Corporate Presentation

November 2021

HOMOLOGY Medicines, Inc.

Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including statements regarding expectations about our competitive position, business strategy, prospective products, timing, design, results and likelihood of success of studies and/or clinical trials, including the Phase 1/2 pheNIX trial, including the expansion phase and the potential for conversion to a registrational trial, the Phase 1 pheEDIT trial, the Phase 1 juMPStart trial, and IND-enabling studies and/or planned clinical studies for MLD and MPS II (Hunter syndrome), timing for regulatory feedback, the potential of our gene therapy and gene editing platforms, including our new GTx-mAb platform, plans and objectives of management for future operations, manufacturing facility capabilities, the market opportunity for our product candidates, and the potential future uses and effects of our product candidates. These forward-looking statements are based on management's current expectations. These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, the following: the fact that we have incurred significant losses since inception and expect to incur losses for the foreseeable future; our need for additional funding, which may not be available; raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or drug candidates; our limited operating history; failure to use our novel genetic medicines platform to identify additional product candidates and develop marketable products; adverse public perception of genetic medicine, and gene editing in particular, may negatively impact regulatory approval of, or demand for, our potential products; the early stage of our development efforts with all programs in the research or preclinical stage; our failure or the failure of our collaborators to successfully develop and commercialize drug candidates; the regulatory approval processes of the FDA and comparable foreign authorities are lengthy, time-consuming and inherently unpredictable; delays or difficulties in the enrollment of patients in clinical trials; our product candidates may cause serious adverse events, side effects, toxicities or have other properties that may delay or prevent their regulatory approval; interim, topline and preliminary data may change as more patient data become available, and are subject to audit and verification procedures that could result in material changes in the final data; inability to maintain any of our collaborations, or the failure of these collaborations; our reliance on third parties to conduct our preclinical studies and manufacture our drug candidates; our inability to obtain required regulatory approvals; the fact that a Fast Track or Breakthrough Therapy designation by the FDA for our drug candidates may not actually lead to a faster development or regulatory review or approval process; the inability to obtain orphan drug exclusivity for drug candidates; failure to obtain marketing approval in international jurisdictions; failure to obtain U.S. marketing approval; ongoing regulatory obligations, continued regulatory review and any post-marketing restrictions or withdrawals from the market; effects of recently enacted and future legislation; failure to comply with environmental, health and safety laws and regulations; failure to achieve market acceptance by physicians, patients, or third-party payors; failure to establish sales, marketing and distribution capabilities on our own or in collaboration with third parties with such capabilities; effects of significant competition; unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives; product liability lawsuits; failure to retain key personnel and attract, retain and motivate qualified personnel; difficulties in managing our growth; the possibility of system failures or security breaches; failure to obtain and maintain patent protection for or otherwise protect our technology and products; effects of patent or other intellectual property lawsuits; the price of our common stock may be volatile and fluctuate substantially; significant costs and required management time as a result of operating as a public company; the impact of the COVID-19 pandemic on our business and operations, including our preclinical studies, ongoing and planned clinical trials and ability to access capital; and any securities class action litigation. These and other important factors discussed under the caption "Risk Factors" in our Quarterly Report on Form 10-Q for the quarter ended September 30, 2021, and our other filings with the Securities and Exchange Commission could cause actual results to differ materially from those indicated by the forward-looking statements made in this presentation. Any such forward-looking statements represent management's estimates as of the date of this presentation. While we may elect to update such forward-looking statements at some point in the future, we disclaim any obligation to do so, even if subsequent events cause our views to change. These forward-looking statements should not be relied upon as representing our views as of any date subsequent to the date of this presentation.

This presentation also includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties or us. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. All of the market data used in this presentation involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. While we believe these industry publications and third-party research, surveys and studies are reliable, we have not independently verified such data. The industry in which we operate is subject to a high degree of uncertainty, change and risk due to a variety of factors, which could cause results to differ materially from those expressed in the estimates made by the independent parties and by us.

HOMOLOGY Medicines, Inc.

Homology Medicines' Mission:

Cure Genetic Disease

HOMOLOGY Medicines, Inc.

Fully Integrated Gene Therapy and Gene Editing Company With Three Clinical Programs in 2021

Technology

15 novel AAVHSCs; potential to **expand**

Equity investments from Pfizer and Novartis

Extensive I.P. portfolio

Clinical Trial Execution

Positive PKU gene therapy data;
Phase 2 dose expansion enrolling

Phase 1 **gene editing PKU trial**

Phase 1 **Hunter syndrome trial**

Rare Disease Experience

Team has developed and/or launched **11 rare disease drugs with >$2B in annual revenue**

Discovery, Research & Development

5 development candidates

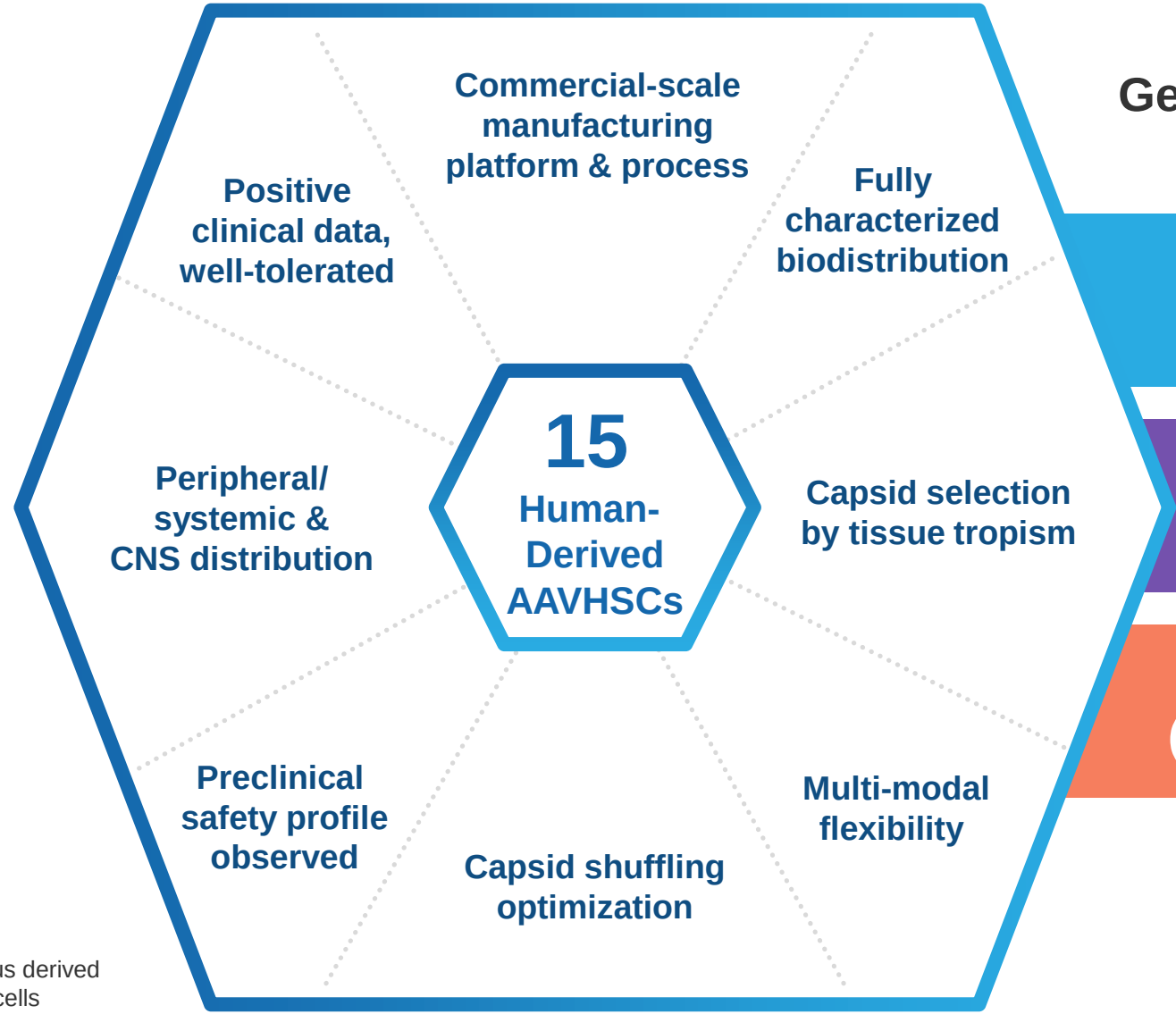
Manufacturing Expertise

25,000 sq. ft. internal **GMP facility**

Commercial platform and process scaled to 2,000L

HOMOLOGY Medicines, Inc.

AAVHSC Platform: The Complete Package



Genetic Approaches

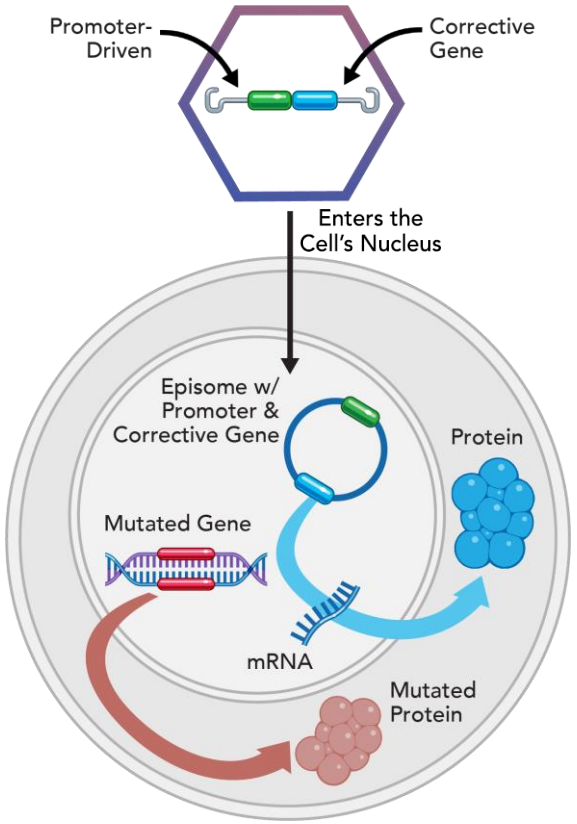
- Gene Therapy
- GTx-mAb
- Gene Editing (Nuclease-Free)

AAVHSC = adeno-associated virus derived from human hematopoietic stem cells

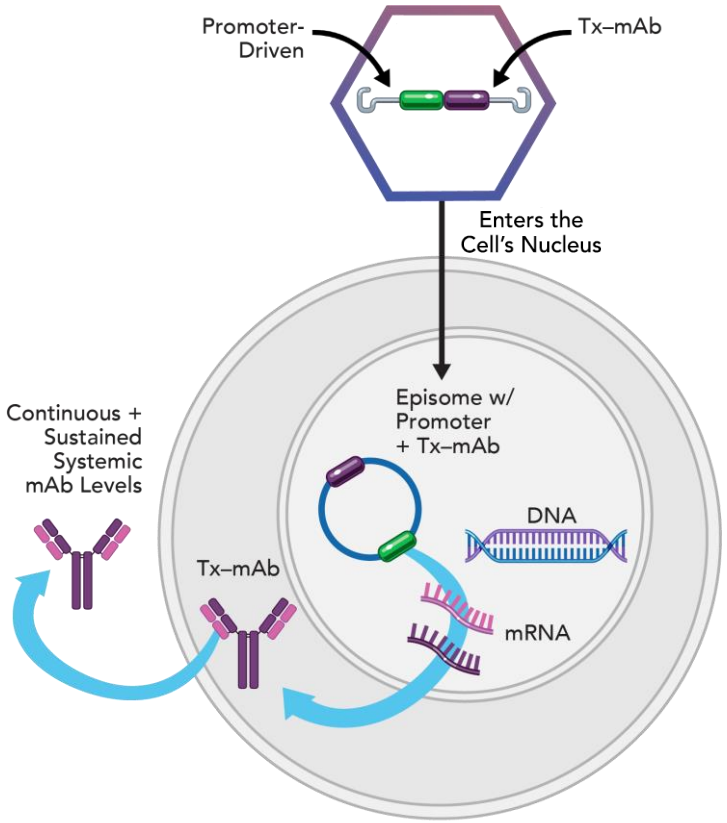
HOMOLOGY Medicines, Inc.

Flexible AAVHSC Platform Designed To Address Rare Genetic Disorders and Diseases With Larger Patient Populations

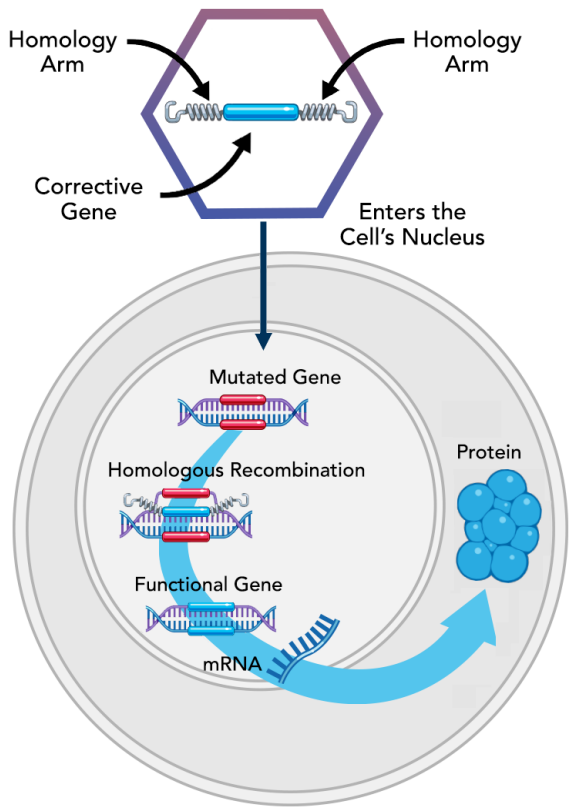
Gene Therapy (Adds a Gene)



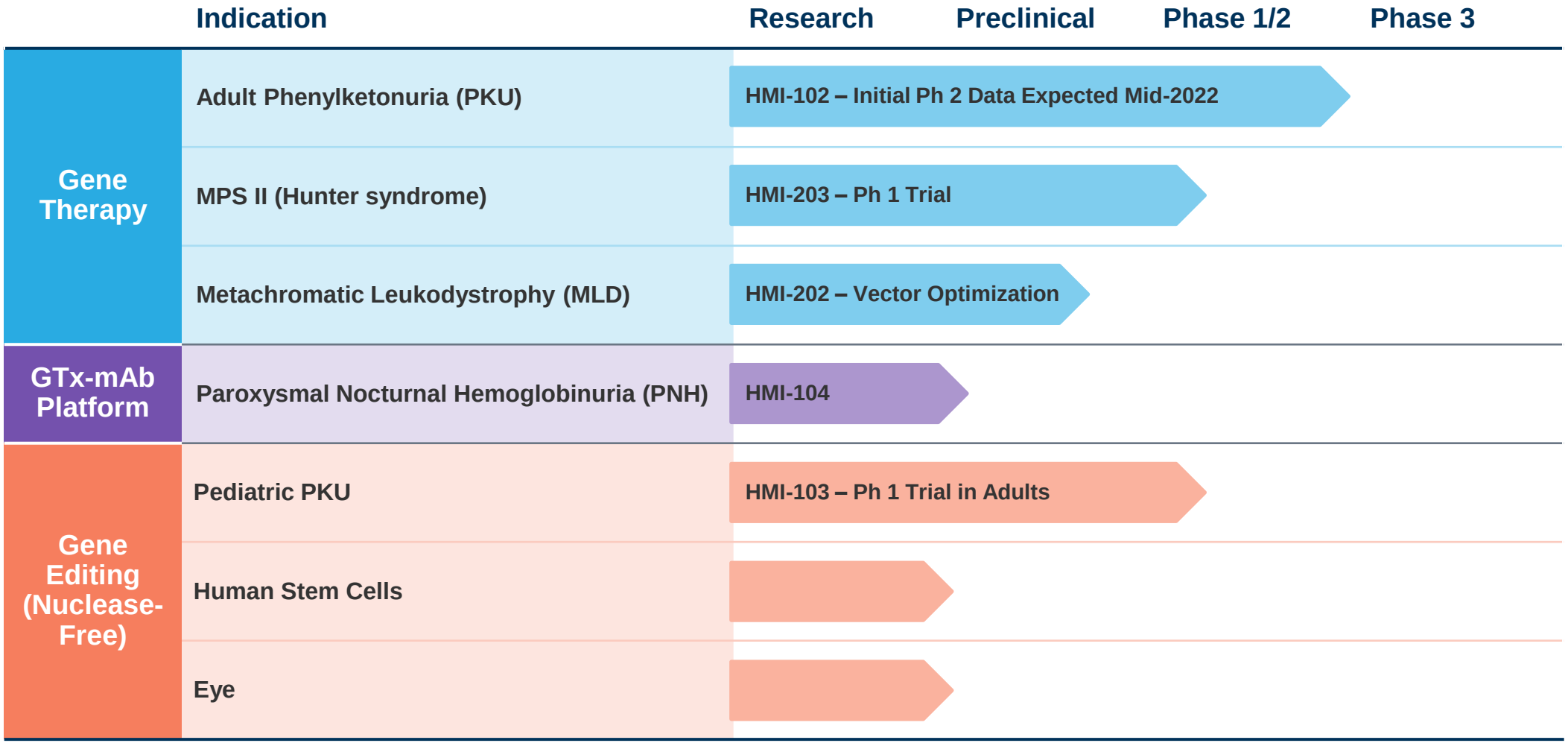
Gene Therapy (GTx-mAb)



Gene Editing (Nuclease-Free)



Homology's *In Vivo* AAVHSC Genetic Medicines Pipeline

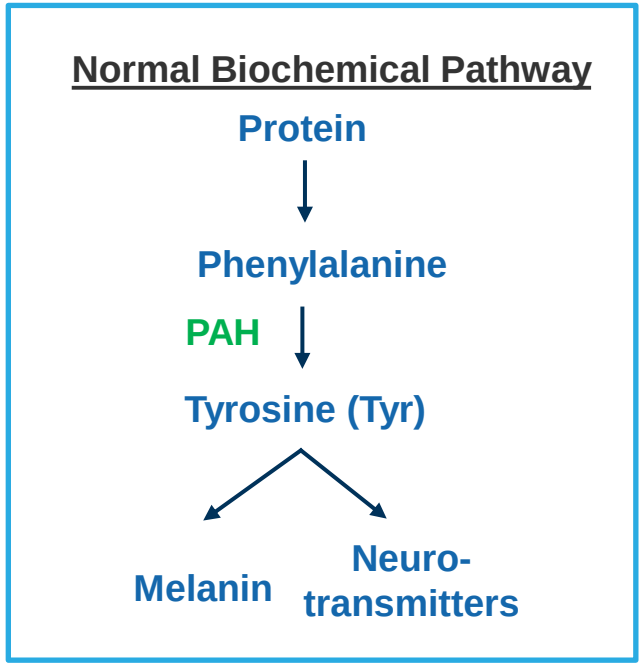


Effective PKU Treatment Remains a High Unmet Medical Need

- **Inborn error of metabolism** caused by mutations in the *PAH* gene
- Results in **loss of function of phenylalanine hydroxylase** responsible for metabolism of phenylalanine (Phe)
- If **untreated**, **toxic levels of Phe accumulate** and result in progressive and severe neurological impairment

Unmet Need

- Standard of care → onerous low Phe **diet has poor compliance**
- **Diet not sufficient** to reduce Phe levels to within ACMG targets (120-360 µmol/L) or EU targets (120-600 µmol/L)
- **Therapeutics do not reconstitute normal biochemical pathway for ~95% of patients**; all require **chronic dosing vs. a potential one-time treatment**
- **Physicians, patients seek new treatment options**



Target sources: Vockley J et al. Genetics in Medicine 2014; Levy H et al. Molecular Genetics and Metabolism 2019; van Spronsen FJ et al. Lancet Diabetes Endocrinol 2017.
ACMG = American College of Medical Genetics and Genomics

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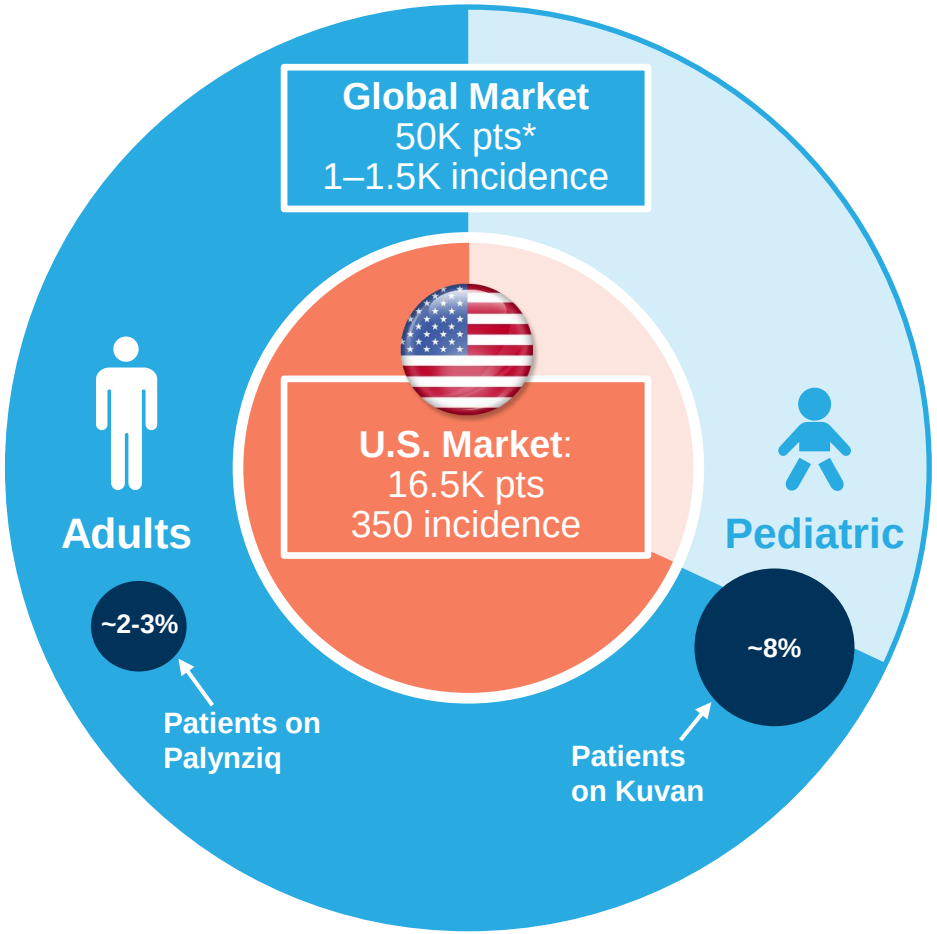
PKU: One of the Largest Established Rare Disease Commercial Markets With Only ~10% of Patients Treated With a Therapeutic



- **Unmet need** remains with current therapeutics:
  - **Kuvan:** Daily oral treatment for patients with BH4-responsive PKU; requires low Phe diet
    - 2020 sales: $457.7M (4K patients globally, 2.5K in U.S.)
  - **Palynziq:** Daily subcutaneous injection of plant-based lyase that does not reconstitute normal biochemical pathway; black box warning
    - 2020 sales: $171M (~1K patients, with significant proportion of Palynziq clinical trial and Kuvan user conversions)
    - Projected peak sales of $500M - $1B

Homology's dual approach to PKU has potential to **treat adult and pediatric patient populations**

***Classical PKU is most severe** form (~2/3 of PKU population)

Untreated population source: PKU population from NORD, NPKUA and sales of two approved PKU treatments
Palynziq sales analysis based on an average of 14 BioMarin analyst reports

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Plans to Report Initial Data From Expansion Phase of pheNIX Clinical Trial Mid-2022

HMI-102

One-time gene therapy designed to restore natural biochemical pathway, including production of PAH enzyme that converts Phe to Tyr, a precursor to neurotransmitters

- Physicians, patients **excited about positive Ph 1/2 dose-escalation data**
  - **Generally well-tolerated** with no treatment-related serious adverse events (SAEs)
  - **Achieved target Phe levels** per treatment guidelines* in one of two patients at two different doses
  - Tyr increases and Phe-to-Tyr ratio decreases **consistent with PAH enzymatic activity**, even while patients self-liberalized diet
- **Applied learnings** from dose-escalation phase to dose expansion phase; **enrollment ongoing with both doses generally well-tolerated and evidence of biological activity****
- Onboarded **additional sites for a total of 13 with more sites expected shortly**
- Plans to **report initial safety & efficacy data** from expansion phase by mid-2022

*Target sources: Vockley J et al. Genetics in Medicine 2014; Levy H et al. Molecular Genetics and Metabolism 2019; van Spronsen FJ et al. Lancet Diabetes Endocrinol 2017.
**As of Sept 30, 2021

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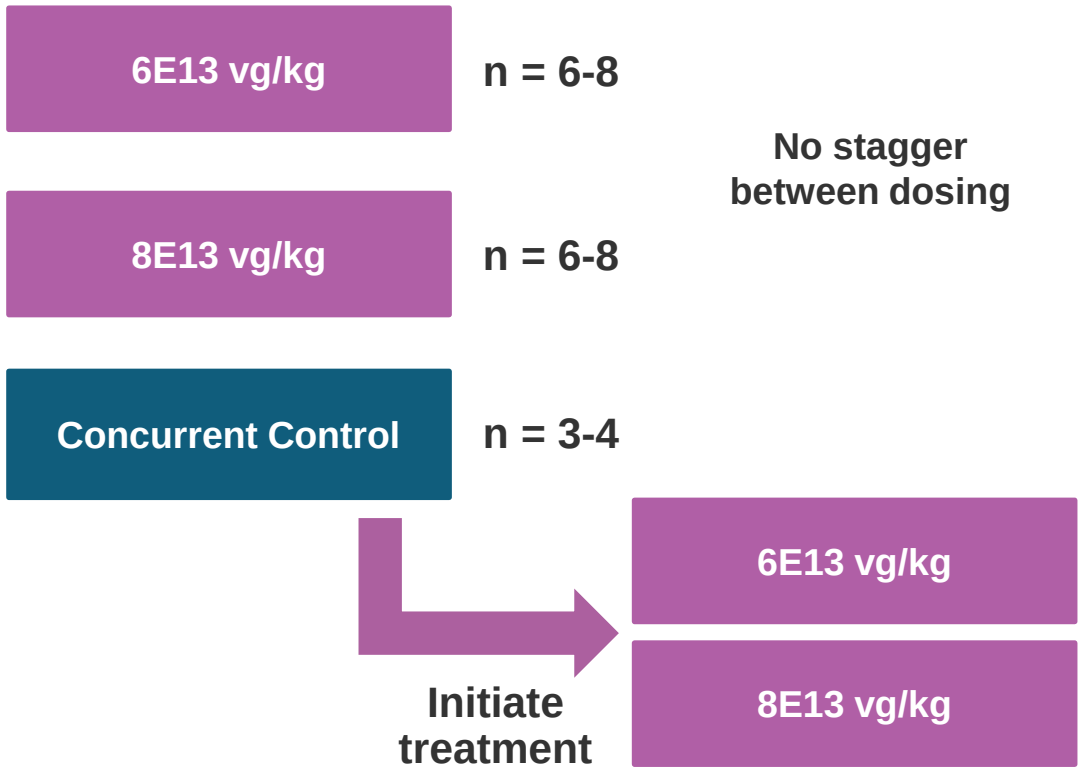
pheNIX Dose Expansion Phase Has Potential to Convert to Registrational Trial

HMI-102

pheNIX
CLINICAL STUDY FOR PATIENTS WITH PKU



- Adults with classical PKU
- Randomized, concurrently controlled
- Single I.V. administration
- Prophylactic tapering steroid regimen

ENDPOINTS

Primary:

Change from baseline in mean plasma Phe

Secondary:

- Incidence of plasma Phe concentrations
- Change in diet
- Neurocognitive evaluation

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pheEDIT Trial: First Nuclease-Free Gene Editing Study for PKU

HMI-103

- **Product candidate designed to maximize PAH expression in liver with one-time treatment**
- **Developed to integrate functional *PAH* gene into genome using natural DNA repair process of homologous recombination (HR)**
  - **Unlike nuclease-based technologies that cut DNA and can introduce unwanted mutations (insertions, deletions)**

- **pheEDIT: Gene editing Phase 1 dose-escalation trial in adults with PKU**
  - Goal to **move to pediatric patients** to address rapidly dividing livers
- Utilizes **AAVHSC15**, same vector as HMI-102, which has been generally well-tolerated in ongoing pheNIX clinical trial*
- **Engaging with multiple clinical trial sites**

*As of Sept 30, 2021

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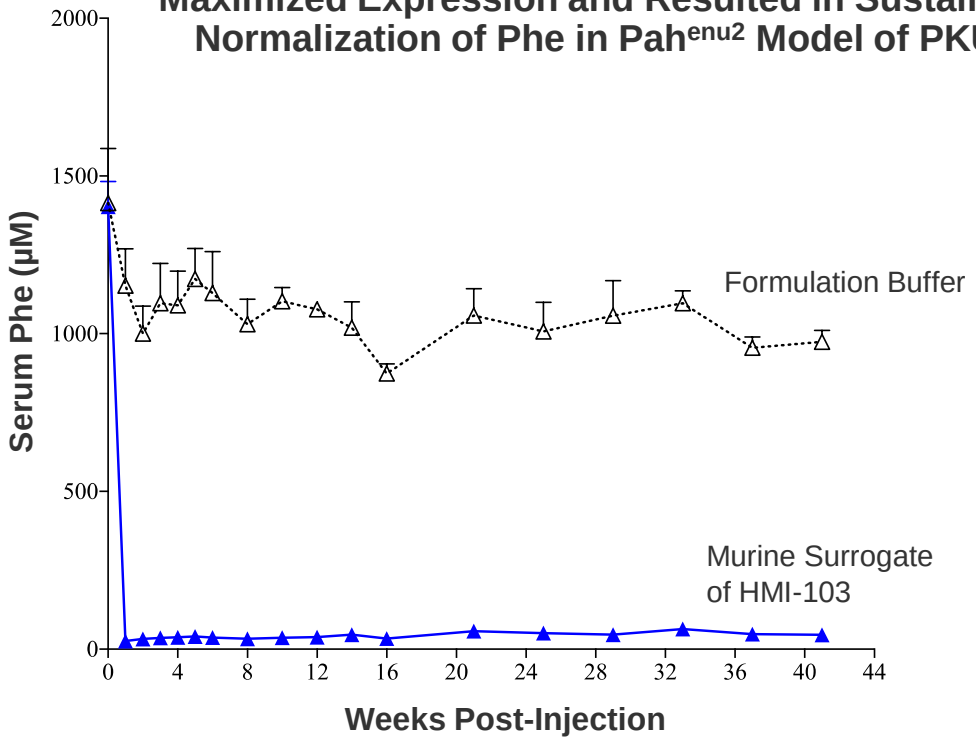
Encouraging Preclinical Data Support Advancing HMI-103 Into Clinical Trials

HMI-103

Human-specific gene editing vector integrated into human *PAH* locus at rates shown to result in sustained reduction of serum Phe in the PKU murine model

Maximized Expression and Resulted in Sustained Normalization of Phe in Pah^{enu2} Model of PKU



Molecular methods demonstrated no unwanted on-target mutations following *in vivo* editing of humanized murine model

Method	Outcome
Sequencing across homology arm of integrated alleles Sequence coverage >10,000 reads per base	**No *de novo* mutations** introduced
Long-read sequencing to capture entire sequence from inserted DNA ➔ homology arm ➔ native genome	**No inverted terminal repeats (ITRs)** detected

Chen H-M, et al. Molecular characterization of precise in vivo targeted gene integration in human cells using AAVHSC15. PLOS ONE (2020).

Source: Homology internal data

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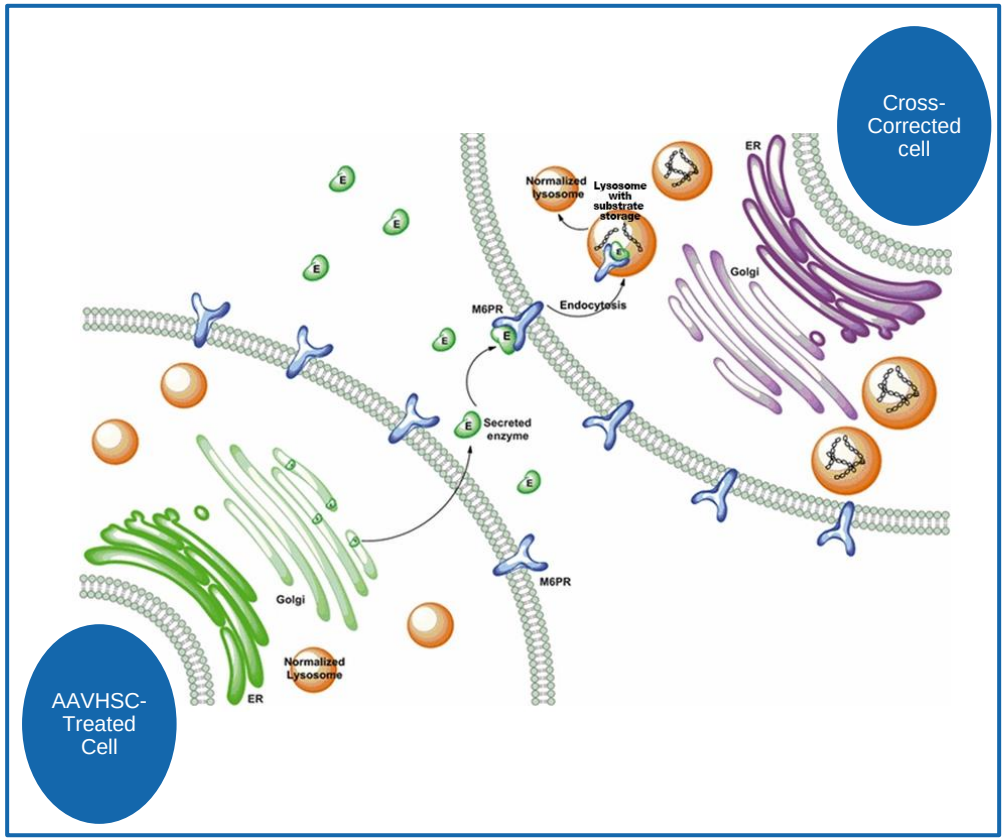
Investigational Gene Therapies for Lysosomal Storage Disorders

MPS II (Hunter syndrome)

- Caused primarily by *IDS* gene mutations
- Leads to **toxic lysosomal accumulation of glycosaminoglycans** (GAGs)
- Severe form includes **progressive debilitation and intellectual decline followed by death** in 10–20 years
- Prevalence: **1 in 100,000 to 1 in 170,000*; primarily males**



Broad Distribution With AAVHSCs Resulted in Both Cellular Transduction and Cross-Correction of Neighboring Cells

Metachromatic Leukodystrophy (MLD)

- Caused primarily by *ARSA* gene mutations
- Results in **destruction of myelin-producing cells**
- Late infantile form includes **rapidly progressive motor and cognitive decline** followed by **death in 5–10 years**
- Prevalence: **1 in 40,000***

*Prevalence: National MPS Society, MLD Foundation
Image Source: D'Avanzo et al., *International Journal of Molecular Sciences*, 2020

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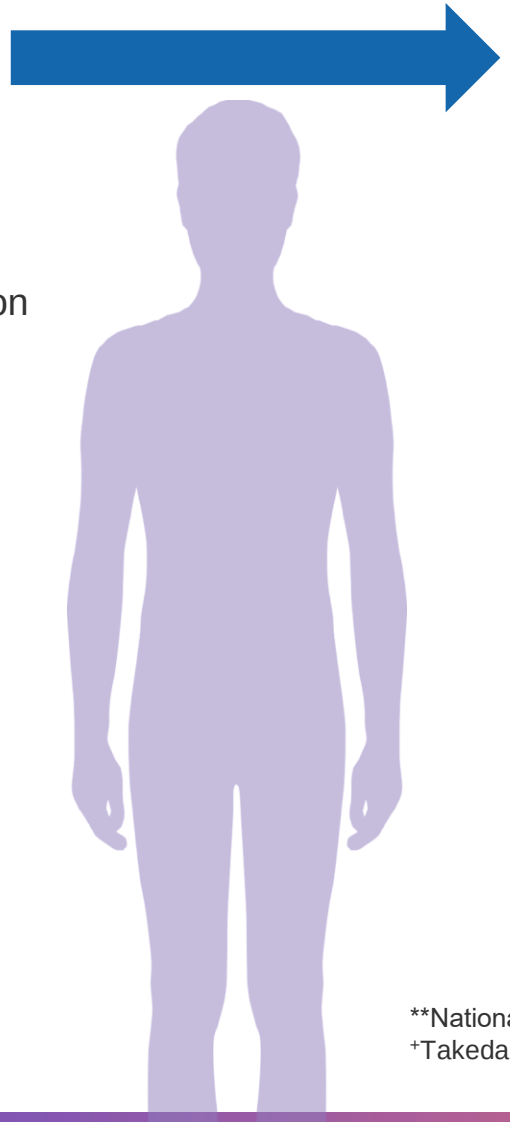
High Unmet Need for MPS II Treatment That Addresses Peripheral and Cognitive Effects

HMI-203

Peripheral

- **Patients on existing ERT continue to experience*:**
  - Increased mortality, sleep apnea, chronic and joint pain, lung and cardiac conditions, hearing loss, limited mobility/range of motion
  - Anxiety caused by uncertainty of disease progression, life expectancy
- **Non-neuronopathic form fatal by 30–40 years**



CNS

- **ERT does not cross blood-brain-barrier (BBB); Patients continue to experience**:**
  - Decreased cognitive function, seizures, cerebrospinal fluid accumulation, carpal tunnel syndrome
- **3-5 years to evaluate CNS endpoints⁺; Need to treat patients <3 years**
- **GAG reduction ≠ CNS function**
- **Neuronopathic form fatal by 20 years**

*ASHG 2021, Haroldson, J., et al.

**National MPS Society. "A Guide to Understanding MPS II."
⁺Takeda WORLD*Symposium*™ data

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juMPStart Trial: Homology's Differentiated Clinical Development Strategy to Evaluate Systemic Gene Therapy Candidate for MPS II

HMI-203

- **One-time *in vivo* gene therapy candidate**
- **Designed to deliver functional copies of *IDS* gene to peripheral organs and CNS**
- **First systemic gene therapy to be evaluated in clinical trials for MPS II**

- AAVHSC biodistribution studies in NHPs showed single I.V. dose **targeted peripheral organs** and **crossed BBB**
- **IND-enabling studies in MPS II murine model** demonstrated:
  - **Long-term transduction and expression** in brain and other organs
  - **Sustained secretion of I2S** into serum
  - **Reduced GAG-HS** in all tissues tested, **including CSF**
  - Phenotypic **correction of joints and skeletal features**
- **Phase 1 juMPStart to focus on unmet need in ERT-treated adults with a one-time treatment**
  - Evaluate peripheral manifestations as measured by registerable endpoint – 6-minute walk test
  - Other endpoints to include I2S levels and GAG reduction in serum, urine, CSF
  - Plans for ERT discontinuation

NHP = non-human primate; BBB = blood-brain-barrier; GAG-HS = glycosaminoglycan heparan sulfate; CSF = cerebrospinal fluid

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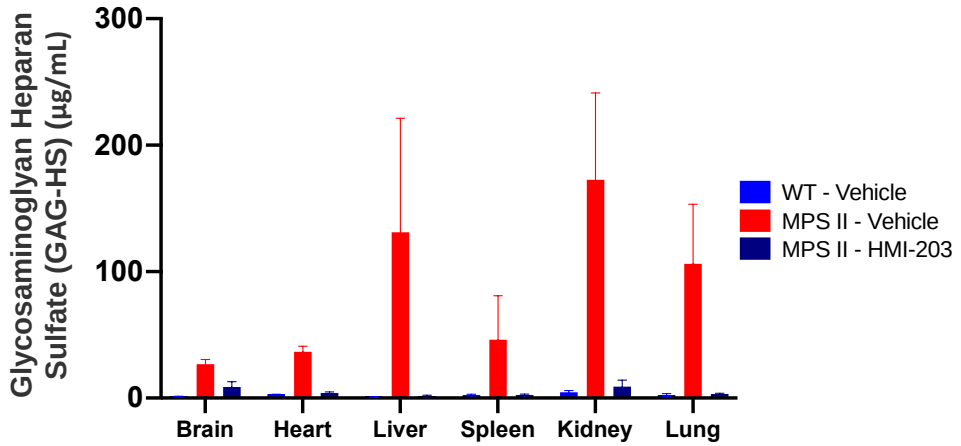
Biochemical and Phenotypic Correction in MPS II Murine Model

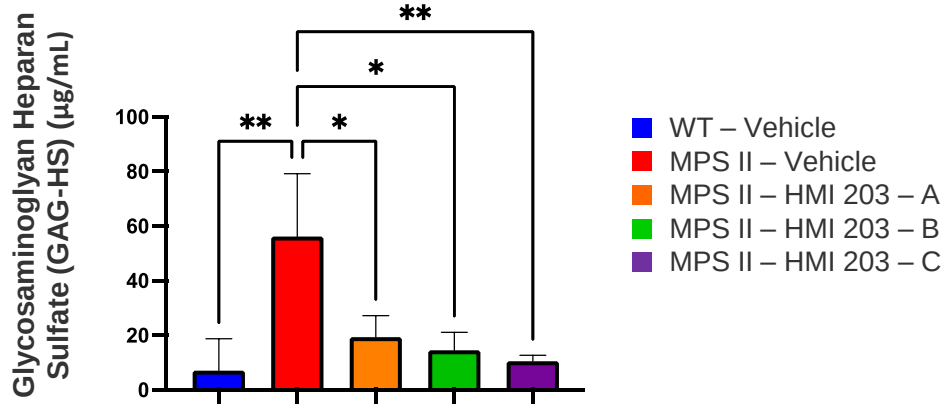
HMI-203

Biochemical Correction

HMI-203 Tissue GAG-HS (at 52 Weeks)



CSF GAG-HS Levels (at 12 Weeks)

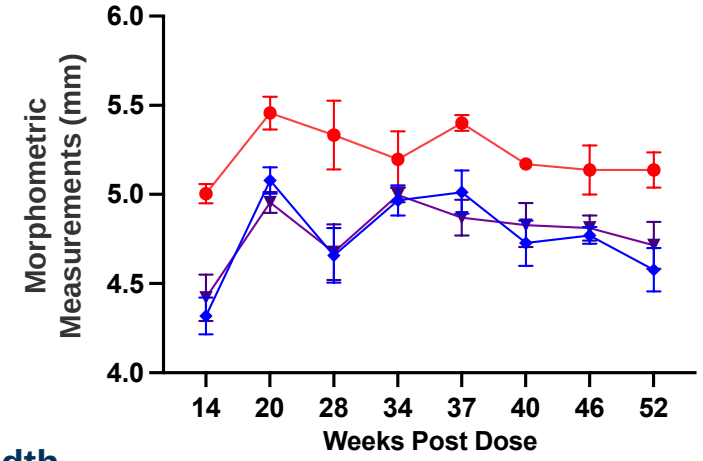


* p>0.05; ** p>0.01; *** p>0.001; “ns” = no significance.

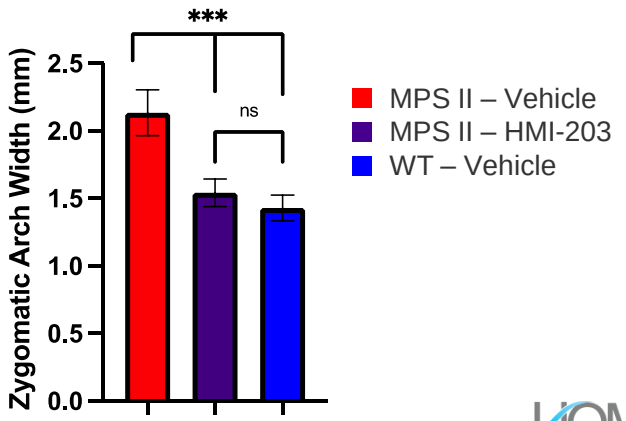
ASGCT 2021. Smith, et al.

Phenotypic Correction

Paw Width



Arch Width



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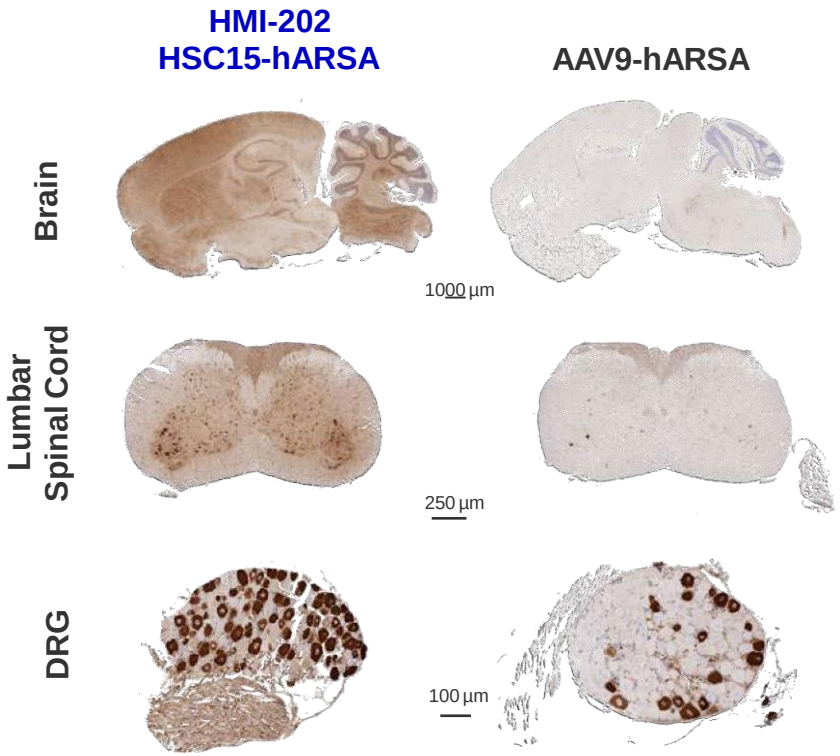
HMI-202 Demonstrated Superior Biodistribution Compared to AAV9 and Motor Benefit in Two Cohorts in *Arsa* KO MLD Mice

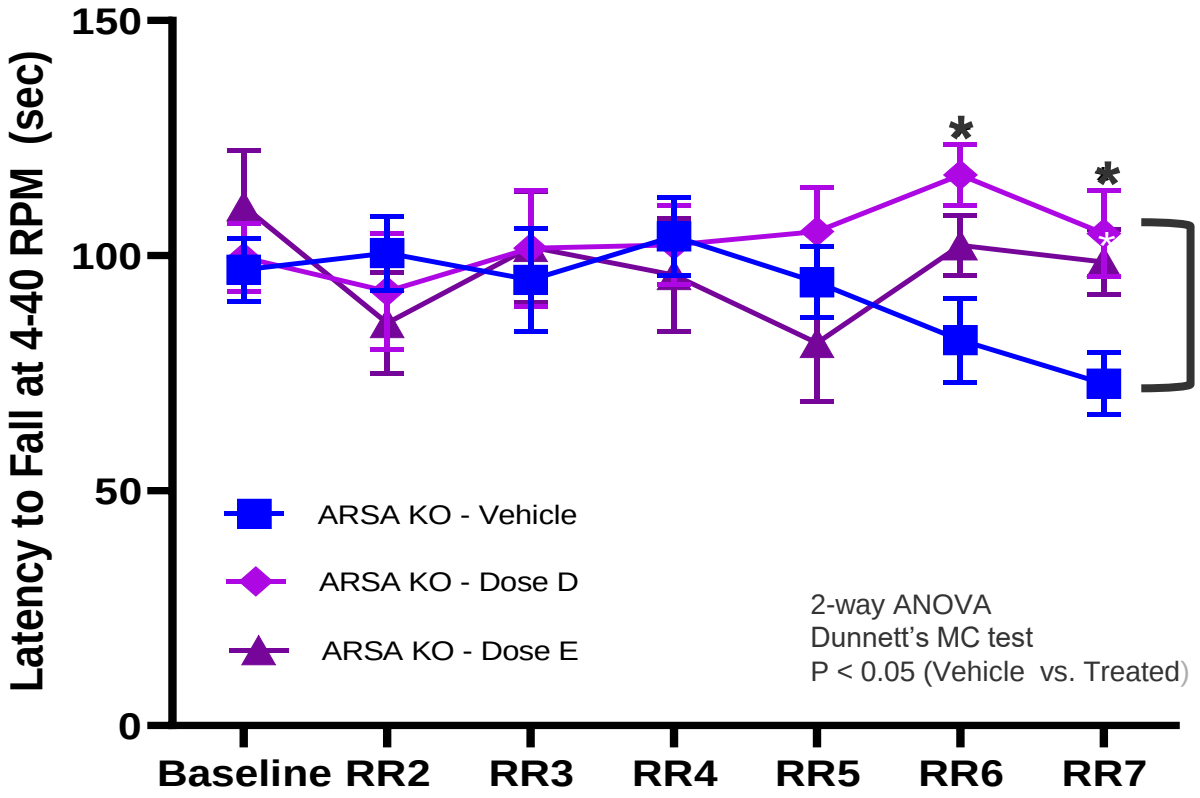
HMI-202

Nervous System Biodistribution of HMI-202 is Broader Than AAV9-hARSA



- **HMI-202 & AAV9-hARSA cross the blood-brain and blood-nerve barriers (BBB and BNB, respectively)**

Rotarod Assay

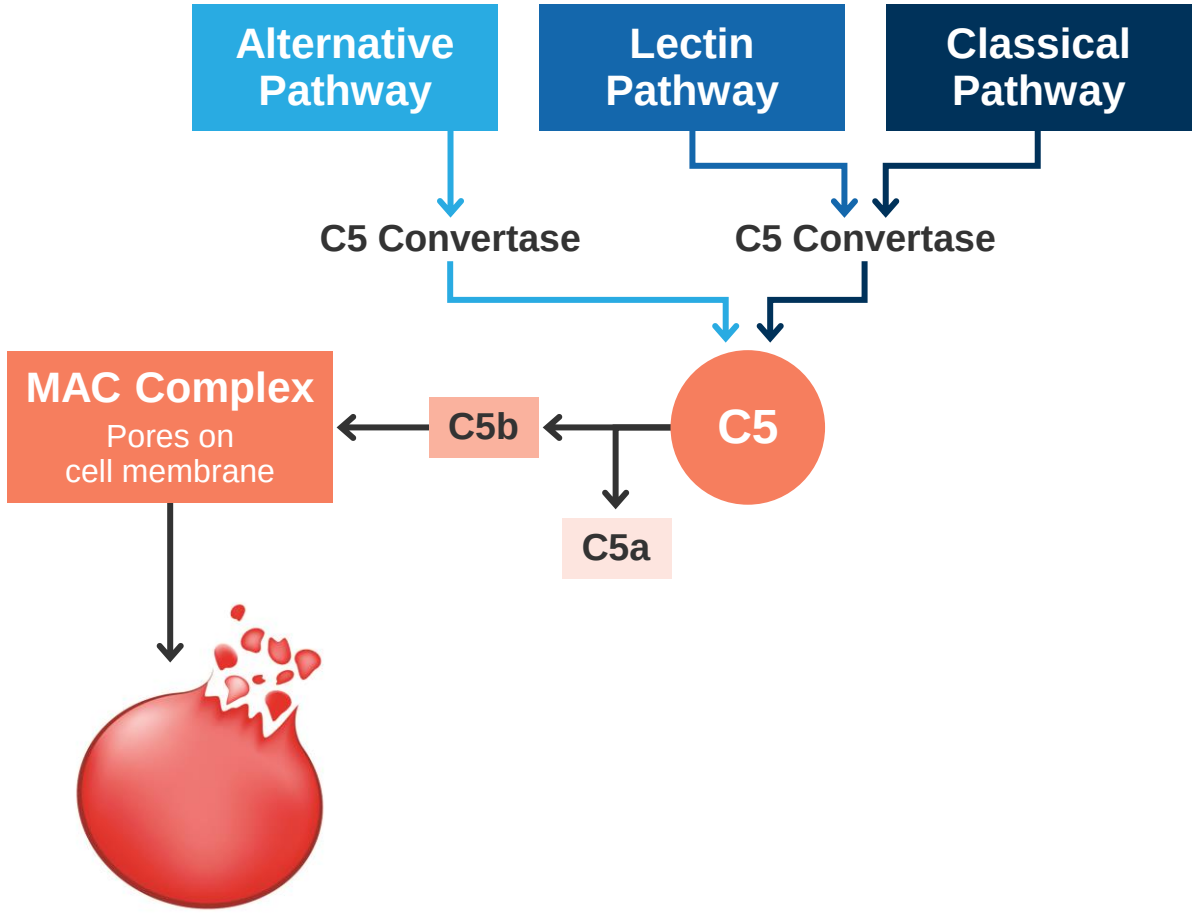


ASGCT 2021. Gingras, et al.

Leveraging Gene Therapy with GTx-mAb Platform

Targeting the Complement Pathway in Paroxysmal Nocturnal Hemoglobinuria (PNH) as Proof of Concept for GTx-mAb

All Complement Pathways Cleave and Activate C5



PNH: Rare, Acquired, Life Threatening Blood Disease, Treatable by Targeting C5

- PIGA mutations result in intravascular hemolysis (RBC destruction) mediated by uncontrolled activation of complement system
- Chronic dosing with anti-C5s imperfect; patients struggle with conditions, including:
  - Fatigue
  - Anemia (~25%)
  - Repetitive infusions (~25%)
  - Hospitalizations
  - Infection risk

*Homology Medicines Market Research & Analysis / KOL Interviews

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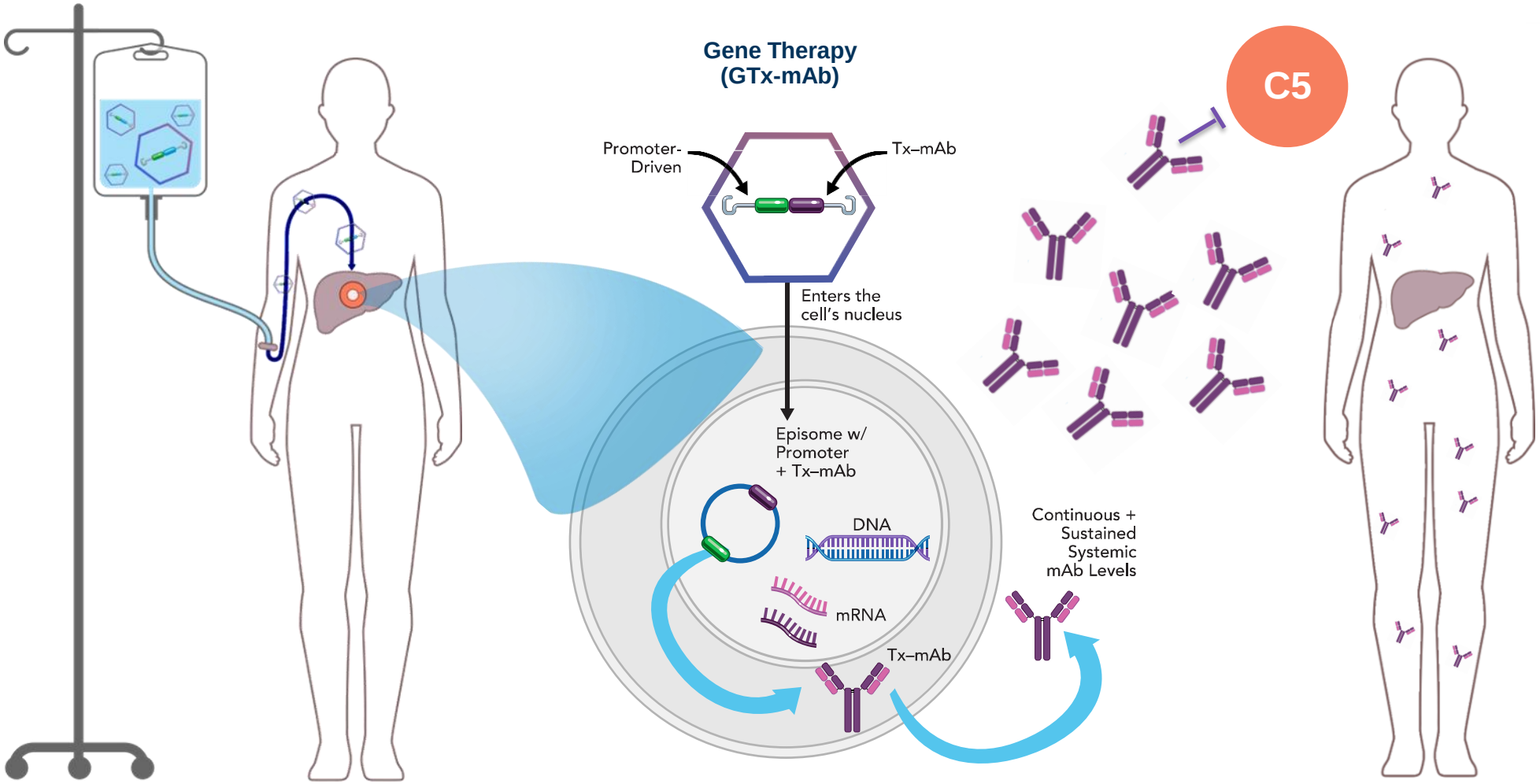
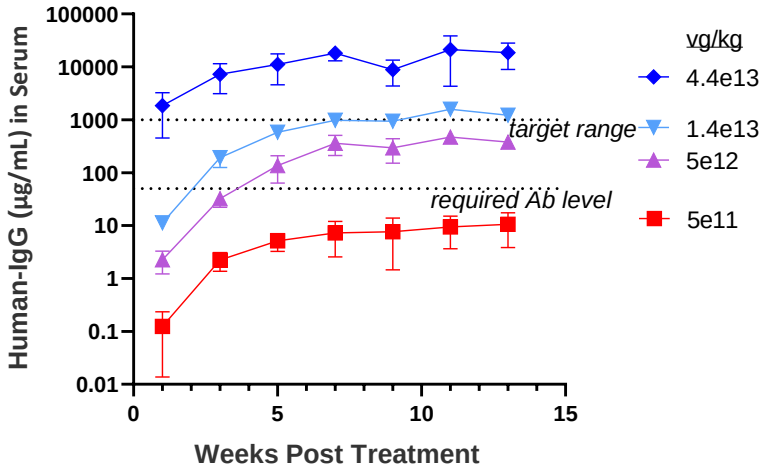
Approach to Target C5: Systemic Delivery Results in Continuous and Sustained mAb Levels

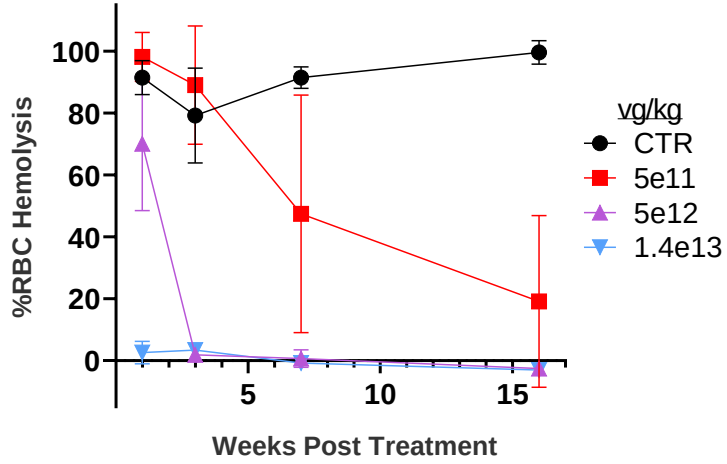


C5 Data Demonstrated Potential as a Sustained, Low Dose One-Time Treatment

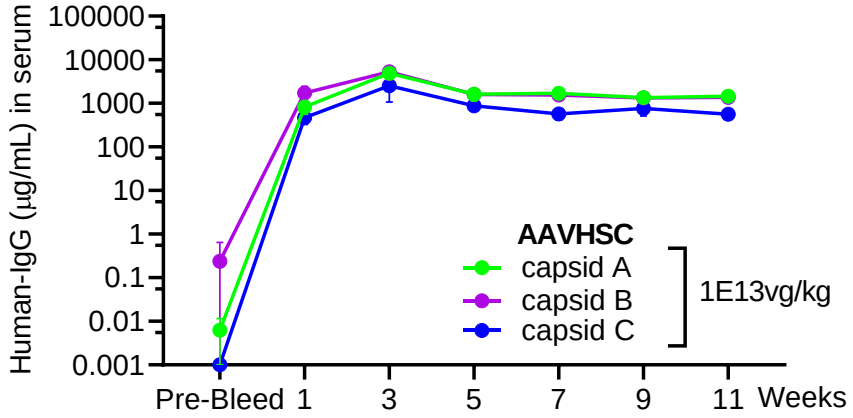
Generated C5mAb in Serum of NOD-SCID* Treated Mice in Target Range



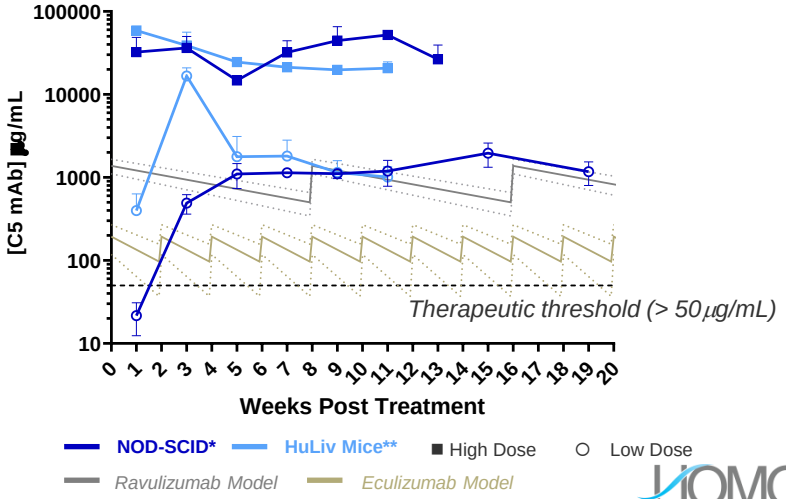
C5mAb Protected Against Erythrocyte Hemolysis



C5mAb in Serum of HuLiv** Treated Mice – Proof of Concept for Human Liver



Model for Comparator mAbs Based on C_{max}, C_{trough} & Dosing Schedule for PNH Patients Showed Sustained, Continuous Production



*Non-obese diabetic/severe combined immunodeficiency |**Humanized Liver Model from Yecuris are FRG® KO
ASGCT 2021. Sharma, et al..

Gatault et al (2015) *maBs* 7:6 1205-1211; Wijnsma et al (2019) *Clinical Pharmacokinetics* 58:858-874.
Dosing: https://alexion.com/Documents/Soliris_USPI.pdf; https://alexion.com/Documents/Ultomiris_USPI.pdf

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Single I.V. Dose of GTx-mAb AAVHSC in Mice Showed Expression of Full-Length Antibodies Consistent With Anti-C5 Therapeutic Levels

HMI-104

- Proprietary vector designed to express a full-length antibody against C5 was **delivered via AAVHSCs and expressed in the liver**
- **Sustained, robust IgG expression *in vivo*** was demonstrated for duration of study (up to 20 weeks)
- *Ex vivo* hemolytic assay showed *in vivo* vector-expressed C5mAb had **potent functional activity**

One-time GTx-mAb could provide consistent levels of functional antibody and reduce the risks of peaks and troughs inherent with chronic antibody treatments

Named HMI-104 Development Candidate for PNH

ASGCT 2021. Sharma, et al.

HOMOLOGY Medicines, Inc.

2021 Anticipated Milestones: Progress Three Clinical Programs and Pipeline

PKU Gene Therapy HMI-102
- Enrolling for Phase 2 dose expansion gene therapy trial for adults with PKU
- Initial clinical data from Phase 2 anticipated by mid-2022

PKU Gene Editing HMI-103
- Dose-escalation trial in PKU

MPS II Gene Therapy HMI-203
- Dose-escalation trial in MPS II

MLD Gene Therapy HMI-202
- Optimizing HMI-202 vector for MLD

PNH GTx-mAb HMI-104
- Introduced new GTx-mAb platform and shared first in vitro and in vivo data at ASGCT 2021
- Named development candidate HMI-104 for PNH

Manufacturing
- Leveraging internal GMP commercial process and platform for clinical and pipeline supply; scaled to 2,000L with 3,500L total active capacity

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Power of the Platform

AAVHSCs for Broad Range of Diseases

PLOS ONE

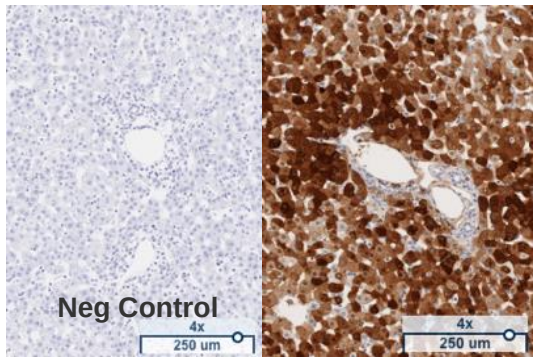
Clade F AAVHSCs cross the blood-brain barrier and transduce the central nervous system in addition to peripheral tissues following I.V. administration in NHPs

Muscle	CD34s	Liver	CNS	Lung	Retina

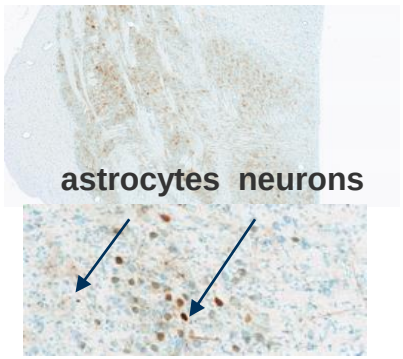
A single AAVHSC can transduce multiple organs with one administration

Certain diseases require multi-tissue tropism, incl. Friedreich's Ataxia, MPS II, MLD, etc.

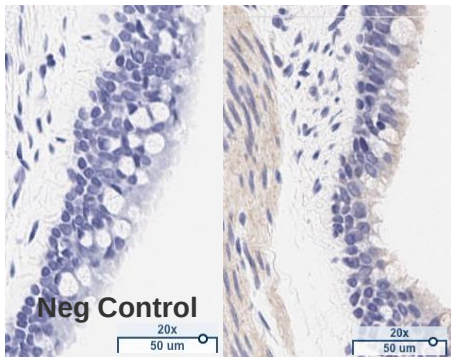
Liver



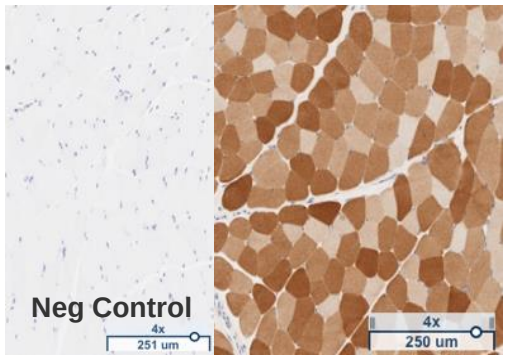
Brain



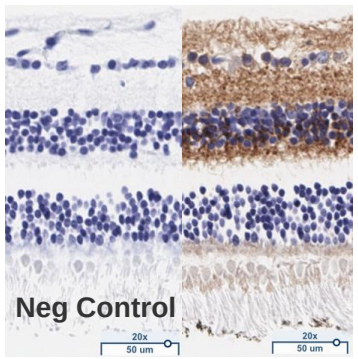
Lung



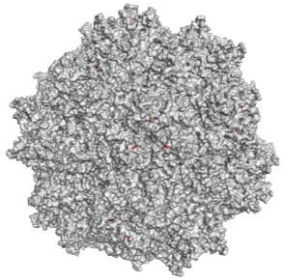
Skeletal Muscle



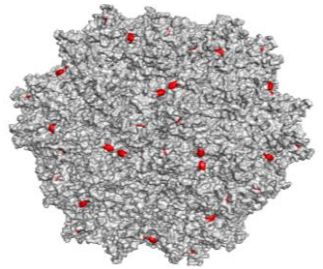
Retina



AAVHSC15



Two amino acid differences in VP3 result in significant variations externally and in biodistribution patterns



AAVHSC16

Biodistribution photos from NHPs two weeks post-dosing with single I.V. injection of AAVHSC15

HOMOLOGY Medicines, Inc.

Single Manufacturing Platform for Gene Therapy, Gene Editing and GTx-mAb Technology

Homology's Team of Technical Operations Experts

- 25,000 sq. ft. internal GMP facility
- Commercial process and platform
- Consistent plug and play model to produce GMP materials rapidly
- Scalable from research to commercial
- 1,500L active capacity (3x500L), scaled to 2,000L
- Process development and vector characterization

Homology's 2,000L Bioreactor

 |

HOMOLOGY Medicines, Inc.

Realizing Substantial Efficiencies from Homology's Manufacturing Platform and Outlook for the Future

- Well-established platform across **gene therapy, gene editing & GTx-mAb**, as well as portfolio of AAVHSCs and constructs, enables rapid development and delivery of **GMP quality vector for clinical and pipeline supply**
- Further optimization of **'plug and play'** manufacturing process and platform created **greater than 50% efficiencies** in subsequent programs and significantly reduced expense for trial materials
- Taking production performance to the next level:
  - Shifting from **frozen to cold** storage
  - Increasing **yield & product quality**
  - Supporting **broader and larger** therapeutic areas
  - Enhancing analytical characterization capabilities to **drive further product quality improvements** and/or understanding

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