Q4 / YE'21 Financial Results and Corporate Update

March 30, 2022

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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 constitute forward-looking statements and may include, but are not limited to, the Company’s expectations 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 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 Libmeldy and the Company’s product candidates; and (xi) expected financial performance and financial condition. 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; 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 public filings with the U.S. Securities and Exchange Commission (the “SEC”), including in the Company’s quarterly report on Form 10-K filed with the SEC on March 30, 2022, 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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Joining Today's Call

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

Braden Parker
Chief Commercial Officer

Frank Thomas
President & Chief Operating Officer

Fulvio Mavilio, Ph.D.
Chief Scientific Officer

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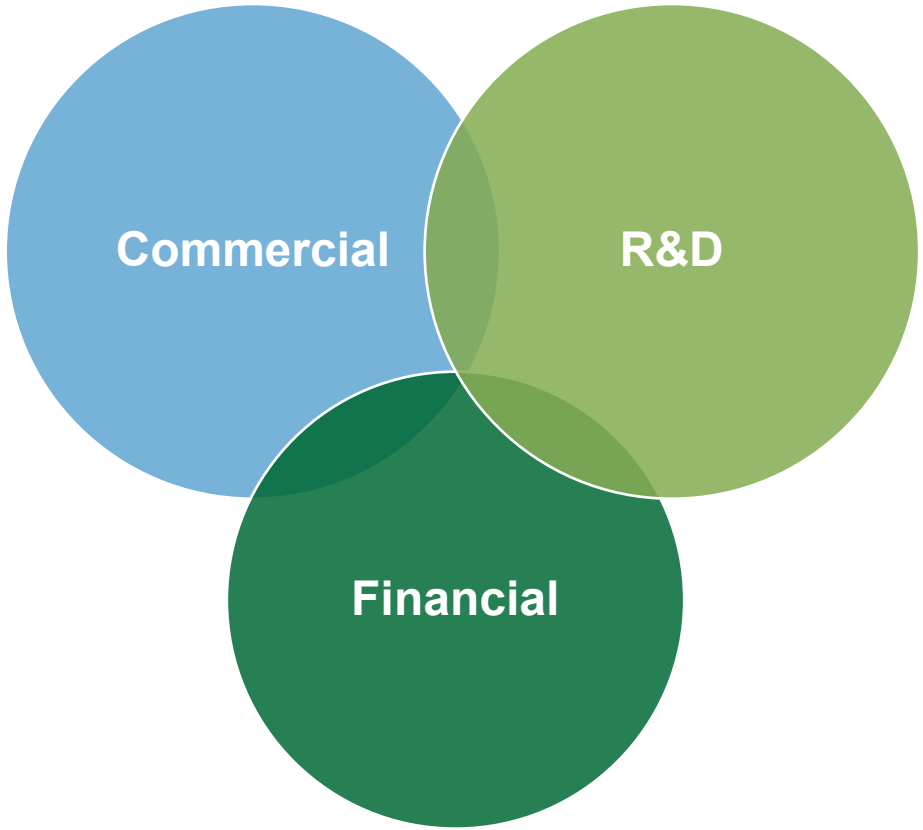
Responding to Broader Environment and Focusing Where HSC Gene Therapy is Scientifically and Clinically Differentiated



- Prioritize investment in Libmeldy (OTL-200)
  - Establish commercial business model
  - Gain U.S. regulatory approval
  - Support diagnostics, screening and market expansion
- Realize manufacturing, regulatory and commercial synergies within neurometabolic portfolio
- Advance research programs in larger indications to enable value creation and potential partnerships
- Discontinue investment in and seek alternatives for rare primary immune diseases programs
- Financial profile built to support milestone achievement

Extending Runway into 2024

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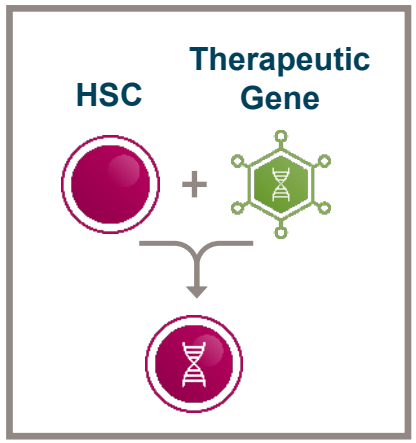
Leveraging One of the Most Extensive Datasets in Gene Therapy



Clinical PoC in MLD & MPS

Neurodegenerative disorders

GRN-FTD

Multilineage potential of HSCs

HSC-generated Tregs
Vectorized mAbs

Clinical PoC in Rare PIDs

Immunological disorders

NOD2- Crohn's
HAE

Commercial Infrastructure

Manufacturing Innovations

Enabling Technologies

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Libmeldy and MPS Programs

Near-term revenue, regulatory progress and geographic expansion

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Neurometabolic Rare Disease Programs Provide Platform Validation and Potential Near-term Milestones

Capture value with Libmeldy as an established commercial asset addressing a devastating disease

- EU launch and geographic expansion
- U.S. BLA submission, approval and launch over next 12-24 months
- Investment in diagnostics and newborn screening to maximize commercial opportunity

Mature next wave of neurometabolic programs to value-creating milestones

- OTL-203 (MPS-IH) pivotal trial initiation by YE 2022
- OTL-201 (MPS-IIIA) proof-of-concept trial ongoing with data by YE 2022
- MPS diseases often referred and treated by same KOL's and treatment centers

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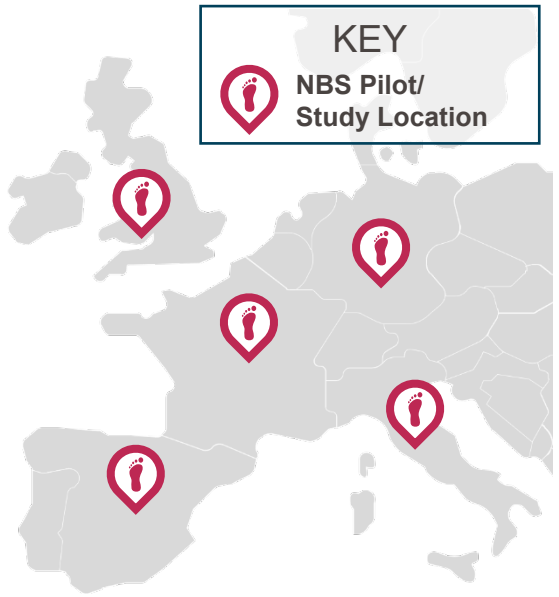
Commercial Priorities to Maximize Libmeldy's Value

Three eligible patients treated in commercial setting to date; 5 treatment centers established

Market Access & Reimbursement

- **England/Wales:** Reimbursement secured for all eligible MLD children
- **Germany:** Highest possible therapeutic benefit rating in pre-symptomatic patients
- **France:** Reimbursed early access program secured
- **Italy:** Approved to treat patients travelling to Italy

Newborn Screening



Geographic Expansion

- EMEA
- U.S. / Canada
- LATAM
- APAC

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Advancing U.S. Regulatory Discussions for OTL-200

REGULATORY STRATEGY

BLA expected late 2022 / early 2023

- ✓ RMAT meeting with confirmation of expected clinical package (June 2021)
- ✓ Productive Type B CMC meeting (Nov 2021)
- ✓ Clarity on manufacturing facility FDA inspection readiness (early 2022)
- ✓ Treatment of patients in the U.S. on compassionate use basis (with EU CDMO manufacturing) (2021)
- ○ NEXT STEP: Pre-BLA submission meeting with U.S. FDA

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Synergies among Neurometabolic Disorders for Next in Line MPS Program

Libmeldy Platform Synergies

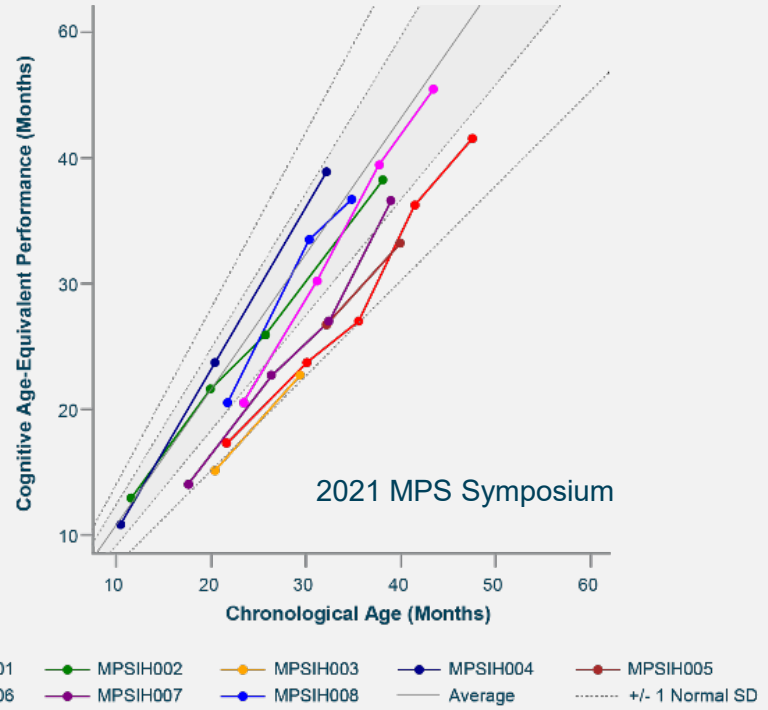
- Manufacturing, distribution, supply chain
- Regulatory learnings
- Treatment sites and referral network

MPS-IH

- 1:100,000 live births; NBS established in some geographies, incl. U.S.
- Current SOC: HSCT and/or ERT as a bridging or chronic therapy

Neuropsychological Tests over Time

Cognitive Age-Equivalent Score (Overall)



OTL-203 Program Status

- POC data published in NEJM
- Conducted parallel scientific advice meeting with EMA and FDA
- Obtain necessary regulatory clearance (mid-2022) to enable global registrational study by year-end

SD = Standard Deviation; IQ(C) = Intelligence Quotient (Cognition); See 2021 MPS Symposium for further details

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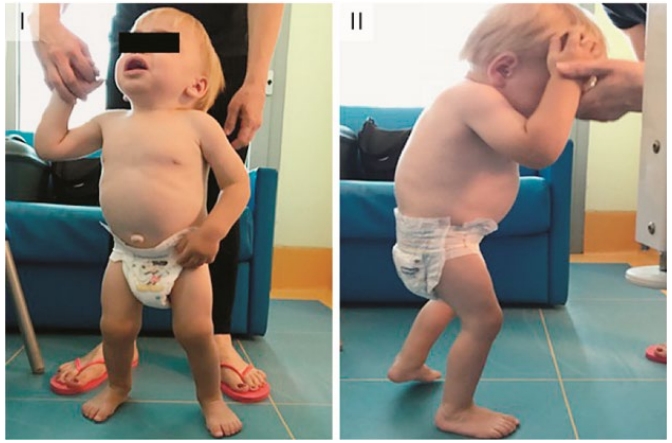
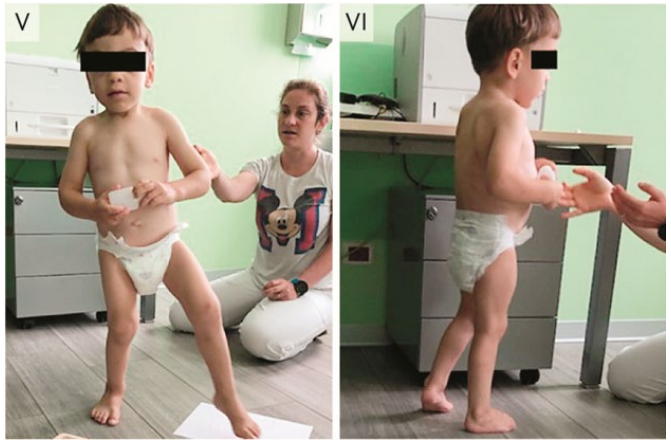
Interim Proof-of-concept Study Results of OTL-203 for Hurler Syndrome

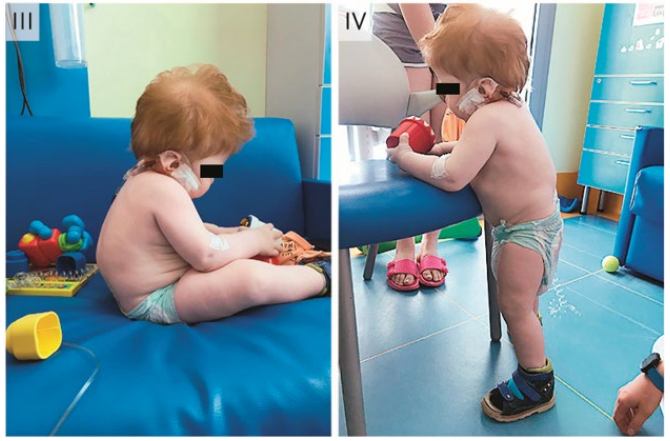
Before Gene Therapy (Patient A)



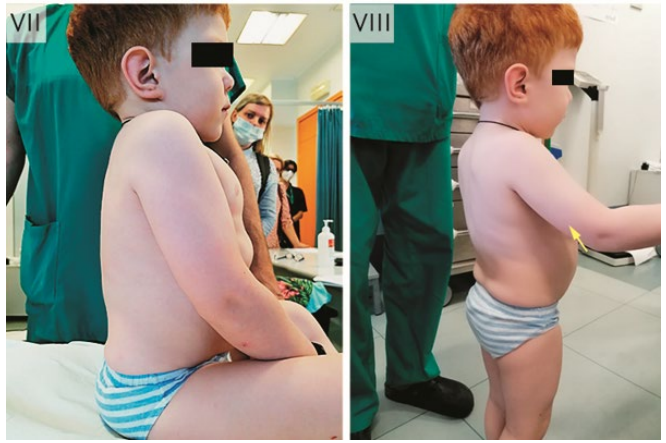
1Y after Gene Therapy (Patient A)



Before Gene Therapy (Patient B)



1.5Y after Gene Therapy (Patient B)



Results post-treatment showed:

- Improved facial features
- Resumed longitudinal growth
- Reduced kyphosis
- Improved locomotion & visual-motor integration
- Regression of corneal clouding and upper airway congestion
- Safety profile consistent with chosen conditioning regimen

 N Engl J Med 2021; 385:1929-1940 DOI: 10.1056/NEJMoa2106596

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Research Pipeline

Maturing the science to fuel sustainable mid- and long-term growth

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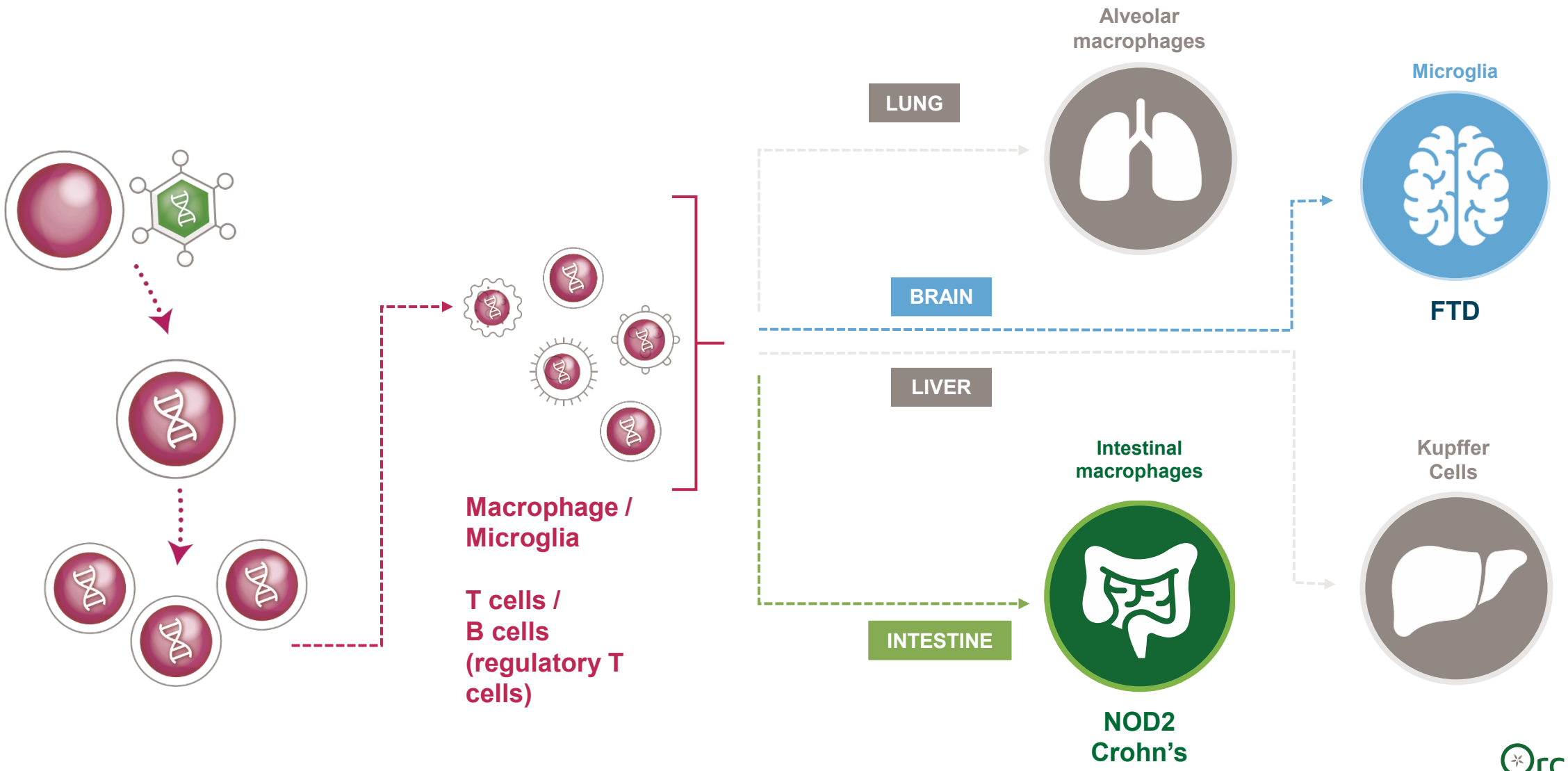
The Power of HSC Gene Therapy: *Differentiation & Migration*



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Research Spotlight: OTL-104 for NOD2 Crohn's Disease

Program Highlights

- NOD2 mutations associated with Crohn's disease severity
- Up to 200,000 estimated patients with two mutated NOD2 alleles (7-10% of all Crohn's disease) in the U.S. and EU[1,2,3]

Preclinical Data Summary

Restoration of NOD2 protein expression in murine and human stem cells can rescue a defective myeloid immune response to microbial peptides

Correction of NOD2 defective inflammatory functions is achievable by LV-mediated NOD2 gene transfer in HSCs

Functional reconstitution of NOD2 activity in a NOD2-ko murine disease model and in NOD2-Crohn's patient-derived cells is in progress

Report preclinical PoC by year end 2022 and submit IND in 2024

[1,2] CD prevalence estimates: Centers for Disease Control and Prevention; European Crohn's and Colitis Organisation (ECCO)
[3] NOD2: Ashton, James J et al. *Clin Transl Gastroenterol*. 2020 Feb

Priorities for Research Activities and Enabling Technologies

Progressing key research programs to INDs

- OTL-104 for **NOD2 Crohn's disease**
- OTL-204 for progranulin-deficient frontotemporal dementia **(GRN-FTD)**
- OTL-105 for hereditary angioedema **(HAE)**

Broadening platform application

- **Engineered Treg cells** for autoimmune diseases (e.g., multiple sclerosis)
- **Vectorized antibody delivery** (e.g., brain tumors)

Enabling larger indications

- Industrialized platform for large-scale manufacturing
- Reduced-toxicity and brain-specific conditioning

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The Journey Ahead

Our path to becoming the global HSC gene therapy leader

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Strengthened Financial Position Moving Forward

$220M

Approximate cash and investments as of December 31, 2021

Extending runway >1 year into 2024

- Discontinuation of programs for rare primary immune deficiencies:
  - OTL-103 for WAS
  - OTL-102 for X-CGD
  - Strimvelis® for ADA-SCID
- 30% proposed workforce reduction

Removes near-term financing need and provides runway for revenue growth and partnership

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Extended Runway Covers Multiple Anticipated Milestones of Significance to 2024

Spanning Commercialization and All Phases of Development

1H'22	2H'22	2023	2024
Commercial	**Development**	**Regulatory**	**Preclinical**
Libmeldy: Reach reimbursement agreement with at least two countries ✓ NHS agreement securing access in England / Wales	**OTL-203:** Initiate global registrational trial for MPS-IH by year end **OTL-201:** Report data from ongoing MPS-IIIA POC trial by year end **OTL-104**: Report preclinical POC data for NOD2-CD	**OTL-200:** Pre-BLA for MLD in late 2H 2022 **OTL-200:** Planned BLA submission for MLD in late 2022 / early 2023 **OTL-200:** Potential FDA approval for MLD by year end 2023	**OTL-104:** Submit IND filing in NOD2-CD

Libmeldy commercialization and revenue generation

Advance preclinical pipeline (OTL-105 for HAE, OTL-204 for GRN-FTD and work in Tregs)

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Compelling Fundamentals Driving Near-term Value Creation and Long-term Growth

Commercial Model	Diagnostics and Newborn Screening	Future Approvals	Manufacturing Capabilities	Evolution to Larger Indications
Establish foundation	Develop markets	Succeed with FDA	Develop a sustainable platform	Build for the future

All based on a validated HSC GT scientific and clinical platform

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Q&A