Reaching New Heights, Looking to New Horizons

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Orchard therapeutics

From Clinician to CEO: The Evolution of HSC Gene Therapy

Photo courtesy of Great Ormond Street Hospital

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We aspire to end the devastation caused by genetic and other severe diseases through the curative potential of HSC gene therapy.

2022: Reaching New Heights, Looking to New Horizons

Reaching New Heights

Looking to New Horizons

The Journey Ahead

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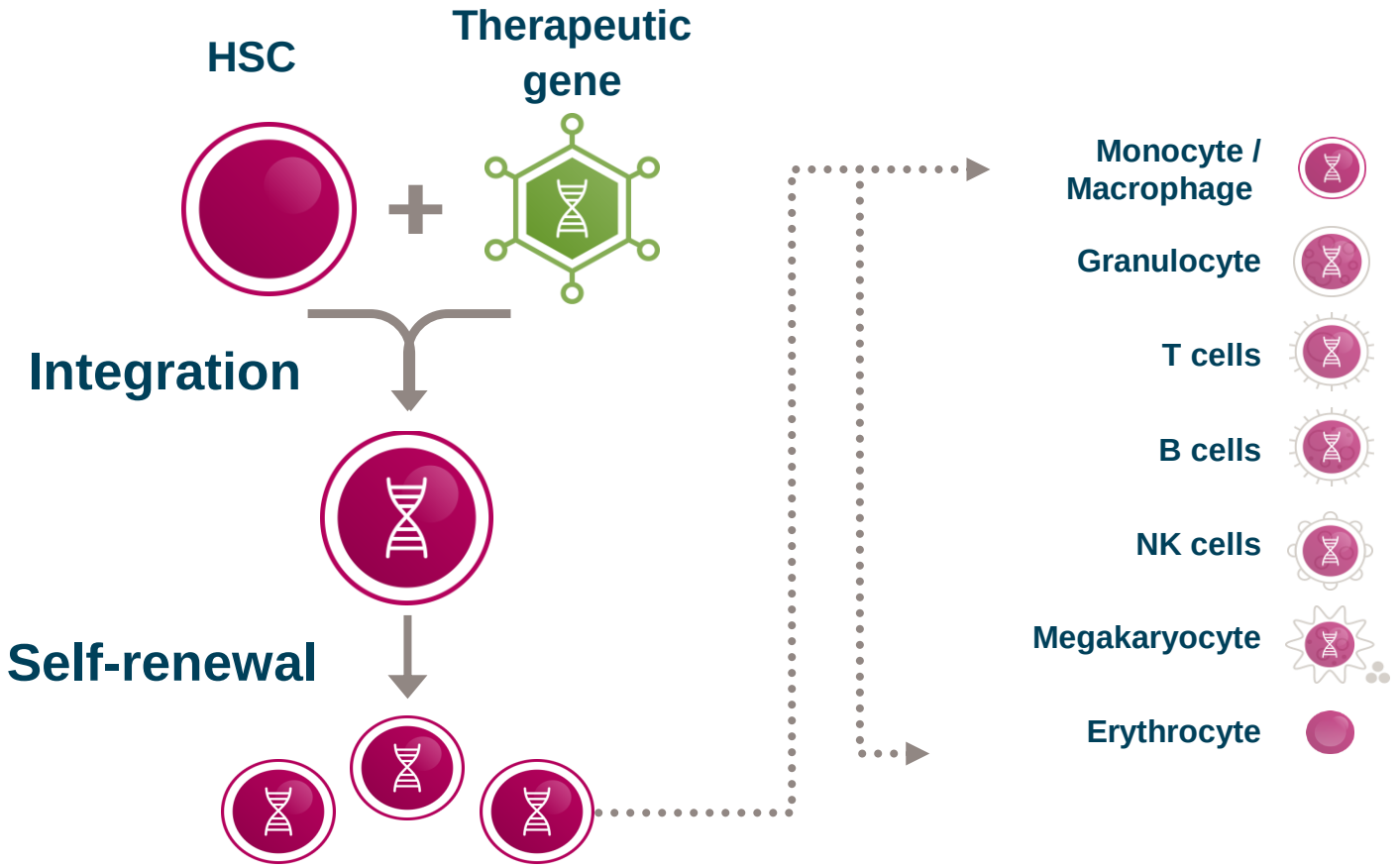
Forward-looking Statements

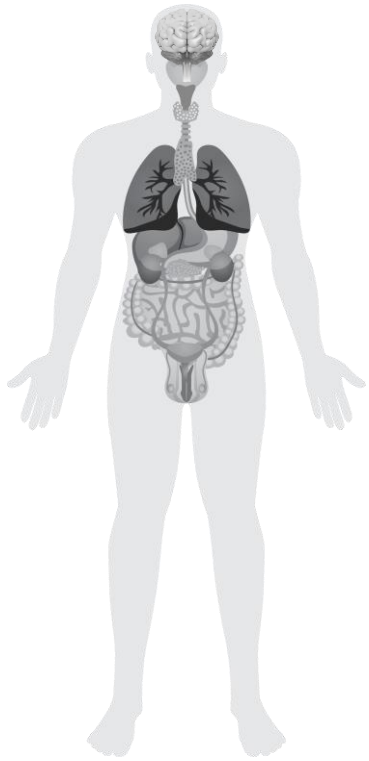
Certain information set forth in this presentation and in statements made orally during this presentation contain “forward-looking statements”. Except for statements of historical fact, information contained herein constitute forward-looking statements and may include, but are not limited to, the Company’s 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 Orchard’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 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-Q filed with the SEC on November 4, 2021, 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.

HSC Gene Therapy Offers a Highly Differentiated Approach



- Monocyte / Macrophage
- Granulocyte
- T cells
- B cells
- NK cells
- Megakaryocyte
- Erythrocyte



- Brain
- GI

High area of focus

- Other Organ Systems

Areas for potential future expansion

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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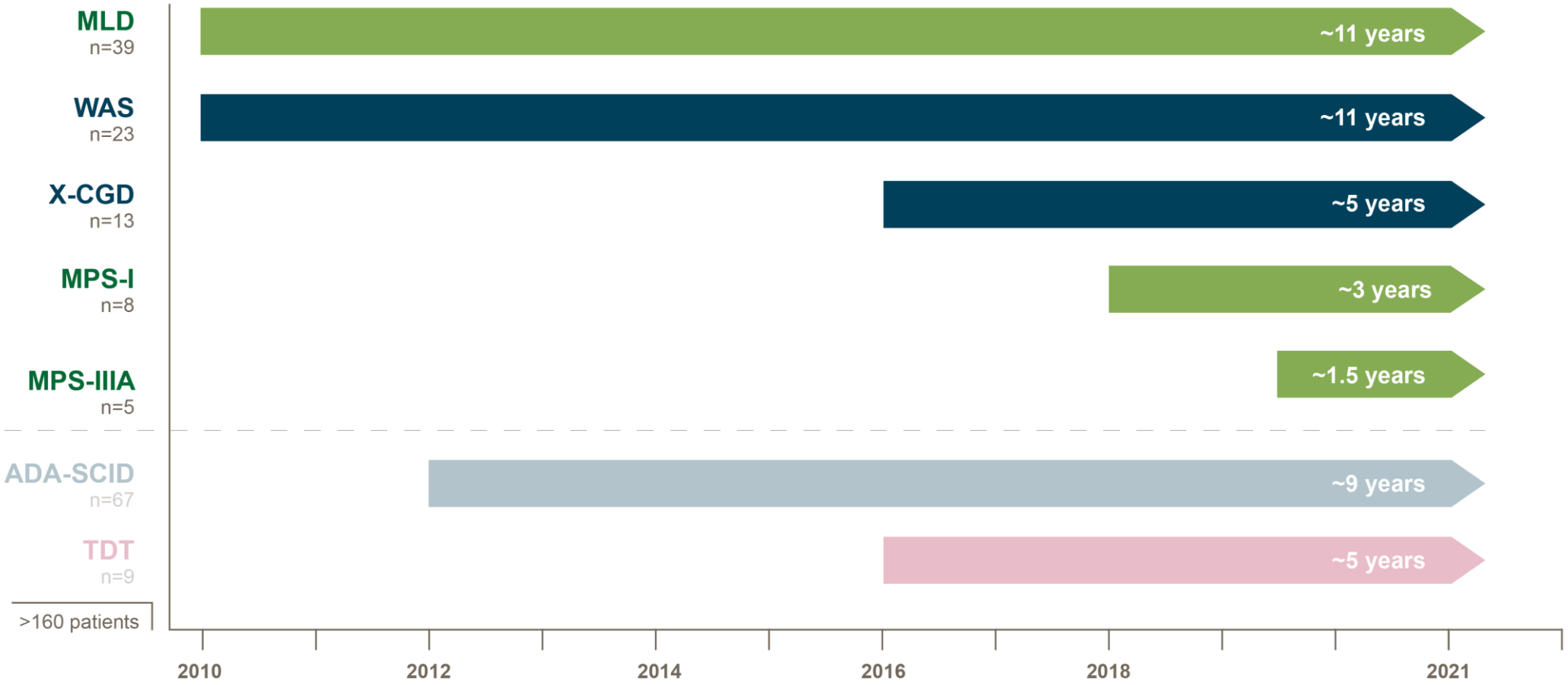
Durability of Response Demonstrated via Longest Patient Follow-up with Orchard's HSC Gene Therapy



- Patients treated in the development phase, including in clinical trials and under pre-approval access (defined as any form of pre-approval treatment outside of a company-sponsored clinical trial, including, but not limited to, compassionate use, early access, hospital exemption or special license).
- Data based on in-house data as of February 2021 and comprises all patients treated with CD34+ hematopoietic stem cells transduced *ex vivo* with vector of interest, inclusive of current and former programs.

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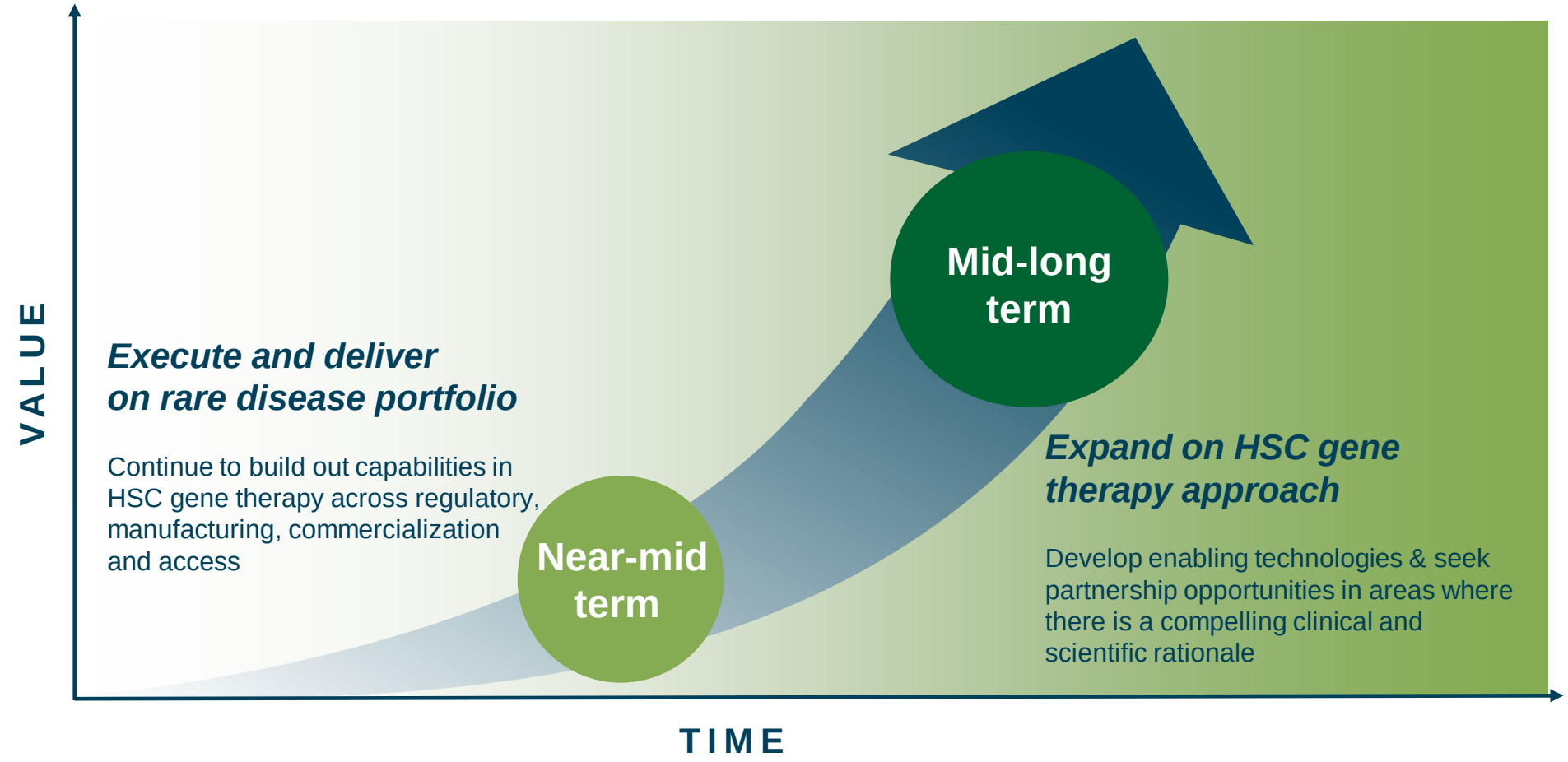
Accelerating Long-term Growth and Value Creation By Expanding into Other Neurodegenerative and Immunological Diseases



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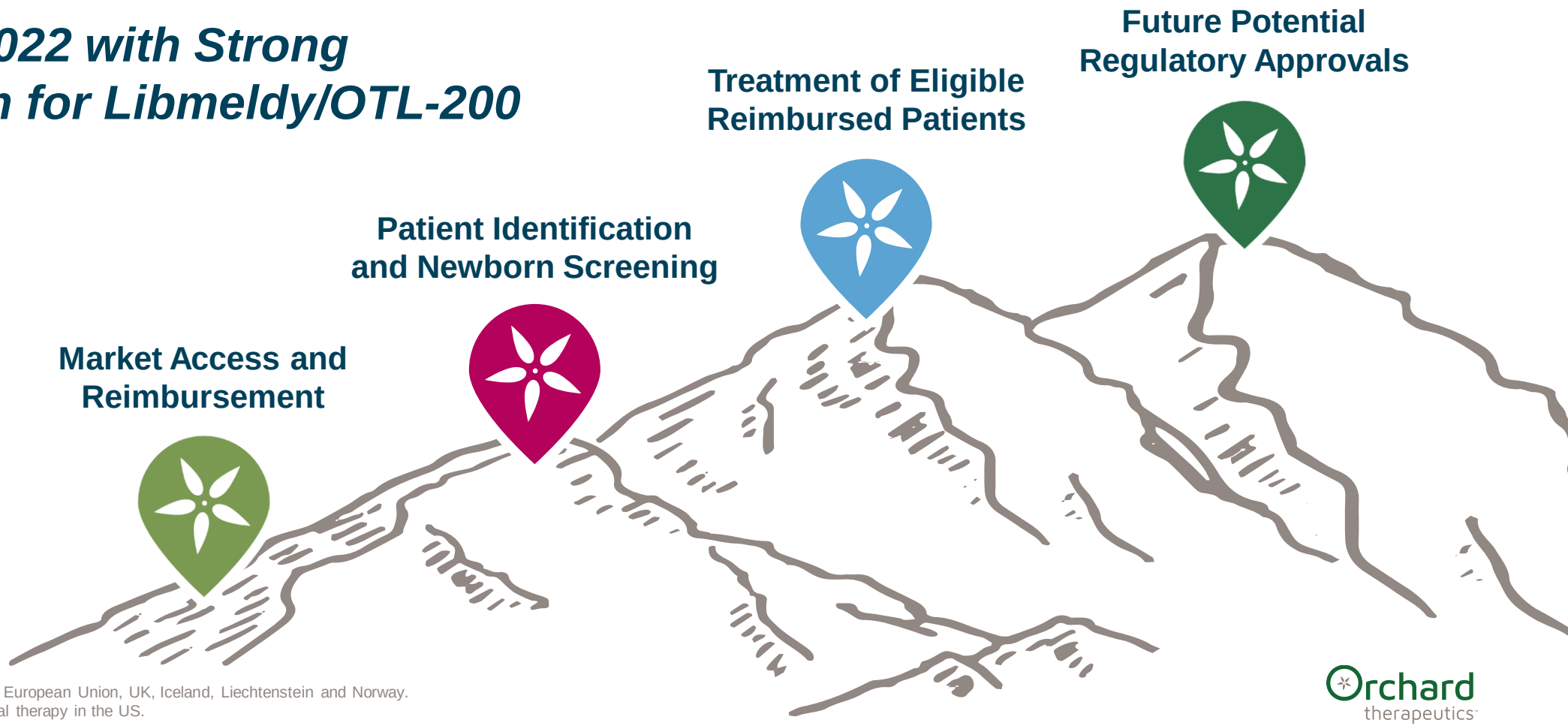
Reaching New Heights

Entering 2022 with Strong Momentum for Libmeldy/OTL-200



Libmeldy is approved in the European Union, UK, Iceland, Liechtenstein and Norway.
OTL-200 is an investigational therapy in the US.

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European HTA and Reimbursement Discussions Progressing Well

Broad Recognition of Libmeldy's Clinical Impact

Achieved highest possible therapeutic benefit rating in pre-symptomatic patients in Germany

Granted approval for reimbursed early access program in France

Ongoing collaboration with NICE and NHS England in advance of Final Evaluation Determination

Approved to treat patients travelling to Italy from countries outside Europe; negotiating final pricing & reimbursement for native patients

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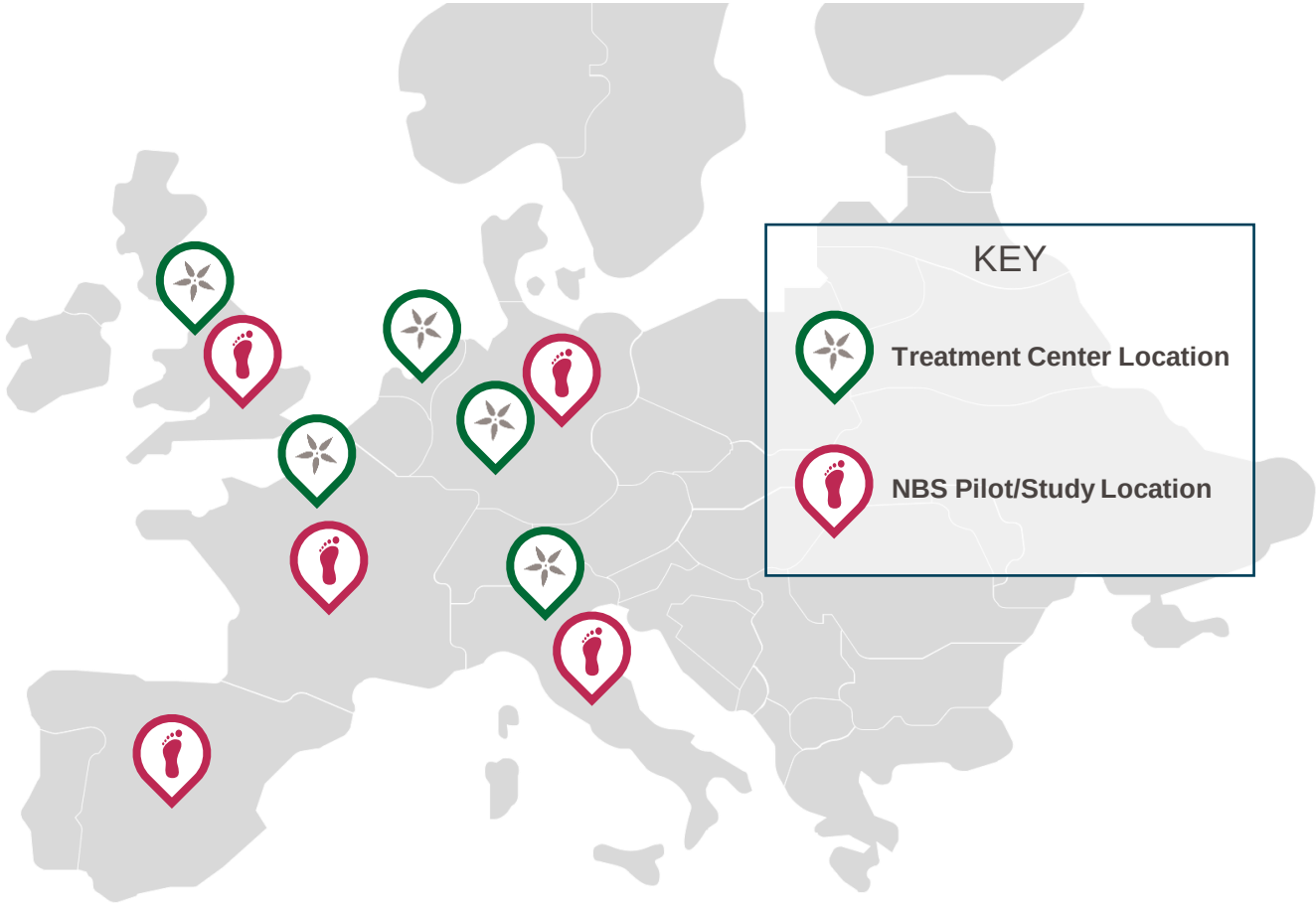
Utilizing Our Commercial Infrastructure to Identify, Treat and Secure Reimbursement for Eligible Patients in Europe

2 eligible patients in process of reimbursed treatment

4 centers treatment ready

5 Newborn screening (NBS) pilots/studies launched or planned



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OTL-200 (MLD): Advancing U.S. Regulatory Discussions

BLA expected late 2022 / early 2023

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

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Looking to New Horizons

Deliver on rare disease portfolio

Meet the need in genetic and other severe diseases

Expand HSC gene therapy approach

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OTL-103 for WAS: Progressing Toward Regulatory Submissions in Europe and the U.S.

- ✓ Productive rapporteur / co-rapporteur interactions
- ○ MAA filing planned for mid-2022

- ✓ Active IND / RMAT designation
- ○ FDA interaction planned for early 2022

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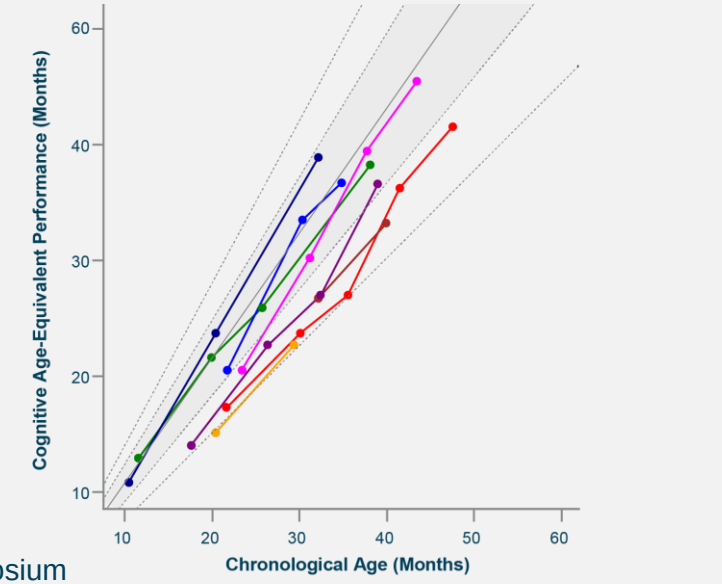
OTL-203 for MPS-IH: Stable Cognitive Function and Growth within the Normal Range in Proof-of-concept Study

Neuropsychological Tests over Time

Cognitive Age-Equivalent Score (Overall)



2021 MPS Symposium

Recent Program Achievements and Next Steps

- ✓ Proof-of-concept study results published in *The New England Journal of Medicine*
- ✓ Conducted parallel scientific advice meeting with EMA and FDA
- ○ Obtain necessary regulatory clearance in mid-2022 to enable global registrational study
- ○ Initiate global registrational trial by year end

Note: SD = Standard Deviation; IQ(C) = Intelligence Quotient (Cognition); For Bayley III, the IQ(C) is the cognitive composite score as collected. For WPPSI, the IQ(C) is defined as the performance scales score. For Bayley II: Cognitive Age-Equivalent will be defined as the Mental developmental Age recorded on the CRF. For Bayley III: Cognitive Raw Scores will be compared to the tabulated values in the Bayley III manual to calculate the Cognitive Age-Equivalent. For WPPSI, Age-Equivalent = (IQ*Chronological Age)/100.

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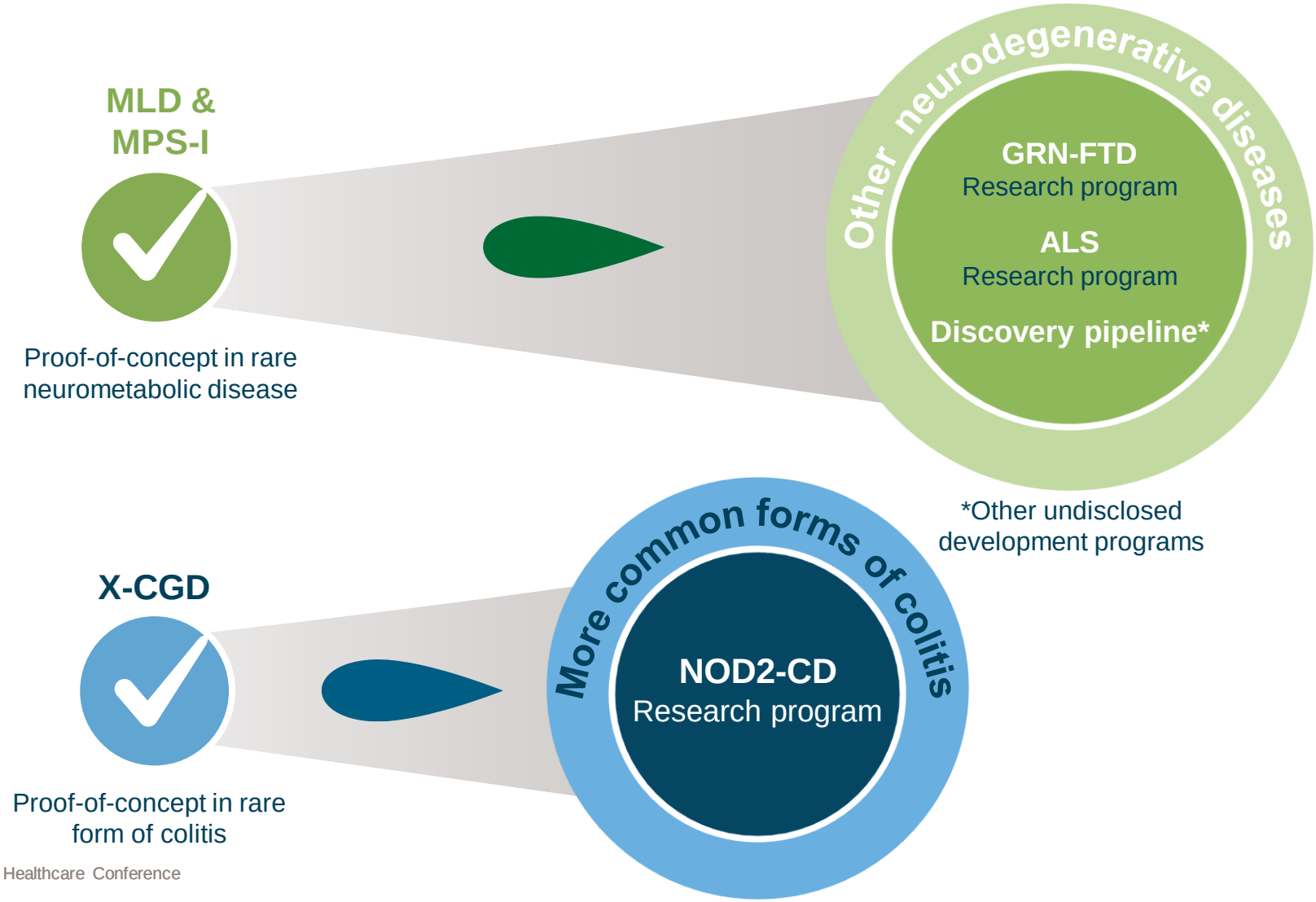
Rare Disease Portfolio Provides Clinical Proof-of-concept in More Prevalent Neurodegenerative and Immunological Diseases



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Orchard's Discovery and Early Research Program Highlights

Neurodegenerative disorders

- Approach leverages success of Libmeldy in **whole-brain secretion of ARSA from fully distributed microglial cells**
- Targets include GRN-FTD, ALS and other indications

Status:
Tech. development and preclinical proof-of-concept models ongoing

NOD2 Crohn's disease

- Orchard is developing OTL-104, an HSC gene therapy product targeting NOD2 mutations associated with Crohn's disease severity
- **Early preclinical data shows potential**

Status:
Preclinical proof-of-concept models ongoing

Future Applications for HSC Gene Therapy

- Two key areas to **expand HSC gene therapy platform:**
  1. Vectorized antibody platform to **deliver mAbs to specific tissues or sites**
  2. HSC CAR-Treg platform as a durable therapy for **autoimmune disorders**

Status:
Exploratory research ongoing

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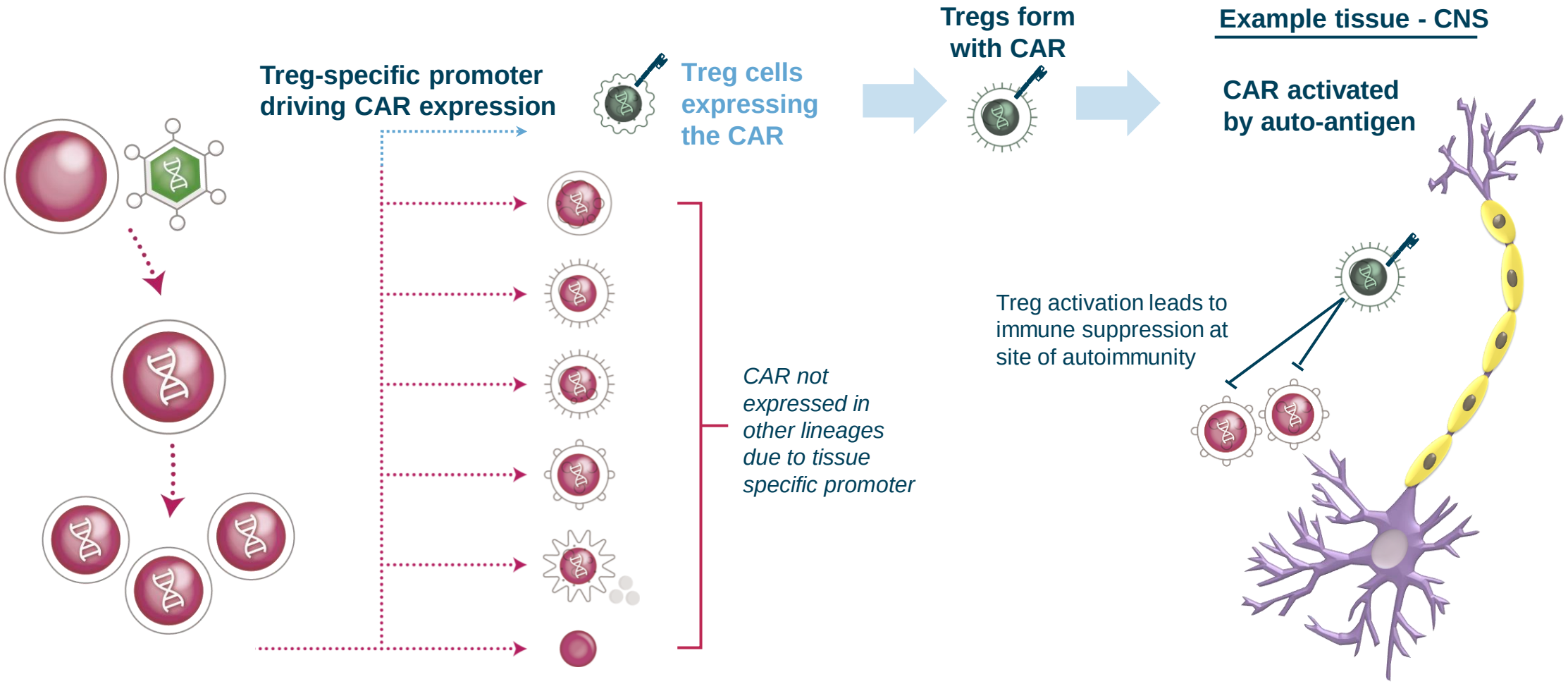
Combining the Proven Durability of HSC Gene Therapy with the Specific Suppressive Potential of CAR-Tregs



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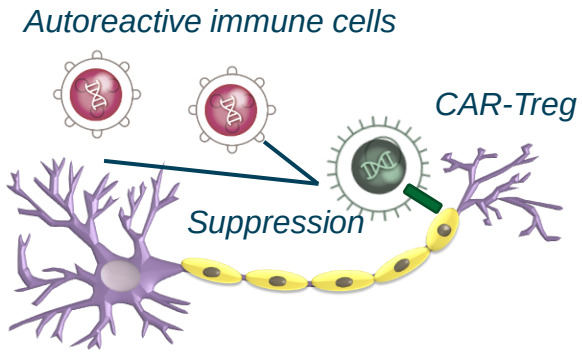
Potential Applications of the HSC CAR-Treg Technology

Multiple sclerosis

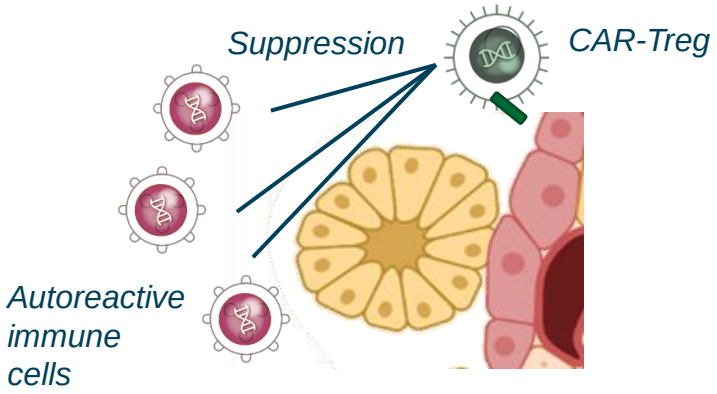
- **Identified antigen:** MOG and MBP
- **Use of HSC transplant:** Yes, 100s per year with limited efficacy
- **Unmet medical need:** High, particularly in progressive disease



Myelin sheath

Type 1 Diabetes

- **Identified antigen:** GAD65, chromogranin A, others
- **Use of HSC transplant:** Yes, but limited efficacy
- **Unmet medical need:** Many patients not reaching HbA1c goals



Pancreatic beta-cells

Rheumatoid arthritis

- **Identified antigen:** Limited, ova is one example
- **Use of HSC transplant:** Yes, but limited efficacy
- **Unmet medical need:** Significant proportion of patients non controlled on existing therapies

Synovial tissue

Image credit: Biorender

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The Journey Ahead

Roadmap for a sustainable future

Maintain strong balance sheet

Well resourced; ended 2021 with approximately $220M of cash and investments

Invest for growth

Utilize global infrastructure for future potential approvals and launches

Leverage HSC GT platform as engine for new indications

Pursue partnership opportunities

Potential for disease-specific or technology driven approaches

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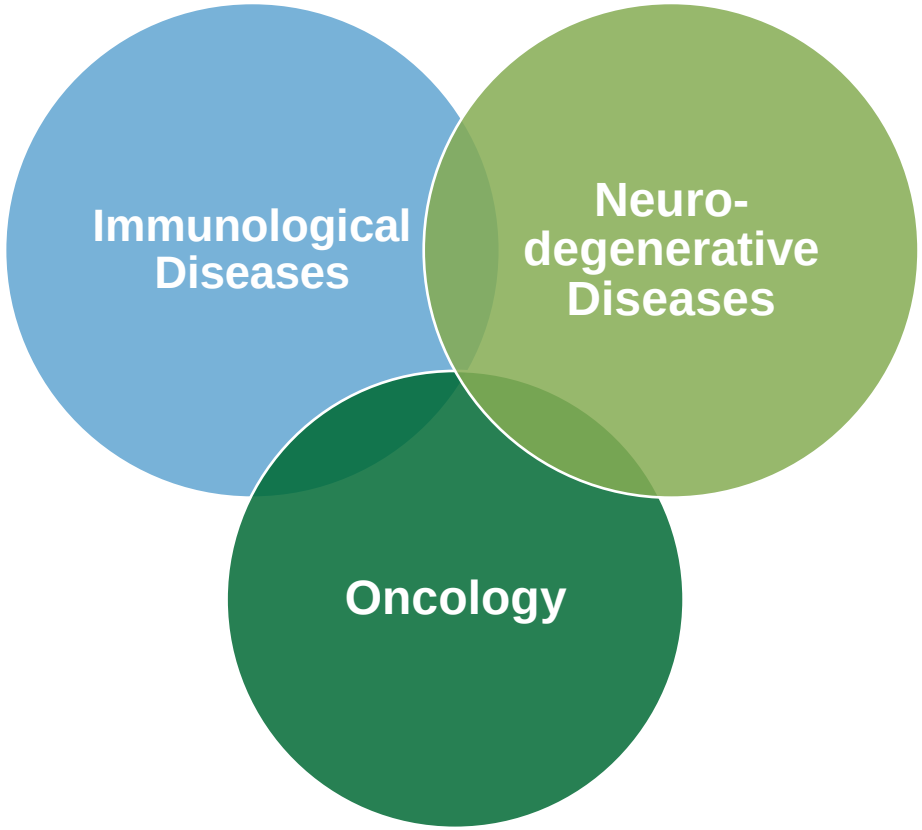
Research Platform Provides Multiple Opportunities for Business Development



Partnerships in specific diseases

- **OTL-105** for HAE partnered with Pharming
- Leveraging ongoing programs in CNS **(FTD/ALS)** and colitis **(NOD2-Crohn's)**

Partnerships built on specific technologies

- **Antigen-specific Tregs** for autoimmune diseases
- **mAb vectorization technology** to target specific tumors or other targets

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Anticipated 2022 Milestones:

A Catalyst-Rich Year Spanning All Phases of Development and Commercialization

Preclinical	Clinical	Regulatory	Commercial
Advance research programs in: • **GRN-FTD** (OTL-204) • **NOD2-CD** (OTL-104) • **HAE** (OTL-105) • **HSC-generated Tregs**	**OTL-203:** Initiate global registrational trial for MPS-IH by year end **OTL-201:** Present data from ongoing MPS-IIIA POC trial in 1H'22	**OTL-103:** MAA filing in WAS in mid-2022; FDA interaction planned in early 2022 **OTL-200:** Planned BLA submission for MLD in late 2022 / early 2023	**Libmeldy:** Reach reimbursement agreement with at least two countries in 1H'22 **Libmeldy:** Continue broadening patient identification and newborn screening initiatives

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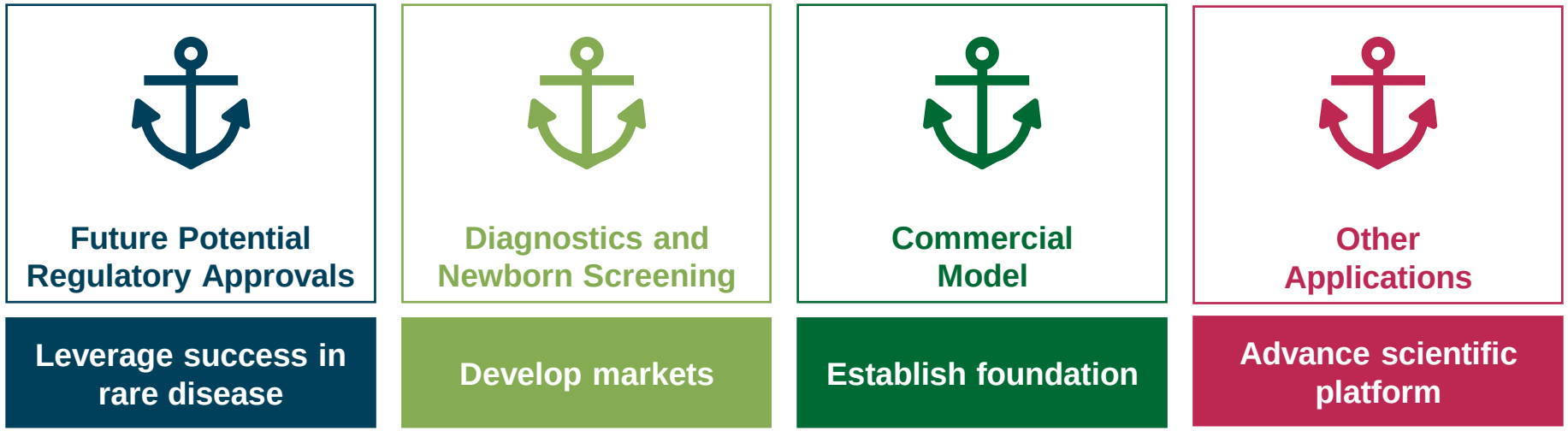
Compelling Fundamentals Driving Near-term Value Creation and Long-term Growth



All based on a de-risked HSC GT scientific and clinical platform

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Thank you!