spain; Orphanet Journal of Rare Diseases · December 2013

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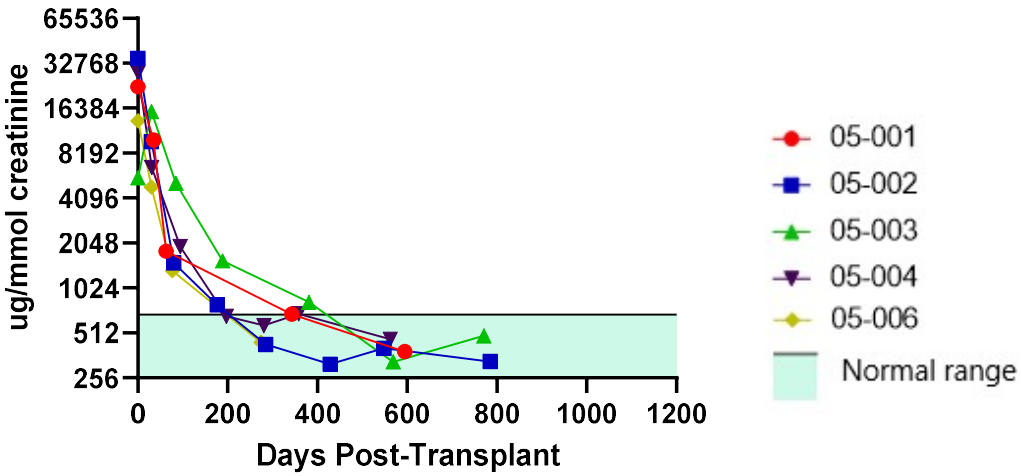
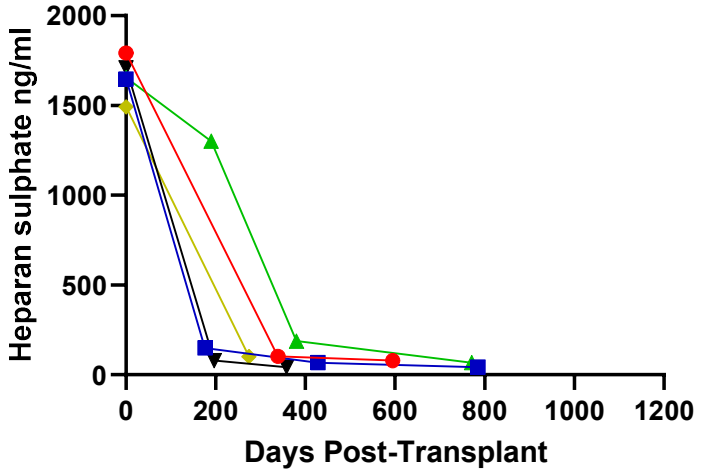
Heparan Sulfate Levels – Reduction in CNS and periphery

Urine HS Levels



CSF HS Levels



Rapid decreases from baseline of heparan sulfate in urine and CSF were seen in all evaluated patients.
Reduction in CSF HS has never been achieved with allogeneic HSCT

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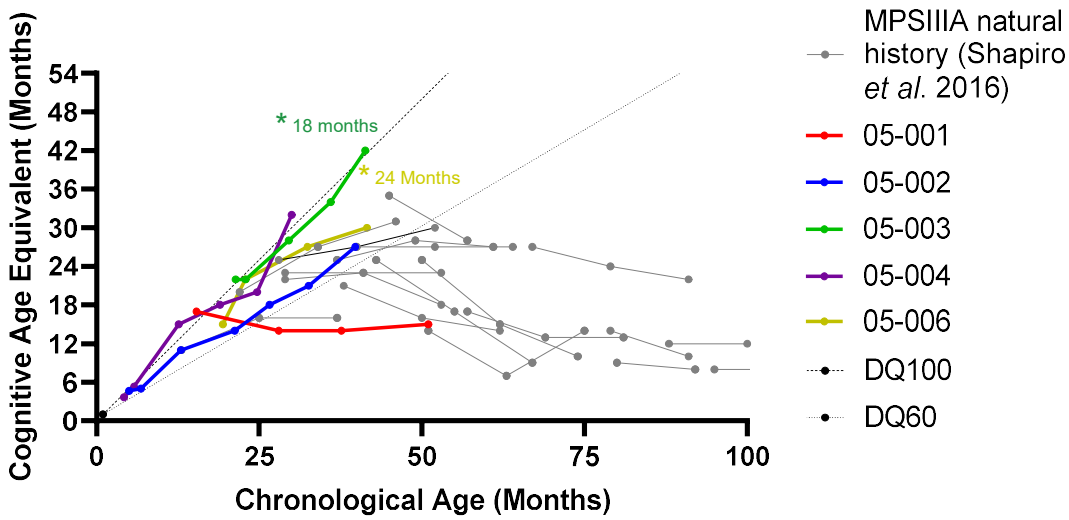
Neurocognitive Outcomes

- Patient 05-003 and 05-006 reached the ceiling of the Bayley scale (BSID-III) at 18/24 months and progressed onto the Kaufmann assessment (KABC-II) at 24/30 months
- Patient 05-003 is the first MPSIIIA patient with rapidly progressive phenotype at Manchester able to complete the Kaufman assessment
- Patient 05-003 is within normal range on Kaufmann scale at both 24- and 30-months post-transplant with gain in skills between assessments

Developmental Age Equivalent



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Neurocognitive Outcomes

Change **in cognitive function (age equivalent scores)** against natural history of MPSIIIA

Change in patient behavior, patient QoL and daily living

Early follow-up in trial patients

- **Gain of skills in line with development of normal children in 4 out of 5 patients**
- Developmental gains not seen in untreated MPSIIIA, e.g. acquisition of speech, continence and complex play
- Longer follow up needed to assess safety and efficacy outcomes

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OTL-201 POC Conclusions

- ✓ **Robust, prompt, sustained, multi-lineage engraftment** of genetically modified cells
- ✓ **Supra-physiological levels** of SGSH enzyme in leukocytes and CSF and rapid and **significant reduction of substrate** observed in all compartments
- ✓ 4 / 5 patients are demonstrating **gain of cognitive skills in line with development in healthy children with two patients progressing to the Kaufman scale of cognitive assessment**

- ○ Early 2024 read-out expected – all patients will have completed 3 years of follow-up and reached at least 3 years of age

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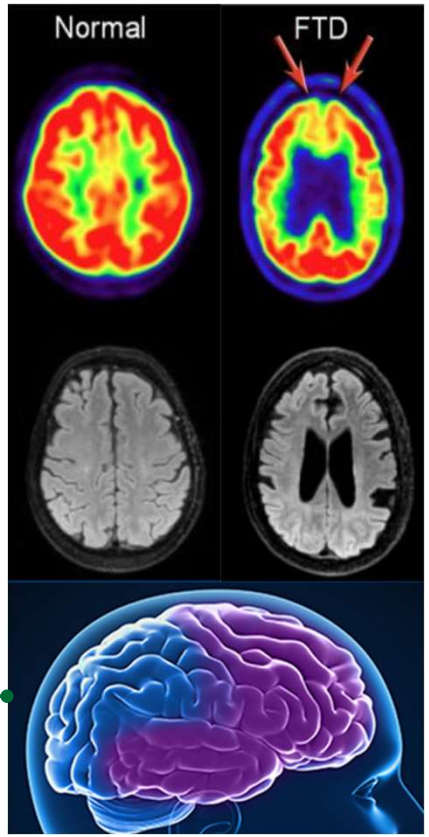
OTL-204 for GRN-FTD Section

Frontotemporal Dementia (FTD) Disease Background

- Second most common dementia in people under 65 after Alzheimer's Disease (onset at ~58)
- Atrophy of frontal and temporal lobes
- Progressive changes in behavior and personality:
  - ***Early*** decline in social and personal interactions, depression, apathy, emotional blunting, disinhibition, language disorders
  - ***Late*** general cognitive decline
- Death within 6-9 years from onset, 3-4 years from diagnosis
- No cure or treatment



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GRN-FTD Represents Large and Growing Opportunity

> 50,000 FTD patients diagnosed in U.S. and EU today

THE OPPORTUNITY

GRN-FTD
is a growing opportunity

- Haploinsufficiency of progranulin *(GRN)* strongly associated with FTD (~5% of cases)
- Mutation known to have high penetrance
- Up to 2,500 GRN-FTD prevalent patients in U.S. and EU[1-3]
- ~800 new cases U.S. / EU per year[1-3]

OUR UNIQUE POSITIONING

HSC gene therapy has demonstrated potential to treat diseases of the brain

- Ideal for targeting single gene mutations
- Mechanism of CNS gene delivery validated by clinical data from MLD, MPS-I, MPS-IIIA
- Gene-modified HSCs enable delivery of *GRN* to brain

Sources: Knopman DS, Roberts RO. *J Mol Neurosci.* 2011, Onyike CU, Diehl-Schmid J. *Int Rev Psychiatry*. 2013 and Riedl L, et al *Neuropsychiatr Dis Treat.* 2014

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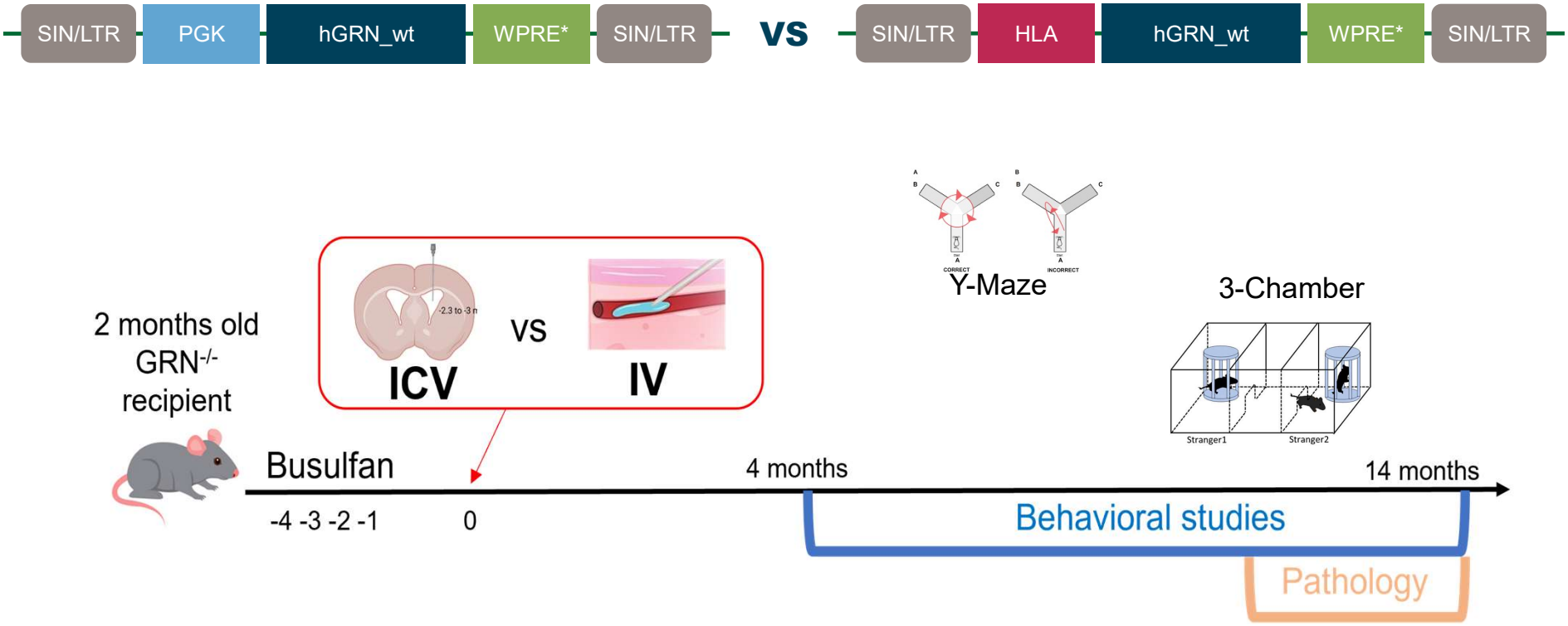
hGRN HSC-GT PoC of efficacy study



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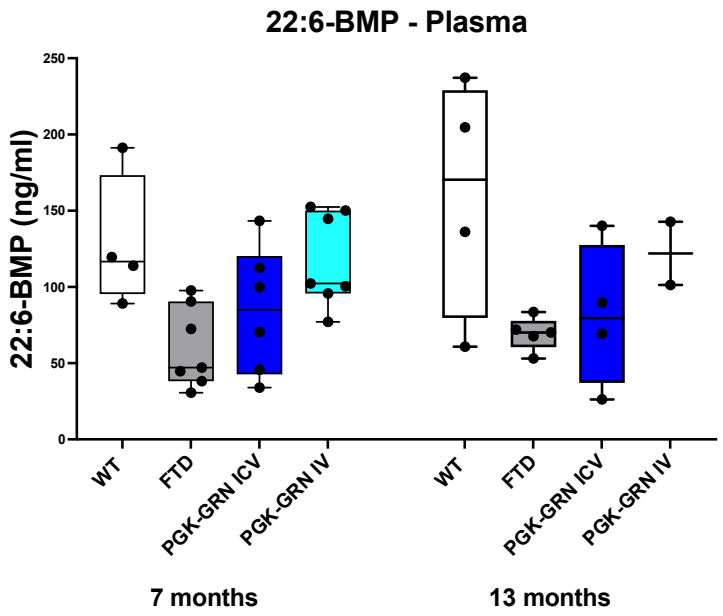
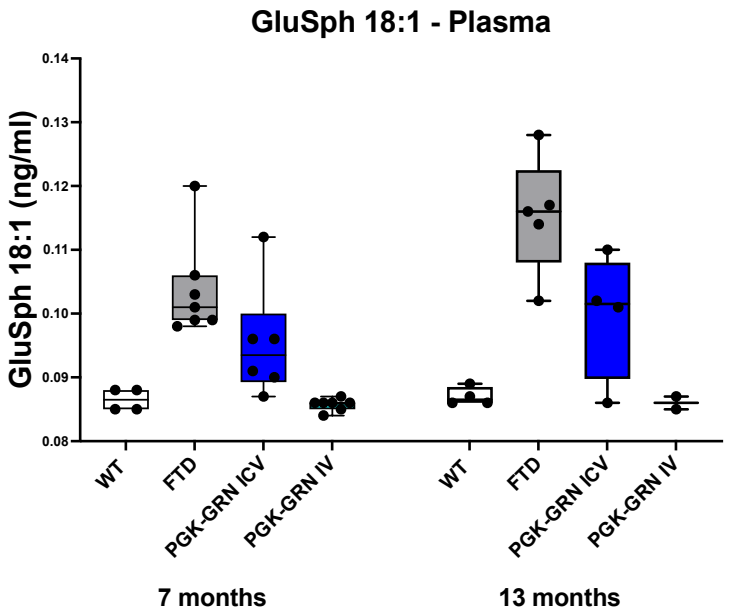
Therapeutic Effect Evidenced by Normalization of Glucosylsphingosine in Transplanted Mice

Plasma glycosphingolipid quantification by LC-MS/MS





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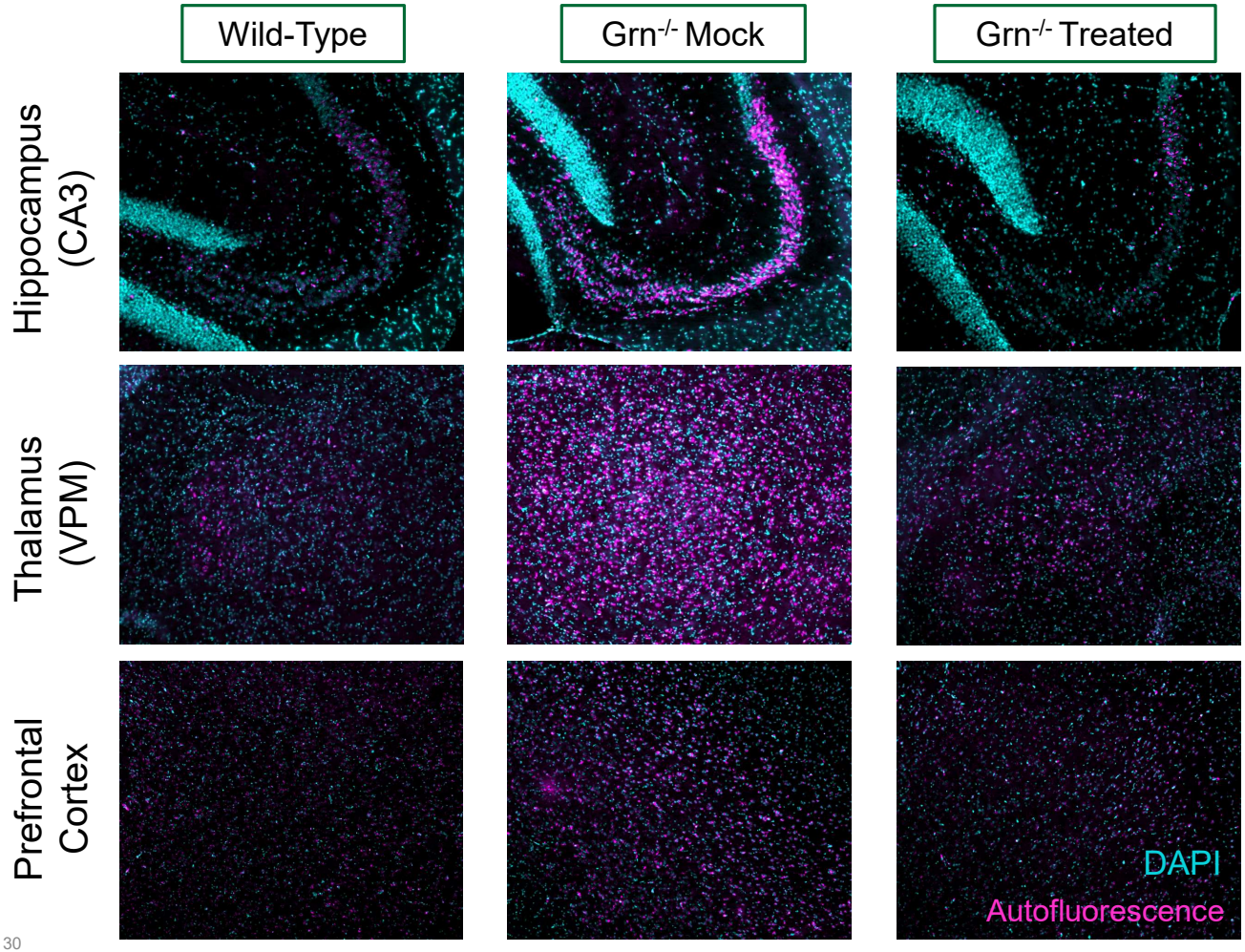
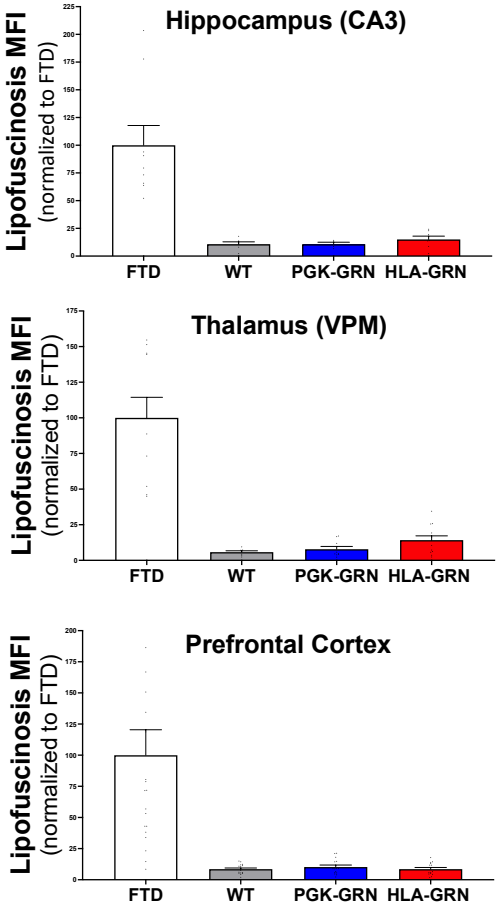
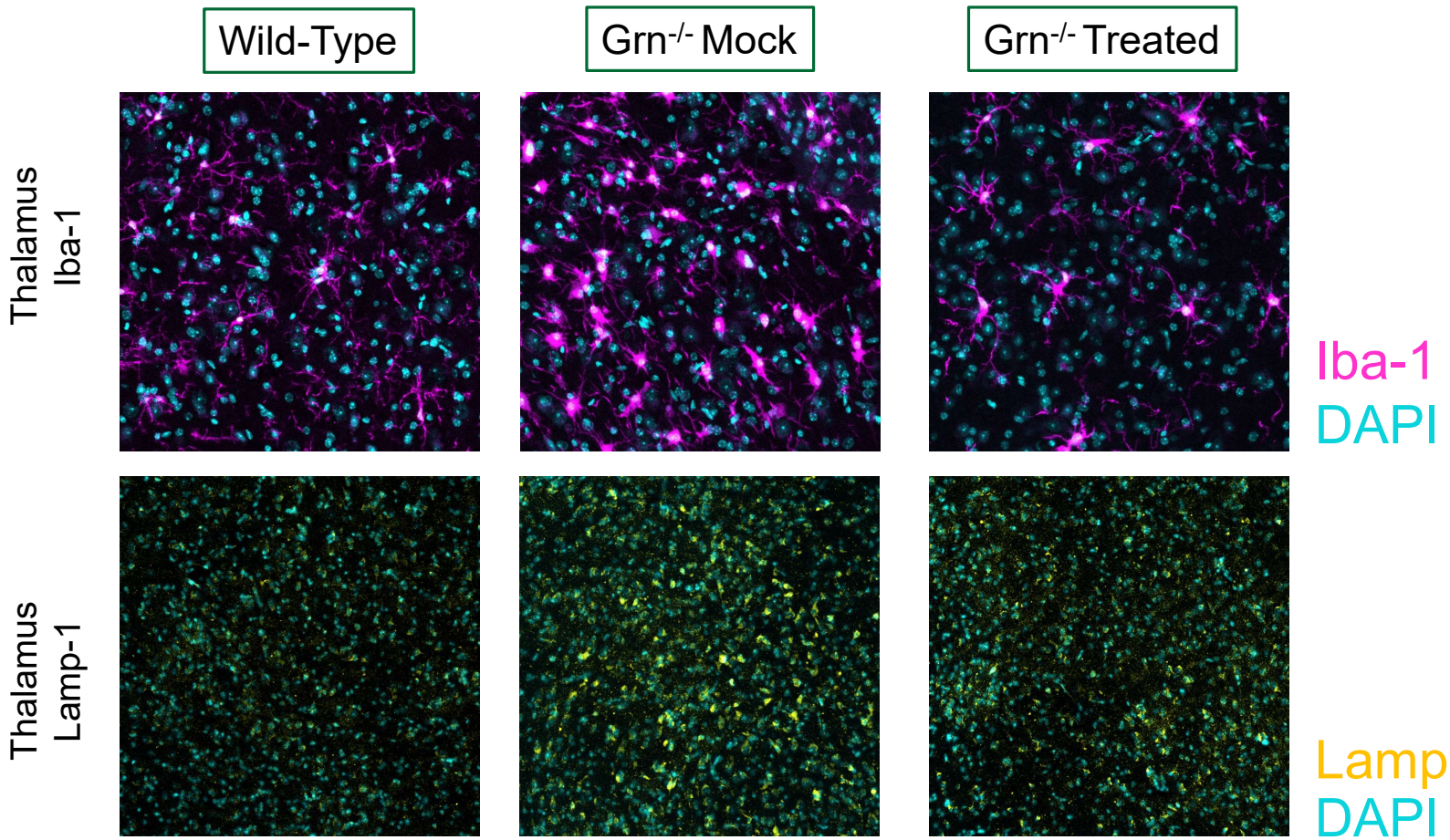
hGRN improves lipofuscinosis in Knockout Mice





Preliminary data

hGRN reduces microgliosis and Lamp-1 immunoreactivity



Preliminary data

Summary and conclusions

First preclinical data for OTL-204 highlight ability of HSC gene therapy to restore microglial function, modulate neuroinflammation, and normalize predictive biomarkers in GRN-FTD

Data from in vivo studies indicate effective GRN protein delivery to the CNS of knockout mice transplanted with gene-modified HSCs.

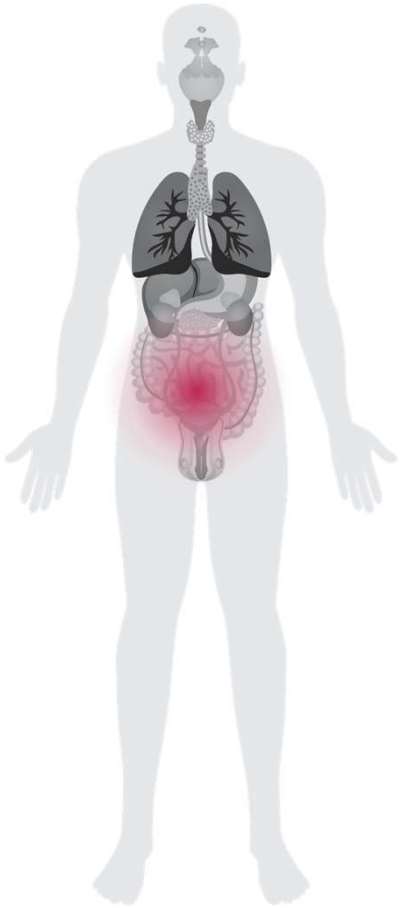
A therapeutic effect in transplanted knockout mice is evidenced by:

- Normalization of glucosylsphingosine, a specific lipid biomarker in the plasma
- Strong reduction of lipofuscinosis and microgliosis
- Decrease of markers of neuroinflammation in the thalamus, hippocampus and prefrontal cortex

Cohorts of knockout mice are being further evaluated both at behavioral and pathological level to accumulate additional evidence supporting the therapeutic approach

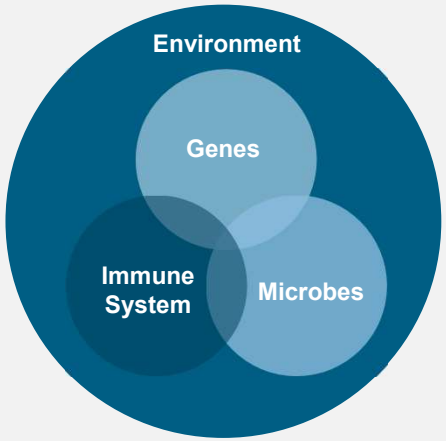
OTL-104 for NOD2-Crohn's Section

Crohn's Disease Overview



- Chronic inflammatory bowel disease
- Primarily affecting ileum
- Symptoms develop from ~15 yrs
- Clinical management by anti-inflammatory medications & surgical resection
- Limited therapies, no cure available
- High prevalence

Contributing causal factors



20-40% of Crohn's patients carry NOD2 mutations

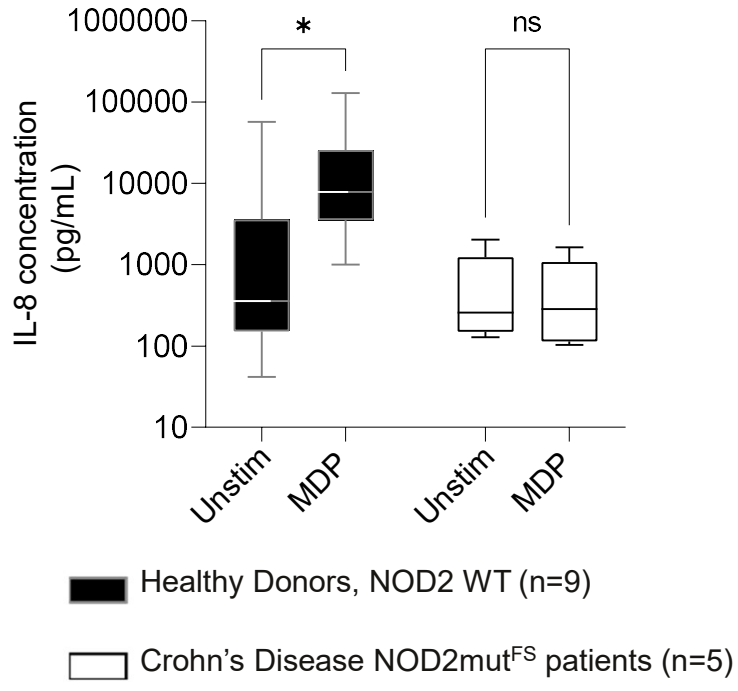
- *NOD2* function: detection of bacterial peptides
- > 60 reported *NOD2* mutations
- 3 SNPs exhibit strongest association
- *NOD2* Crohn's patients are more refractory to therapy & have more severe disease

https://pubmed.ncbi.nlm.nih.gov/28601423/

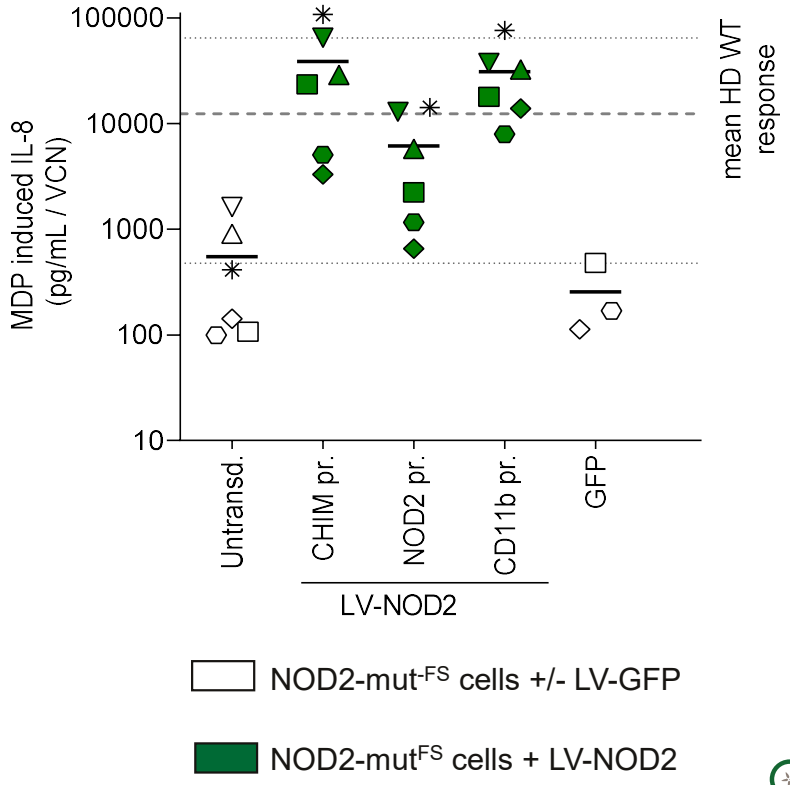
https://www.biorxiv.org/content/10.1101/098574v2.full
https://www.frontiersin.org/articles/10.3389/fimmu.2016.00367/full

Orchard therapeutics

CD34+ HSC derived myeloid cells from NOD2-mutFS CD patients show impaired responses to MDP

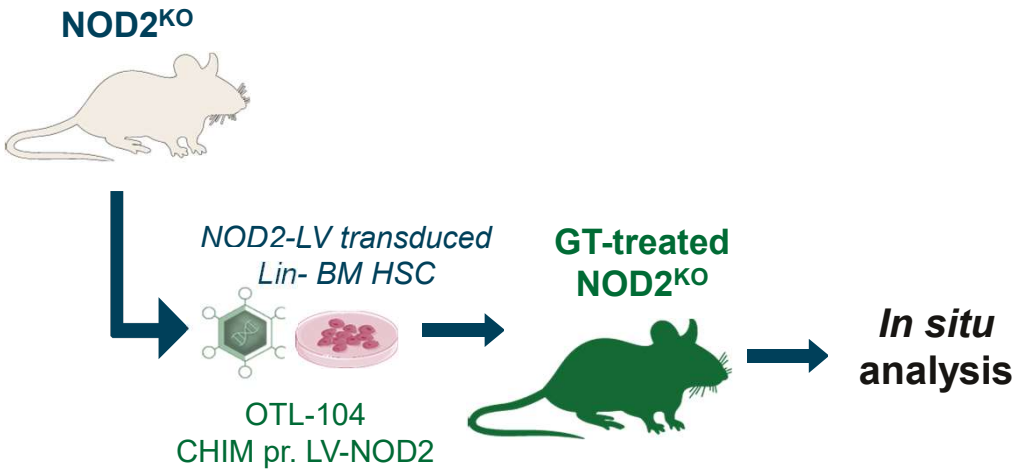


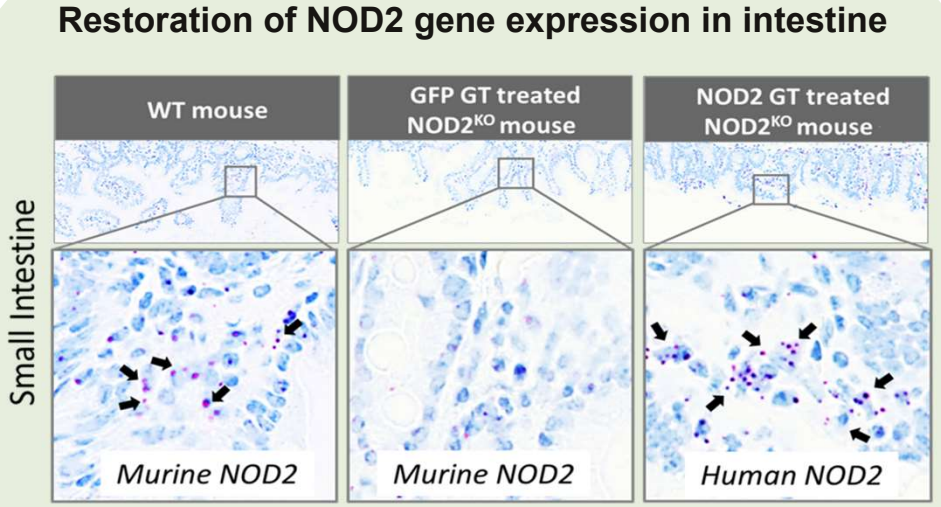
Two-way Anova, p<0.05 (*)



Orchard therapeutics

Gene Therapy treatment of NOD2^{KO} mice reconstitutes normal NOD2 expression within the gut and fully restores NOD2-dependent immune responses *in vivo*



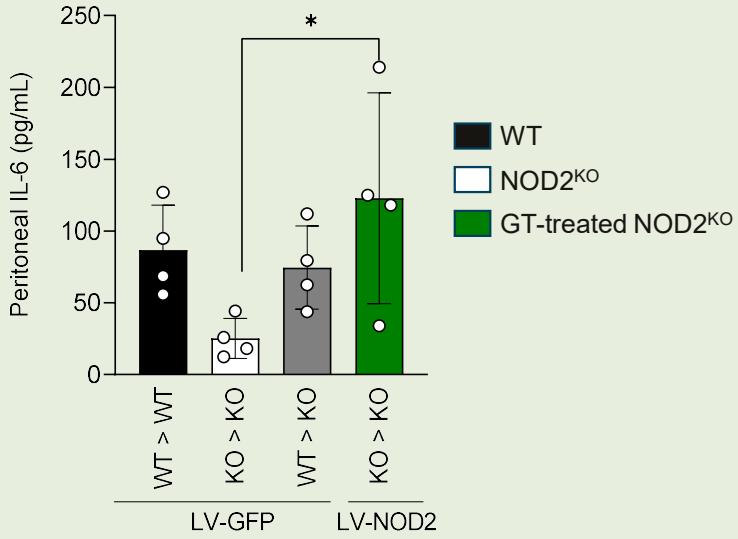


Detection of NOD2 mRNA in situ (RNAScope) in intestinal lamina propria of WT and GT treated NOD2^{KO} mice

Orchard therapeutics

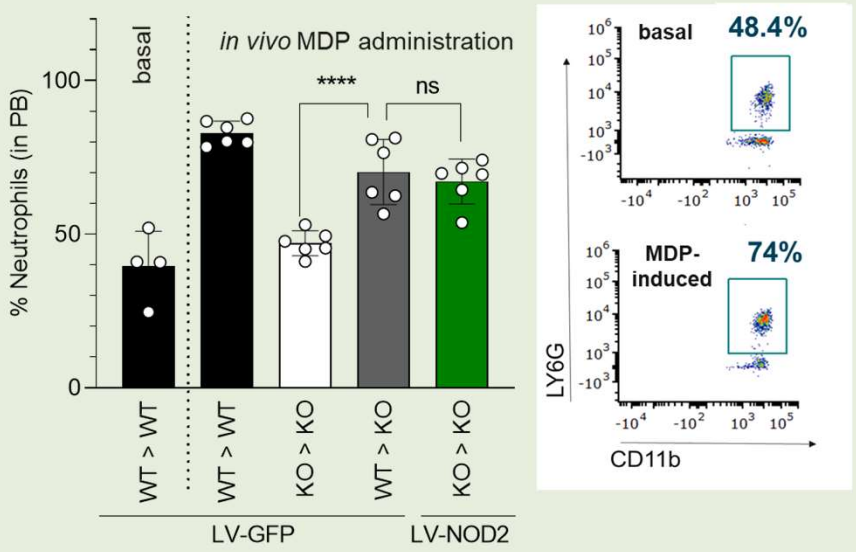
Gene Therapy treatment of NOD2^{KO} mice reconstitutes normal NOD2 expression within the gut and fully restores NOD2-dependent immune responses *in vivo*

Functional reconstitution of NOD2-dependent (MDP-induced) immune activity in myeloid subsets



MDP-induced IL-6 release into peritoneal fluid

Functional reconstitution of NOD2-dependent (MDP-induced) immune activity in myeloid subsets



MDP-induced neutrophil mobilisation

OTL-104 LV-NOD2 CHIM pr. construct shows in vivo efficacy in restoring normal NOD2-dependent myeloid immune functions in GT-treated bone marrow chimeric NOD2^{KO} mice

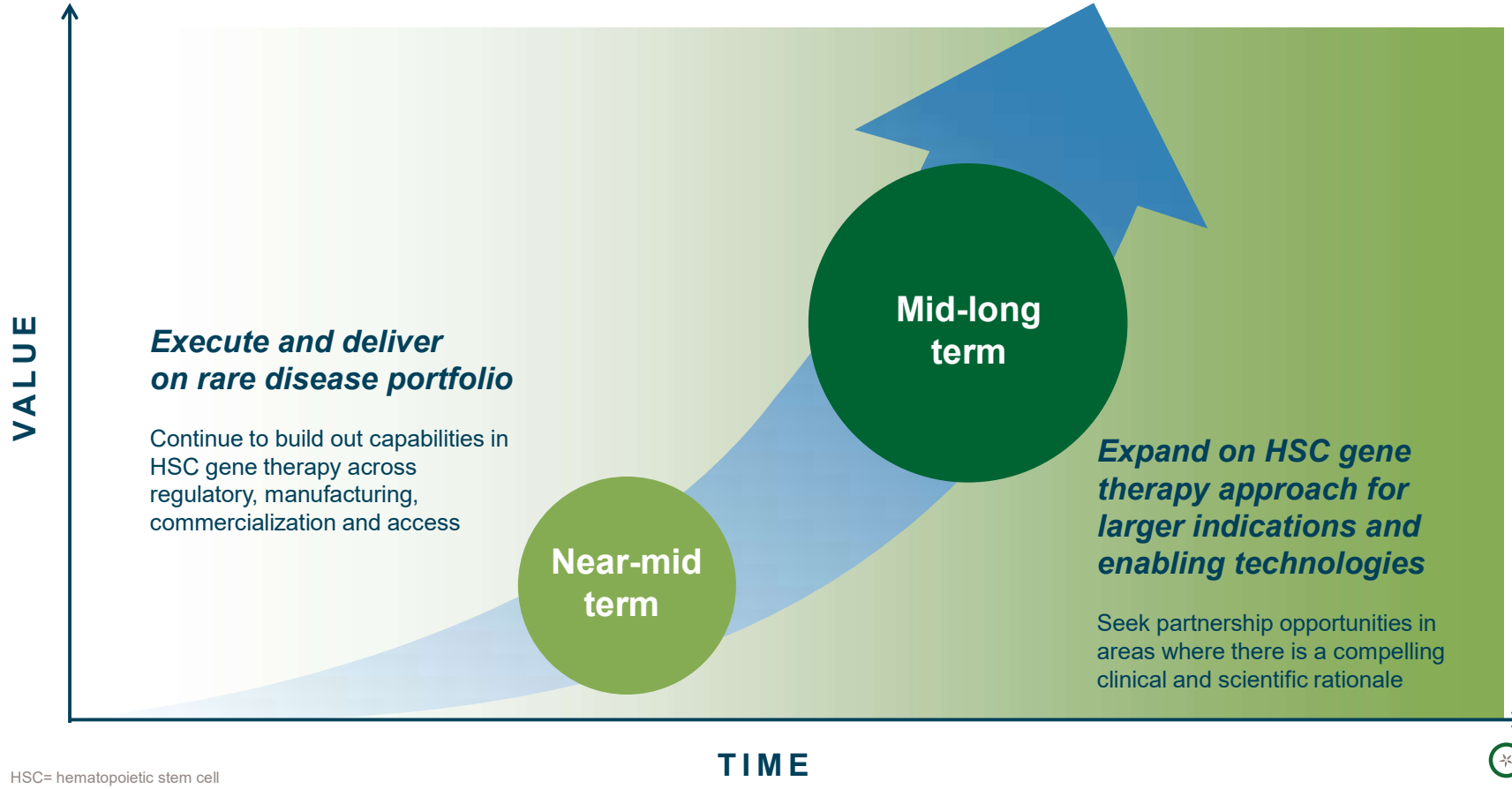
OTL-104 Summary

- ✓ OTL-104, fully restores NOD2-dependent immune responses in macrophages derived from HSCs obtained from Crohn's patients carrying biallelic NOD2 mutations to within the range of healthy donor cells
- ✓ Transplantation of OTL-104 in NOD2 knockout mice reconstitutes NOD2 expression in intestinal tissue resident cells and broadly restores NOD2-dependent innate immune cell functions
- ✓ Results confirm the negative impact of NOD2 deficiency in primary immune activation and support the therapeutic potential of HSC gene therapy to provide long-term correction of NOD2 Crohn's disease

Expect to commence IND- and CTA-enabling studies in the second half of 2023, with a potential filing anticipated in the first half of 2025

Orchard therapeutics

Orchard's Vision to End the Devastation Caused by Severe and other Genetic Diseases



HSC= hematopoietic stem cell

Orchard therapeutics

Key Event Takeaways

OTL-203 for MPS-IH - New PoC data shows extensive metabolic correction in the skeletal system, including normal growth rates, improvement in joint function and progressive acquisition of motor skills

OTL-201 for MPS-IIIA - New data from ongoing PoC study show additional favorable neurocognitive outcomes compared to disease natural history with median follow-up out to 2.5 years

OTL-204 for GRN-FTD - First preclinical data highlighting ability of HSC gene therapy to restore microglial function, modulate neuroinflammation, and normalize predictive biomarkers

OTL-104 for NOD2-CD – Preclinical data confirm negative impact of NOD2 deficiency in primary immune activation and support therapeutic potential to provide long-term correction of NOD2 CD

New areas of research could represent significant commercial opportunities in large indications for Orchard alone or with potential partners interested in utilizing HSC gene therapy platform

Orchard therapeutics

Q&A

Bobby Gaspar, M.D., Ph.D.
Chief Executive Officer

Leslie Meltzer, Ph.D.
Chief Medical Officer

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