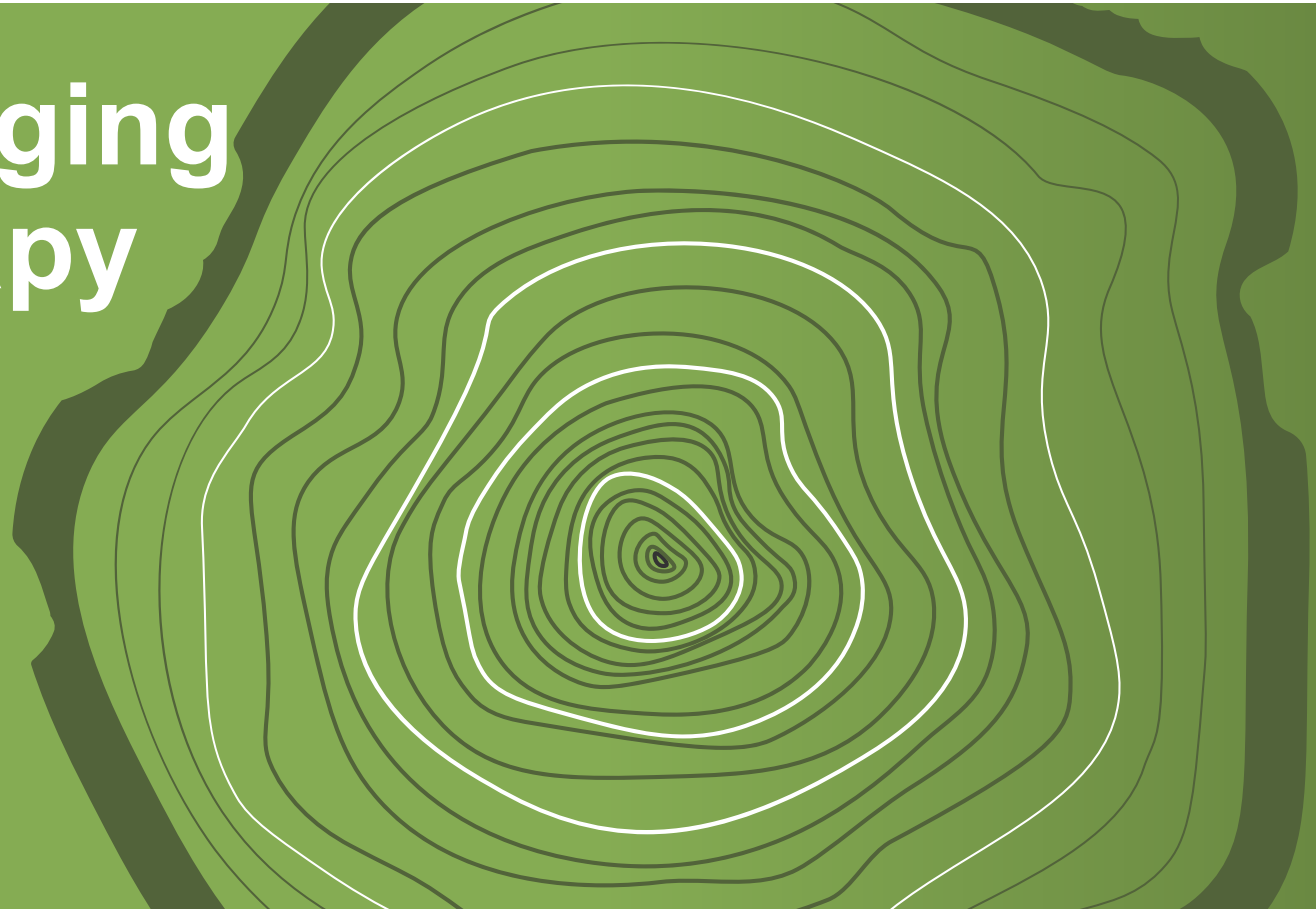
Orchard therapeutics™

Challenges of bringing a cell & gene therapy to the clinic



Piv Sagoo

Director of Translational Research

7th December 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 constitutes forward-looking statements and may include, but is not limited to, the Company’s expectations regarding its product candidates, including their safety and efficacy. The words “may,” “should,” “expects,” “intends,” “plans,” “anticipates,” “believes,” “estimates,” “predicts," 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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Unless explicitly stated otherwise, the products and formulations discussed in this presentation have not yet been proven to be either safe or effective by the U.S. Food and Drug Administration or European Medicines Agency, and any claims of safety and effectiveness can be made only after regulatory review of the data and approval of the label claims.

Orchard therapeutics

Challenges of bringing a cell & gene therapy to the clinic

1

Orchard's HSC Gene Therapy Approach

2

Clinical Translation: Specific Considerations for Gene Therapy

3

Case Study: HSC-GT for MLD Libmeldy ™

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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

Orchard's HSC Gene Therapy Approach

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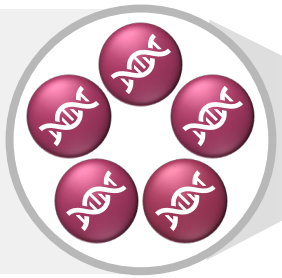
Orchard's Autologous HSC Gene Therapy Platform Approach

Administration:
Genetically-modified cells (drug product) are given back to the patient intravenously

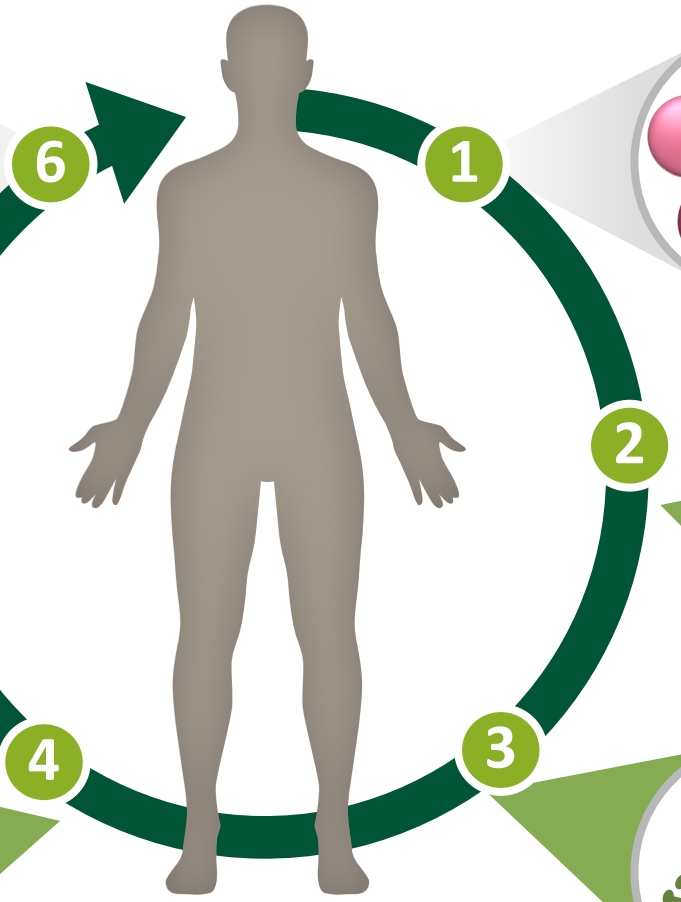


Conditioning:
The patient is given conditioning to permit genetically-modified cells engraftment

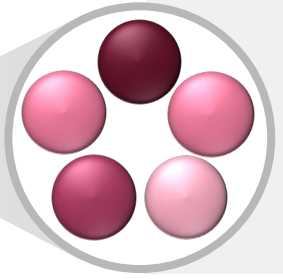
Patient returns to center

Cells shipped back to center

Cryopreserved genetically modified HSPCs:
Drug product is certified that meets manufacturing standards and sterility



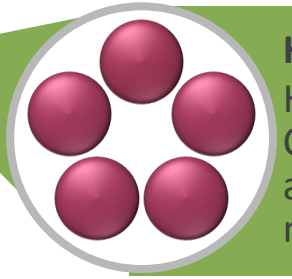
Blood cell collection:
Blood hematopoietic stem and progenitor cells (HSPCs) are taken from the patient via leukapheresis or bone marrow extraction after PBSC mobilization



Patient can return home

Cells travel to manufacturing site

HSC selection & purification
HSPCs, identified by the $CD34^+$ cell surface marker, are selected and purified by magnetic bead selection



Transduction:
HSPCs are genetically modified *ex vivo* via exposure to a lentiviral vector carrying a functional copy of the gene of interest

Occurs at treatment center

Occurs at manufacturing location

Viral vector carrying a copy of the therapeutic gene

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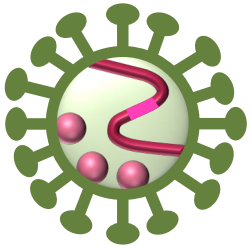
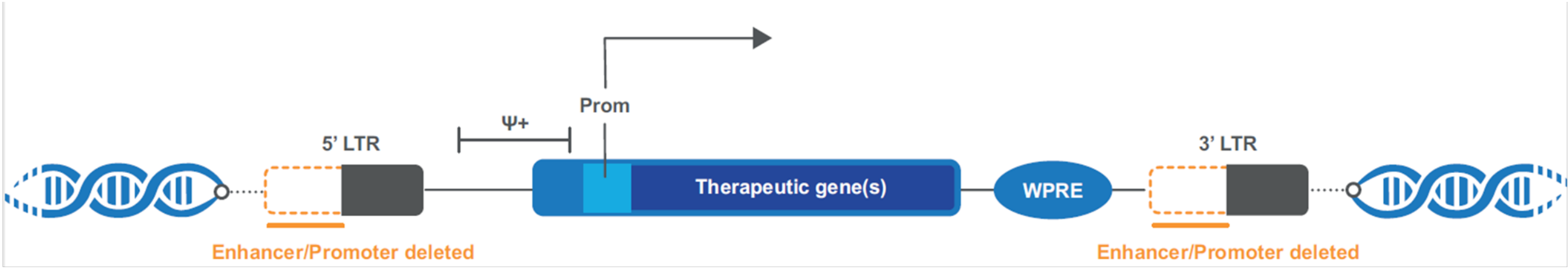
Lentiviral Vector Mediated Gene Therapy: *ex-vivo* Transduction of HSCs





- Self-Inactivating (SIN) lentiviral vectors
- Deletion of viral promoters/enhancer sequences and the use of internal promoters with minimal enhancer and transactivation potential

RNA, ribonucleic acid

Adapted from: Gene Therapy Net.com. Retroviral vectors. Available at: https://www.genetherapynet.com/viral-vector/retroviruses.html. Accessed March 8, 2021.

Cartier N, *et al. Acta Neuropathol* 2014;128:363–380.

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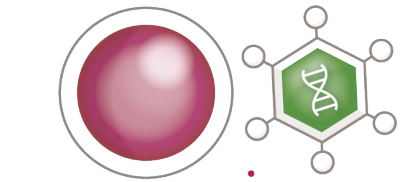
HSC Gene Therapy offers a highly differentiated approach allowing several therapeutic areas to be addressed

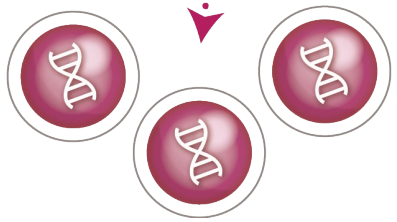


One-time administration

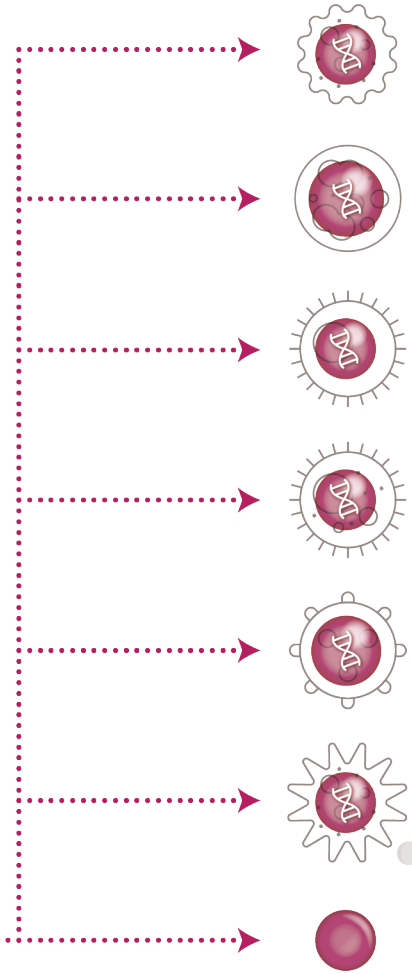
Integration

Potential for permanent disease correction

Self-renewal



Differentiates into multiple cell types



Monocyte / Macrophage / Microglia

Granulocyte

T cells

B cells

NK cells

Megakaryocyte

Erythrocyte

Central Nervous System

- MLD
- MPS-I
- MPS-IIIA

Immune System

- ADA-SCID
- WAS
- X-CGD

Blood Cell & Platelet Lineage

- WAS
- TDT

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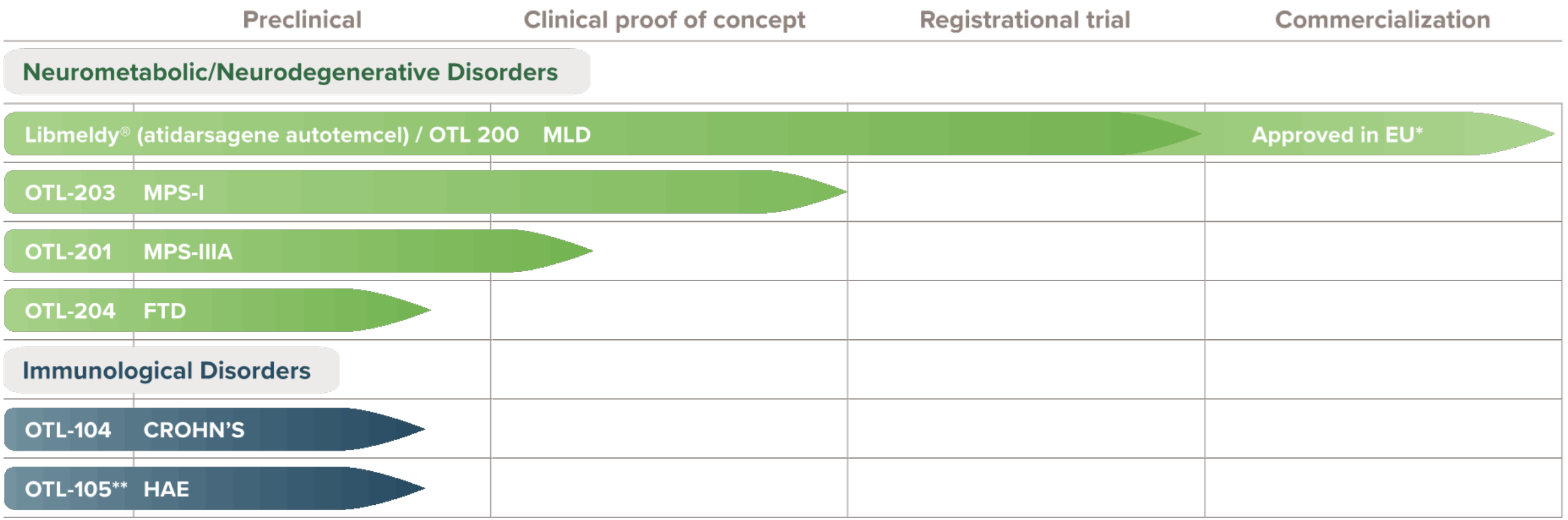
Focusing Where HSC Gene Therapy is Scientifically and Clinically Differentiated



*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.

- 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 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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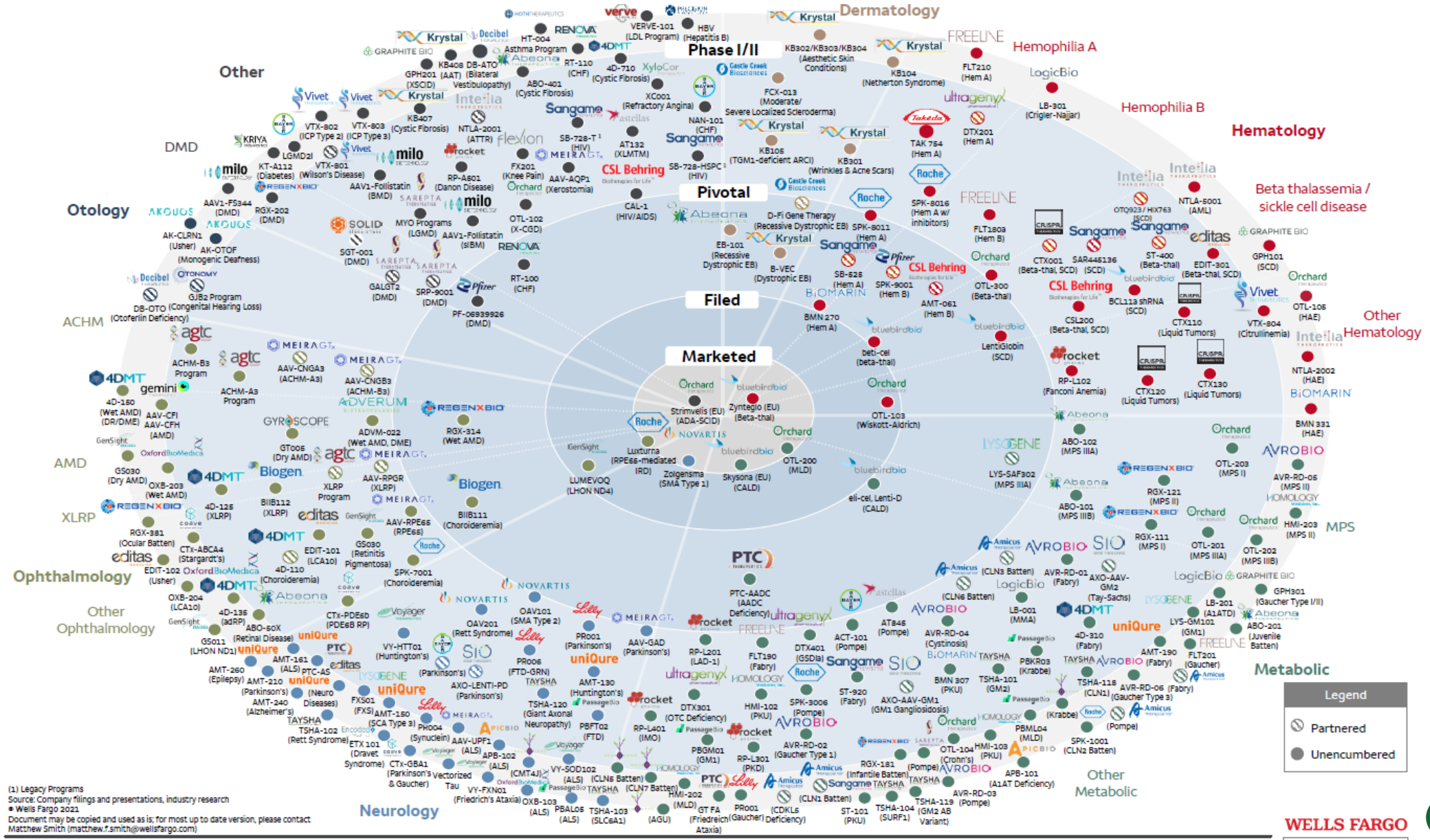
Gene Therapy Landscape 2022



(1) Legacy Programs
Source: Company filings and presentations, industry research
● Wells Fargo 2021
Document may be copied and used as is; for most up to date version, please contact Matthew Smith (matthew.f.smith@wellsfargo.com)

WELLS FARGO
Investment Banking

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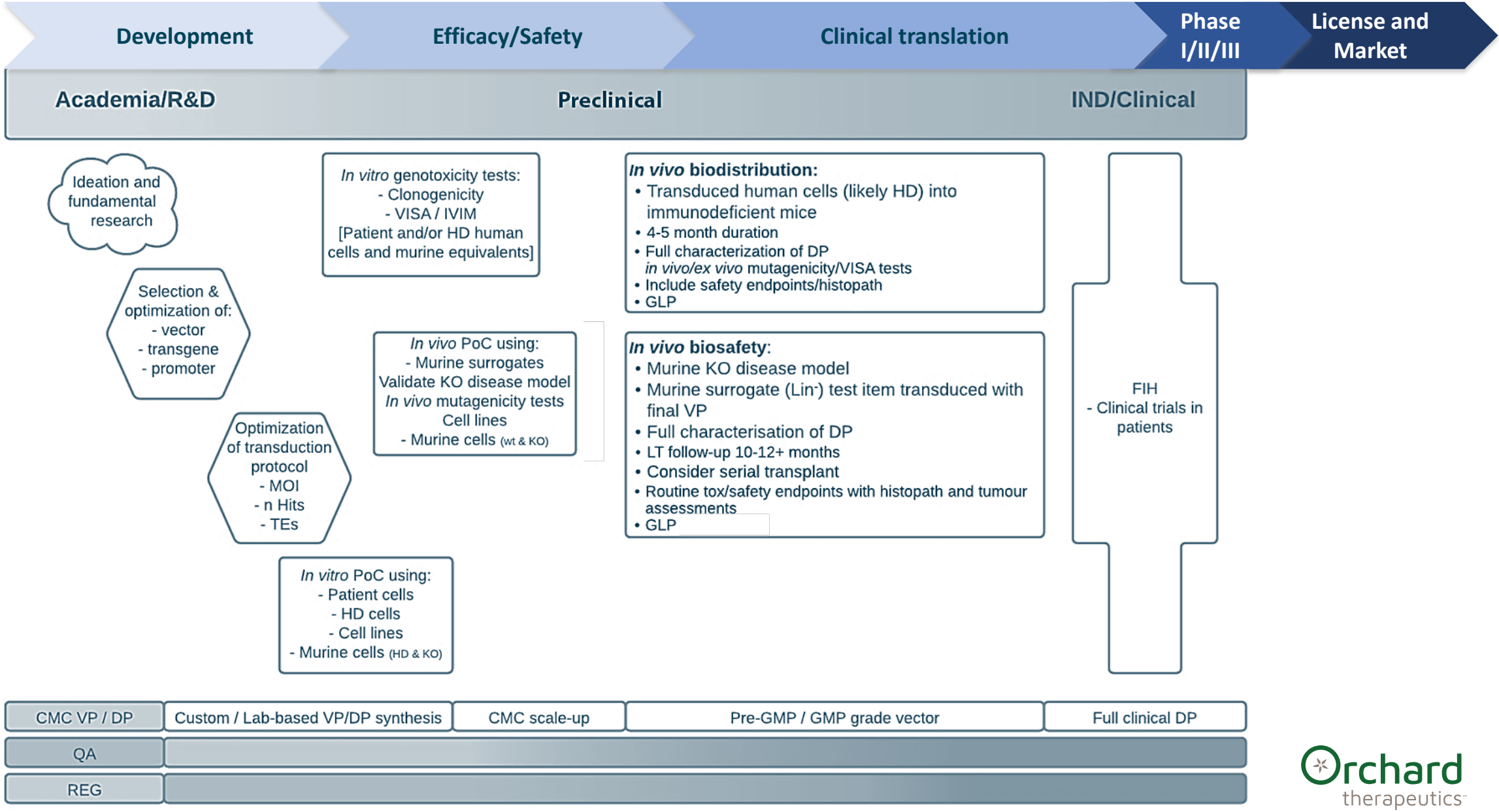
The path to making genetic medicines



Orchard therapeutics

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Navigating primary hurdles in Gene Therapy Clinical Development

- C&GT or ATMPs (EU) are a novel and varied group of therapeutics developed to treat specific conditions for which there are limited or no effective treatments
- The novelty and complexity of this product modality demands a **regulatory risk-based approach** to define a sound development approach

Aim:	To demonstrate the safety & efficacy (POC) of a CG&T product at reversing or preventing disease induction/ progression
Requirement:	Detail the development, manufacturing & quality control, as well as non-clinical and clinical development of a C&GT product

IND/CTA Applications: Identify and mitigate risks for first-in-human and early clinical trials

- Regulatory authorities pay closer attention to the design and conduct of pre-clinical studies in C&GT space
- Aim to demonstrate safety & efficacy in high quality POC studies

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IND/CTA Application: Identifying & mitigating risks for first-in-human & early clinical trials with investigational medicinal products (IMPs)

Quality	Non-clinical Aspects	Dosing FIH & early CTs	Planning FIH & CTs
Strength & potency	Relevance of animal model	Dosing for Heathy volunteers	Study Design & Endpoints
Material qualification	Nature of the Target	Dosing for patients	Selection of subjects
Reliability of small doses	Pharmacodynamic POC	Dose escalation	Assessments & interventions
	Pharmaco & toxicokinetics	Maximum exposure & Dose	Precautions & considerations for cohorts
	Safety pharmacology	Single to Multiple dosing	Stopping Rules/ AE monitoring
	Toxicology	ROA	Site, facilities, personnel

Identifying & mitigating risks for first-in-human & early clinical trials with advanced therapeutic medicinal products (ATMPs/ C&GT)

Quality	Non-clinical Aspects	Dosing FIH & early CTs	Planning FIH & CTs
Strength & potency	Relevance of animal model	~~Dosing for Heathy volunteers~~	**Study Design & Endpoints**
Material qualification	Nature of the Target	**Dosing for patients**	**Selection of subjects**
Reliability of small doses	**Pharmacodynamic POC**	**Dose escalation**	Assessments & interventions
	Pharmaco & toxicokinetics	**Maximum exposure & Dose**	Precautions & considerations for cohorts
	Safety pharmacology	Single to Multiple dosing	Stopping Rules/ AE monitoring
	Toxicology	ROA	Site, facilities, personnel
• Lentiviral Vector (DS) • Therapeutic Transgene • HSC Cell DP	• Expression of correct transgene product & intended biological effect in target organ	• Rationale for dosing for permanent correction • Expression or integration of transgene • Germline transmission	• Exploratory trials > pivotal trials • Multistep therapy considerations > conditioning regimens

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Guidelines relevant for safety evaluation of C&GT products before FIH

- EMA Guideline on human cell-based medicinal products 2008 (EMEA/CHMP/410869/2006)
- EMA Scientific Guidance - Guideline on the non-clinical studies required before first clinical use of GT medicinal products 2008 (EMEA/CHMP/GTWP/125459/2006)
- Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (EMA/CAT/GTWP/671639/2008 Rev. 1) - **MAA**
- **Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials** (EMA/CAT/852602/2018) – **CTA**
- FDA guidance for Industry - Preclinical assessment of investigational cellular and gene therapy products (2013)
- **FDA Guidance for Industry - Human GT for rare diseases. (2020)**
- Draft ICH guideline S12 on nonclinical biodistribution considerations for gene therapy products. (2021)

Regulatory strategies should be built on solid scientific data that also addresses general regulatory recommendations to enable a benefit : risk analysis aligned with the particularities of each CGT product

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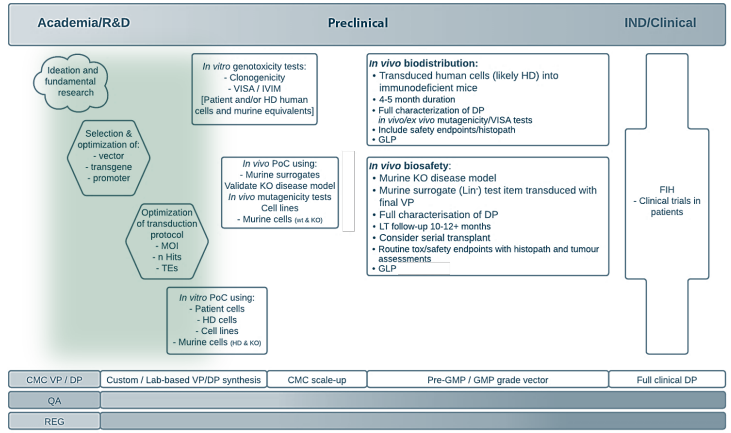
Seeking Early Development Advice FDA/EU/ MHRA



Meeting	FDA INTERACT meeting	EMA Innovation Task Force (ITF) / UK MHRA Innovation office
Purpose	Advice regarding CMC & pharm/tox development plan of novel products with unknown safety profiles	Regulatory advice for development of medicines where new technology or materials are being used for the first time, or where products like GT, CT or nanomedicines are being developed
Points which may be addressed	Robustness of POC data and acceptability of plan for tox studies to support FIH • **Criteria for therapeutic vector selection based on *in vitro* POC data** • **Vector and DP materials & quality profile for the pivotal tox studies**	
What is needed	POC package readiness • Justification of MoA evidence *in vitro* and link to disease physiopathology • Justification for the lack of suitable animal/ large animal model Non-clinical and CMC development plan, including DP characteristics & quality profile	

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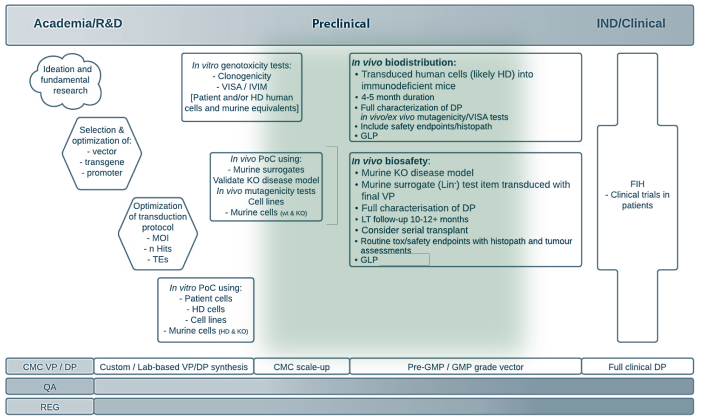
Seeking FDA/MHRA formal advice (preIND/CTA)



Meeting	FDA PRE-IND meeting	UK MHRA / EU Scientific Advice
Purpose	• Confirm agreement on design of animal studies needed to initiate human testing • Discuss the scope and design of FIH POC testing	Non-binding advice on • Suitability of the proposed pharmaceutical and nonclinical package to support initiation of FIH PoC study in patients • Acceptability of design, endpoints and other outlines for the FIH POC study
Points which may be addressed	• **Acceptability of pharmaceutical development plan** • **Acceptability of non-clinical package** intended to support the initiation of the clinical development • **Acceptability of proposed FIH POC study design**, target population, endpoints, safety monitoring, other associated clinical procedures and risks (BM harvesting/ mobilisation/ conditioning)	
What is needed	Non-clinical and CMC development plan Non-clinical package including summary of POC data and preliminary tox data FIH study synopsis developed based on KOL input Country/PI considered for the clinical study to decide Agency to be met	

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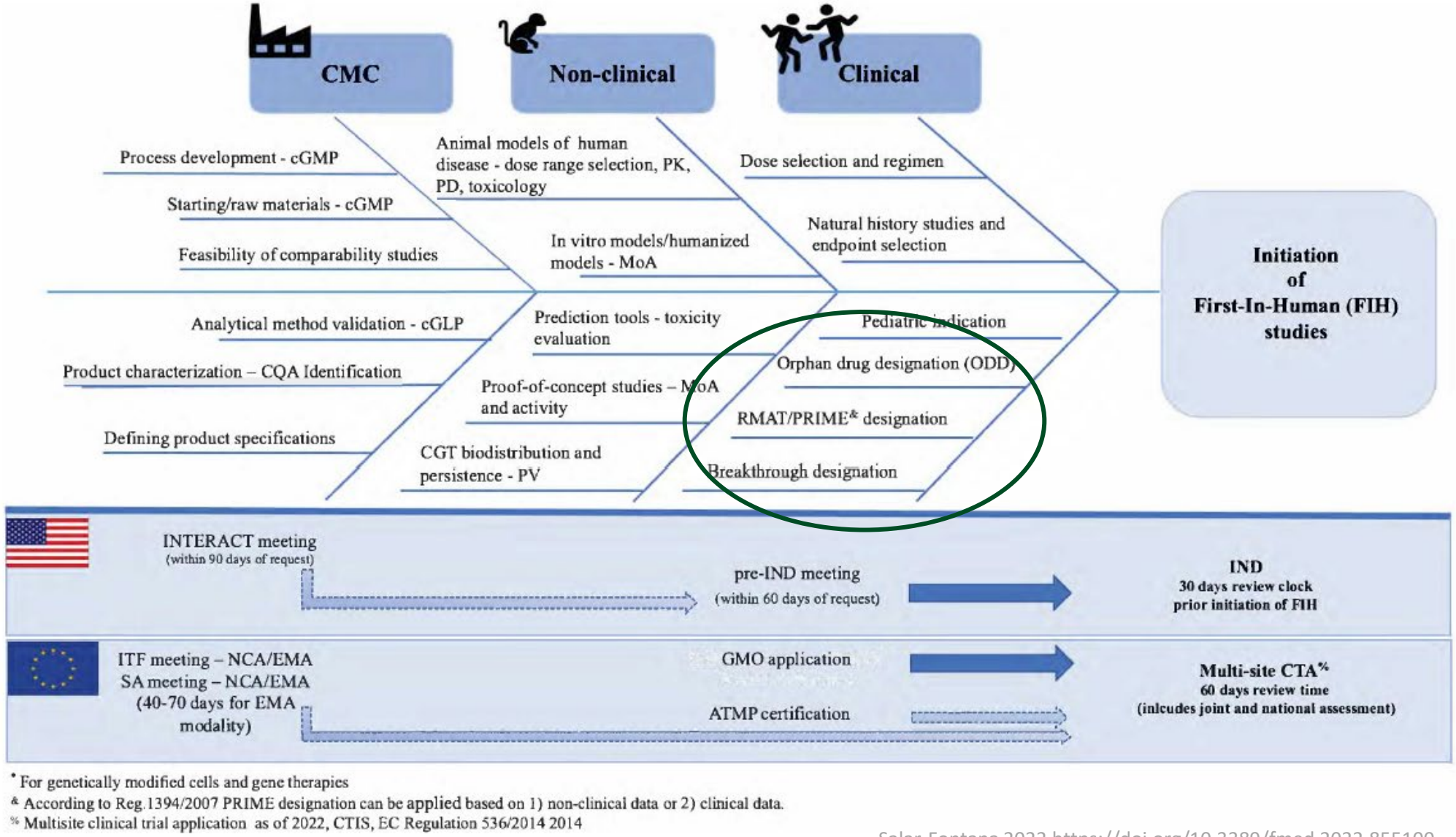
Regulatory Risk Analysis in early ATMP/ CGT development



* For genetically modified cells and gene therapies
& According to Reg.1394/2007 PRIME designation can be applied based on 1) non-clinical data or 2) clinical data.
% Multisite clinical trial application as of 2022, CTIS, EC Regulation 536/2014 2014

Salar-Fontana 2022 https://doi.org/10.3389/fmed.2022.855100

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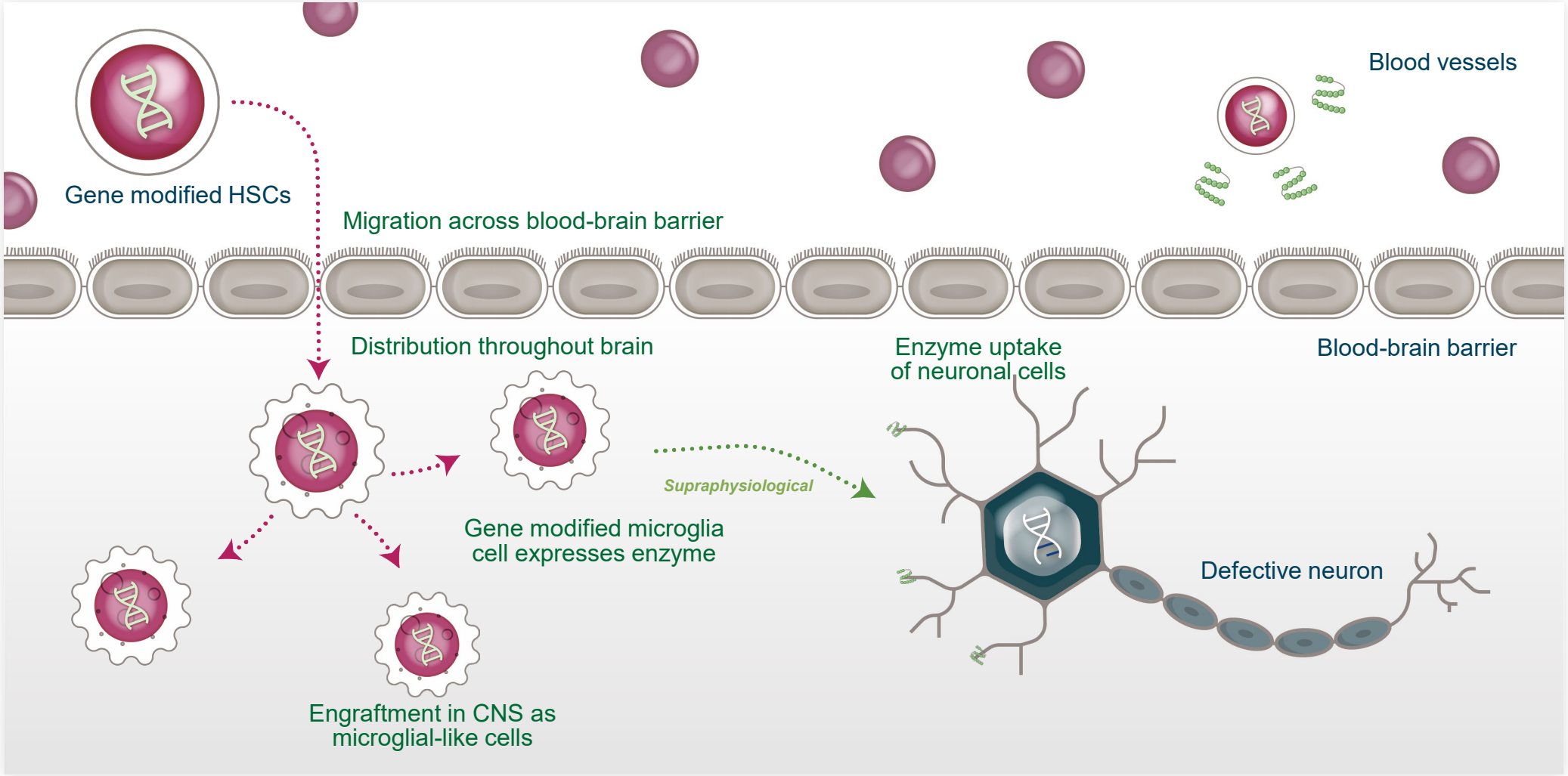
HSC-GT Provides the Potential to Treat Multi-Systemic Neurometabolic Diseases via Cross-Correction



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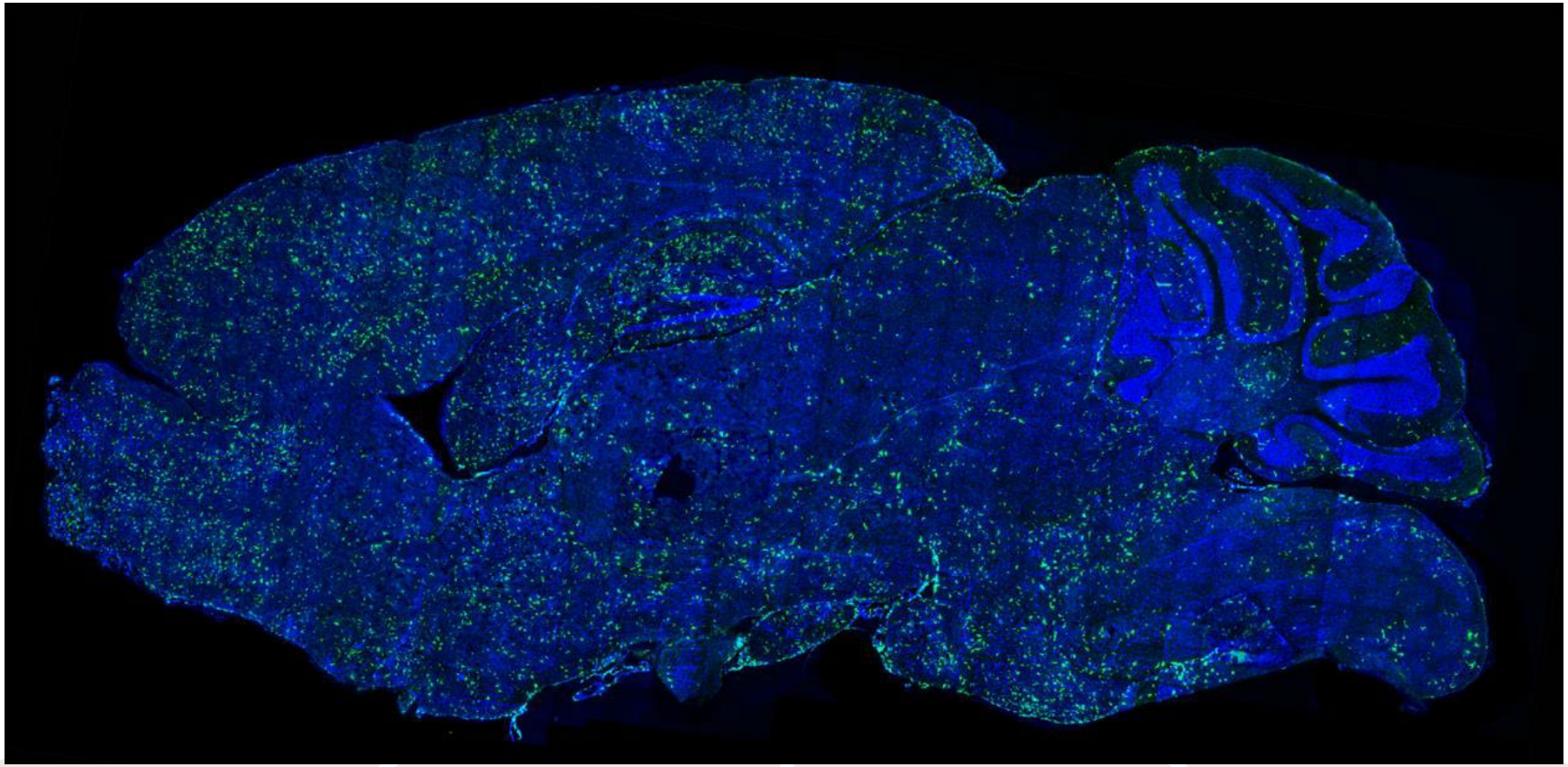
Delivery of genes/RNA/proteins to the brain via ex vivo HSC GT unlocks potential to treat a large number of neurodegenerative diseases

Broad transgene distribution in mouse brain after administration of HSCs transduced with GFP-encoding LV vector



MLD | MPS-I | MPS-IIIA | MPS-IIIB

Potential in multiple additional neurodegenerative diseases (NDDs)

Source: Capotondo et al. PNAS 2012;109:15018-15023; Brain of a wildtype mouse transplanted with GFP-LV transduced HSCs after Busulfan conditioning. **Green** = GFP (green fluorescent protein); **blue** = nuclei staining

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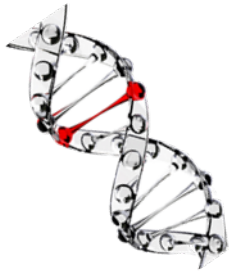
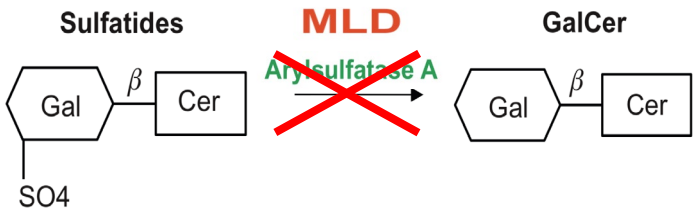
Overview of Metachromatic Leukodystrophy (MLD)

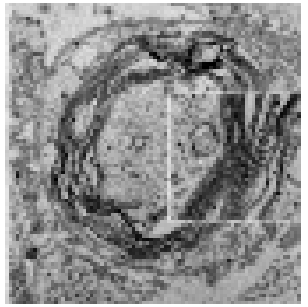
MLD is one of the **most common forms of leukodystrophy**

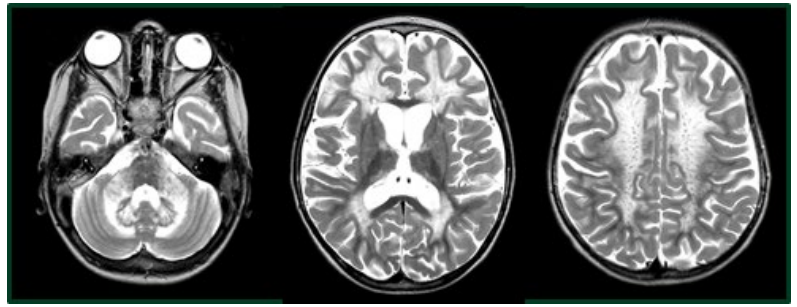
- Rare, autosomal recessive lysosomal storage disorder, caused by a deficiency of arylsulfatase A (ARSA) enzyme[1-4]

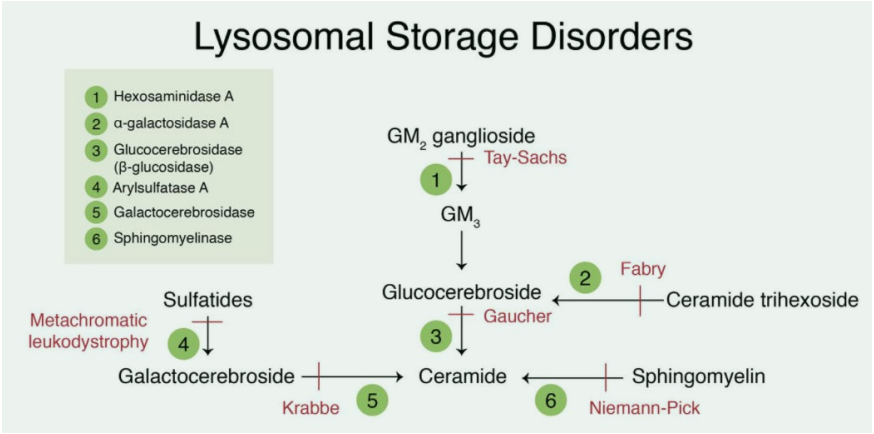
***ARSA* gene mutations** → **Functional deficiency of ARSA (lysosomal enzyme)** → **Intra-lysosomal sulfatide accumulation** → **Progressive demyelination & neurodegeneration**











- ARSA, arylsulfatase A; MLD, metachromatic leukodystrophy.

1. Ferreira C et al. *Translational Science of Rare Diseases* 2 (2017) 1–71. **2.** Gieselmann V, Krageloh-Mann I. *Neuropediatrics* 2010;41(1):1-6. **3.** von Figura K, Gieselmann V, Jaeken J. Metachromatic leukodystrophy. In:. The metabolic and molecular bases of inherited disease, Vol 3, 8th ed. McGraw Hill, 2001:3695,. **4.** Gomez-Ospina N. Arylsulfatase A deficiency. In: GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2018.

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MLD comprises a phenotypic continuum

- Currently classified into distinct phenotypes based on age at disease onset
- MLD is increasingly understood as a disease continuum with a **common pathophysiology** across the clinical spectrum due to variable residual enzymatic activity

	Early Onset MLD (<7 yrs)		Late Onset MLD (≥7 yrs)	
Residual ARSA activity[1,2]				
Phenotype[2,4]	**Late-infantile (LI)**	**Early Juvenile (EJ)**	**Late Juvenile (LJ)**	**Adult Onset**
Age of onset of symptoms[2,4] (Years)	**≤ 30 mo**	**30 mo to 6 yrs**	**7 to 16 yrs**	**17+ yrs**
Initial Presenting Signs & Symptoms[1-4]	Gait abnormality and motor milestones	Gait and motor decline may be accompanied by educational and behavioral symptoms	Inattention, poor school performance, behavioral difficulties	Dementia, emotional & behavioral problems

ARSA, arylsulfatase A; MLD, metachromatic leukodystrophy.

1. Gieselmann V, Krägeloh-Mann I. *Neuropediatrics.* 2010; 41: 1– 6. **2.** Biffi A et al. Clin Genet. 2008;74:349-357. **3** Wang RY et al. *Genet Med.* 2011;13(5):457-484. **4.** Solders M et al. *Bone Marrow Transplant.* 2014; 49(8):1046-1051.

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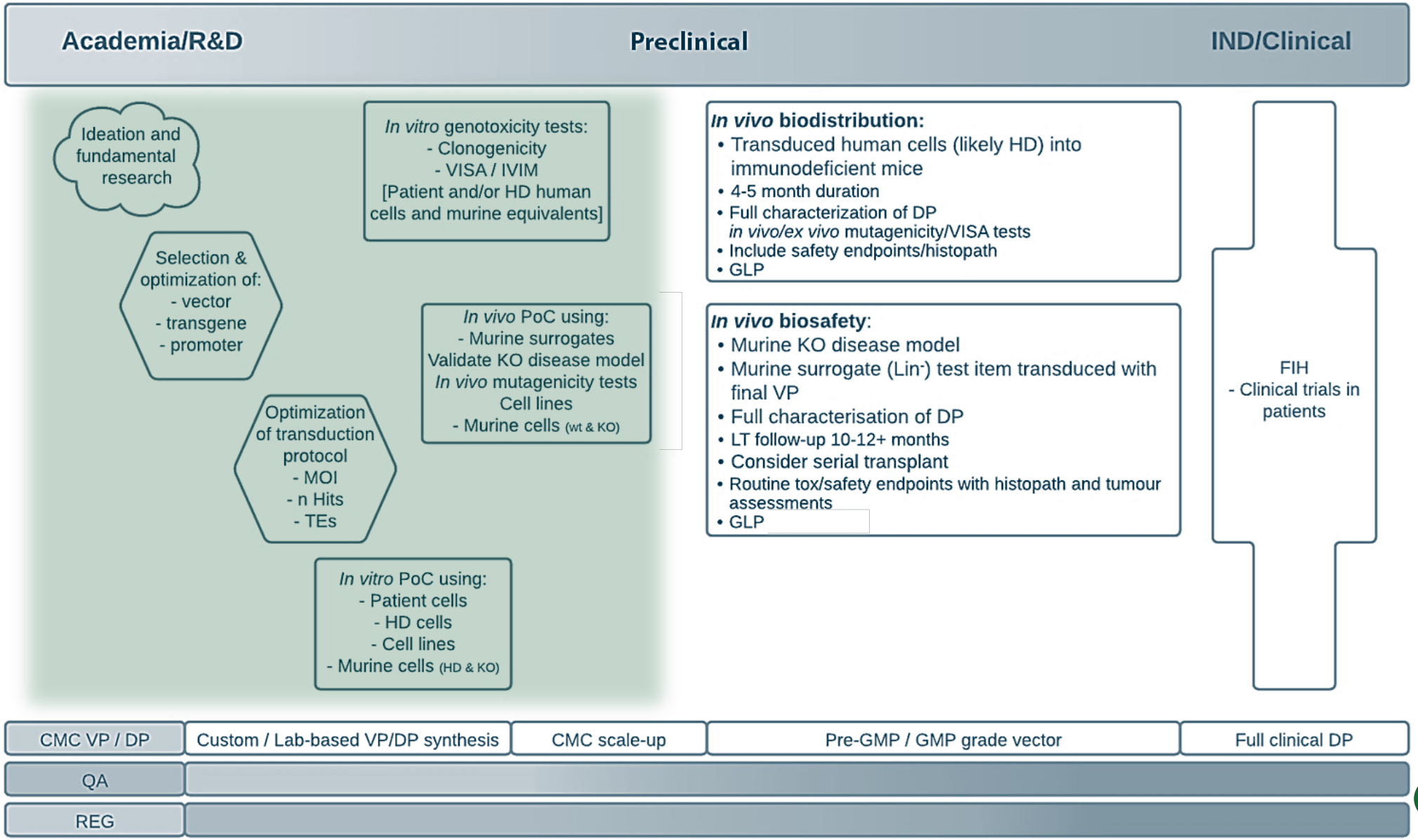
The path to making genetic medicines



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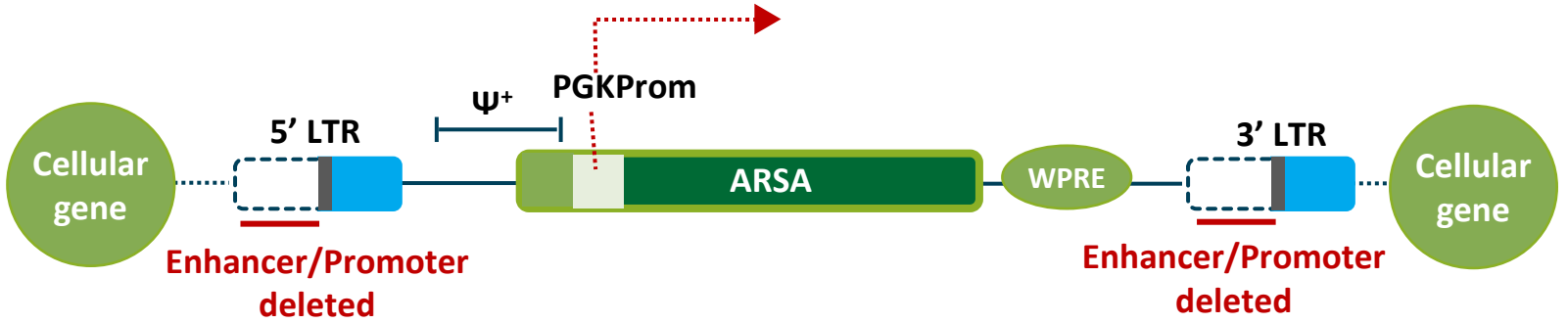
Preclinical Development Autologous HSC Gene Therapy for MLD: Lentiviral Vector Development

3rd Generation self-inactivating lentiviral vector:



- Based on HIV-1 virus
- 3'LTR deletions
- Internal promoter driven expression (constitutive human PGK promoter)
- Reduced potential of insertional mutagenesis
- Infect non-dividing cells

Non-clinical Study Provisions to minimise Risks	
Vector mobilization and germline transmission	• Replication competent lentivirus (RCL) testing • Stability & Detection of Tissue VCN
Insertional mutagenesis	• Insertional site analysis
Transduction efficiency & transgene expression	• Clonogenicity potential in vitro & in vivo, human CD34+ HSC and murine Lineage negative HSPC • Engraftment potential in primary & secondary recipients (human and mouse HSC)
Toxicity related to supraphysiological levels of ARSA expression	

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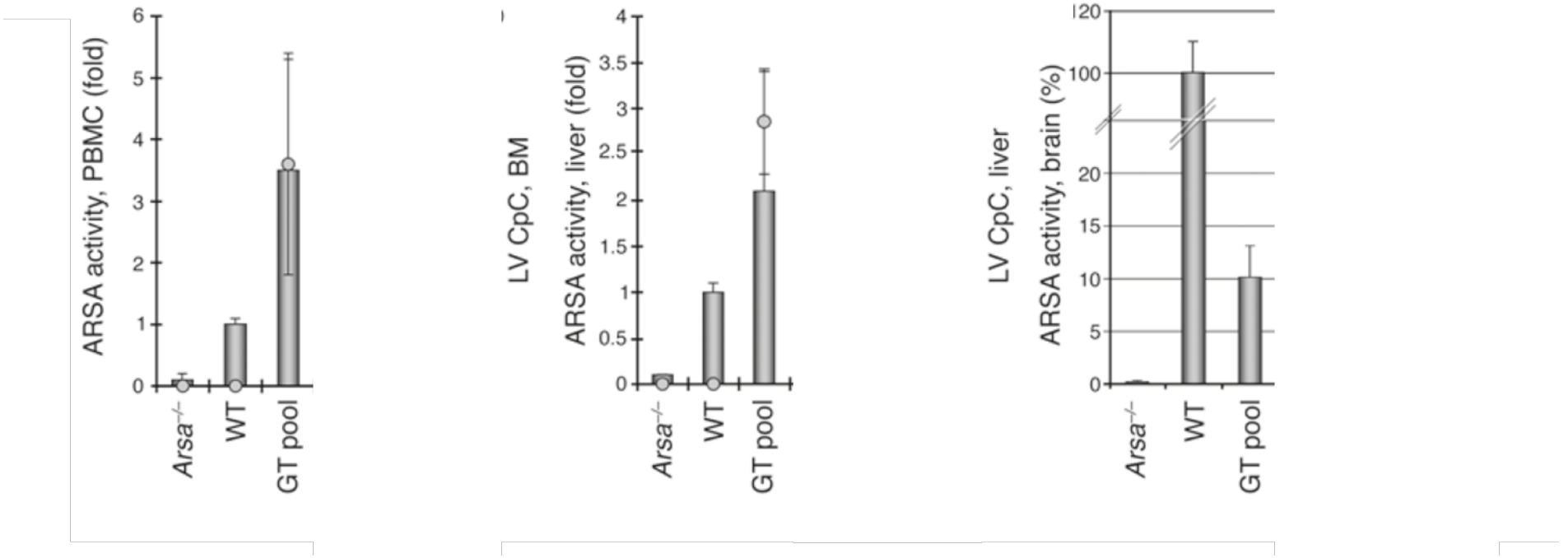
Preclinical Development Autologous HSC Gene Therapy for MLD: Primary Pharmacodynamics

- ARSA activity in PBMC derived from GT-treated mice & LV (copy per cell) content detected in BM
- ARSA activity is expressed as fold increase compared with WT levels and LV content in CpC showing significantly higher (supraphysiological) levels of enzyme production are achieved *in vivo*



Biffi et al JCI 2004 https://doi.org/10.1172/JCI19205 | Biffi et al JCI 2006 https://doi.org/10.1172/JCI28873.

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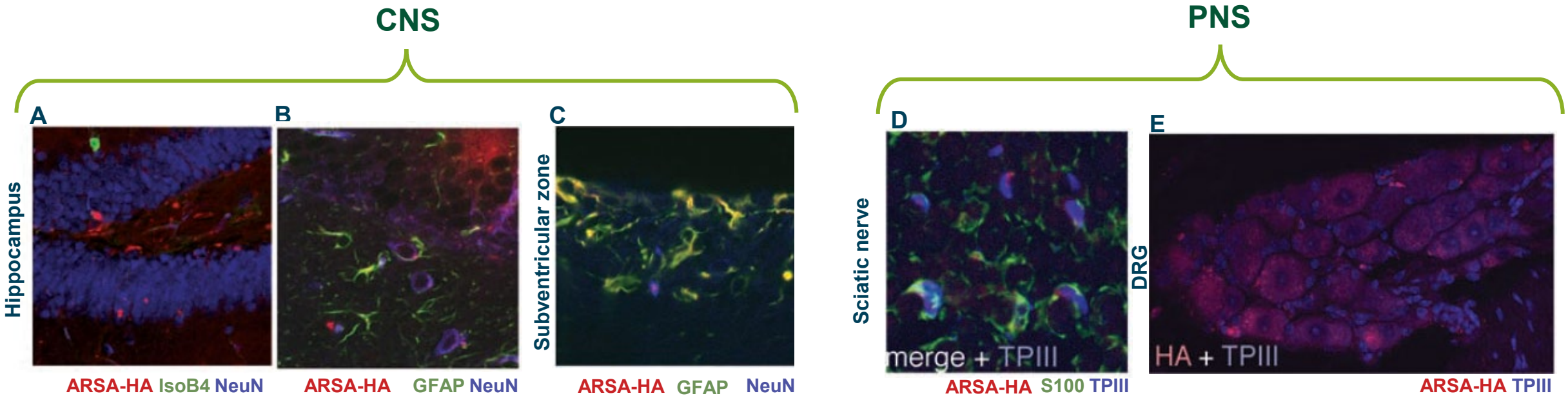
Preclinical Development Autologous HSC Gene Therapy for MLD: Biodistribution

- In pre-clinical studies, genetically-modified myeloid precursors migrated to the brain after GT treatment, with subsequent extensive repopulation of CNS microglia and PNS endoneural macrophages in mouse models of MLD[1,2,4]
- ARSA secreted by gene-corrected cells is taken up by neighbouring neurons and oligodendrocytes via the mannose-6-phosphate receptor pathway, providing cross-correction for enzyme-deficient cells[1-3]



- ARSA, arylsulfatase A; CNS, central nervous system; GFAP, glial fibrillary acidic protein; GT, gene therapy; HA, hemagglutinin tag epitope, MLD, metachromatic leukodystrophy; PNS, peripheral nervous system; DRG, dorsal root ganglia.

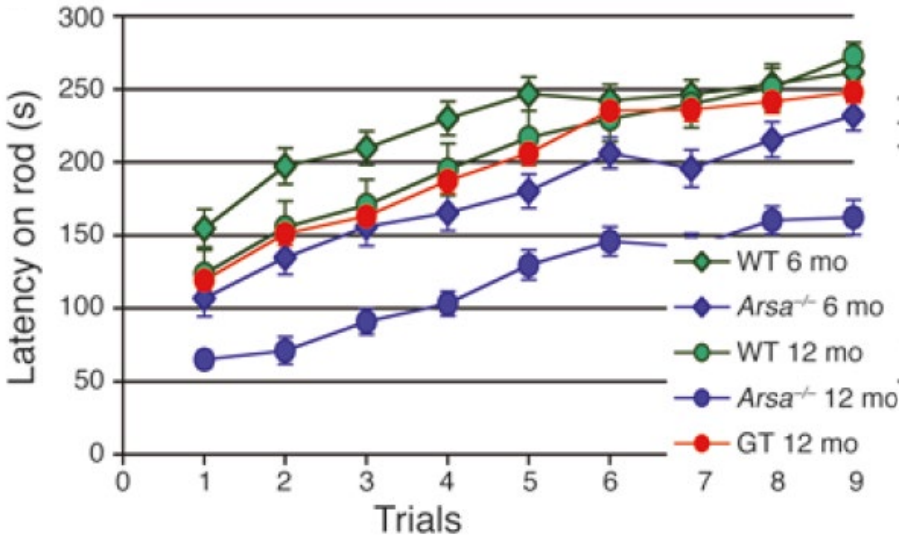
1. Biffi A et al. *J Clin Invest* 2006;116(11):3070–3082. **2.** Neumann H. *J Clin Invest* 2006;116(11):2857–2860. 3. Cartier N et al. *Acta Neuropathol* 2014;128:363–380.

Biffi et al JCI 2004 https://doi.org/10.1172/JCI19205 | Biffi et al JCI 2006 https://doi.org/10.1172/JCI28873.

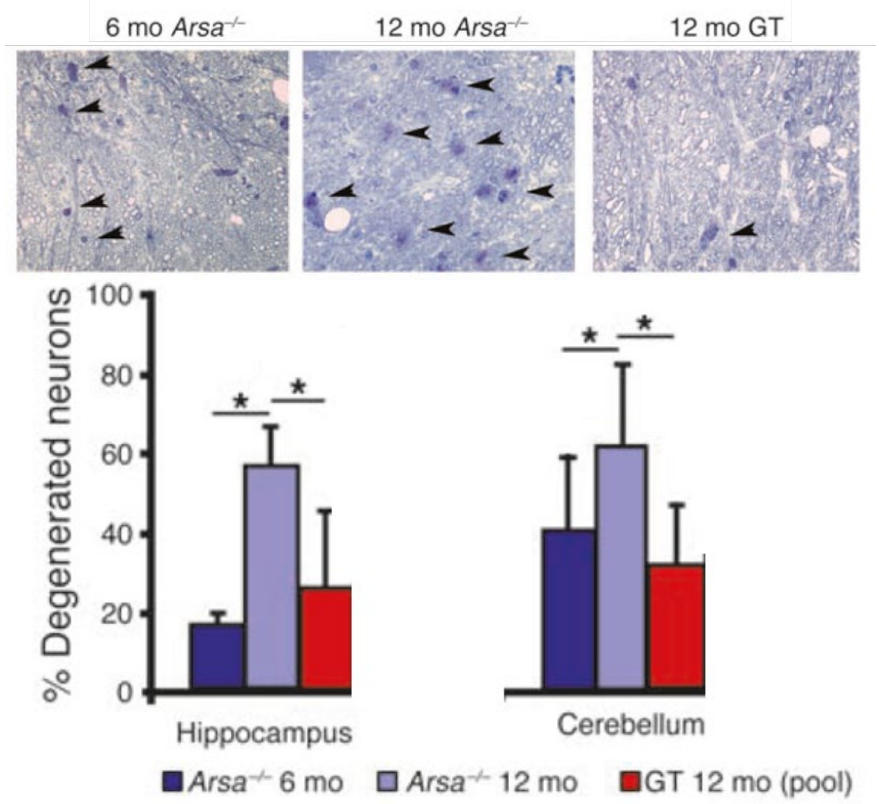
Orchard therapeutics

Preclinical Development Autologous HSC Gene Therapy for MLD: Proof of Concept/ Efficacy

- Behavioural evaluations of GT-treated mice



- Correction of sulfatide accumulation & neuronal damage in the CNS of GT-treated mice



Evidence for Enzymatic reconstitution and correction of neurological defects in *Arsa–/–* mice

Biffi et al JCI 2004 https://doi.org/10.1172/JCI19205 | Biffi et al JCI 2006 https://doi.org/10.1172/JCI28873.

Orchard therapeutics

Preclinical Development Autologous HSC Gene Therapy for MLD: Dose selection/ Potency

Dose-effect relationships in treated *Arsa*$^{-/-}$ mice

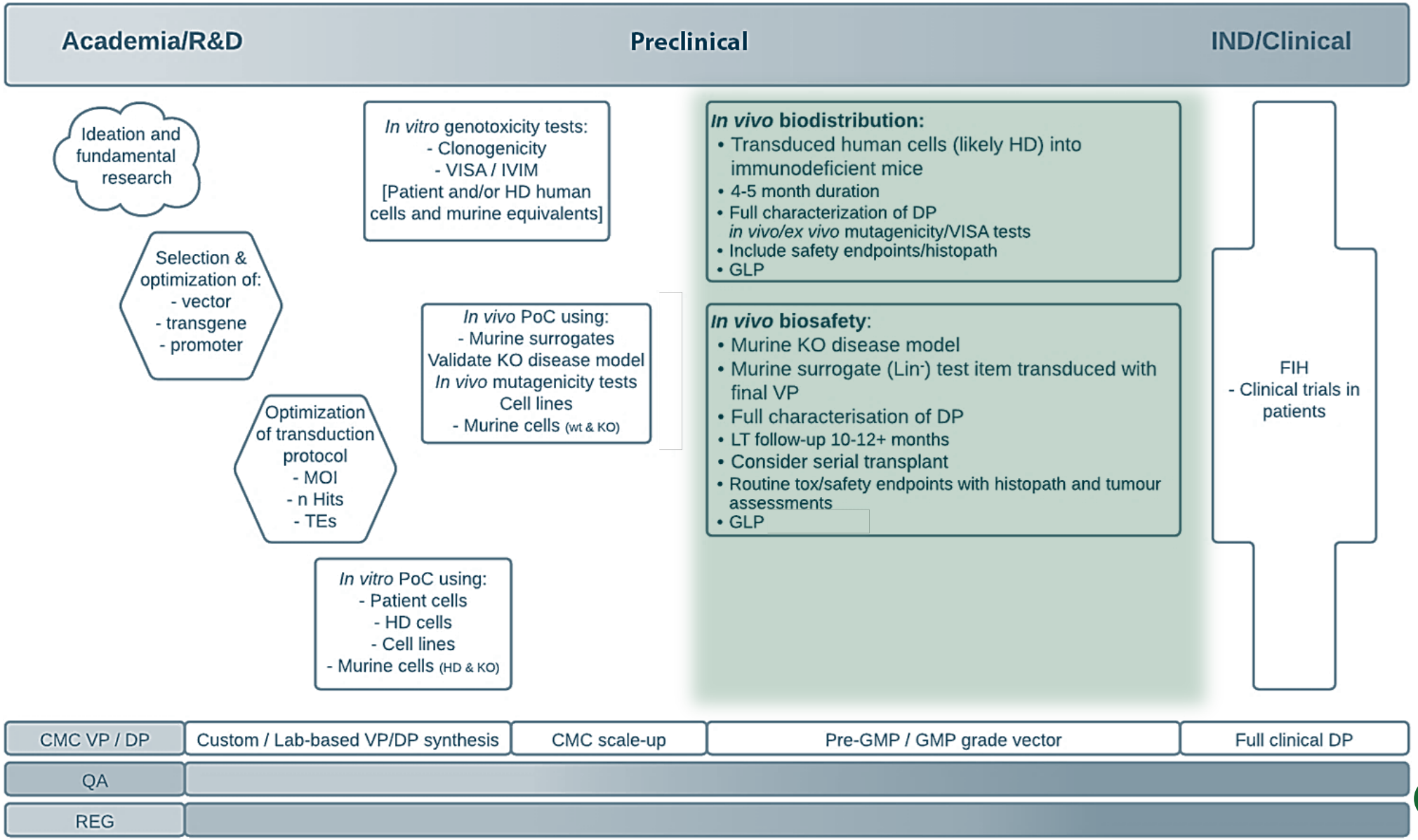
Treatments	*n*	CpC	ARSA activity			Neurophysiology	Rotarod	Hippocampus		Cerebellum	
			PBMC (fold to WT)	Liver (fold to WT)	Brain (% of WT)	CCT (ms)	Latency (s)	Deposits, fimbria (score)	Neu damage, CA2–3 (% deg neu)	Deposits, white matter (score)	Neu damage, Purkinje (% deg neu)
UT *Arsa*$^{-/-}$, 6 mo	36	–	0.3 ± 0.3	0.1	0.1	3.4 ± 0.7^{A}	232 ± 10^{B}	1.5 ± 0.5	17 ± 2.8	1.7 ± 0.5	41 ± 18
MT *Arsa*$^{-/-}$, 12 mo	45	4.5 ± 2	0.3 ± 0.2	0.1	0.1	3.9 ± 0.7^{B,C}	162 ± 12^{B,D}	2.7 ± 0.6^{D}	57 ± 9.8^{D}	2.9 ± 0.7^{D}	62 ± 20^{C}
GT, pool, 12 mo	61	6 ± 3	3.5 ± 1.0^{E}	2.1 ± 1^{E}	10.1 ± 5.3^{E}	3.0 ± 0.3^{C,E}	248 ± 7^{E}	1.5 ± 0.7^{E}	26.5 ± 15^{E}	1.8 ± 0.8^{E}	32 ± 15^{E}
GT, group A, 12 mo	36	4.1 ± 1.8	2.8 ± 0.8	1.2 ± 0.3	7 ± 2.5	3.2 ± 0.45^{E}	223 ± 10^{E}	1.8 ± 0.6^{E}	40.9 ± 18	2.2 ± 0.7	45.5 ± 14
GT, group B, 12 mo	25	7.8 ± 1.4^{F}	4.2 ± 1.0^{F}	2.5 ± 0.9^{F}	12.6 ± 4.2^{E}	2.92 ± 0.1^{C,E}	263 ± 10^{D,E,F}	1.2 ± 1^{E}	18.4 ± 7^{E,F}	1.5 ± 0.8^{E,F}	25.7 ± 8^{D,E,F}
UT WT, 6 mo	29	–	1 ± 0.5	1 ± 0.3	100 ± 2.5	3.0 ± 0.4	262 ± 9	–	–	–	–
MT WT, 12 mo	20	5.1 ± 1.6	1 ± 0.5	1 ± 0.3	100 ± 2.5	2.9 ± 0.5	272 ± 9	–	–	–	–

We analyzed the following groups of mice: untreated (UT) or mock-treated (MT) *Arsa*$^{-/-}$ mice, the latter transplanted with *Arsa*$^{-/-}$ HSPCs transduced with GFP-LV; GT-treated mice (GT, pool and groups A and B; for details, see text); UT and MT WT animals at the indicated age in months. ARSA activity was quantified by p-NC assay on total PBMCs and by Rh-sulfatide test for liver and brain extracts and is expressed as fold increase compared with WT (fold to WT) or percentage (%) of WT levels. LV CpC was quantified by TaqMan on bone marrow DNA from transplanted mice. For rotarod test, the mean latency on rod measured at the ninth trial is reported. For histopathology, the semiquantitative score for white matter deposits and the percentage of degenerated neurons in hippocampal CA2–3 and Purkinje cell layer (neu damage) are reported. For statistical analysis, Student's *t* test and 2-way ANOVA were used for CpC, ARSA activity, and neurophysiology, and for behavior, respectively. $^{A}P < 0.05$, $^{B}P < 0.01$ for comparison with age matched WT groups; $^{C}P < 0.05$; $^{D}P < 0.01$ for comparison with 6-month-old UT *Arsa*$^{-/-}$; $^{E}P < 0.01$ for comparison with 12-month-old MT *Arsa*$^{-/-}$; $^{F}P < 0.05$ for comparison with group A.

Dosing considerations for C&GT: Primary dose optimisation of therapeutic transgene copy number, as HSC dosing informed by extensive allogeneic & autologous BMTx clinical experience

Orchard therapeutics

The path to making genetic medicines

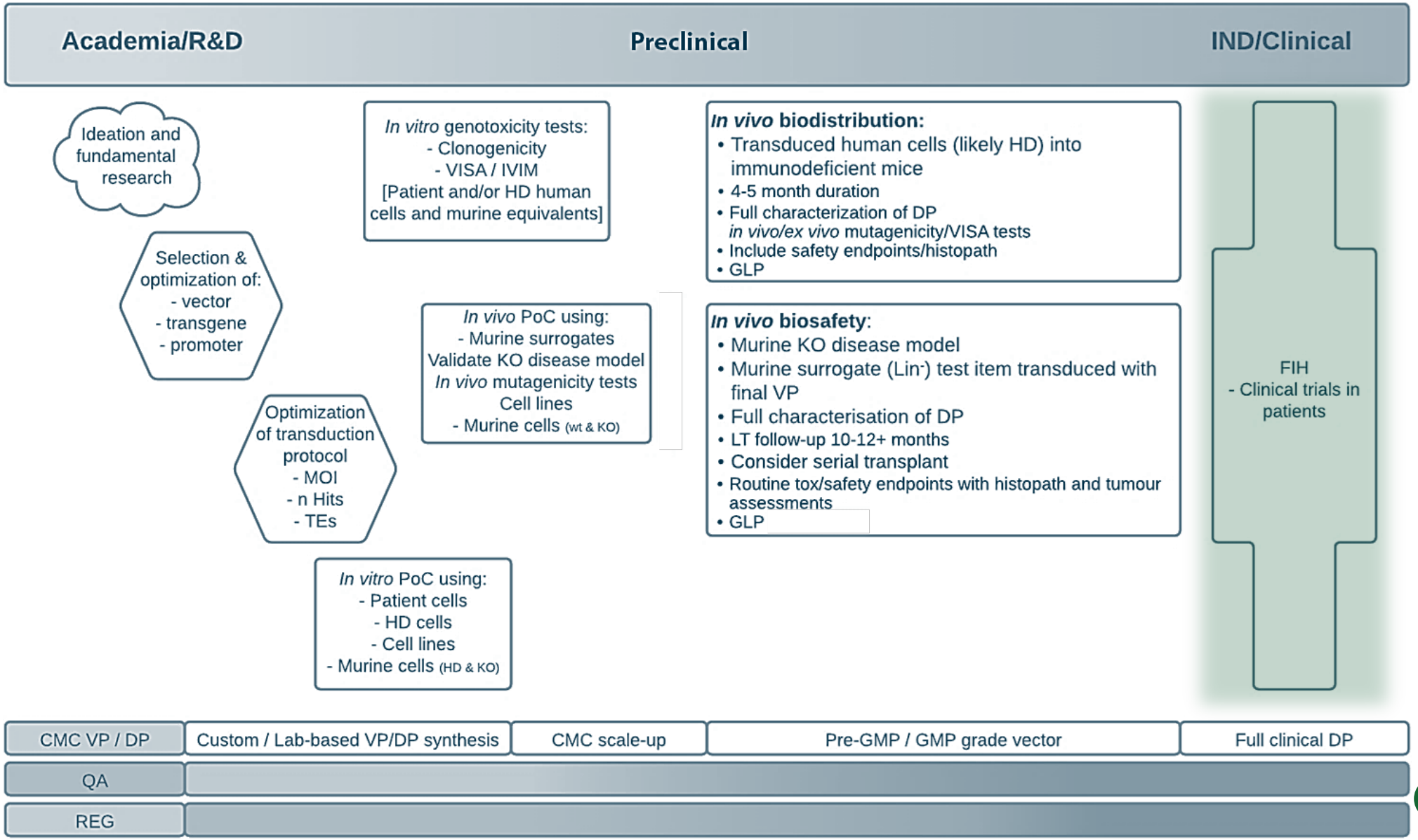


Orchard therapeutics

Toxicity and tumorigenicity: Example study design

***In vitro* characteristics**	-	**VCN (ddPCR)**
	-	**Clonogenic potential (CFU)**
	-	**mRNA (ddPCR) & protein**
***In vivo* observations: clinical signs, body weight, food consumption**	-	Mortality and clinical signs
	-	Food consumption
Proof of dosing	-	**Engraftment and cell differentiation ; chimerism ; VCN**
Therapeutic protein reconstitution	-	mRNA (ddPCR) in CNS, spleen & BM
Clinical pathology and markers of cell differentiation	-	**Serum clinical chemistry**
	-	**Haematology**
	-	Analysis for haematopoietic compartments
Pathological examination	-	Macroscopic examination performed at necropsy
	-	Organ weight: main organs
	-	**Microscopic examination: Extensive list of tissues examined microscopically**
	-	Analysis for haematopoietic subsets in intestine, spleen, thymus and BM if macroscopic abnormalities observed

The path to making genetic medicines



Orchard therapeutics

MLD: Treatment Process

A patient-specific product: autologous CD34⁺ cells encoding *ARSA* gene

STEP 1
Cells are collected from the patient via BM harvest or mPB apheresis

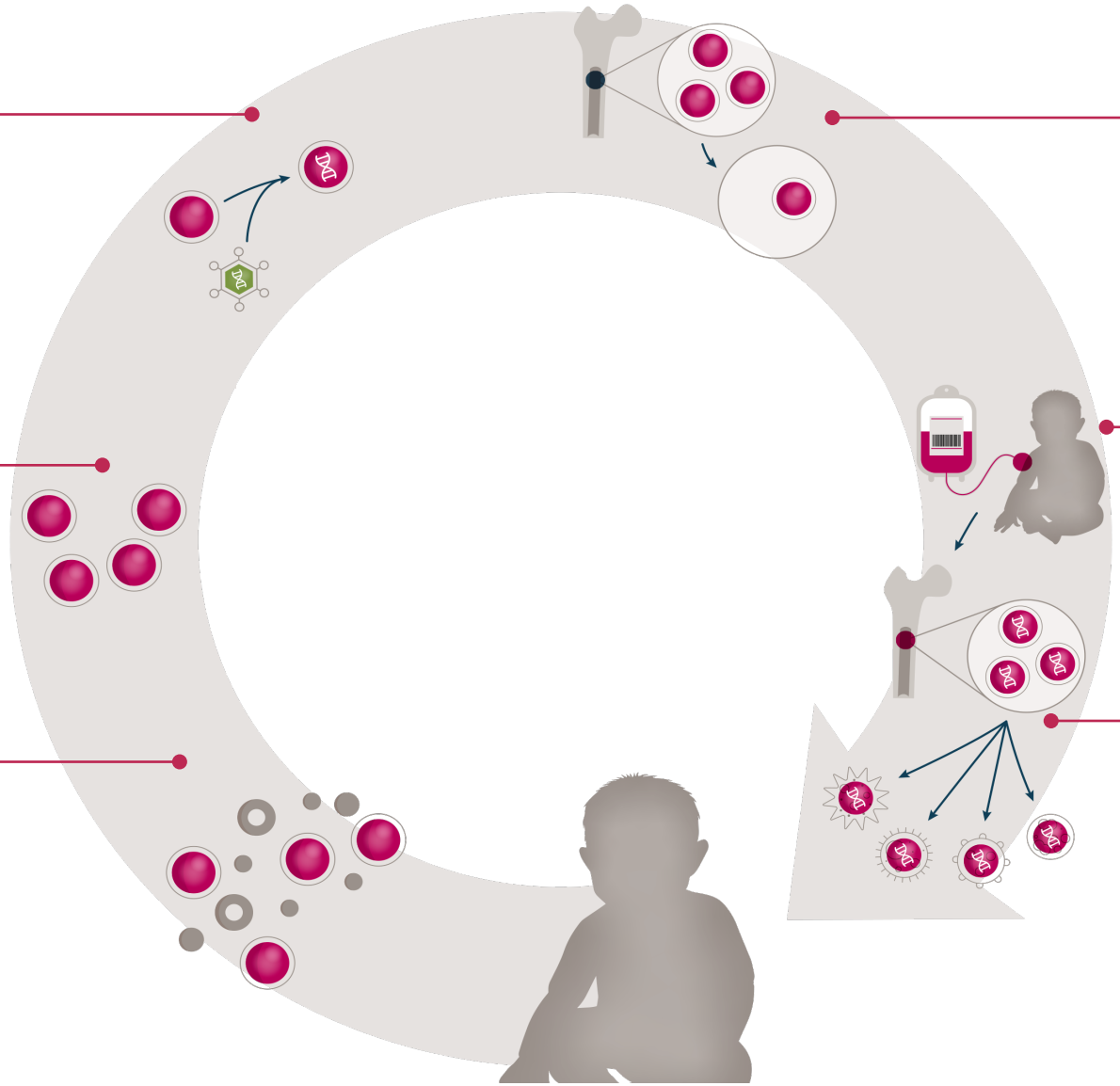
STEP 2
HSPCs, identified by the CD34⁺ cell surface marker, are selected and purified

STEP 3
A working copy of the *ARSA* gene is inserted into the HSPCs *ex vivo* via exposure to a viral vector

STEP 4
Patient is conditioned to receive Libmeldy

STEP 5
Gene-corrected cells are infused into the patient

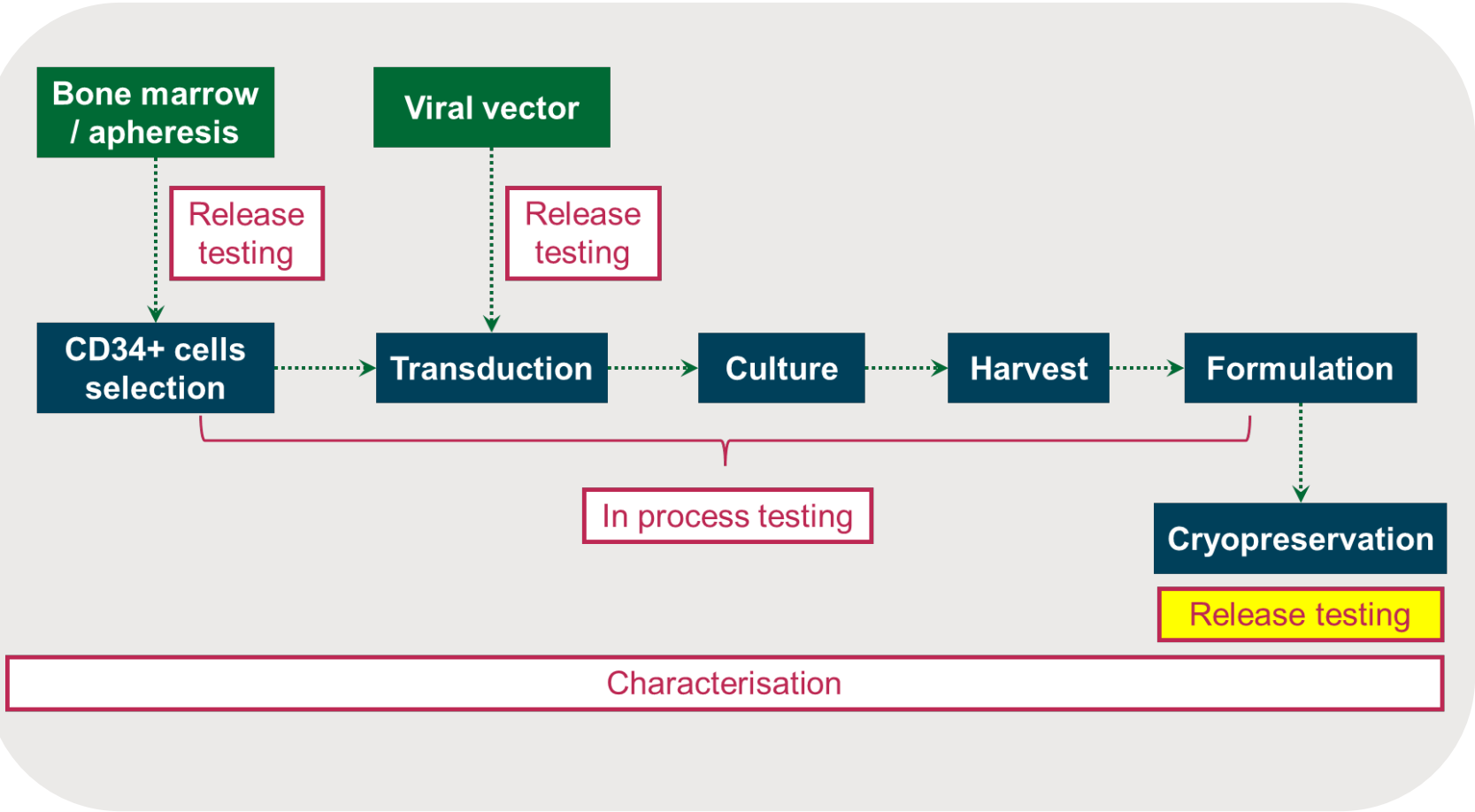
STEP 6
Gene-corrected cells engraft and proliferate



BM, bone marrow; mPB, mobilised peripheral blood; HSPCs, haematopoietic stem and progenitor cells; ARSA, arylsulfatase A

Orchard therapeutics

Additional CMC challenges for development of C&GTs



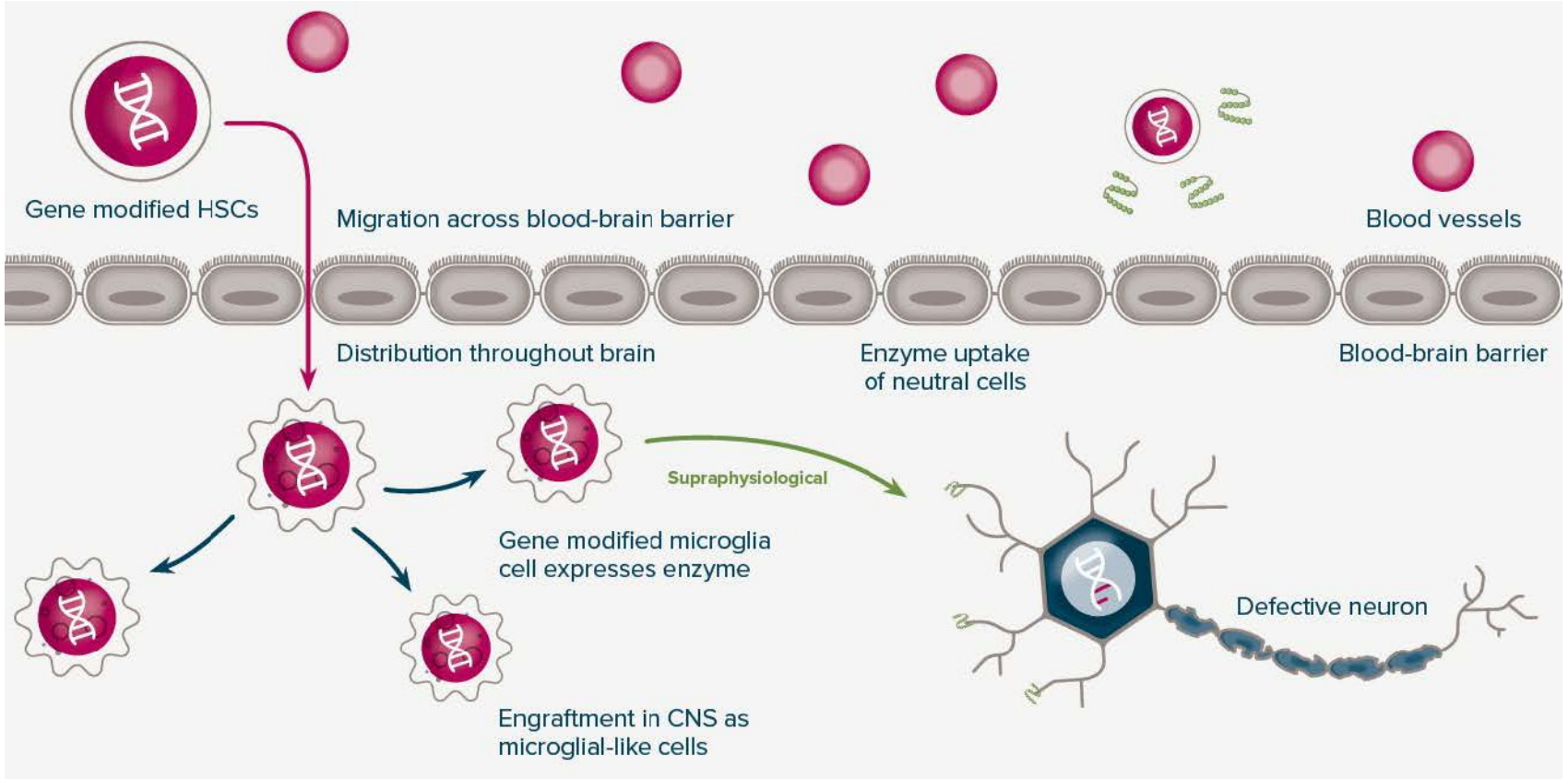
- Product Critical Quality Attributes (CQAs) are defined by the manufacturing process
- QC analytics during manufacturing process (*Not just Drug Product specifications)*
- **Demonstration of Viral & Cell Batch QC & comparability**
- **Potency assay developments**
  - Complex MOA
  - Consider function of cells & of therapeutic protein
  - Limited time-window for DP release

Libmeldy™ Proposed Mechanism of Action

Following myeloablative conditioning, infused **genetically modified cells engraft** and repopulate the haematopoietic compartment.

A subpopulation of the infused HSPCs and/or their myeloid progeny is able to **migrate across the BBB** and **engraft as CNS resident microglia** and **perivascular CNS macrophages** as well as **endoneural macrophages in the PNS**

These genetically modified cells can **produce and secrete the functional ARSA enzyme**, which can be taken up by surrounding cells, a process known as **cross-correction**, and used **to break down, or prevent the build-up, of harmful sulfatides.**



HSPCs, haematopoietic stem and progenitor cells; BBB, blood-brain barrier; CNS, central nervous system; PNS, peripheral nervous system.ARSA, arylsulfatase A; cPPT-CS, central polypurine tract-central termination sequence; LV, lentiviral vector; mRNA, messenger ribonucleic acid; PGK, phosphoglycerate kinase; WPRE, Woodchuck hepatitis virus post-transcriptional regulatory element; LTR, Long terminal repeat

Orchard therapeutics

Clinical Development Autologous HSC Gene Therapy for MLD:

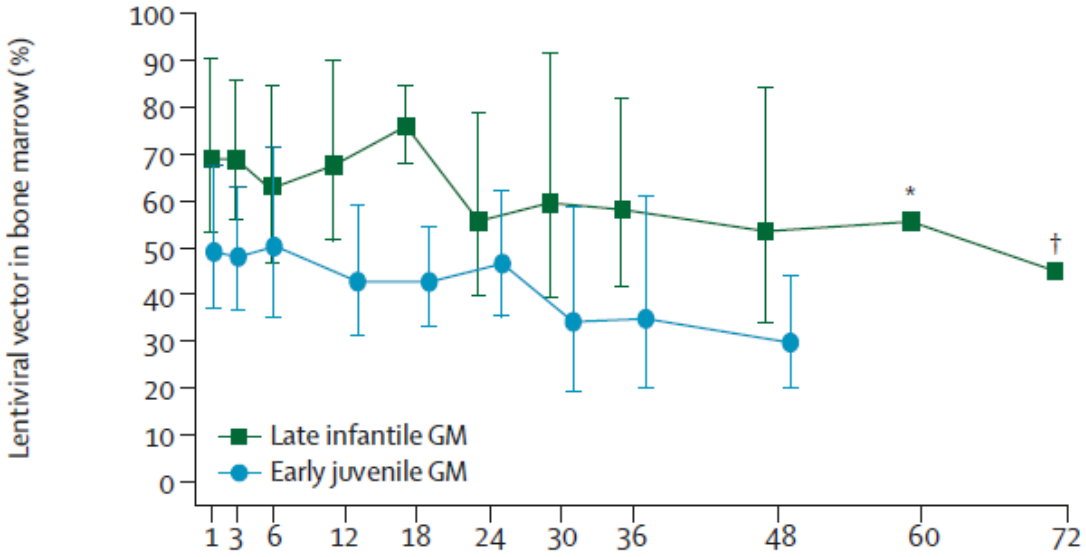
- **Clinical Trial Design: non-randomised, open-label, phase 1/2 trial and expanded access (2010-2017)**
  - Favourable risk : benefit analysis in such a severe disease setting, with natural history comparator group data
  - Greatest potential clinical benefit for paediatric patients
  - Precedence for allogeneic HSCT for MLD, with limited efficacy
  - Relying on safety & efficacy data from Non-clinical studies

Clinical Program	Patient Population (Age at Onset or Predicted Age of Onset)	OTL-200 Formulation	Target Enrollment	Number Enrolled
Phase I/II Registrational Trial • Open label, single arm, prospective (NCT01560182)[1-4,7]	Early-onset MLD (< 7 yrs)	Fresh	n=20	n=20
Expanded Access Programs • Similar treatment protocol to registrational trial[2]	Early-onset MLD (< 7 yrs)	Fresh	N/A	n=9
Natural History Study • Retrospective untreated comparator cohort[2-4,7]	Early-onset MLD (< 7 yrs)	N/A	N/A	n=31
Phase I/II Trial • Open label, single arm, prospective (NCT03392987)[5,6]	Early-onset MLD (< 7 yrs)	Cryopreserved	n=10	n=10

1. https://clinicaltrials.gov/ct2/show/NCT01560182. Accessed June 25, 2020. **2.** Fumagalli F et al. Lentiviral hematopoietic stem cell gene therapy (HSC-GT) for metachromatic leukodystrophy (MLD) provides sustained clinical benefit; Presented at: 2019 Annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM); September 3-6, 2019; Rotterdam, The Netherlands. **3.** Biffi A et al. *Science*. 2013;341(6148):1233158. **4.** Sessa M et al. *Lancet*. 2016;388(10043):476-487. **5.** https://clinicaltrials.gov/ct2/show/NCT033929873 Accessed June 25, 2020 **6.** Calbi V et al. Lentiviral haematopoietic stem cell gene therapy (HSC-GT) for metachromatic leukodystrophy (MLD): Preliminary results from a clinical trial with a cryopreserved formulation of OTL-200 [Poster], Presented at: 27th Annual Congress of the European Society of Gene & Cell Therapy (ESGCT), 22–25 October 2019, Barcelona, Spain **7.** Fumagalli F et al. Lentiviral Hematopoietic Stem and Progenitor Cell Gene Therapy (HSPC-GT) for Metachromatic Leukodystrophy (MLD): Clinical Outcomes from 33 Patients Presented at: 16th Annual WORLD*Symposium,* February 10-13, 2020, Orlando, FL, USA. **8.** https://clinicaltrials.gov/ct2/show/NCT04283227 Accessed June 25, 2020

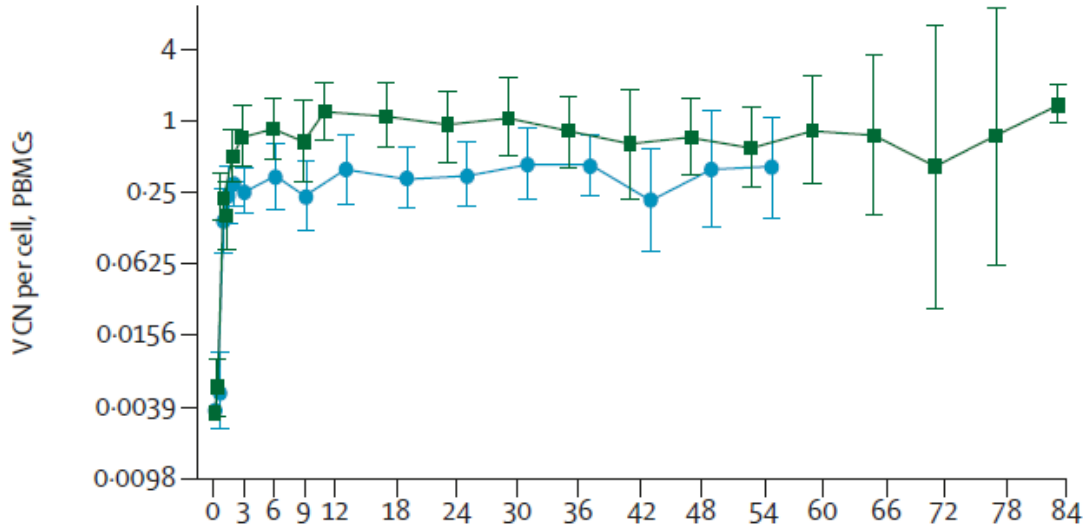
Clinical Development Autologous HSC Gene Therapy for MLD: Engraftment of Gene-Corrected Cells

% Lentiviral-vector positive cells in BM



Number of patients											
Late infantile	12	13	13	12	8	7	7	5	7	4	3
Early juvenile	12	12	10	11	10	9	6	6	3	..	..

Vector Copy Number PBMCs

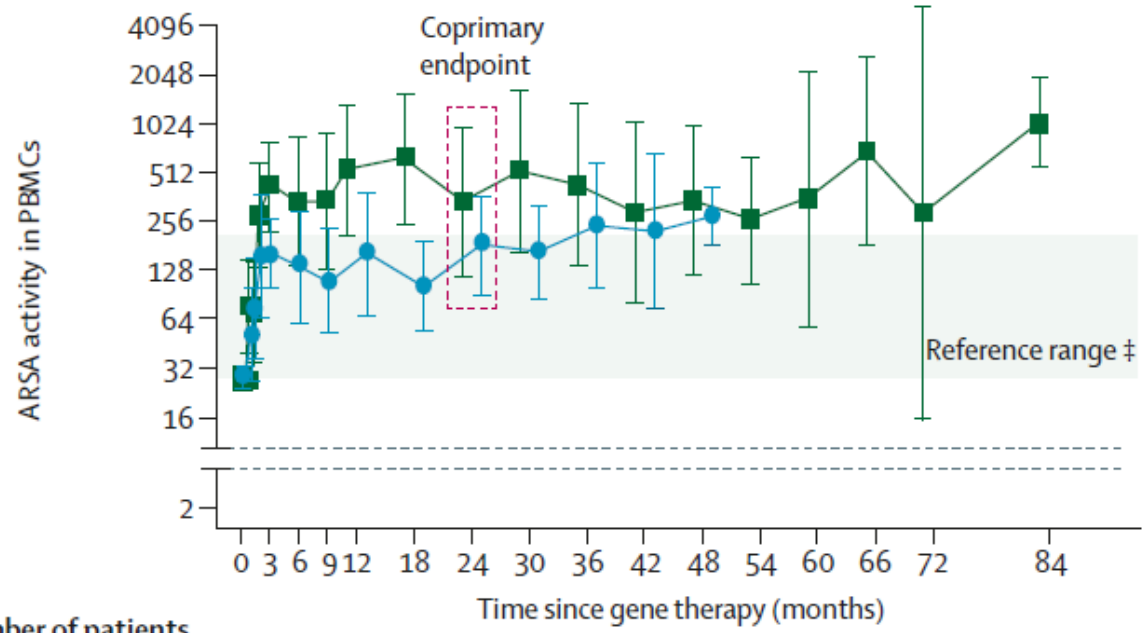


Number of patients																		
Late infantile	16	16	14	10	16	11	11	9	9	6	7	6	5	4	3	3	3	
Early juvenile	13	12	10	10	11	10	10	9	10	6	5	3	..	..	..	..	..	

BM, bone marrow; CI, confidence interval; GM, geometric mean; LV, lentivirus; Note: geometric means and 95% confidence intervals 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; Presented at: 2019 Annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM); September 3-6, 2019; Rotterdam, The Netherlands.

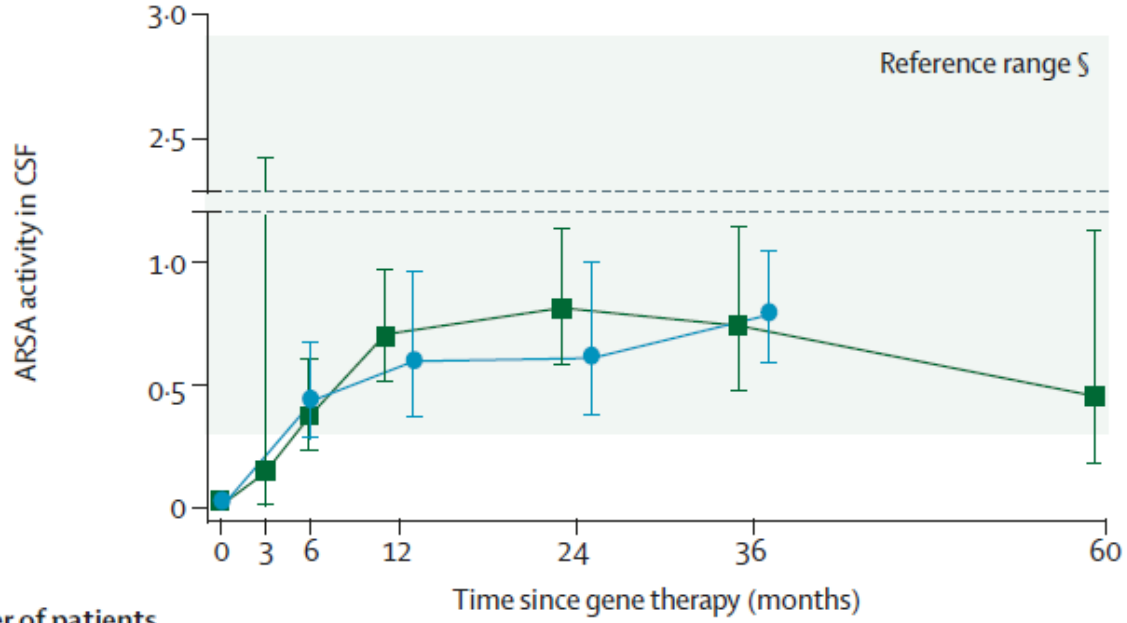
Clinical Development Autologous HSC Gene Therapy for MLD: Reconstitution of ARSA Activity in Peripheral Blood and CSF

ARSA Activity Peripheral Blood Mononuclear Cells



Number of patients													
Late infantile	15	15	11	12	16	11	11	9	10	5	7	6	5	4	3	3
Early juvenile	13	12	10	10	10	10	9	9	9	6	4	..	..	..	..	..

ARSA Activity in Cerebrospinal Fluid



Number of patients							
Late infantile	16	5	10	14	9	8	5
Early juvenile	13	..	9	11	10	8	..

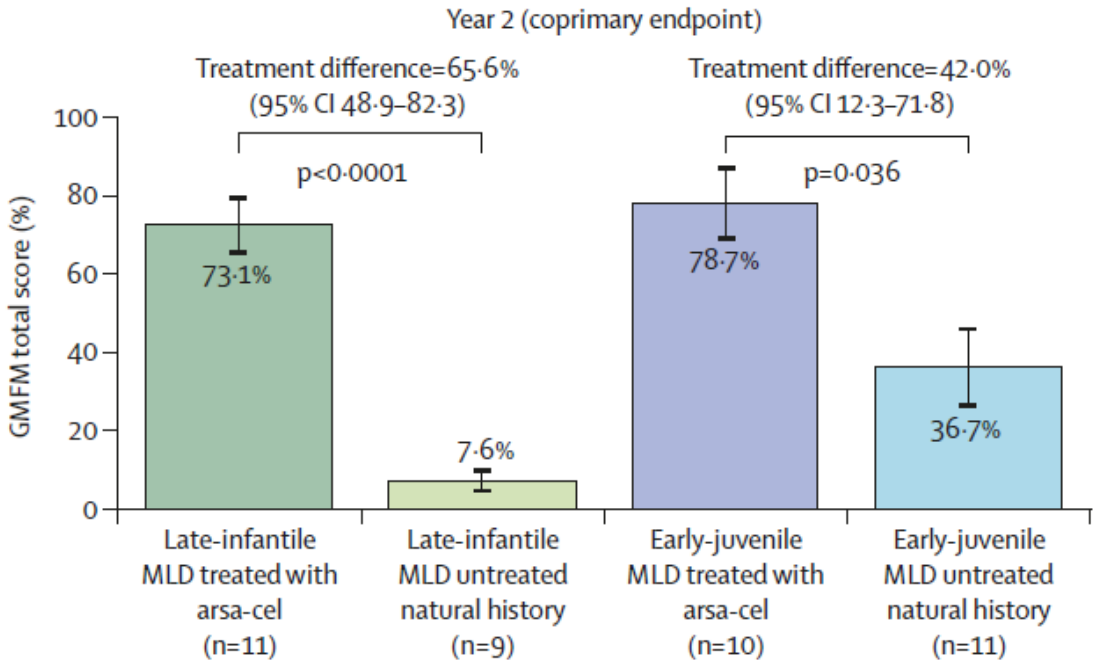
- **Co-primary endpoint: change from baseline of total PBMC ARSA activity at 2 years compared with values before treatment**

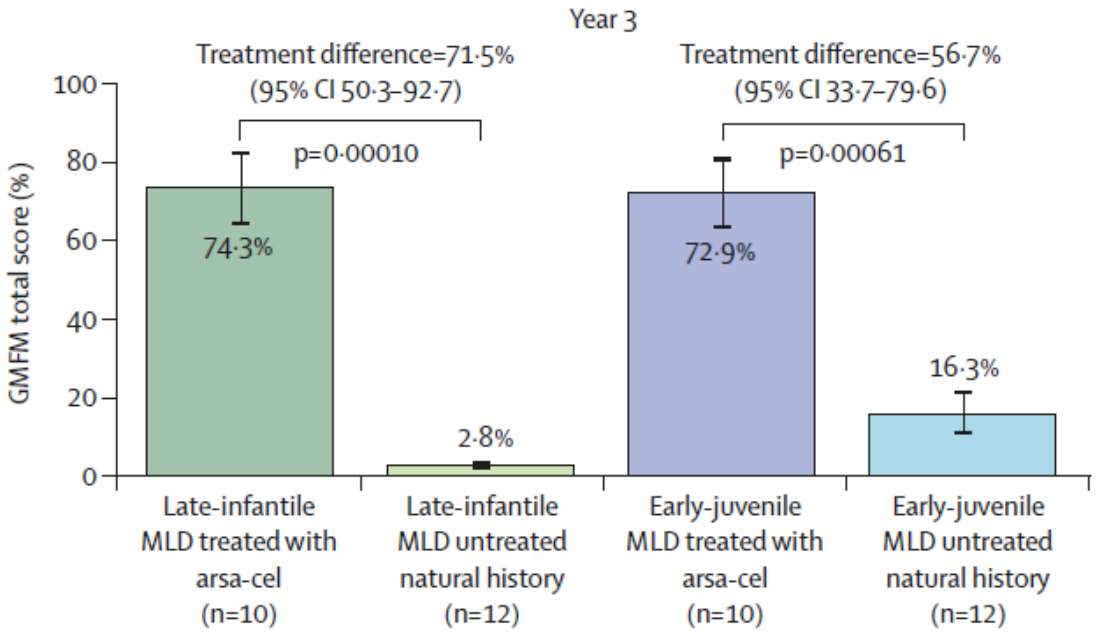
* For PBMCs, Reference range from adult reference donors, For CSF, Reference range from pediatric reference donors

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; Presented at: 2019 Annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM); September 3-6, 2019; Rotterdam, The Netherlands.

Clinical Development Autologous HSC Gene Therapy for MLD: Gross Motor Function Measure

Arsa-cel (OTL-200) vs. Natural History





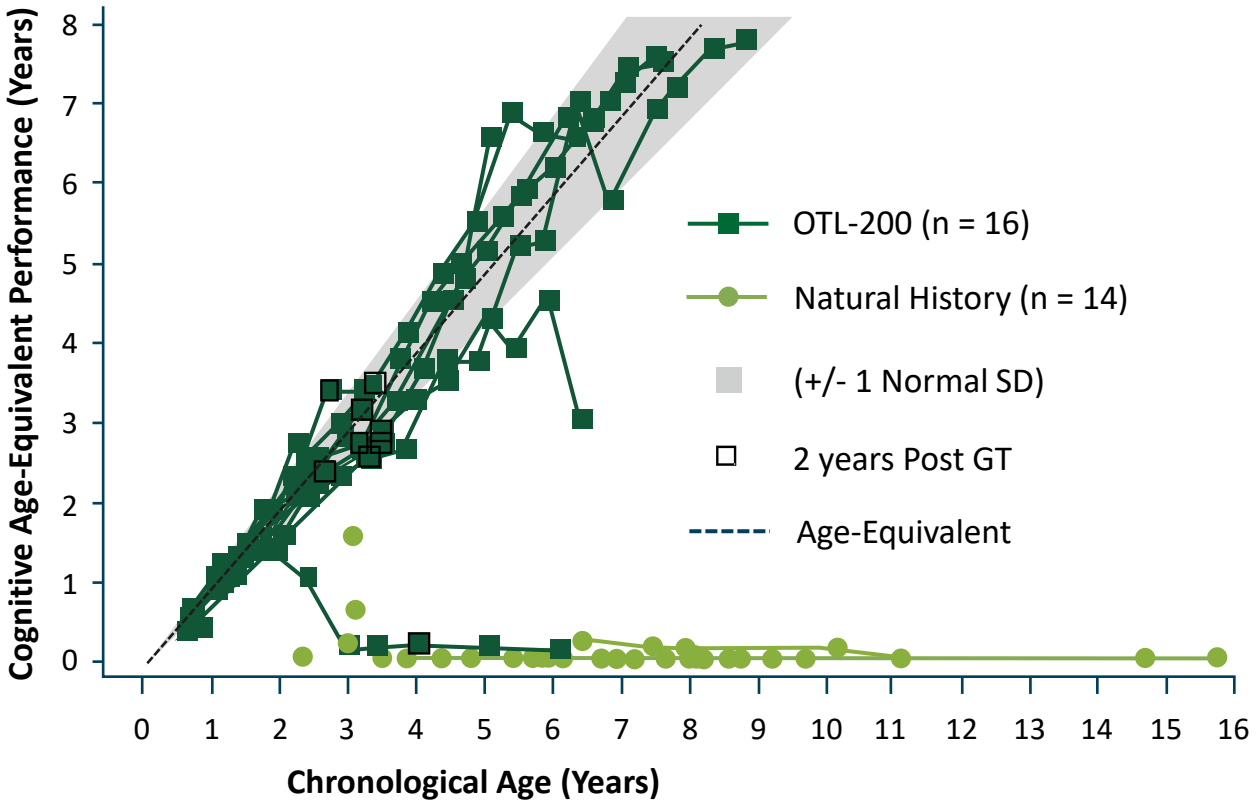
- Co-primary endpoint: **improvement of more than 10% in total gross motor function measure score at 2 years after treatment in treated patients compared with controls**

CI, confidence interval; EJ, early juvenile; GMFM, gross motor function measurement; GT, gene therapy; HSC, hematopoietic stem cell; LI, late infantile; MLD, metachromatic leukodystrophy.Figure from Fumagalli F et al. Lentiviral hematopoietic stem cell gene therapy (HSC-GT) for metachromatic leukodystrophy (MLD) provides sustained clinical benefit; Presented at: 2019 Annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM); September 3-6, 2019; Rotterdam, The Netherlands

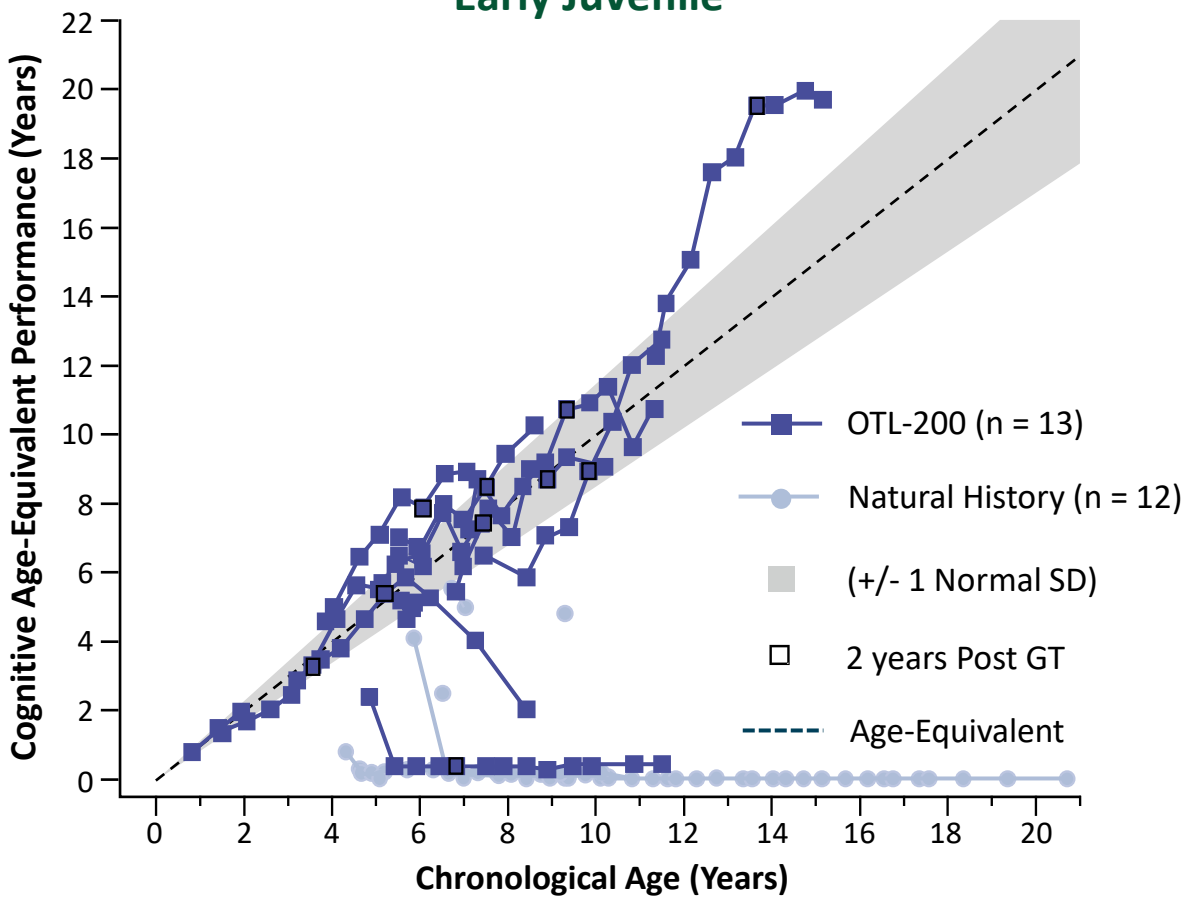
Clinical Development Autologous HSC Gene Therapy for MLD: Cognitive Age-Equivalent (Performance)

Arsa-cel (OTL-200) vs. Natural history

Late Infantile



Early Juvenile

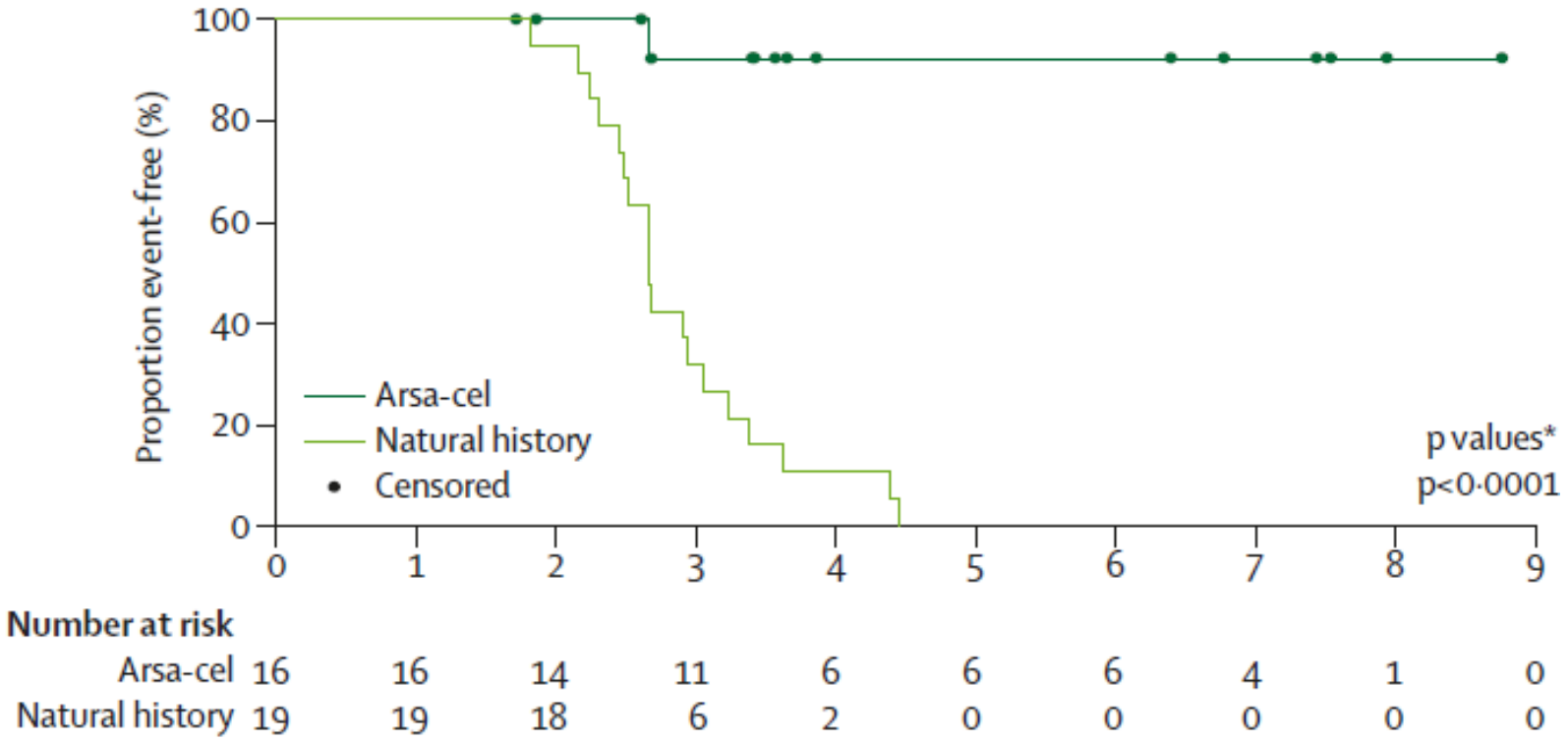


GT, gene therapy; SD, standard deviation.

Figures from Fumagalli F et al. Lentiviral Hematopoietic Stem and Progenitor Cell Gene Therapy (HSPC-GT) for Metachromatic Leukodystrophy (MLD): Clinical Outcomes from 33 Patients Presented at: 16th Annual WORLD*Symposium,* February 10-13, 2020, Orlando, FL, USA

Clinical Development Autologous HSC Gene Therapy for MLD: Clinical Outcome

Kaplan-Meier plot showing age at severe motor impairment or death in patients with late-infantile MLD versus untreated natural history late-infantile MLD controls



Figures from Fumagalli F et al. Lancet 2022, Lentiviral haematopoietic stem-cell gene therapy for earlyonset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase 1/2 trial and expanded access

Orchard therapeutics

Challenges of bringing a cell & gene therapy to the clinic

1

Orchard's HSC Gene Therapy Approach

2

Clinical Translation: Specific Considerations for Gene Therapy

3

Case Study: HSC-GT for MLD Libmeldy ™

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Summary & final thoughts: Accelerating clinical translation of C&GT

Regulatory agencies are expanding regulatory review capacity for GT

Provision of draft guidance for ATMPs/ C&GTs should continue to pave a clearer path to approval for pharma/biotech

Although innovative clinical trial designs enabled by (or required) small patient populations & high unmet need allow an **accelerated pathway, yet some clinical questions are unresolved**

Long-term follow-up is essential to ensure the durability of response or long-term safety & address ongoing concerns about genomic integration and off-target effects

Clinical development will need to adjust to a new paradigm of **compressed clinical development timelines & long-term follow-up**

Equates to significant investment beyond CT launch, to monitor safety & efficacy over extended time periods

CGT Products are **complex** and not yet fully defined or understood

Investments in automation are required to reduce manual labour, variability, & cost of goods; also allowing a platform approach to some elements of C&GT product manufacture

Orchard therapeutics

Thank you!

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