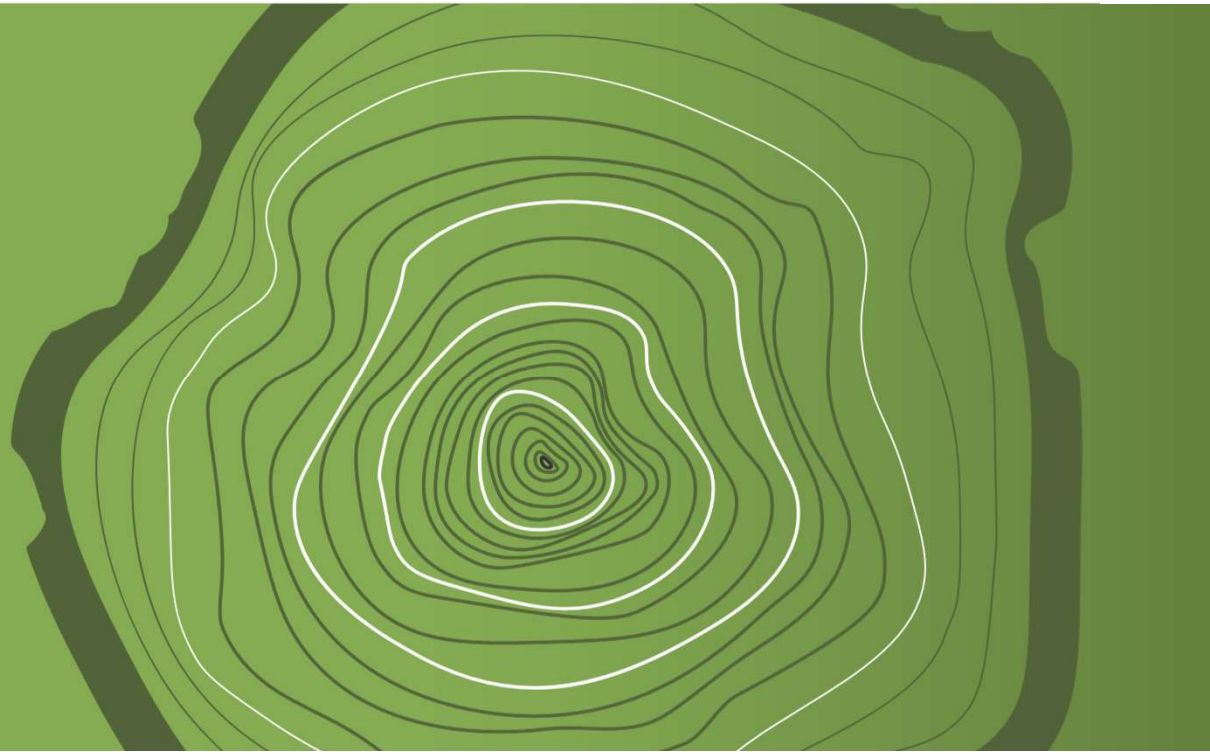
Orchard therapeutics™

New Horizons in HSC Gene Therapy

R&D Investor Event

November 13, 2020



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Certain information set forth in this presentation and in statements made orally during this presentation contains “forward-looking statements”. Except for statements of historical fact, information contained herein constitutes forward-looking statements and may include, but is not limited to, the Company’s expectations regarding: (I) the safety and efficacy of its product candidates; (II) the expected development of the Company’s business and product candidates; (III) the timing of regulatory submissions for approval of its product candidates; (IV) the timing of interactions with regulators and regulatory submissions related to ongoing and new clinical trials for its product candidates; (V) 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; (VI) the timing and likelihood of approval of such product candidates by the applicable regulatory authorities; (VII) the adequacy of the Company’s manufacturing capacity and plans for future investment and commercialization; (VIII) execution of the Company’s vision and growth strategy, including with respect to global growth; (IX) the size and value of potential markets for the Company’s product candidates; and (X) projected 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.

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Q&A Session How-to

Q&A

Please use this link to submit your questions and interact with the speakers:

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Delivering Now; Building for the Future

Bobby Gaspar, M.D., Ph.D.

Chief executive officer

Today's Agenda

TIME	AGENDA TOPIC	SPEAKER
9:00 – 9:15am	Delivering Now; Building for the Future	Bobby Gaspar
9:15 – 9:35am	HSC Gene Therapy for Frontotemporal Dementia & Amyotrophic Lateral Sclerosis	Alessandra Biffi
9:35 – 9:55am	HSC Gene Therapy for Crohn's Disease	Bobby Gaspar & Piv Sagoo
9:55 – 10:10am	Q&A	
10:10 – 10:30am	Scaling Manufacturing for Larger Indications	Ran Zheng & Bobby Gaspar
10:30 – 10:45am	Revisiting Delivering Now; Building for the Future	Frank Thomas
10:45 – 11:00am	Q&A	

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New Horizons in HSC Gene Therapy

What you will see and hear today

- HSC gene therapy has the potential to treat a broad range of severe diseases
- Clinical validation in rare disorders builds confidence for larger indications
- FTD, Crohn's and ALS programs are backed by strong scientific rationale
- Prioritizing innovation in manufacturing to accelerate profitability and scale-up
- Building commercial capabilities to leverage with future products

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Dedicated to **transforming** the lives of people with rare diseases.

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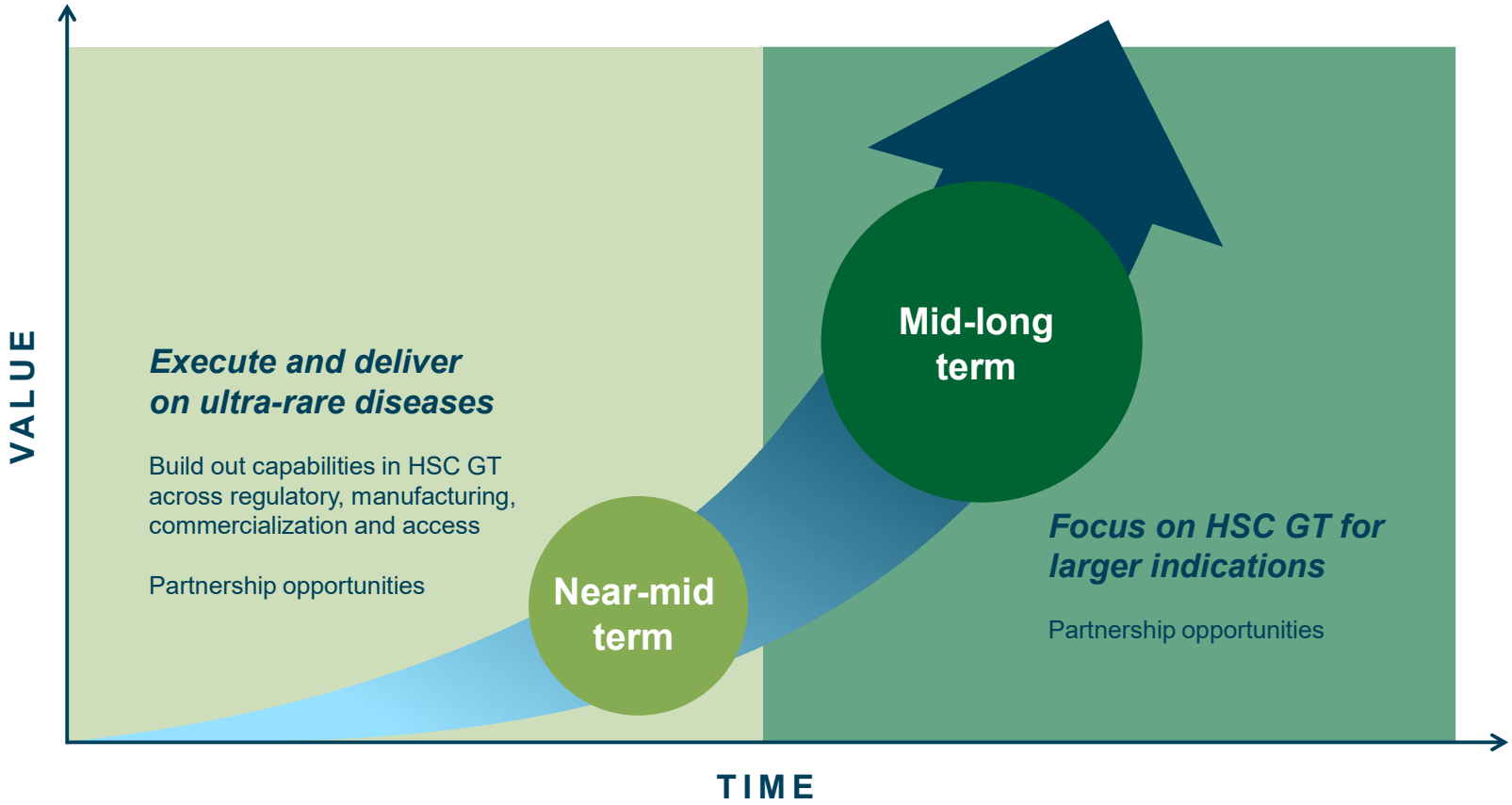
Evolving from Rare to Larger Indications



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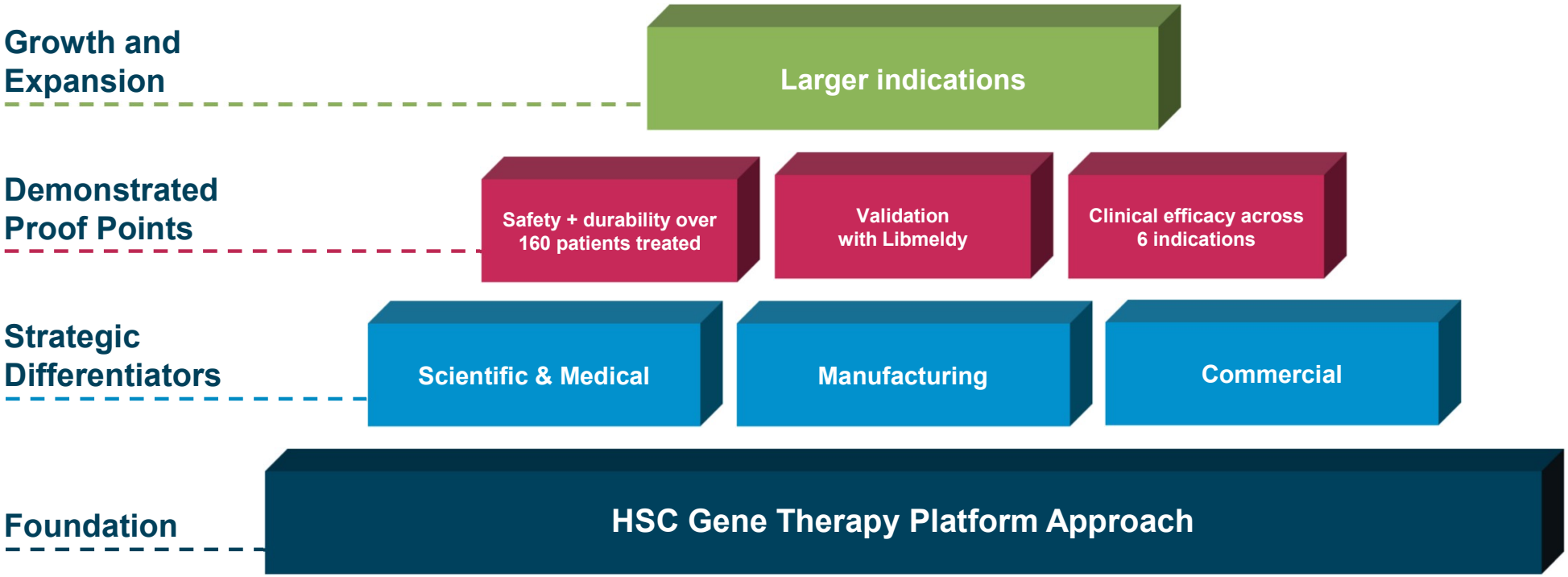
Delivering Now; Building for the Future



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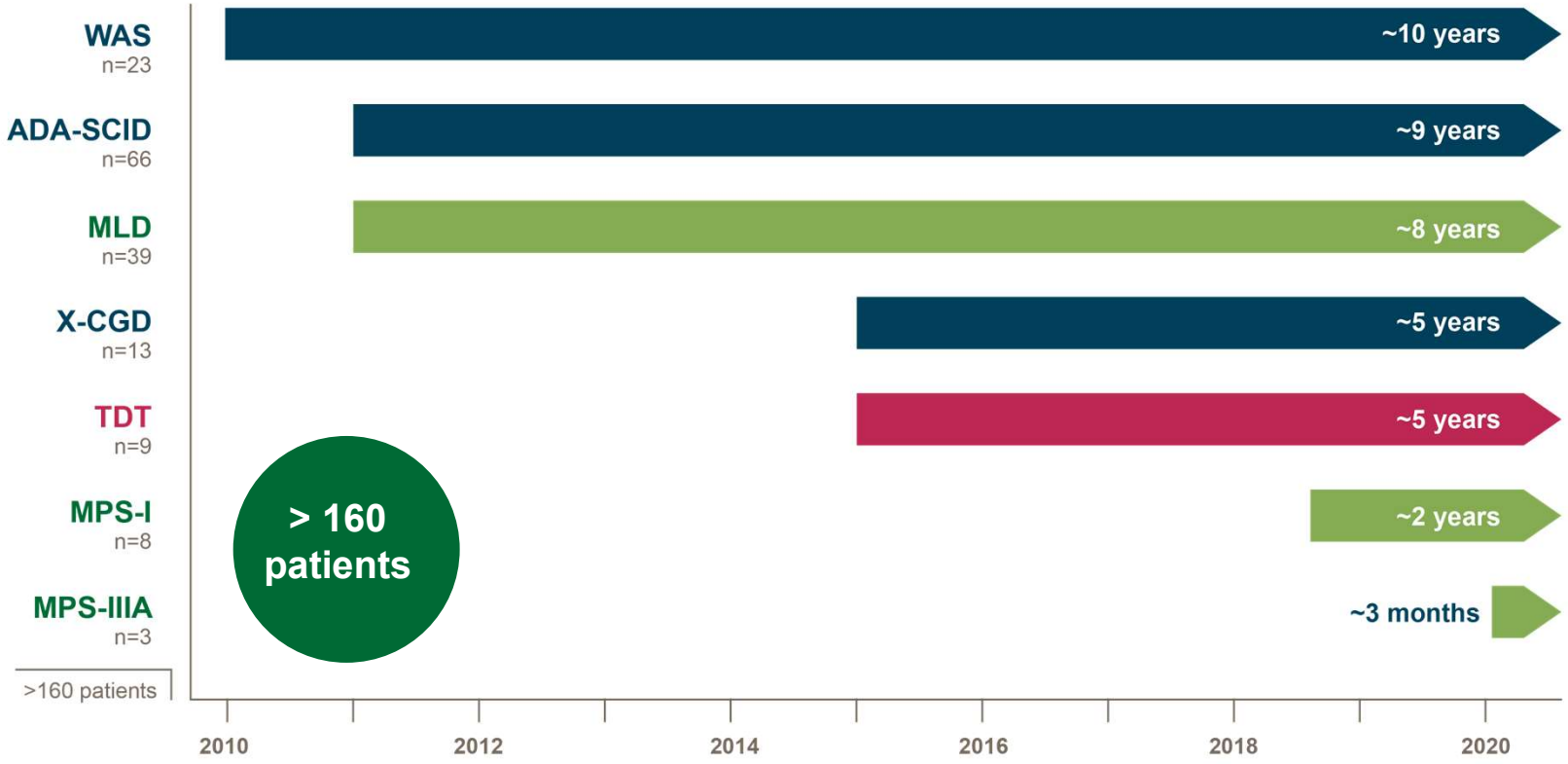
Durability of Response with Lentiviral HSC Gene Therapy Demonstrated via Longest Patient Follow-up



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 December 2019. Data include all patients treated with CD34+ hematopoietic stem cells transduced ex vivo with vector of interest.

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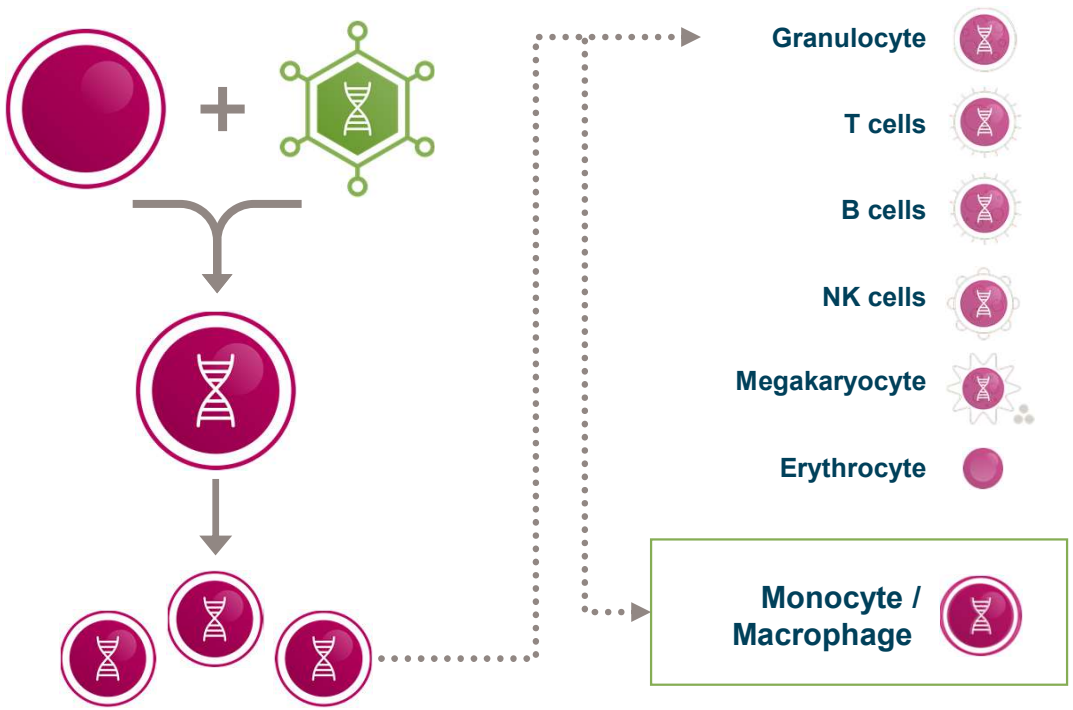
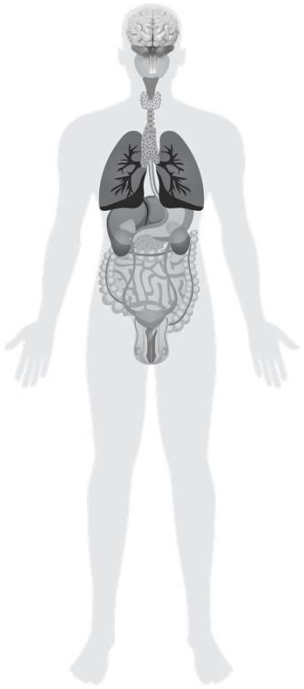
Expanding the HSC Gene Therapy in Larger Indications





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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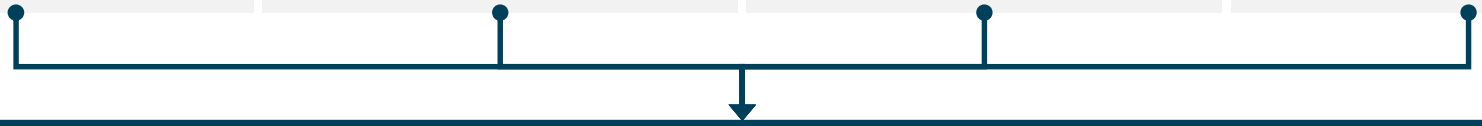
Selection of New Indications is Strategic and Science-Driven

Etiology	Underlying genetic association / causation	Clinical experience	High level of unmet need
• Dysfunctional cell is progeny of HSCs or can be corrected through interaction with HSC progeny	• *Ex 1: NOD2* mutation strongly associated with Crohn's disease • *Ex 2: GRN* mutation strongly associated with FTD	• Human or animal study data that cellular phenotype can be corrected by HSCT or by HSC gene therapy	• Benefit / risk profile • Refractory to current therapies • Lack of available treatment options



Potential for HSC Gene Therapy to Become Standard of Care

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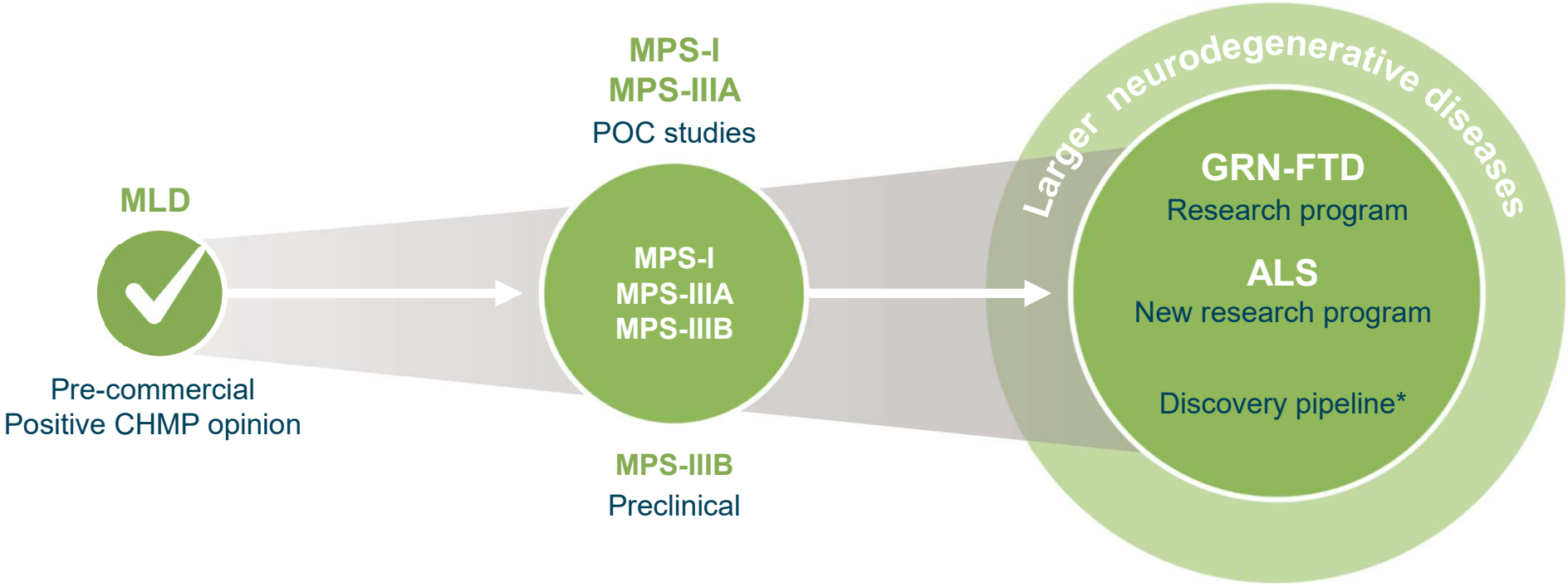
Clinical Validation in Rare Disorders Supports Application in Larger Populations such as GRN-FTD and ALS



*Other undisclosed development programs

Today's Agenda

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HSC Gene Therapy in GRN-FTD and ALS

Alessandra Biffi

Professor and chair of the Pediatric Hematology, Oncology and Stem Cell Transplant Division at University of Padua, faculty of pediatrics at Harvard Medical School and co-director of the Gene Therapy Program at Dana Farber/Boston Children's Cancer and Blood Disorders Center

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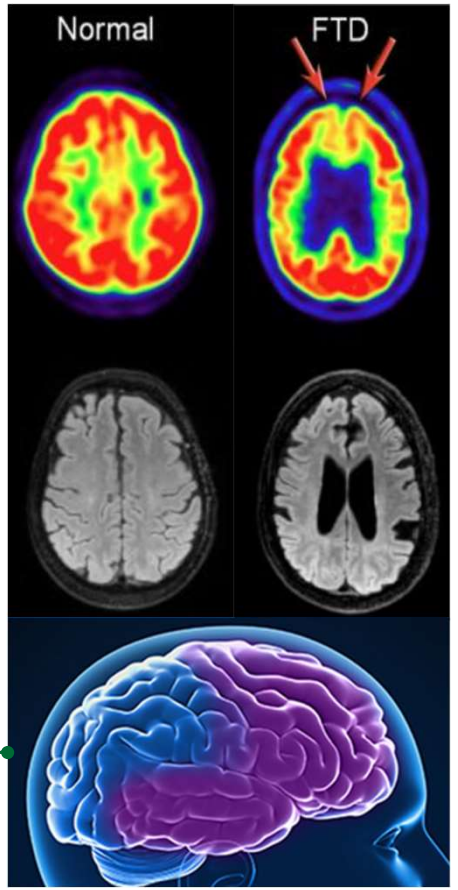
Frontotemporal Dementia (FTD) Disease Background

- 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



www.ninds.nih.gov

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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
- ~800 new cases U.S. / EU per year

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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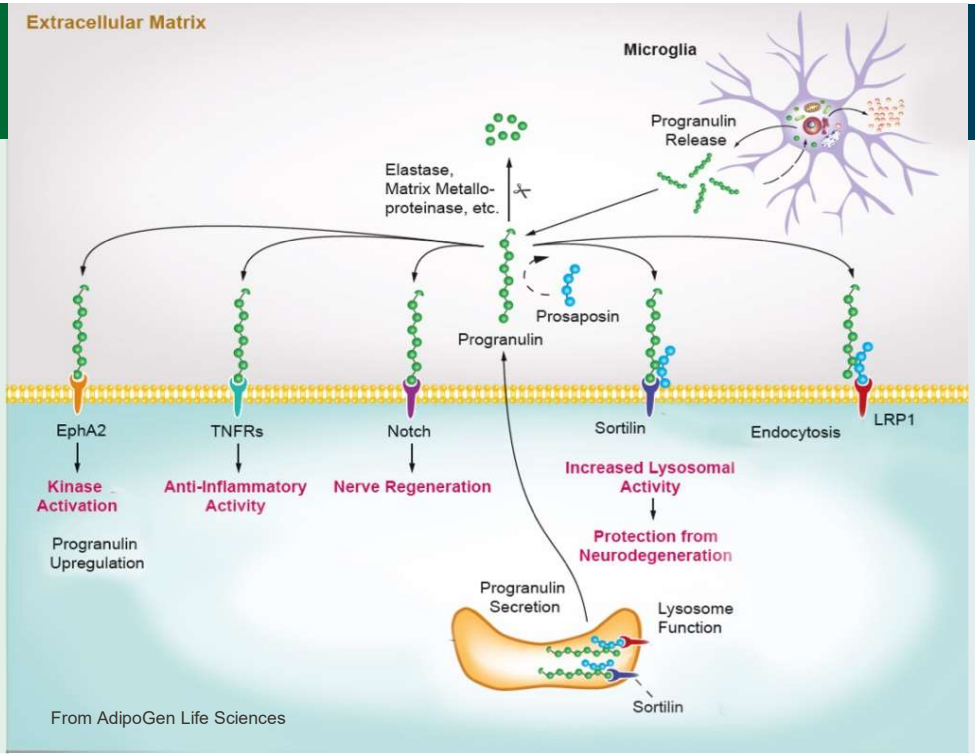
Progranulin Carries Important Neurotrophic, Anti-inflammatory and Lysosomal Functions

Progranulin function in the CNS

- Secreted glycosylated 593-aa protein, 7.5 tandem repeats of highly conserved granulin motifs, can be cleaved into granulins
- In the brain, *GRN* is expressed mainly in neurons and microglia
- Neurotrophic, anti-inflammatory and lysosomal functions



Consequences of lack of progranulin

- Sustained pro-inflammatory microenvironment and neurodegeneration
- Microglia and astrocyte activation
- Excessive complement production and synaptic pruning
- Enhanced caspase activation, lower cell survival, lysosomal dysfunctions, increased vulnerability to oxidative stress, oxygen and glucose deprivation

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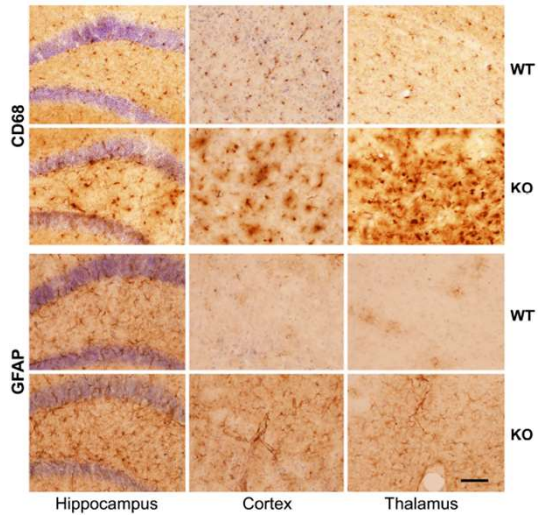
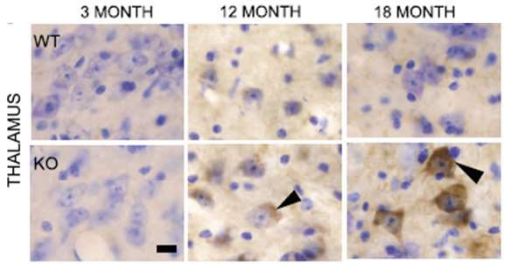
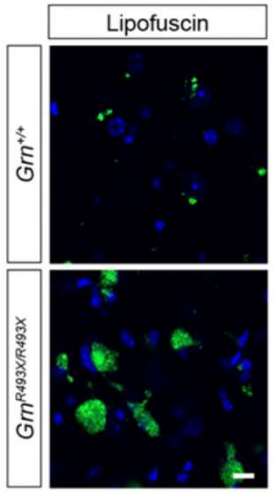
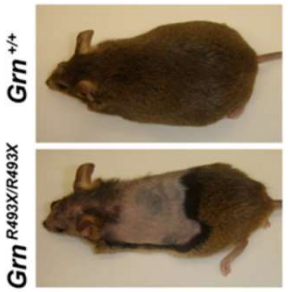
Knockout Mouse Models Recapitulate Human Phenotypes

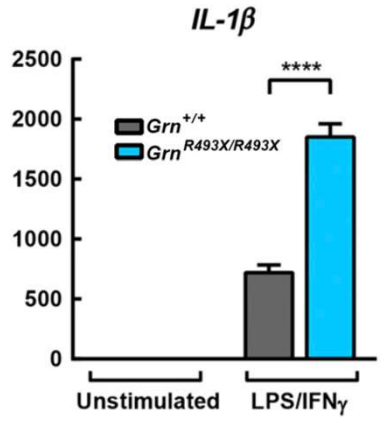
- Microgliosis
- Lipofuscinosis
- Hyperinflammatory macrophages
- Cytoplasmic pTDP43
- Excessive grooming behavior
- Reduced survival due to infections

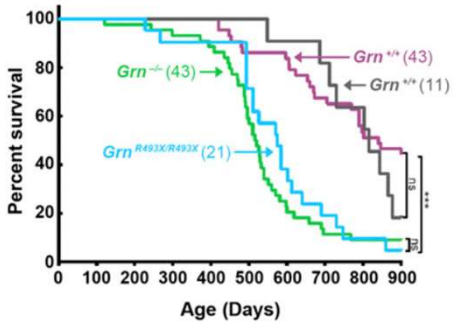












Nguyen (2018) PNAS, Yin (2010) FASEB J, Yin (2010) J Exp Med

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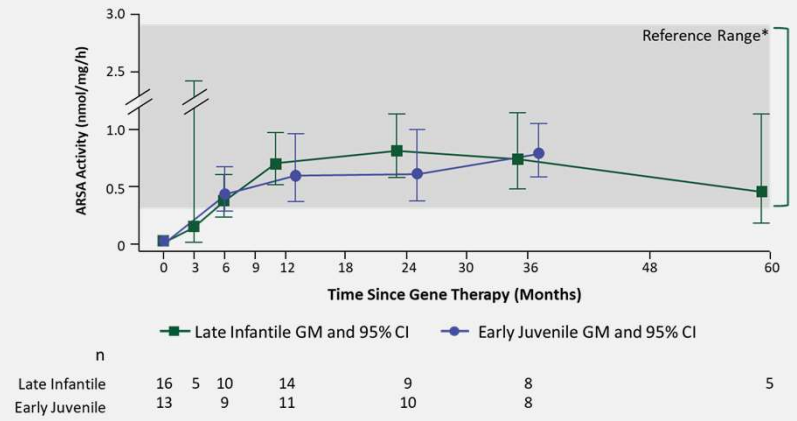
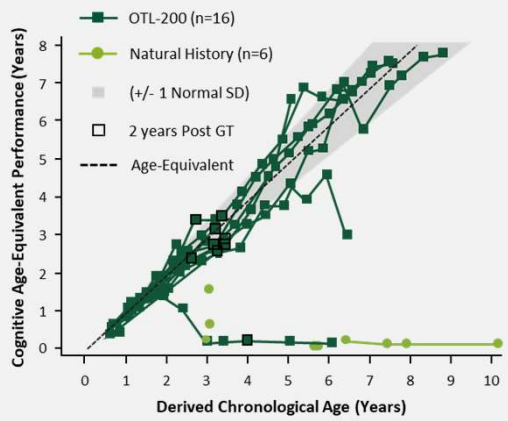
OTL-204
ex vivo HSC Gene Therapy Program for GRN-FTD

Strong Evidence of Durable, Whole Brain Effect of *Ex Vivo* HSC Gene Therapy Supported by OTL-200 Clinical Dataset

OTL-200 ARSA Activity in Cerebrospinal Fluid



Cognitive Age Equivalent Performance OTL-200 vs. Natural history, Late infantile



Evidence from OTL-200 development program suggests durable CNS engraftment of genetically-corrected cells and sustained clinical efficacy

ARSA, arylsulfatase A; CI, confidence interval; GM, geometric mean; GMs and 95% CIs are presented where there are at least 3 patients with non-missing data; Figure from Fumagalli F et al. Lentiviral hematopoietic stem cell gene therapy (HSC-GT) for metachromatic leukodystrophy (MLD) provides sustained clinical benefit; ARSA Activity in CSF Presented at: 2019 Annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM); September 3-6, 2019; Rotterdam, The Netherlands; Cognitive Age-Equivalent at each visit has been derived as follows: For WPPSI and WISC: (DQp x Chronological Age)/100. For Bayley III: Cognitive Raw Scores have been compared to the tabulated values in the Bayley III manual to calculate Cognitive Age-Equivalent. For Bayley II: Cognitive Age-Equivalent is based on Mental Development Age as reported on the CRF. The Psychological Corporation. 2006.Bayley N. Bayley scales of infant and Toddler Development. Third Edition. San Antonio. Cognitive Age Equivalent Performance Presented at: 2019 Annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM); September 3-6, 2019; Rotterdam, The Netherlands.

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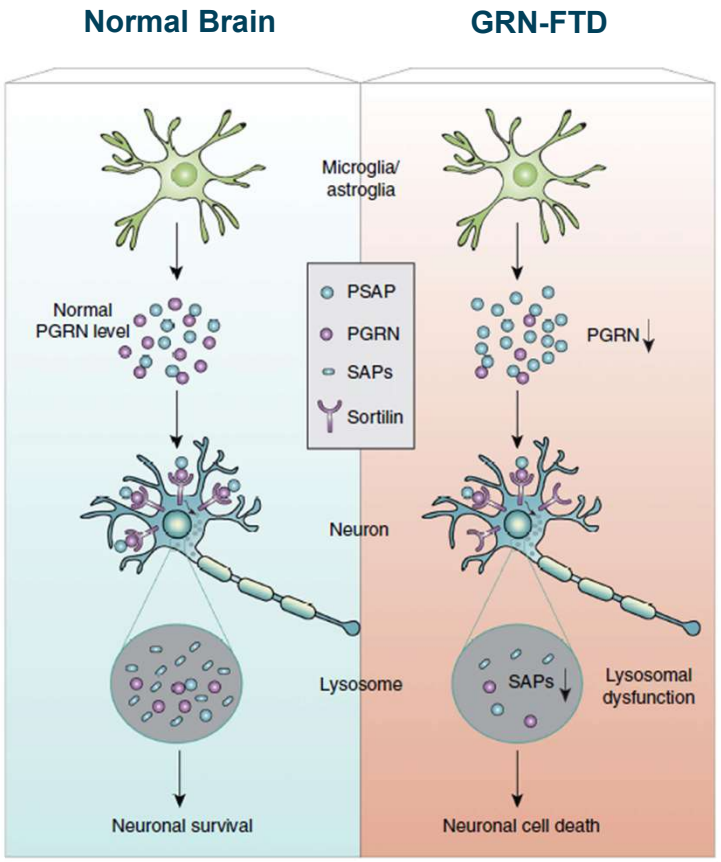
Microglia Cells Are the Ideal Therapeutic Target in GRN-FTD

Autologous HSCs transduced with a *GRN*-encoding LV for the treatment of FTD

Engrafted microglia cells would provide a long-lasting endogenous source of *GRN* directly in the CNS

Locally secreted *GRN* would cross-correct neighboring neurons and at the same time mediate the uptake of prosaposin (PSAP) by neurons via the Sortilin receptor.

Saposin peptides (SAPs) are essential for lysosomal function and neuronal survival.
PSAP+/- mice have FTD-like glial activation and behavioral phenotypes



Zhou (2017) Nat Commun

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OTL-204 Is Highly Suited for GRN-FTD

		OTL-204	AAV approaches	Biologics	Small molecule approaches
Efficacy	Directly restores wild type *GRN*	✓	✓ ✗ mAb	✗	✗
	Correct microglia phenotype	✓	✗	✗	✗
	Whole brain effect	✓	?	?	✓
	Restores neuronal function via cross-correction	✓	✗	✗	✗
Safety	Low risk of immunogenicity	✓	?	?	✓
	Myeloablative conditioning	?*	N/A	N/A	N/A
Administration	Single	✓	✓	✗	✗
	Durability	✓	?	N/A	N/A

*Ongoing developments to provide safe, brain targeted conditioning

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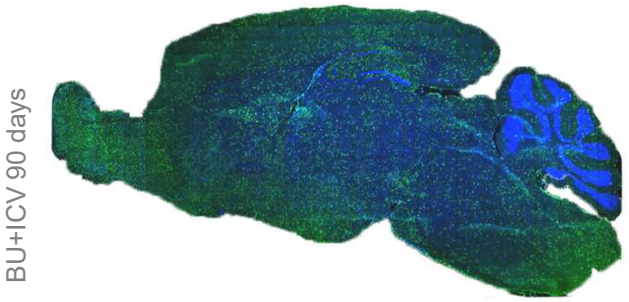
Ongoing Developments to Enhance Efficacy and Safety of OTL-204 Through Route of Delivery and Conditioning Regimen

- Conditioning is necessary to eliminate pre-existing microglia progenitors and “make space” for HSCs to engraft
- Systemic conditioning with alkylating agents has proved to allow efficient brain engraftment in other diseases (MLD, MPS-I) with strong risk/benefit rationale
- Following conditioning, HSC gene therapy delivered via ICV injection would enable efficient and targeted myeloid cell engraftment in the CNS
- Ongoing developments in brain-specific conditioning agents target maintenance of brain engraftment potential but with lower systemic impact



Capotondo (2017) Sci Adv

Peviani (2019) Biomaterials; ICV=intracerebroventricular (

Status of OTL-204 Development Plan

Stage 1
in vitro

Completed

Selection and validation of the transgene for *in vivo* study

- *GRN*-negative cell lines (human HeLa and HAP1, mouse MEF) were transduced with LVs carrying the *GRN* gene
- Single clones were isolated by flow cytometry, expanded and VCN assessed by ddPCR
- Clones with increasing VCN were tested for GRN expression, GRN release and cross-correction of *GRN*-negative cell lines
- Murine HSPCs were transduced with LVs carrying the *GRN* gene, expressed hGRN and cross-corrected *GRN*-negative cell lines and primary cells

Stage 2
in vivo

Ongoing

Generation of the experimental cohort and analysis of phenotypic readouts

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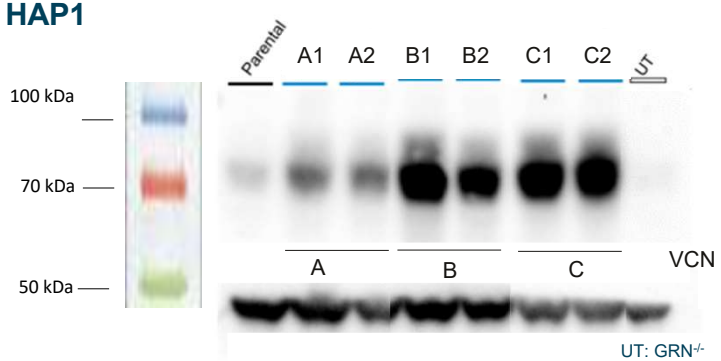
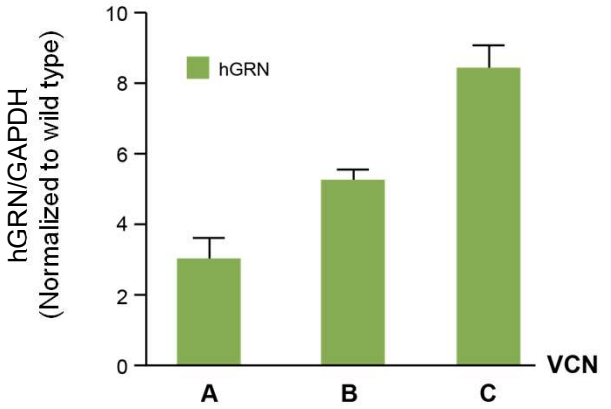
hGRN Is Efficiently Expressed in Transduced Cells *In Vitro*

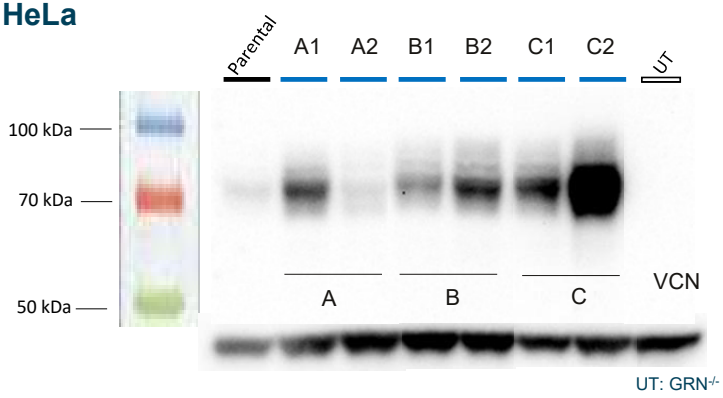
GRN$^{-/-}$ human cell lines were stably transduced with *hGRN*_LV and expressed hGRN at high levels after gene transfer

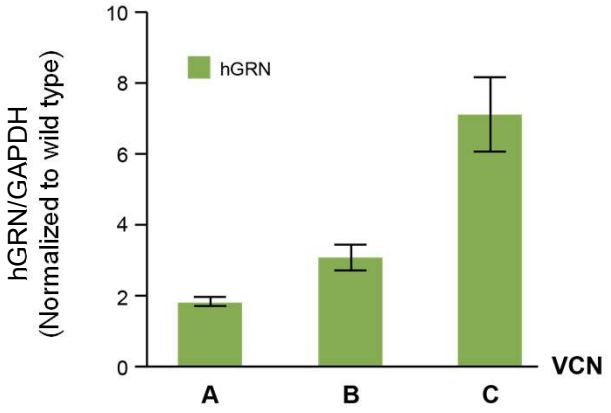
HAP1





HeLa





Data on file

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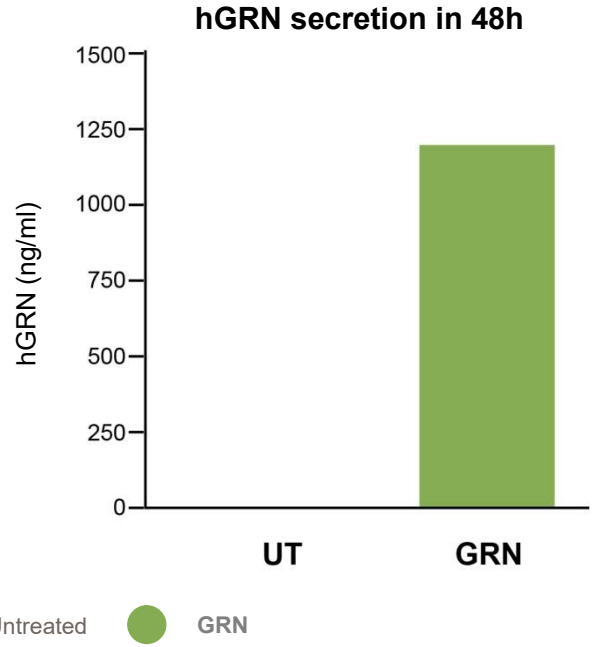
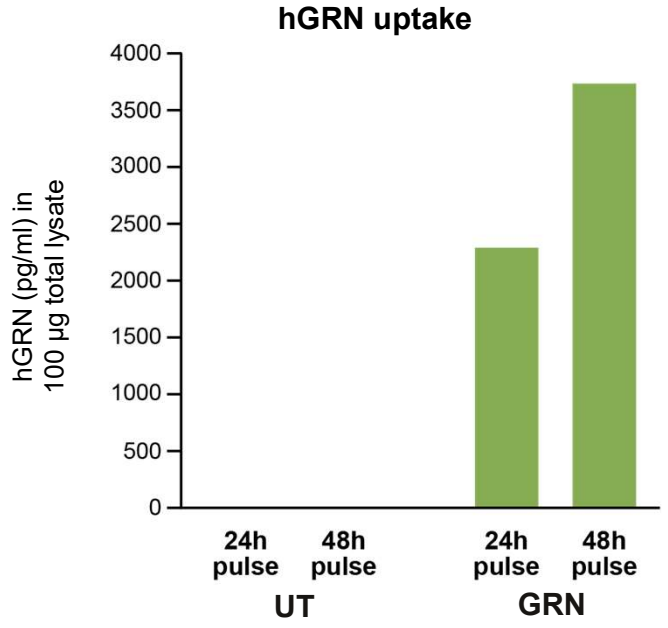
Evidence of Cross-correction of *GRN*$^{-/-}$ cells

hGRN effectively secreted by transduced *GRN*$^{-/-}$ cell clones in culture medium



UT=Untreated GRN

Secreted GRN taken up by *GRN*$^{-/-}$ cells from conditioned medium 48h>24h



Data on file

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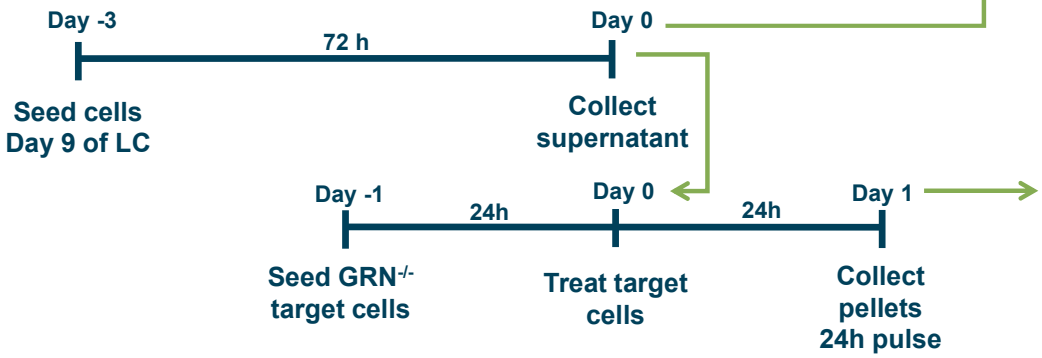
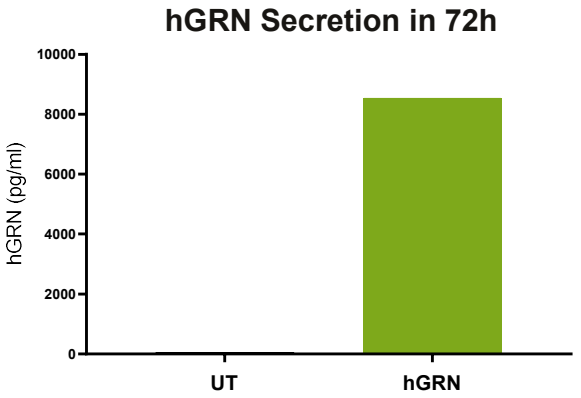
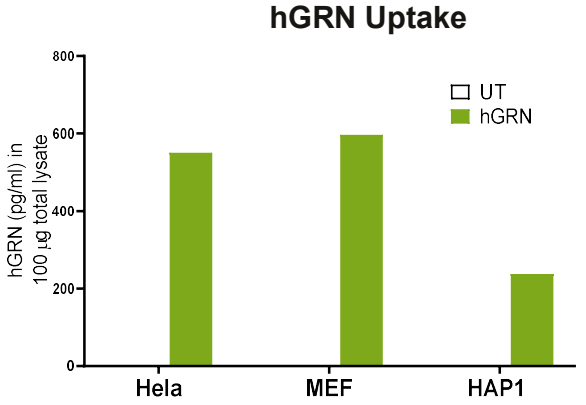
Transduced mHSPCs Secrete hGRN and Cross-correct *GRN*$^{-/-}$ cells

- Wt Lin- HSPCs transduced with *hGRN*_LV and cultured for 9 days
- hGRN secreted over 3 days of culture used to pulse *GRN*$^{-/-}$ human cell lines and murine fibroblasts for 24h
- Secretion and uptake of hGRN measured by ELISA







ELISA=enzyme-linked immunosorbent assay

Data on file

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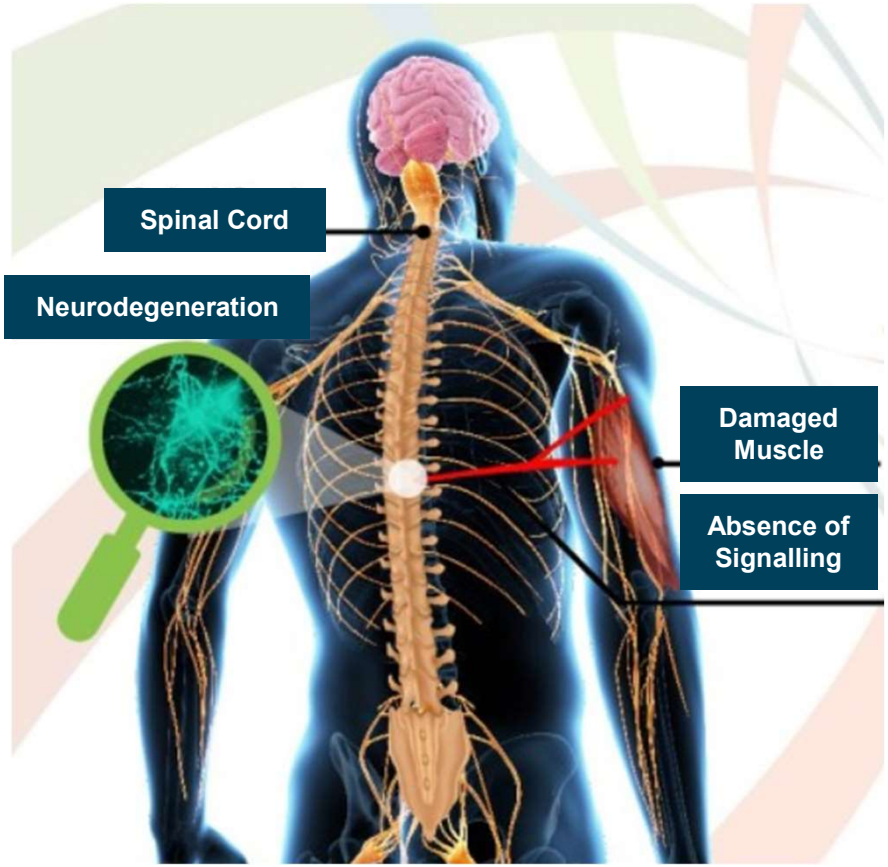
OTL-205
ex vivo HSC Gene Therapy Program for ALS

Amyotrophic Lateral Sclerosis (ALS) Disease Overview

- Progressive degeneration of upper and lower motor neurons
- Muscular weakness, twitching and atrophy cause difficulty speaking, swallowing, breathing
- 80-90% sporadic (onset at 58-63)
  10-20% familial (onset at 47-52)
- No effective treatment
  Survival 2-4 years from onset, 1-2 years from diagnosis
- Incidence: 2.1-3.8 per 100k (EU) and 1.0-2.6 per 100k (US), for a total of 12-15k patients per year
- Prevalence: 30-40k patients in the U.S. and EU



Source: Taylor, J. Paul, Robert H. Brown, and Don W. Cleveland. "Decoding ALS: from genes to mechanism." Nature 539.7628 (2016): 197-206.

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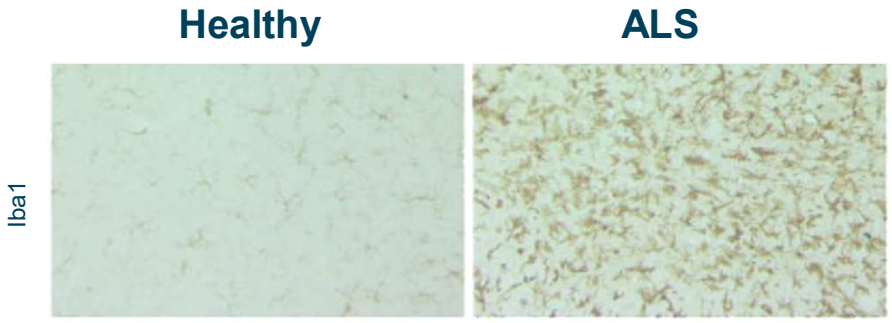
Microglia Cells Contribute to ALS

Mutations in different genes lead to abnormalities in RNA metabolism, DNA repair, protein homeostasis and endosomal trafficking, which cause glial dysfunction and motor neuron axonopathy

Characteristic **strong neuroinflammation** with reactive gliosis, lymphocyte infiltration, secretion of inflammatory cytokines and oxidative stress accumulation

Microglia cells are a major contributor to neuronal loss



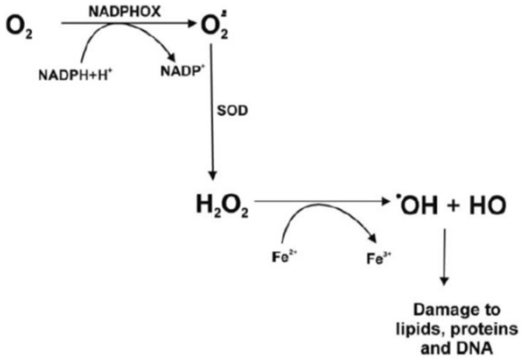
Boillee (2006), Science

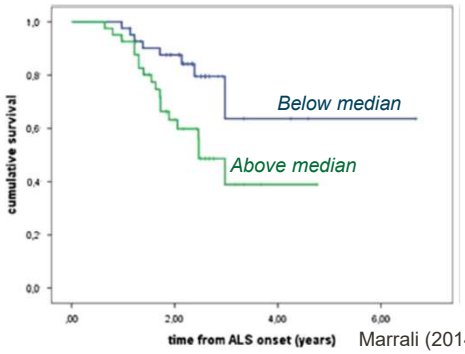
Restoring healthy non-activated microglia by transplant of genetically modified HSCs has potential to improve symptoms and prolong survival by favorably modulating neuroinflammation

Hardiman (2017) Nat Rev Dis Prim

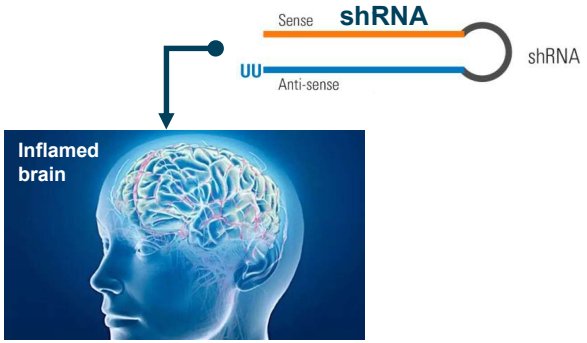
Orchard therapeutics

Depleting NOX2 with HSC GT Could Reduce Oxidative Stress





Marrali (2014) J Neurol



Oxidative stress is one mechanisms by which motor neuron death occurs in ALS

Nox2 is part of the NADPH oxidase complex, which induces oxidative stress and damage to molecules and organelles

Lower Nox2 activity correlates with increased survival in ALS patients

shRNA-mediated Nox2 depletion with HSC GT could benefit all ALS patients, in contrast to those with a specific genetic susceptibility

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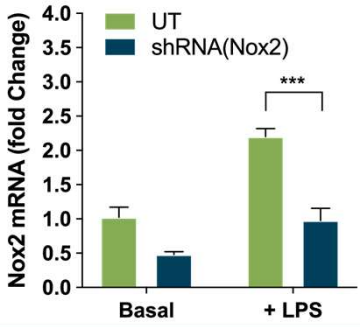
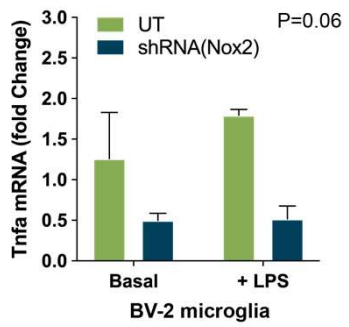
Early *In Vitro* Experiments Show Potential to Reduce Multiple Neuro-inflammation Markers

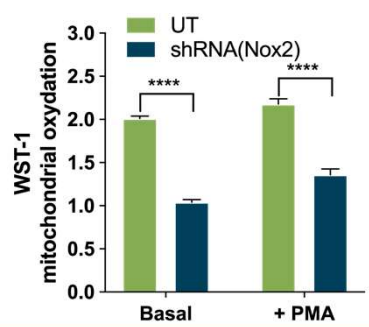
NOX 2



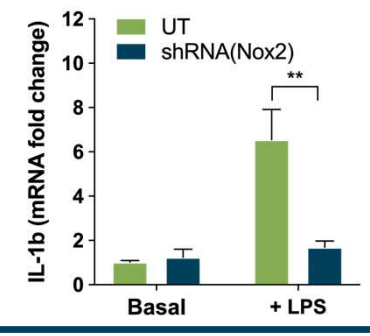
TNFA



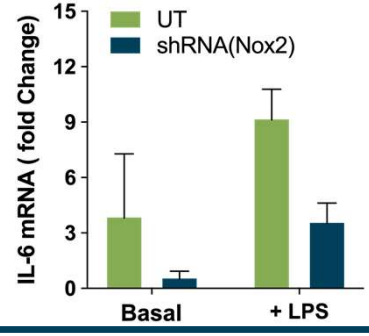
ROS (mt)



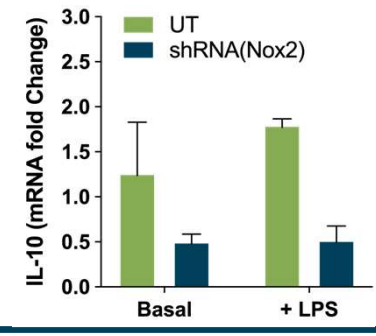
IL-1b



IL-6



IL-10



Data on file

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HSC GT Provides Compelling Opportunity in GRN-FTD and ALS

Our Approach	Opportunity	Current status	Next steps
Ex vivo HSC gene therapy restores **healthy microglia function** and **rescues neuronal phenotype** via secretion of therapeutic gene products and cross-correction	• GRN-FTD market opportunity represents **up to 2,500 patients** and growing • **Large market opportunity in ALS**	• Gene modified HSCs lead to **GRN expression and secretion** in the culture medium and **uptake by GRN negative cells for cross-correction** • Expression of an shRNA targeting NOX2 can **downregulate neuroinflammatory responses in ALS**	Murine studies in GRN-FTD and ALS designed to establish *in vivo* effect of HSC gene therapy for severe neurodegenerative conditions

Orchard therapeutics

Today's Agenda

TIME	AGENDA TOPIC	SPEAKER
9:00 – 9:15am	Delivering Now; Building for the Future	Bobby Gaspar
9:15 – 9:35am	HSC Gene Therapy for Frontotemporal Dementia & Amyotrophic Lateral Sclerosis	Alessandra Biffi
9:35 – 9:55am	HSC Gene Therapy for Crohn's Disease	Bobby Gaspar & Piv Sagoo
9:55 – 10:10am	Q&A	
10:10 – 10:30am	Scaling Manufacturing for Larger Indications	Ran Zheng & Bobby Gaspar
10:30 – 10:45am	Revisiting Delivering Now; Building for the Future	Frank Thomas
10:45 – 11:00am	Q&A	

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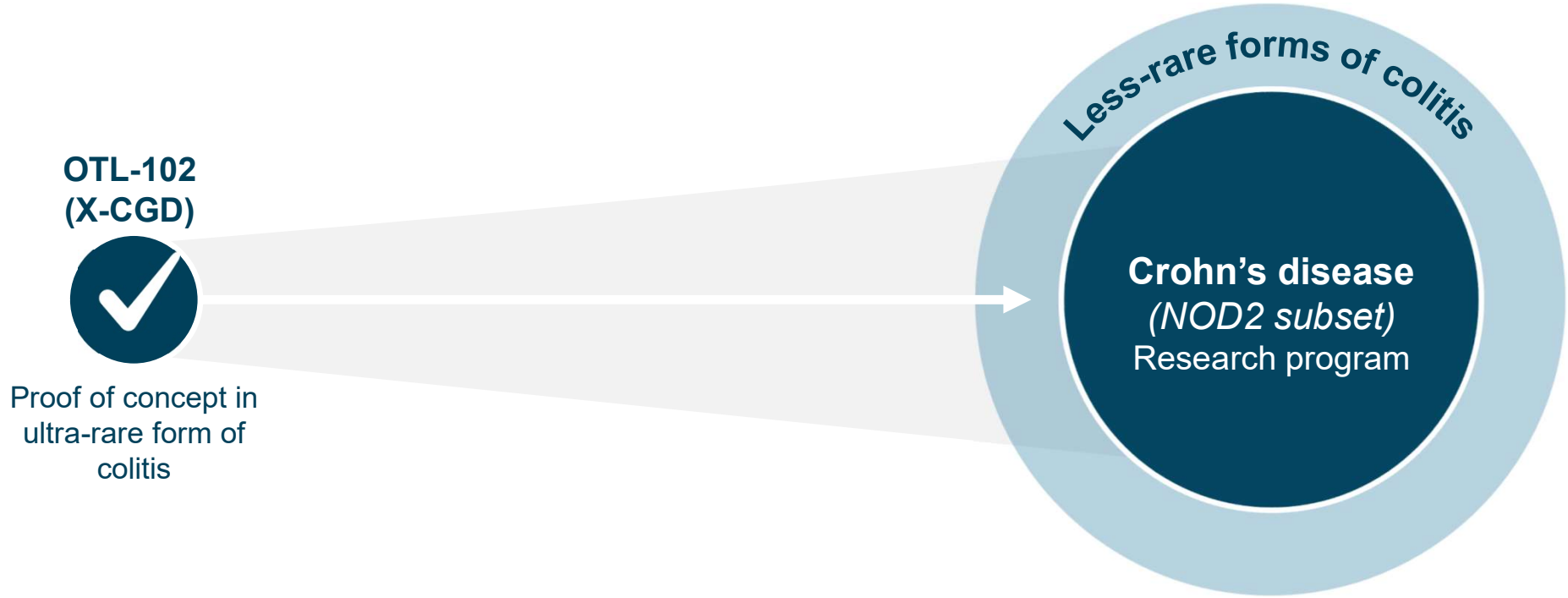
HSC Gene Therapy for *NOD2* Crohn's Disease

Bobby Gaspar, M.D., Ph.D.

Chief executive officer

Clinical Validation with OTL-102 for X-CGD Indicates Potential for Application in Crohn's Disease



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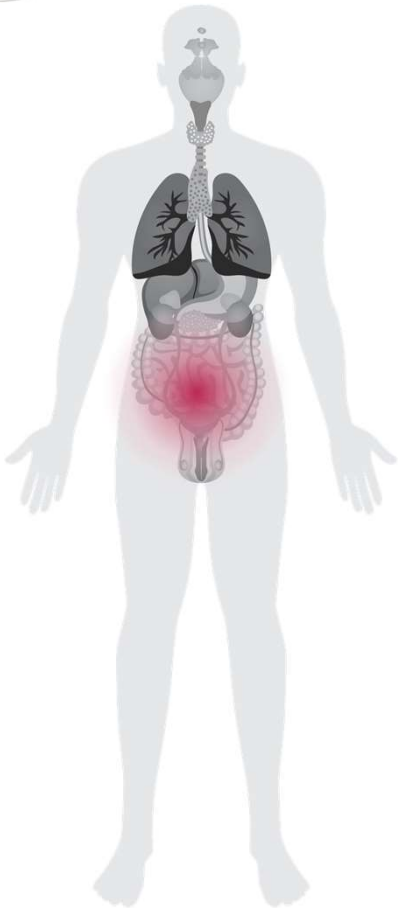
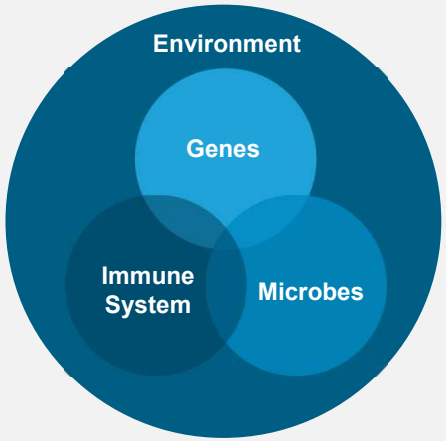
Crohn's Disease Overview



- 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

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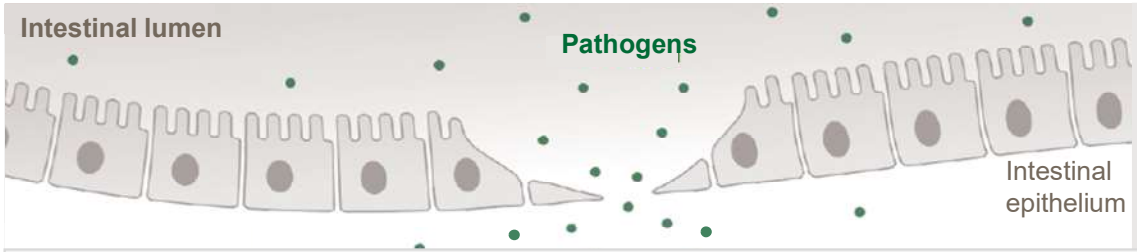
NOD2 Associated Crohn's Disease Is Driven by Impaired Intestinal Pathogen Sensing and Clearance



Phase 1:
The trigger:
gastrointestinal infection

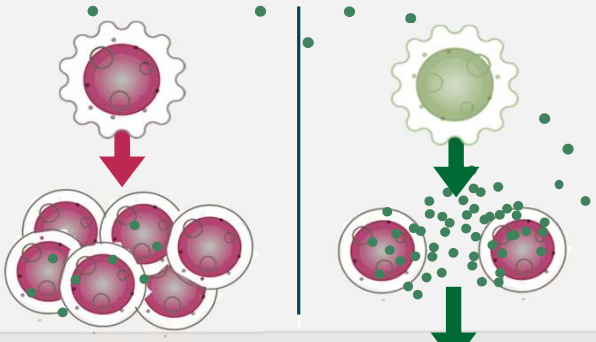
Normal Subject

Acute Inflammation

Crohn's Subject

NOD2-mediated pathogen sensing & macrophage activation

Effective proinflammatory response promotes neutrophil & monocyte recruitment

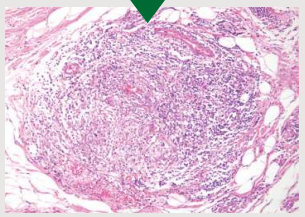


Defective pathogen detection

Limited innate immune cell recruitment & pathogen clearance

Phase 2:
NOD2- associated impaired acute inflammatory response to bacteria in tissue

Infection resolved



Lymphocytic & sclerotic granuloma formation

Phase 3:
A compensatory chronic adaptive immune response generates granulocytic lesions

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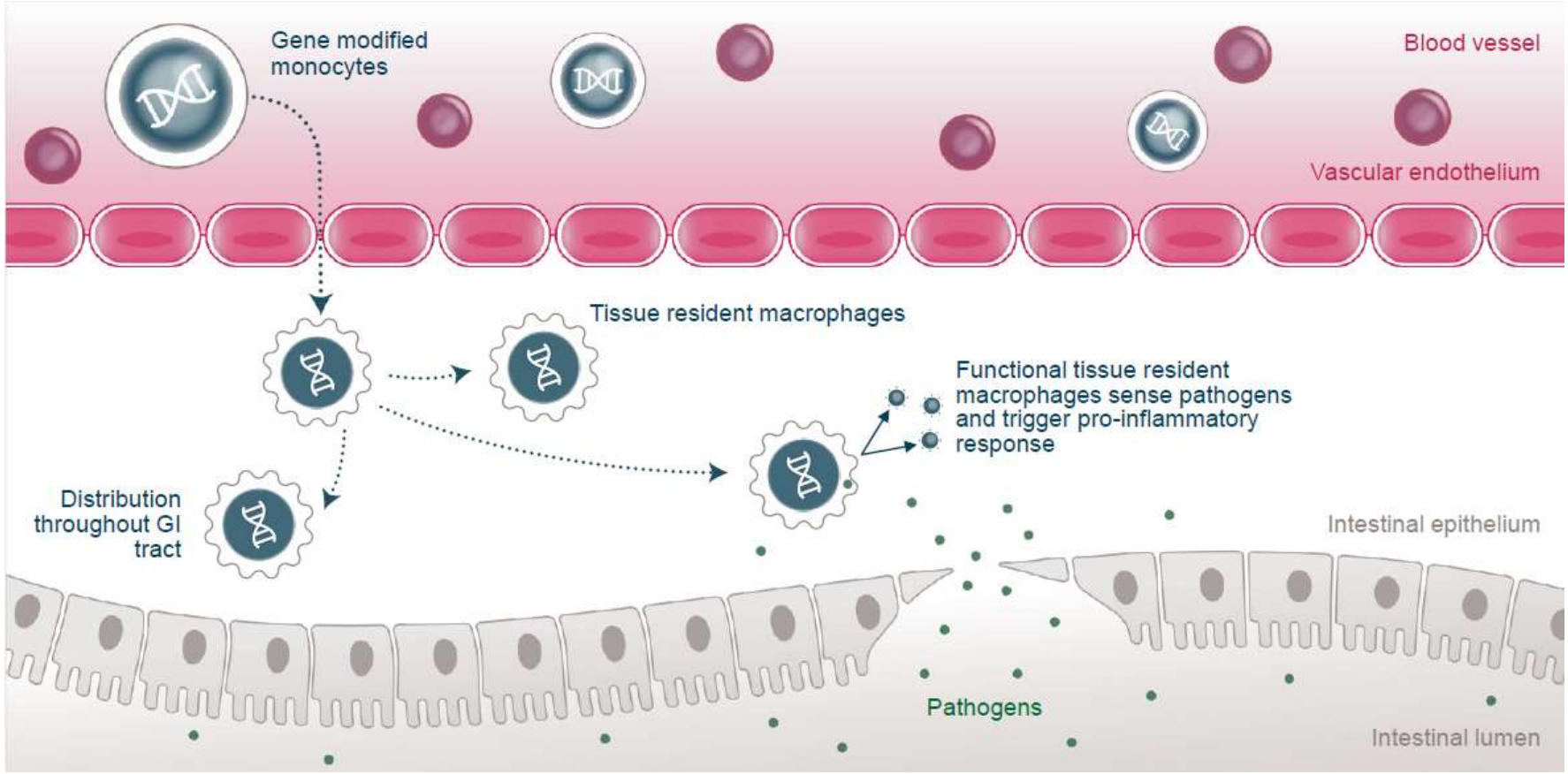
HSC Transplants Give Rise to Tissue Macrophages with the Potential to Reconstitute Functional Gut Innate Immunity



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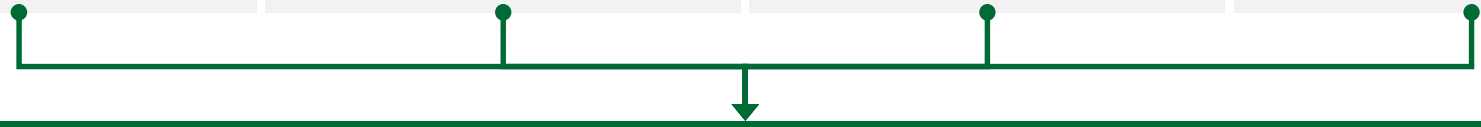
HSC GT Approach for Crohn's Disease Is Supported by Numerous Factors

Etiology	Underlying genetic association	HSCT clinical experience	High level of unmet need
Clear link between dysfunctional immune cells, which are the progeny of HSCs, and Crohn's disease	*NOD2* defect strongly associated with Crohn's disease	Previous autologous HSCT clinical trials Allogeneic HSCT corrects X-CGD and IL10 deficiency[1]	No efficacious treatments for severe, refractory disease



Potential HSC GT solution (OTL-104)

[1]https://jamanetwork.com/journals/jama/fullarticle/2475462; 2https://www.nejm.org/doi/full/10.1056/nejmoa0907206

Orchard therapeutics

NOD2-Crohn's Represents a Significant Commercial Opportunity

THE OPPORTUNITY

NOD2-Crohn's

is a significant segment of Crohn's disease

- 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]
- NOD2-CD is increasingly recognized as a monogenic form of CD

OUR UNIQUE POSITIONING

HSC gene therapy has already demonstrated potential to treat other forms of colitis

- HSC GT and HSCT correct colitis in X-CGD + other monogenic PIDs
- NOD2-CD disorder of monocytes / macrophages in GI wall
- NOD2 patients often have severe relapsing disease despite immunosuppressive therapy
- Severe CD already associated with need for autologous HSCT

[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

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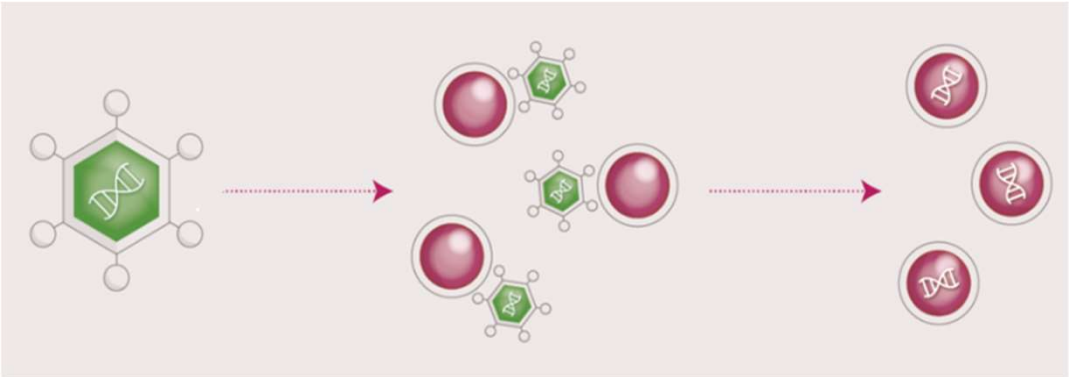
OTL-104
ex vivo HSC Gene Therapy Program for NOD2 Crohn's Disease

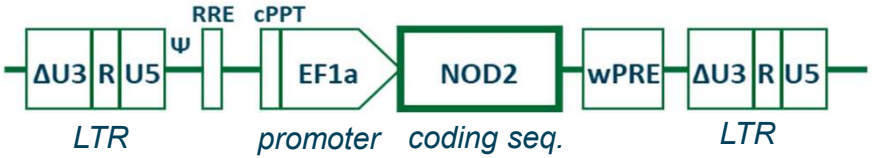
Piv Sagoo

Director, gene and cell therapy research

Gene Therapy Approach to Restore NOD2

HSC Lentiviral Gene Therapy: Insertion of functional NOD2





- Restoration of functional NOD2 expression using Orchard's lentiviral vector technology
- Sequence & promoter development to achieve
  - Cell-specific expression
  - Optimised gene expression

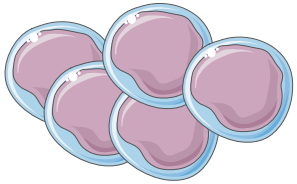
Internal Discovery Research program underway: *Preclinical PoC development*

Discovery Research		Preclinical (IND enabling studies)
• Target identification	✓	• CMC process – Vector
• Demonstration of Mode of Action	✓	• CMC process – Drug Product
• Candidate therapeutic selection	*ongoing*	• Assay Development
• *In vitro* & *In vivo* efficacy	*ongoing*	• GLP Tox & Biodistribution

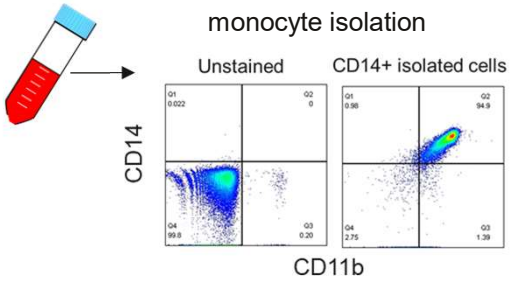
NOD2 Activation Drives Robust Inflammatory Cytokine Release by Monocytes

Experimental schema

human monocytic cell line (THP-1)

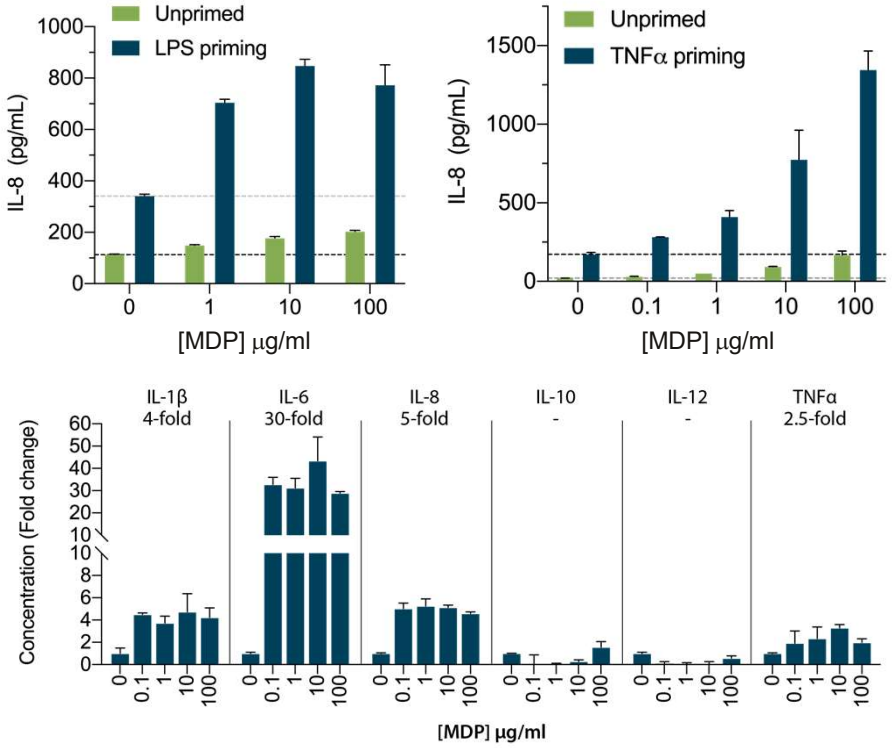


Healthy donor peripheral blood



Monocyte priming & activation of NOD2 by bacterial MDP treatment (muramyl dipeptide)

Cytokine response profiling



NOD2 activation by MDP recapitulates a classical innate proinflammatory response required to orchestrate effective neutrophil recruitment

Data on file

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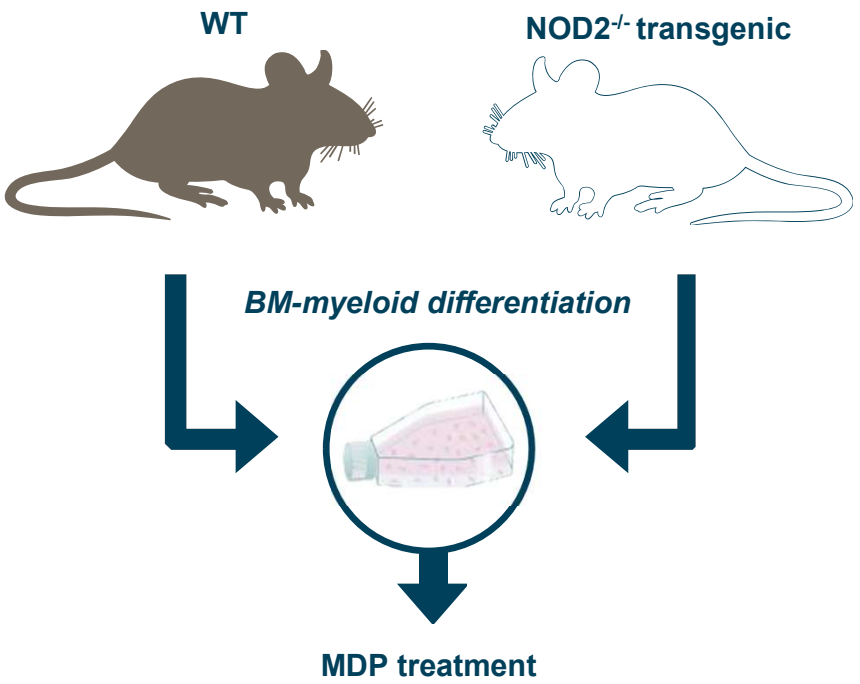
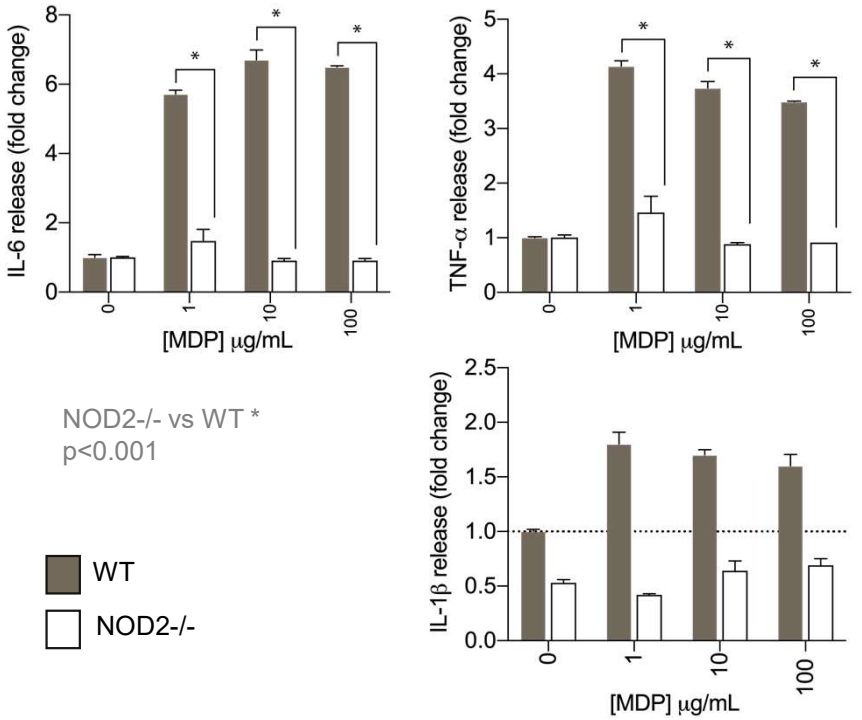
NOD2 Deficiency in Mouse Renders Monocytes Unresponsive to Bacterial MDP

Experimental schema



Cytokine response profiling



NOD2-/- monocytes and DCs lack broad proinflammatory cytokine release essential for induction and recruitment of cellular immune responses to infection

Data on file

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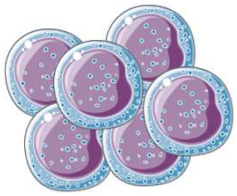
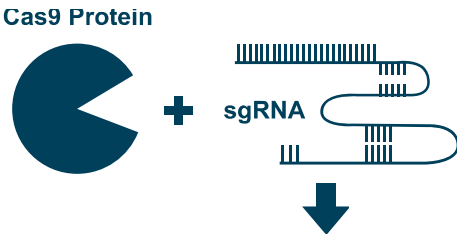
Modeling Human NOD2-deficiency Demonstrates Defective MDP Sensing and Cytokine Output

Experimental schema

Healthy donor mobilised blood isolated CD34+ HSC



CRISPR-Cas9 KO protocol developed for targeted NOD2 disruption



HSC differentiation to myeloid lineages

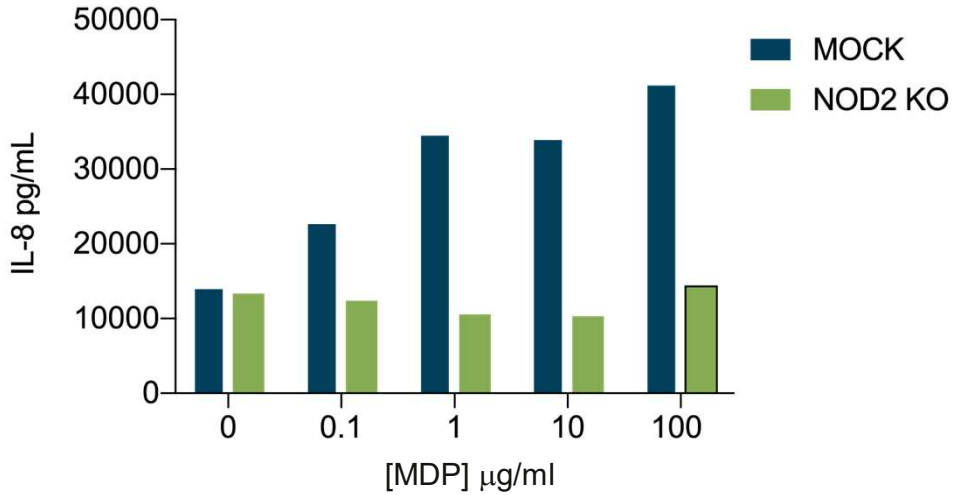
MDP treatment

Efficiency of NOD2 disruption in HSC

ICE analysis	% indels	KO score
Exon 2	78%	70%
Exon2 Multi-gRNA	87%	70%
Exon 4	42%	14%
Exon 8	38%	27%
Exon 11	23%	23%

Cytokine response profiling

Healthy subject & NOD2 disrupted CD34+ derived monocyte responses to MDP



Mock : RNP only process

NOD2 KO: Exon2 multi-gRNA (82% KO efficiency)

Data on file

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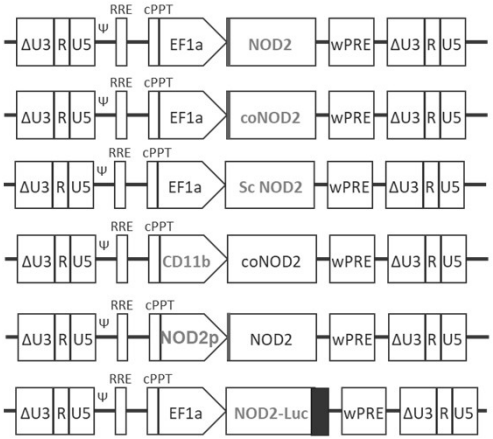
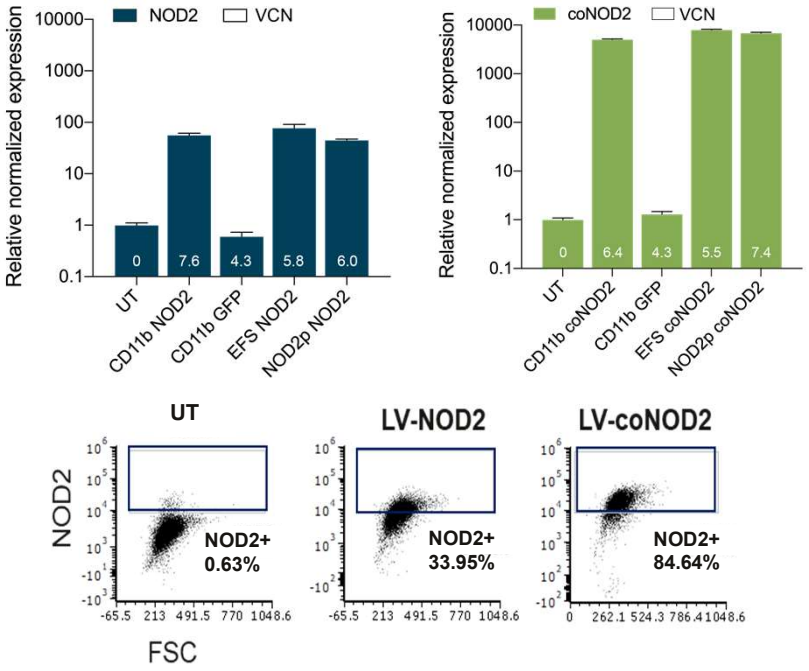
Lentiviral Vector Development for Restoration of Functional NOD2

Therapeutic vectors designed & generated for evaluation

- Minimal vector components (Orchard backbone)
- **Transgene:** Codon optimized & WT cDNA, scrambled NOD2
- **Promoter:** myeloid, constitutive, endogenous (NOD2+NFkBre)
- **Reporters:** Luciferase & fluorescent reporter transgenes



LV derived NOD2 transcript & protein expression



Data on file

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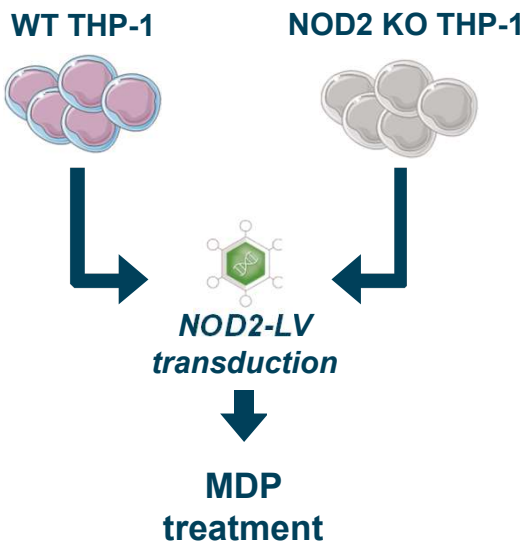
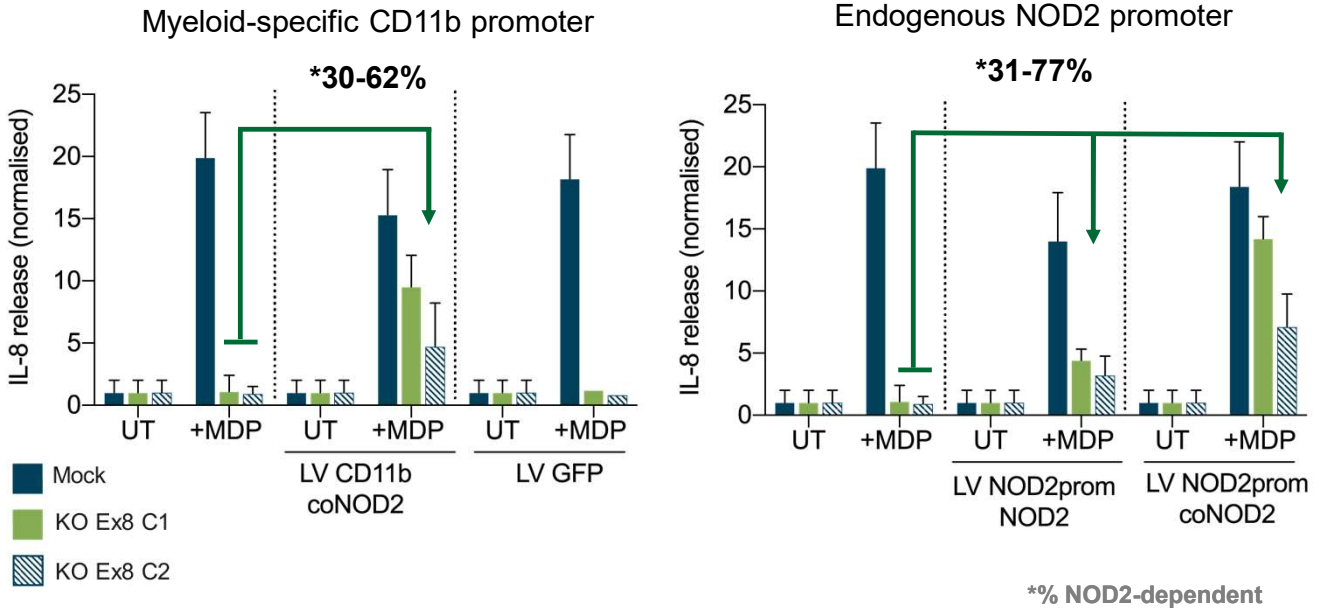
LV Transduction of NOD2 Deficient Human Monocytes Restores Inflammatory Responses to MDP

Experimental schema



Cytokine response profiling



LV transduction of THP-1 ~42-62 % transduction, mean cell VCN range 3-6 copies

***% NOD2-dependent Cytokine output restored**

- Regulation of NOD2 cellular sensitivity to MDP
- Codon optimized transgenes deliver improved NOD2 expression and function
- Ongoing profiling of other immune cellular functions on LV mediated NOD2 expression

Data on file

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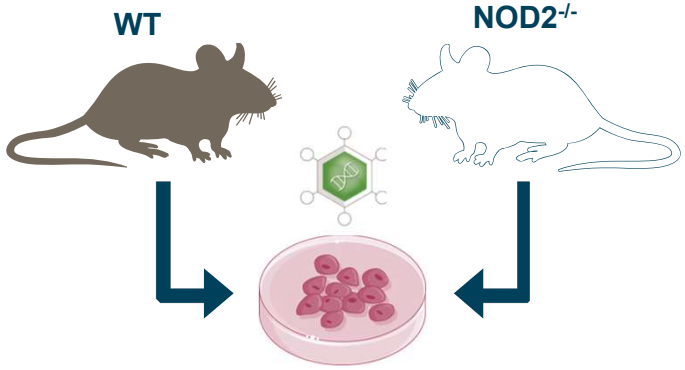
Lentiviral Transduction of NOD2 -/- Mouse HSC Restores Monocyte Inflammatory Responses to MDP

Experimental schema



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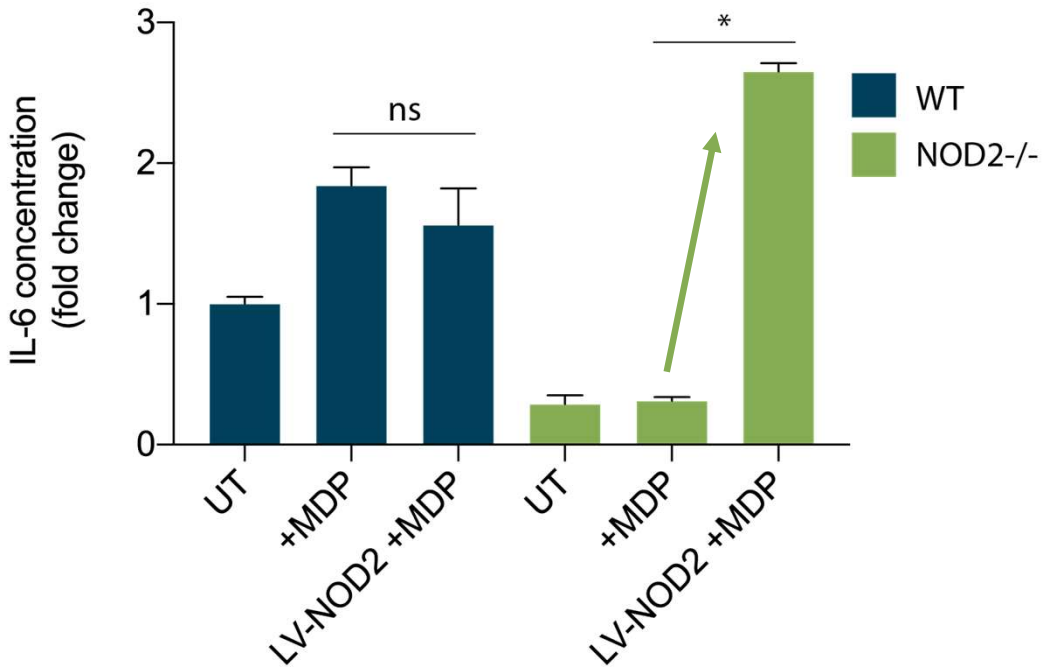

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OTL-104 for NOD2 Crohn's Disease Conclusions

- NOD2 function is an important driver of the innate cellular immune response to bacterial infection
- Evidence that defective NOD2 function results in impaired proinflammatory cytokine release
- Essential research tools established and sourced for i) target validation and ii) evaluation of therapeutic approaches
- Lentiviral vectors compatible for clinical gene modification designed and generated
- Demonstrate restoration of NOD2 protein expression in murine and human cells can rescue a defective immune response to microbial peptides

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10:30 – 10:45am	Revisiting Delivering Now; Building for the Future	Frank Thomas
10:45 – 11:00am	Q&A	

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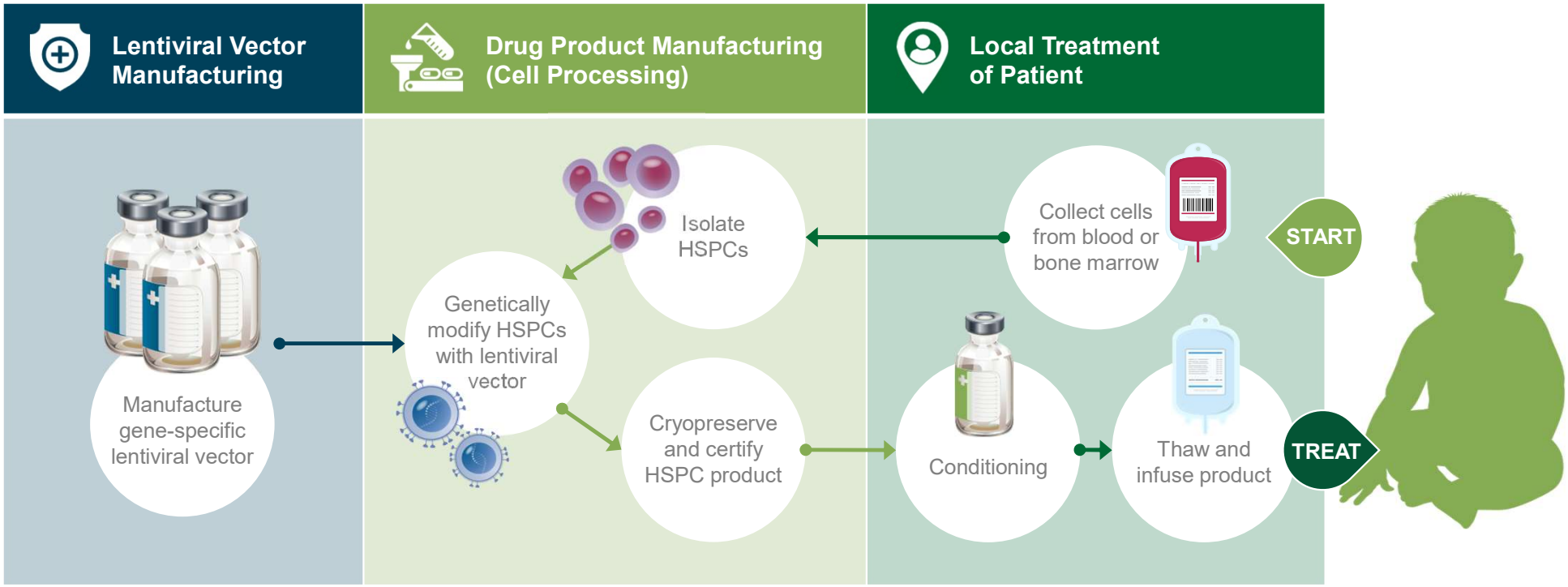
Q&A

Approaches to Transform Commercial Scale Gene Therapy

Ran Zheng
Chief technical officer

Bobby Gaspar
Chief executive officer

Overview of Current HSC Gene Therapy Manufacturing Process



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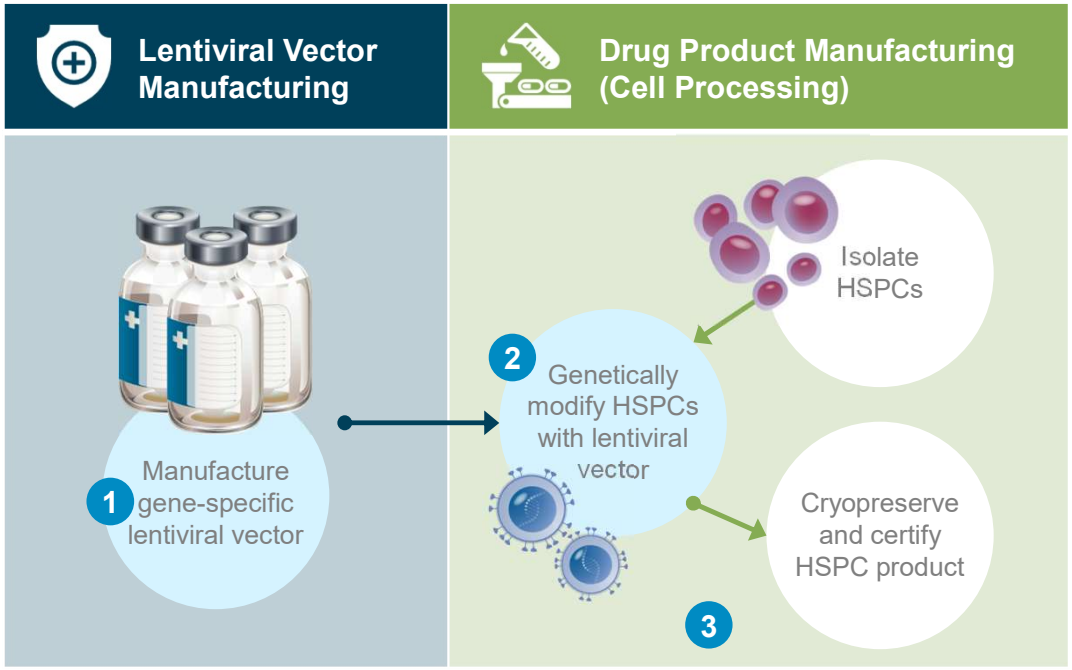
Improving the HSC Gene Therapy Manufacturing Process



		Technology innovations
1	Vector Production	Scalable suspension culture with stable producer cell line
2	Stem Cell Transduction	Transduction enhancing compounds
3	Drug product process	Fully closed, automated cell processing

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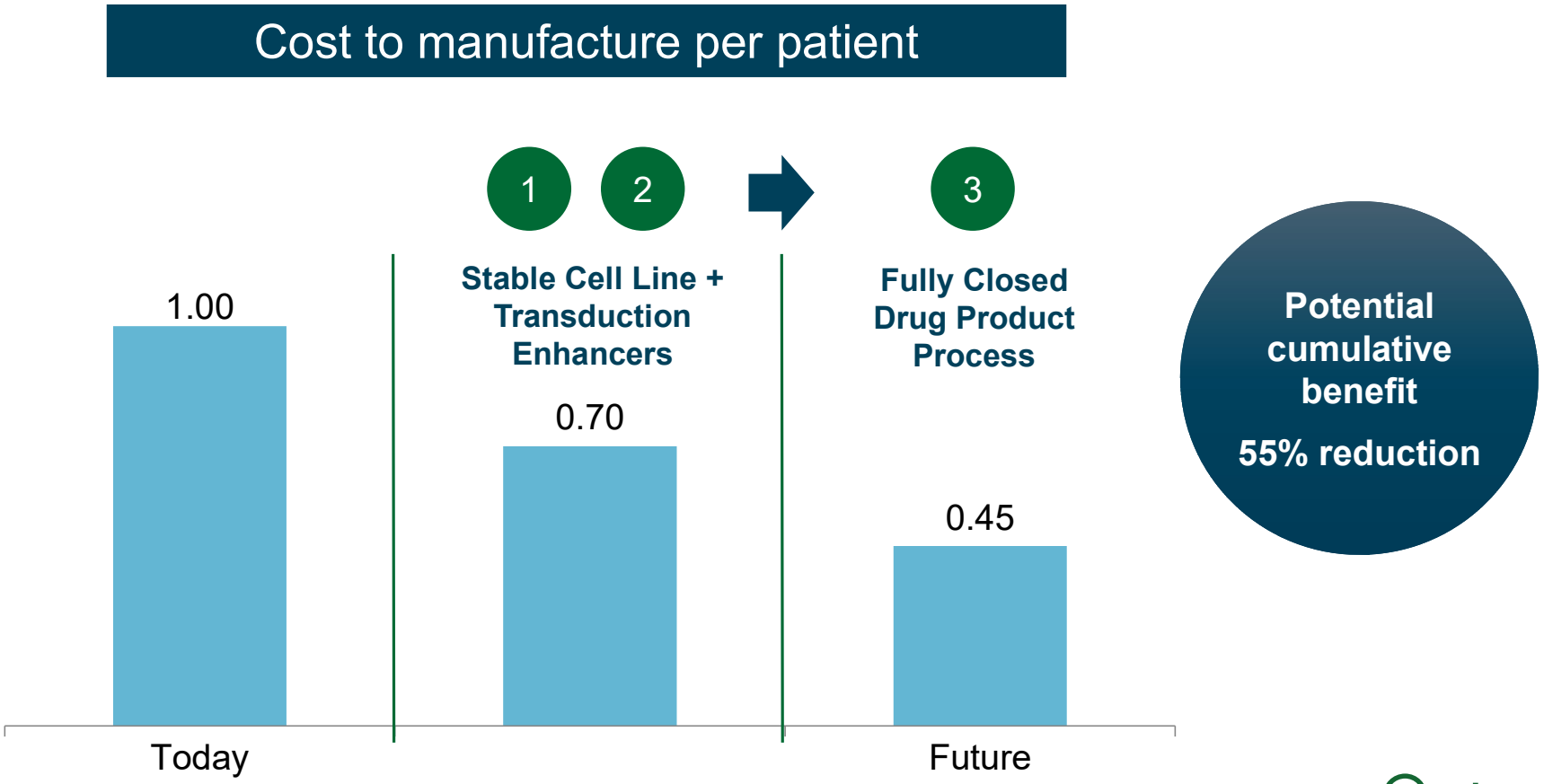
Potential to Reduce Manufacturing Costs By > 50% Through Innovation



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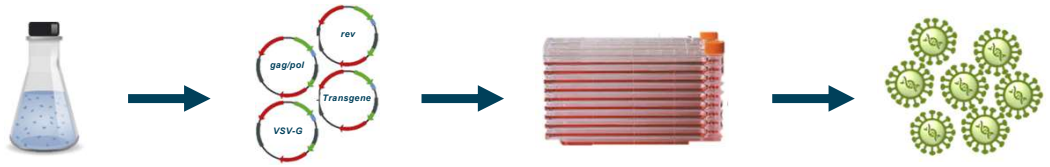
Scalable Stable Vector Producing Cell Line

SCL Technology Provides a More Scalable Manufacturing Process

1 Clinical-scale LVV production

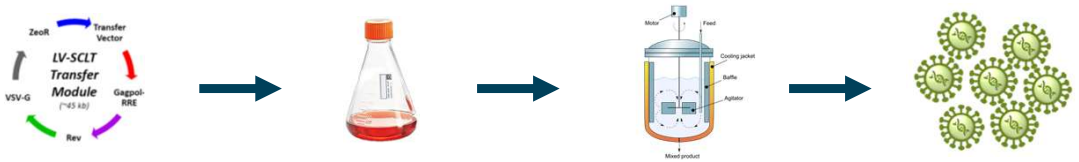
- **Simplified and more scalable** batch manufacture process
- **Obviate recurrent** need to produce GMP-grade plasmids
- Vials of stable producer cell lines are expanded & induced for viral production
- Suspension adapted host cells are easier to scale up using bioreactor production systems

Current adherent cell vector manufacture process:



Plasmid manufacture → Transient transfection → Adherent cell supernatant purified → Downstream processing

Stable cell line creation and vector manufacture process:



BAC cloning → Creation of clonal BAC cell line → Bioreactor scale-up → Downstream processing

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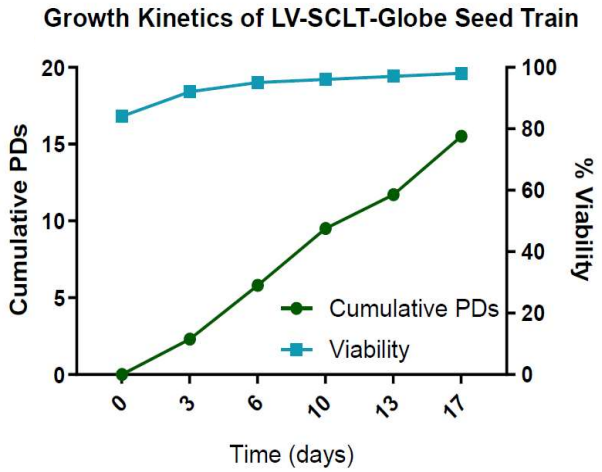
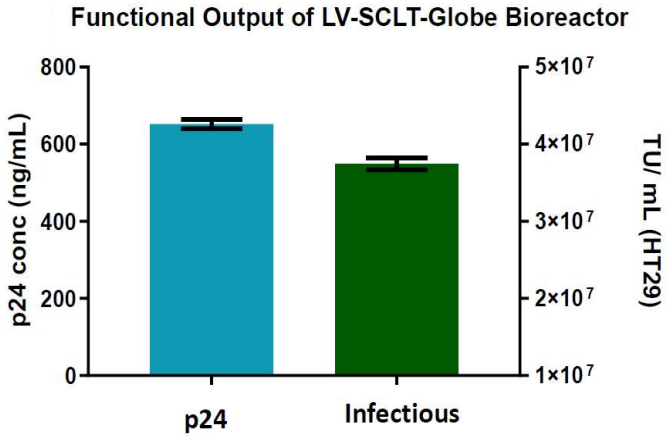
BAC Platform Bioreactor Evaluation Shows Vector Performance Comparable to Validated Current Adherent Process at Small Scale

1 Clinical-scale LVV production

Results recapitulate transient transfection (i.e. current process) anticipated titers and compare to clinical scale transient processes productivity-wise





Vector	Shake flask	3L Bioreactor
P24 ng/ mL	790	660
TU/mL HT29 ddPCR	4.7E+07	3.7E+07

See also: Chen, Yu Hua, et al. "Rapid lentiviral vector producer cell line generation using a single DNA construct." Molecular Therapy-Methods & Clinical Development 19 (2020): 47-57.

BAC= bacterial artificial chromosome
TU/mL = transducing units / mL, a measure of viral particles
PDs = population doubling time

Data on file

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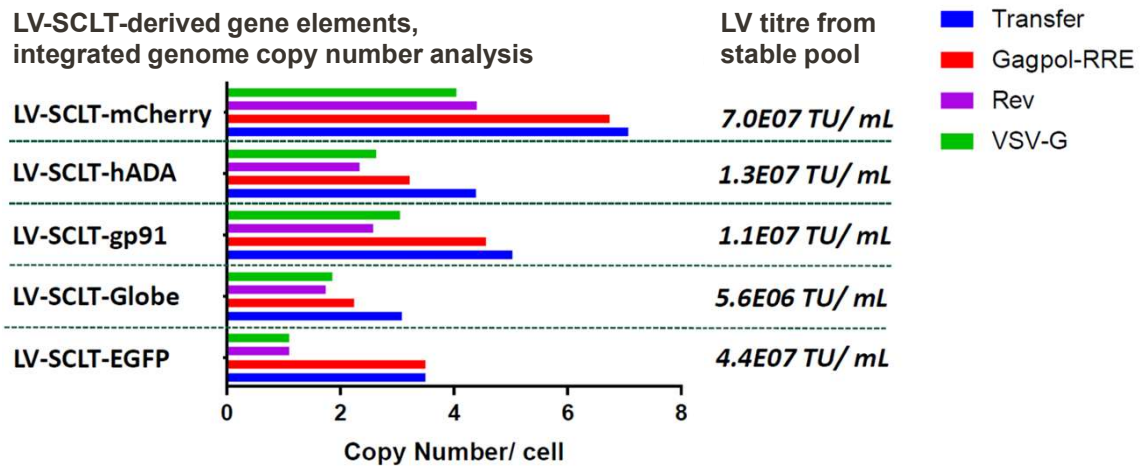
Application of BAC Platform to Orchard's LV Vectors

Successful creation of multiple new SCLs using BAC technology

1 **Clinical-scale LVV production**

- SCL pools (not clonal line); further clonal selection will identify highest expressing clones (often log-fold higher than pool average)
- Copy number of LVV components reflect BAC integration process
- LV titres show functional virus produced from all vectors
- **Optimized workflow** allows single high titre clone **selection in 3 months**

Creation of SCLs with different Orchard vectors



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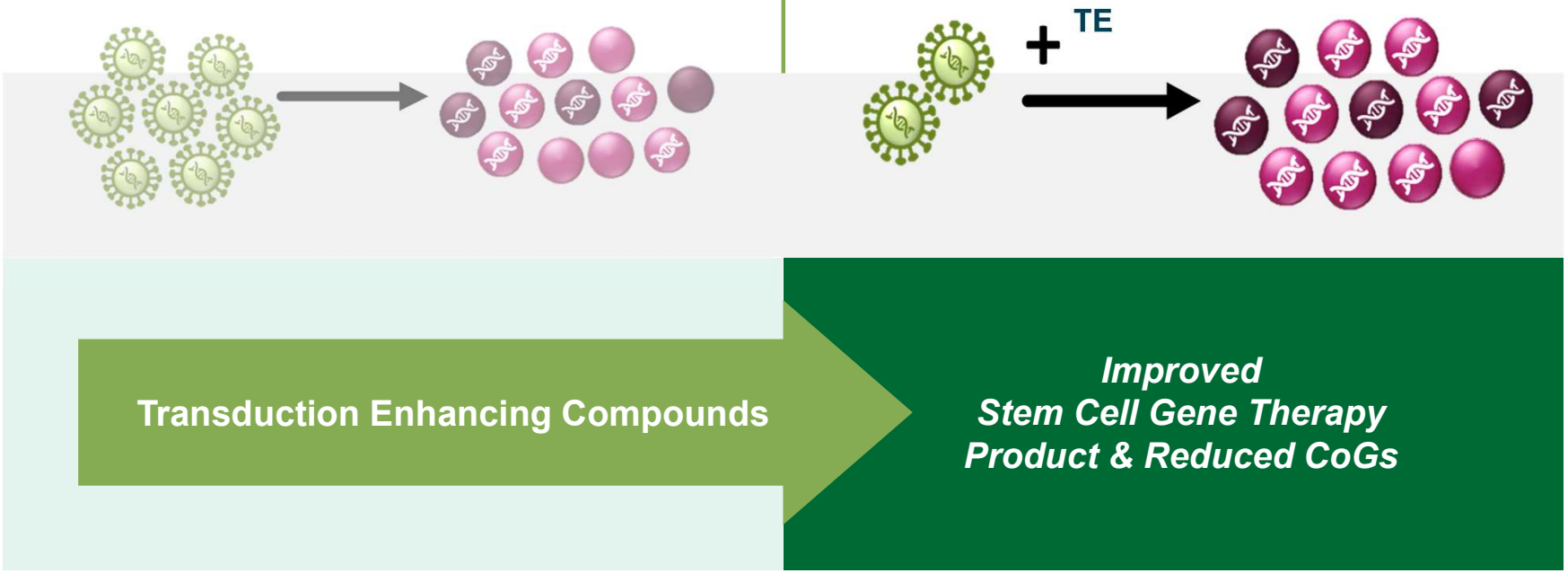
Transduction Enhancing Compounds

Addition of Transduction Enhancers (TE) Compounds During Transduction Process Can Greatly Reduce Vector Requirements

Compounds identified that can significantly reduce the multiplicities of infection (MOI) required to achieve a comparable VCN



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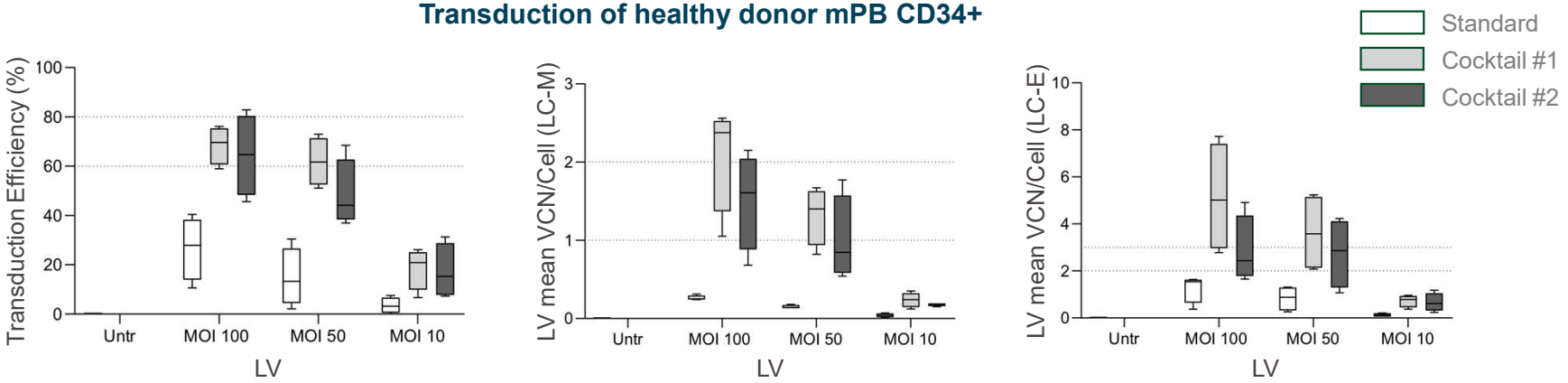
Orchard Proprietary Transduction Enhancer Combinations Permit >50% Reduction in Vector Requirements

2 Transduction Enhancing compounds

Transduction of healthy donor mPB CD34+



Transduction conditions	Mean % Transduction	Fold increase Transduction	mean VCN (range) in Eryth. LC	mean VCN (range) in Myel. LC	n=
Standard	26% (10-40)	_	1.27 (0.4-1.64)	0.26 (0.25-0.31)	4
TE1	69% (59-77)	2.4	5.13 (3.6-7.72)	2.09 (1.1-2.6)	4
TE2	67% (46-83)	2.3	3.2 (1.65-4.91)	1.51 (0.7-2.2)	4

VCN = vector copy number, TE = transduction efficiency

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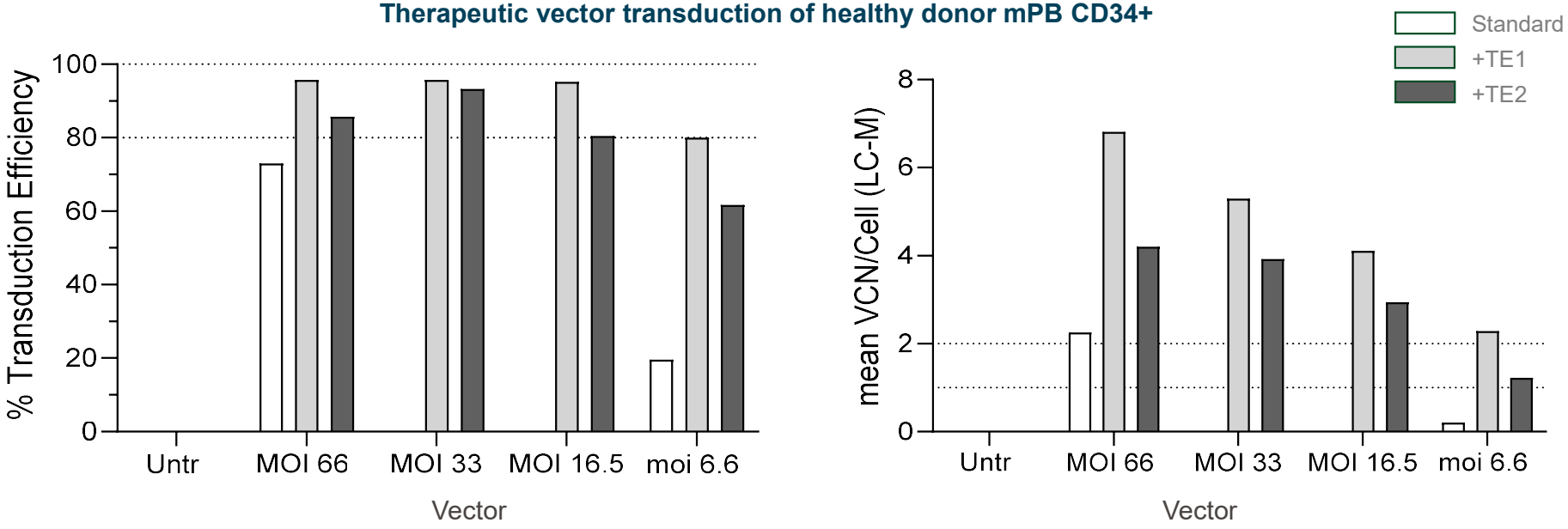
Transduction Enhancers Effective with All Therapeutic Lentiviral Vectors Tested

2 Transduction Enhancing compounds

Therapeutic vector transduction of healthy donor mPB CD34+



Target drug product values achieved using a 75-90% reduction in vector

VCN = vector copy number, TE = transduction efficiency

Data on file

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Fully Closed, Automated Drug Product Process

Automation Provides Opportunity for Increased Throughput with Reduced Labor

3 **Fully closed, automated drug product process**

Steps to be automated

- **Processing of starting material**
  - Automated processing for HSC selection and enrichment
- **Automation and closed processing**
  - For lentiviral vector addition and HSC transduction
- **Formulation and freezing**
  - Automated/closed washing after harvest and filling

Miltenyi CliniMACS Prodigy

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Technology Advancements Are Being Developed for the Next Generation of Orchard Programs

Technology improvements	Shorter term (1-3 years)	Longer term (3+ years)
1 **Scalable stable Vector producing cell line**	• Scale-up, UPS + DPS process optimization	• Further improvements and optimization • Evaluate implementation into existing clinical programs as needed
2 **Transduction enhancing compounds**	• Incorporate into all new programs	• Further improvements and optimization • Evaluate implementation into existing clinical programs as needed
3 **Fully closed, automated drug product process**	• Evaluate implementation into existing and new programs	• Further improvements and optimization as needed

Technology development Technology implementation

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Today's Agenda

TIME	AGENDA TOPIC	SPEAKER
9:00 – 9:15am	Delivering Now; Building for the Future	Bobby Gaspar
9:15 – 9:35am	HSC Gene Therapy for Frontotemporal Dementia & Amyotrophic Lateral Sclerosis	Alessandra Biffi
9:35 – 9:55am	HSC Gene Therapy for Crohn's Disease	Bobby Gaspar & Piv Sagoo
9:55 – 10:10am	Q&A	
10:10 – 10:30am	Scaling Manufacturing for Larger Indications	Ran Zheng & Bobby Gaspar
10:30 – 10:45am	Revisiting Delivering Now; Building for the Future	Frank Thomas
10:45 – 11:00am	Q&A	

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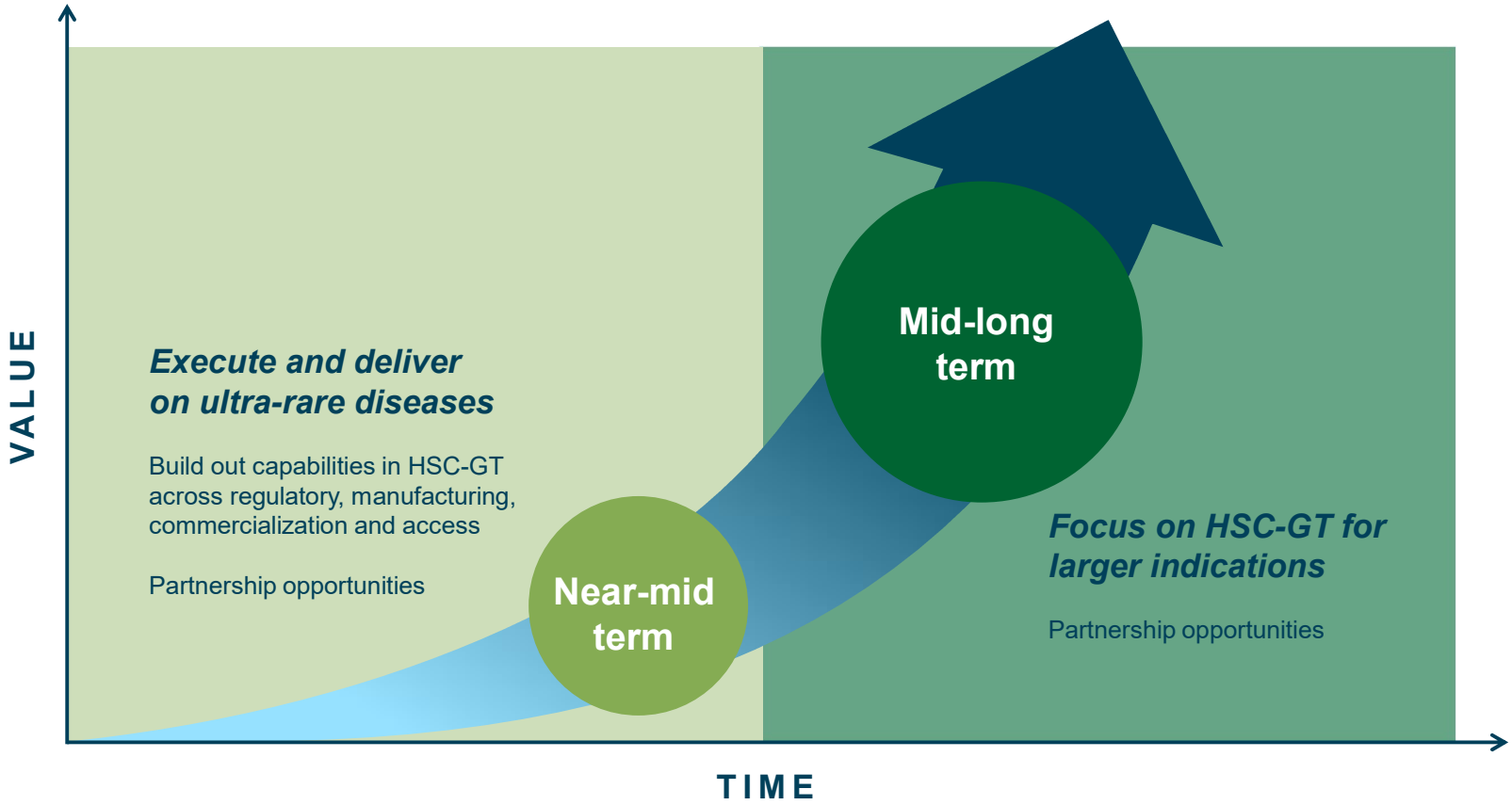
Revisiting
Delivering Now; Building for the Future

Frank Thomas

President and chief operating officer

Delivering Value Now and for the Future



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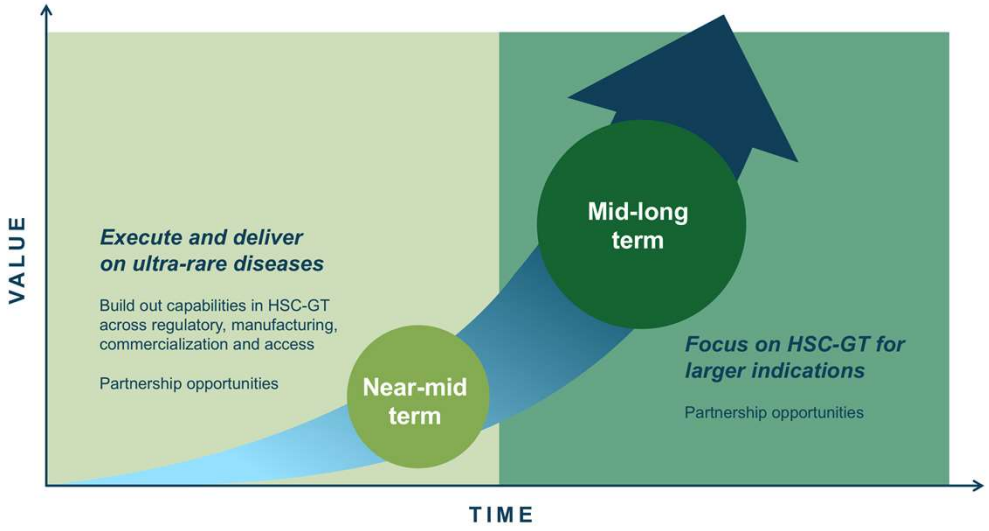
Multiple Potential Success Factors Driving Valuation



1. Improving patient ID and diagnosis rates
2. Expanding global regulatory approvals
3. Achieving reduction in manufacturing costs
4. Gaining market access and reimbursement
5. Capital efficiency and non-dilutive capital

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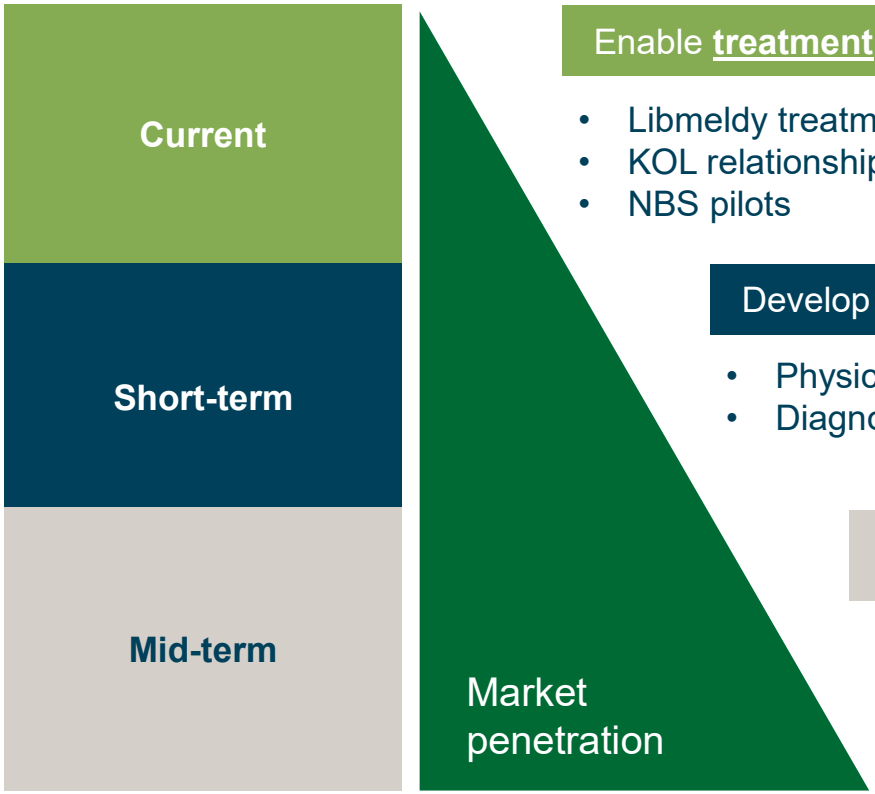
Staged Investment in EU Commercial Infrastructure for Libmeldy

Leverage this infrastructure for future launches



Enable treatment

- Libmeldy treatment centers
- KOL relationship building
- NBS pilots

Develop urgency to diagnose and refer

- Physician awareness
- Diagnostic capabilities and availability

Implement newborn screening

- NBS on the national level

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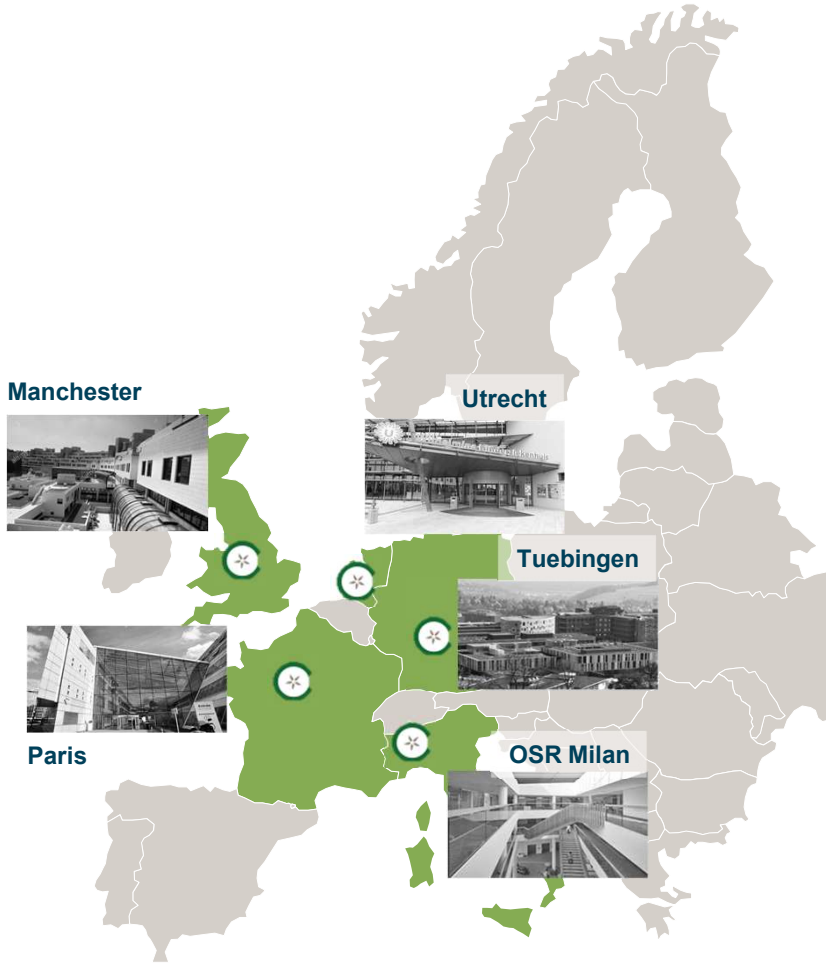
Planned Treatment Centers Preparing for EU Launch of Libmeldy in 2021

Key centers of excellence for lysosomal storage disorders and transplant identified; site qualification ongoing

- *Germany*
- *Italy*
- *France*
- *UK*
- *The Netherlands*

Serve as foundation for next wave of neurometabolic programs (MPS-I, MPS-IIIA)

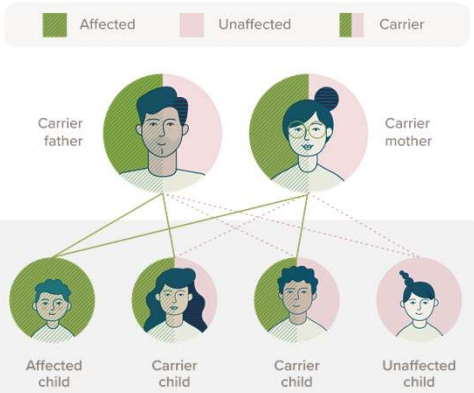


Accelerating MLD Diagnosis from EU Launch of Libmeldy

Disease awareness

Provider education,
web, media

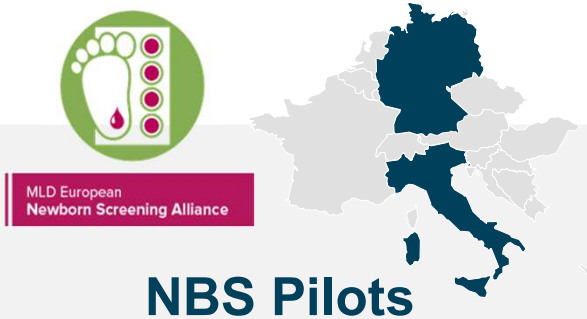
Educating physicians, caregivers and general public



Diagnostic initiatives

No-charge testing
& sibling screening

Facilitating biochemical and genetic testing



NBS Pilots

Universal NBS

Pilots underway/ready to start

Fostering a stakeholder network and generating data

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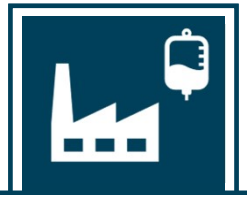
EU Commercial Supply Chain in Place for Libmeldy



Secured Manufacturing Capacity

- Supply agreement signed with AGC Biologics (formerly MolMed) for long term lentiviral vector and drug product supply
- Milan facility EMA approved
- Prior commercial supply experience with Strimvelis

Treatment Center Qualification

- Five hospitals in Europe are becoming Qualified Treatment Centers (QTC)
- Delivering approved product information and manual to QTCs

Inventory and Logistics Management

- Sufficient vector inventory to support launch
- Partnered with BeTheMatch Biotherapies to deliver Libmeldy

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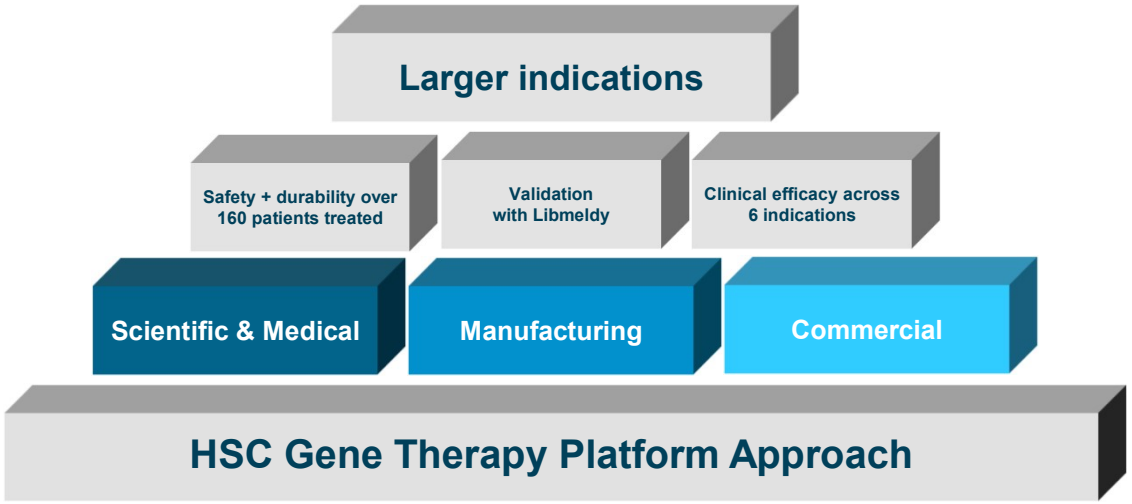
Building Competitive Strengths

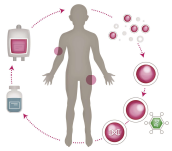
Building Competitive Strengths



Scientific & Medical

libmeldy™ atidarsagene autotemcel

Manufacturing



Commercial

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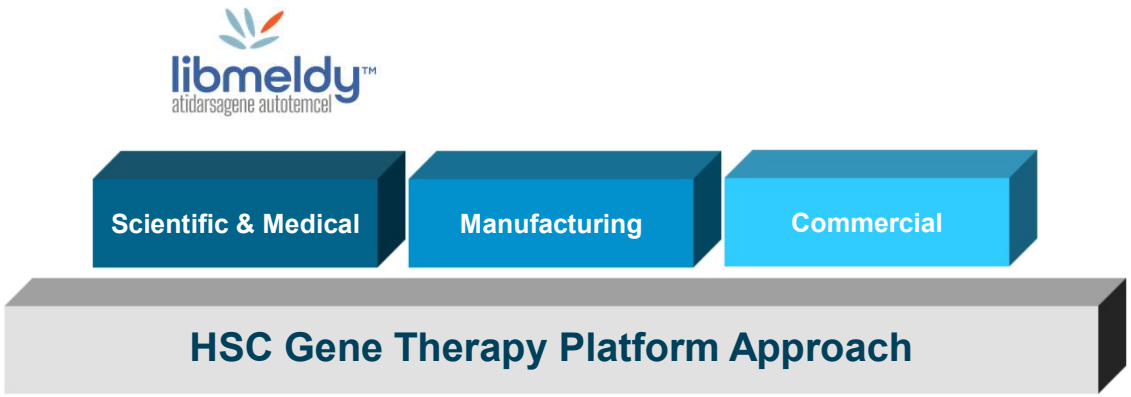
Select Indications With Strong Scientific and Medical Rationale

Building competitive strengths with our platform



Scientific & Medical

- Etiology of disease
- Genetic association
- Disease profile and unmet need

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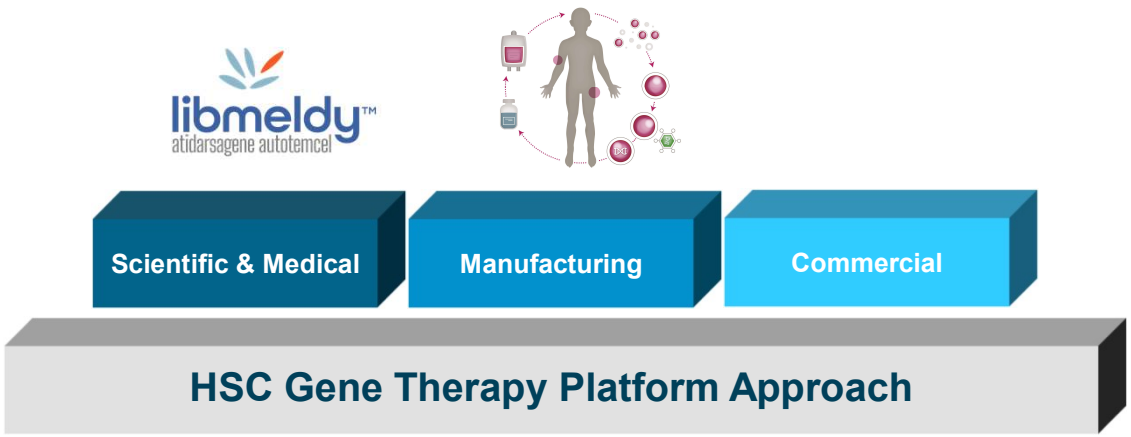
Use Innovation to Drive Efficiency and Build Capacity

Building competitive strengths with our platform



Scientific & Medical

- Etiology of disease
- Genetic association
- Disease profile and unmet need

Manufacturing

- Innovate for process efficiency
- Support capacity with partners
- Build capabilities within Orchard

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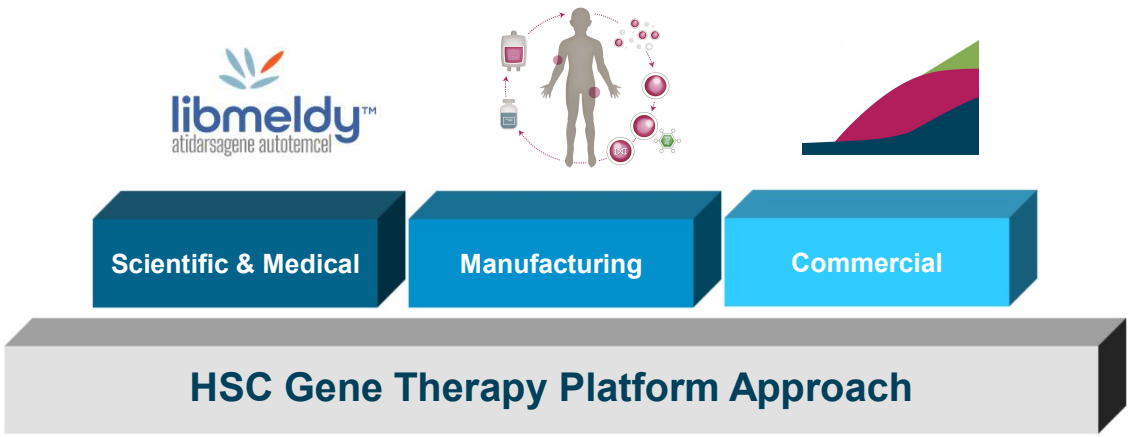
Build A Global Commercial Model That Can Support Multiple Products

Building Competitive Strengths With Our Platform Approach



Scientific & Medical

- Etiology of disease
- Genetic association
- Disease profile and unmet need

Manufacturing

- Innovate for process efficiency
- Support capacity with partners
- Build capabilities within Orchard

Commercial

- Enable treatment at centers of excellence
- Create urgency to diagnose
- Enhance patient identification

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Capital Allocation Strategy

Capital Allocation Strategy to Manage Growth and Dilution

1	**Maintain Strong Balance Sheet**	• Access equity markets following inflection points; supplement with non-dilutive capital
2	**Invest for Growth**	• Focus on highest value indications • Stage investments in additional rare disease programs • Allocate R&D capital for larger indications
3	**Leverage Partnership Opportunities**	• Consider partners for programs based on disease expertise and commercial footprint • Leverage platform as engine for new indications with partners

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New Horizons in HSC Gene Therapy

What you saw and heard today

- HSC gene therapy has the potential to treat a broad range of severe diseases
- Clinical validation in rare disorders builds confidence for larger indications
- FTD, Crohn's and ALS programs are backed by strong scientific rationale
- Prioritizing innovation in manufacturing to accelerate profitability and scale-up
- Building commercial capabilities to leverage with future products

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Q&A