



**CYPRIMUM**  
THERAPEUTICS

**Corporate Presentation**

December 2021

## ► Forward Looking Statements

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# ► Company Highlights

- **Cyprium Therapeutics** is an orphan disease company with a focus on the development and commercialization of novel therapies for Menkes disease, a rare and fatal pediatric disease in copper metabolism.



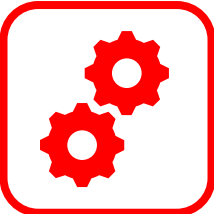



- **CUTX-101 (Copper Histidinate Injections)** ODD FT RPD BTD OMP
  - Rolling NDA submission to the FDA initiated in December 2021 – NDA submission expected to complete in mid-2022.
  - Potential to be the first FDA-approved treatment for Menkes Disease
  - Reported positive topline clinical efficacy data, showing a nearly 80% reduction in the risk of death (Hazard Ratio = 0.21,  $p < 0.0001$ ). Recent data presentation at AAP 2021
  - Intermediate-size Expanded Access protocol ongoing
  - FDA granted Breakthrough Therapy, Orphan Drug, Fast Track, and Rare Pediatric Disease Designations → Eligible for the Rare Pediatric Disease Priority Review Voucher.
  - EMA COMP granted Orphan Medicinal Product Designation
  - Development and Asset Purchase Agreement signed with Sentyln Therapeutics in February 2021



- **AAV-ATP7A Gene Therapy** ODD
  - Preclinical and already has Orphan Drug Designation from FDA
  - Expects to nominate candidate for clinical development in 2022

# ▶ Copper is Required in Human Development and Health

	Biological Functions	Copper Containing Proteins
	<b>Brain Development</b>	
	Catecholamine production	Dopamine $\beta$ -hydroxylase
	Mitochondrial respiration	Cytochrome C oxidase
	Iron and copper transport	Ceruloplasmin
	Peptide amidation	Peptidylglycine $\alpha$ -amidating monooxygenase
	Antioxidant defense	Superoxide dismutase
	Connective tissue formation	Lysyl oxidase
	Pigment formation	Tyrosinase

Source: de Bie, et al, 2007; Image source: freepik.com

# ▶ Menkes Disease is a Rare Pediatric Disease

## Menkes Disease

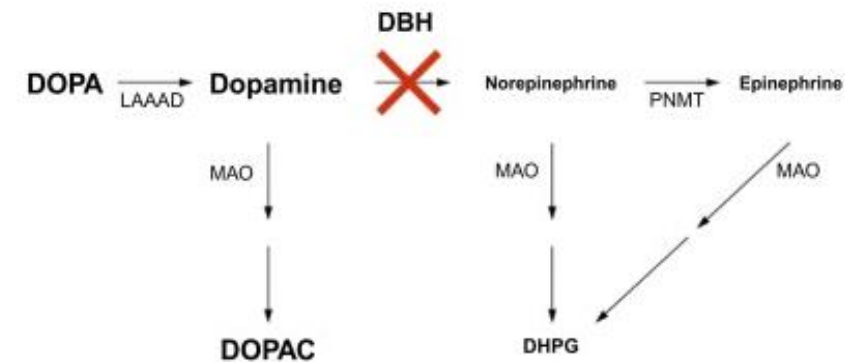
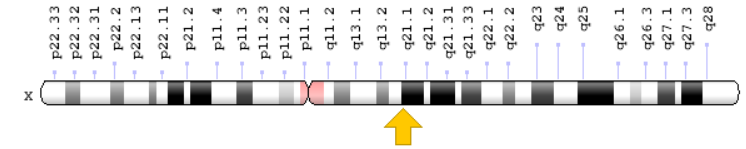
- First described by Dr. John Menkes in 1962
- X-linked recessive disease: affecting mostly boys
- Minimum birth prevalence for Menkes disease believed to be 1 in 34,810 live male births, but could potentially be as high as 1 in 8,664 live male births, higher than previously recognized
- Disorder of copper metabolism caused by mutations in the Copper transporter ATP7A
- **If untreated, premature death ~ 3 years**

## Distinctive clinical phenotypes

- Sparse, depigmented hair (“kinky hair”)
- Onset of neurologic symptoms: seizures, hypotonia, and developmental delays
- Failure to thrive
- Connective tissue problems

## Diagnosis

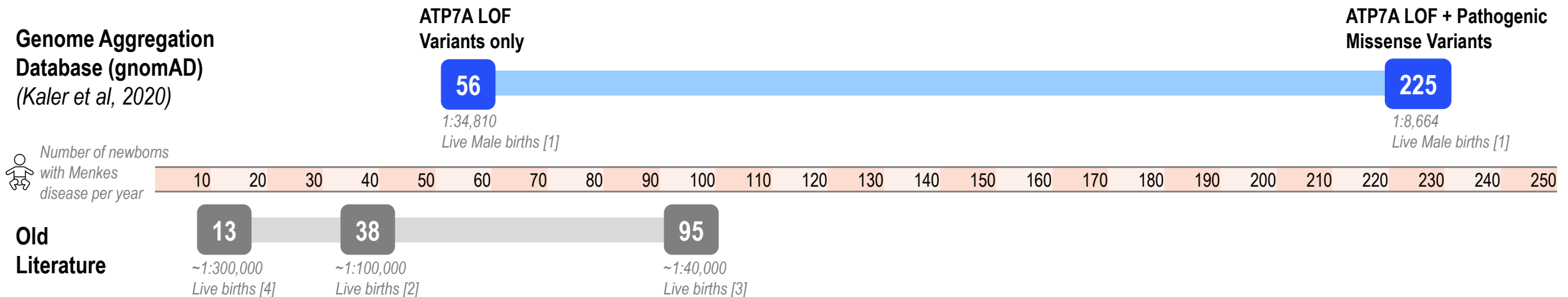
- Low serum copper and ceruloplasmin levels
- Abnormal catecholamine levels
- ATP7A gene sequencing confirmation



# ▶ Menkes Disease is Under-estimated and Under-diagnosed

## New study estimated birth prevalence of Menkes disease based on the Genome Aggregation Database

- Accessed Genome Aggregation Database (gnomAD) at MIT/Broad Institute → over 200,000 ATP7A alleles
- Identified 1,106 ATP7A variants
  - 4 Loss-of-Function (LOF) variants → 4 alleles → 1:34,810 live male births → 56 patients per year
  - 28 potentially pathogenic missense variants (PolyPhen-2) → 12 alleles with high confidence (REVEL >0.85)
  - Including both LOF and pathogenic missense variants → 1:8,664 live male births → 225 patients per year
- Newborn screening (NBS) will likely increase the number of Menkes disease patients identified and allow early diagnosis and treatment with CUTX-101



References: [1] Kaler, et al, 2020; [2] Kaler, SG, 1998; [3] Danks DM, 1971; [4] Tonnesen et al 1991

# Potentials of gnomAD and Newborn Screening to Discover More Patients in Rare Pediatric Diseases

- Kaler 2020 study applied the same approach to a different X-linked recessive disorder, Duchenne Muscular Dystrophy (DMD), for which incidence data are better established due to longer lifespan.
- Analysis of gnomAD database entries for the DMD locus indicated 19 unequivocally loss-of-function alleles out of a total of 204,738 sequenced → predicted birth prevalence of DMD equals 1 in 7,246 live male births, in reasonable agreement with population-based estimates (1 in 5,000 newborn males) [1]
- Newborn screening detected a higher than previously estimated prevalence:
  - **Fabry Disease:** 1 in 8,454 in NBS [2] vs 1 in 40,000 to 60,000 males [3]
  - **Pompe Disease:** 1 in 21,979 in NBS [2] vs 1 in 40,000 births [4]

## References:

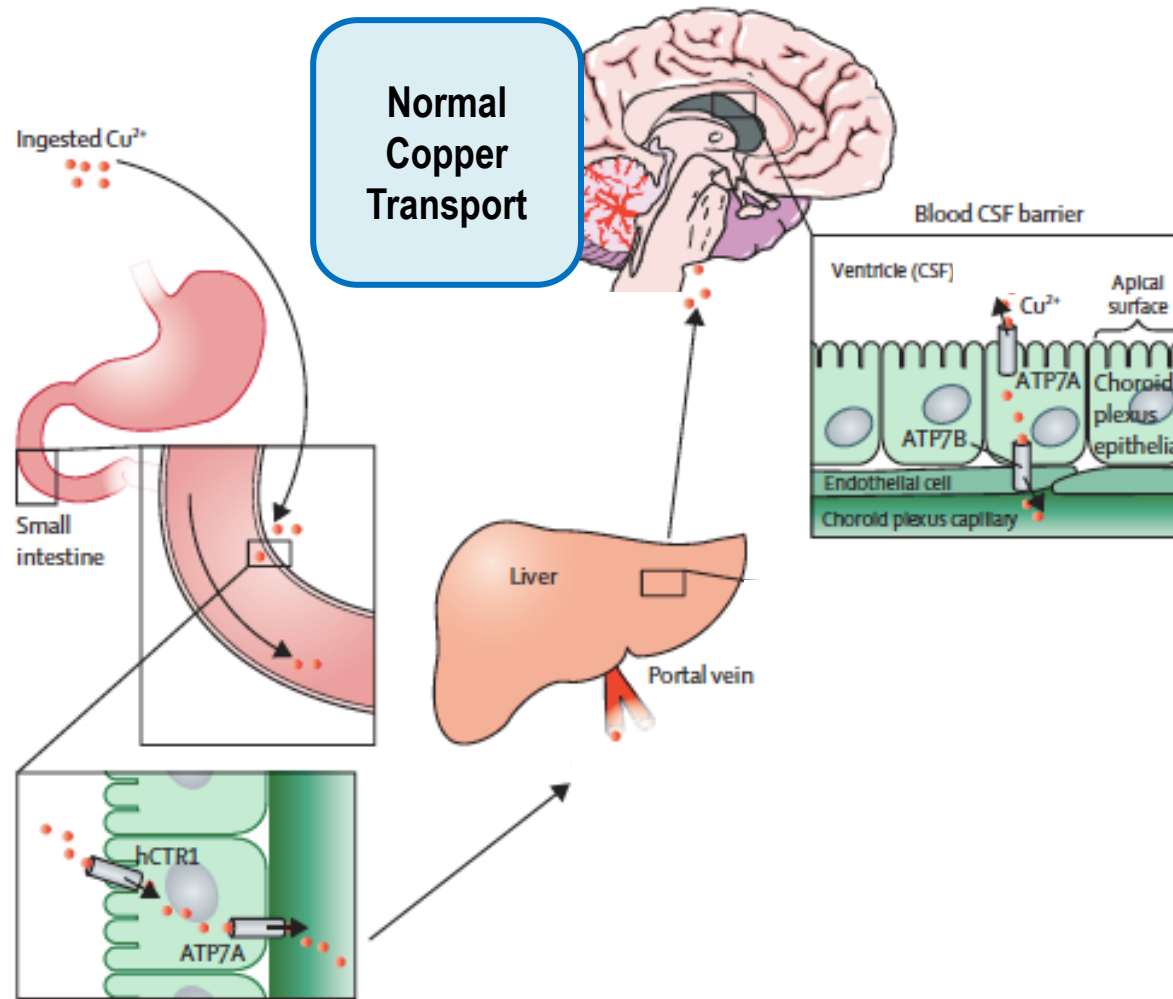
[1] Kaler, et al, 2020

[2] Burton et al, 2017

[3] <https://rarediseases.org/rare-diseases/fabry-disease/>

[4] <https://rarediseases.org/rare-diseases/pompe-disease/>

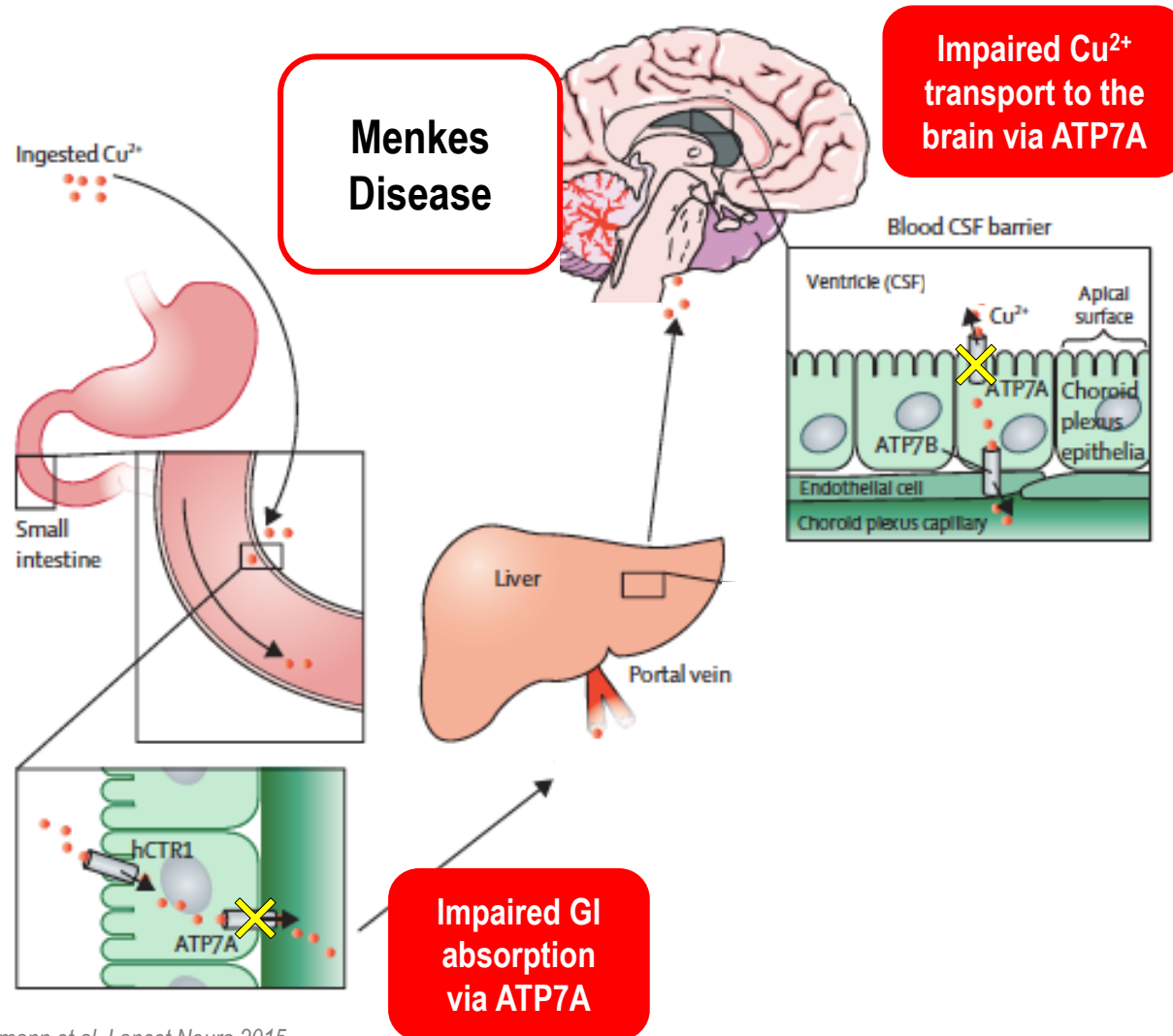
# ▶ ATP7A is Critical for Copper Transport to the Brain & GI



Adapted from: Bandmann et al, Lancet Neuro 2015

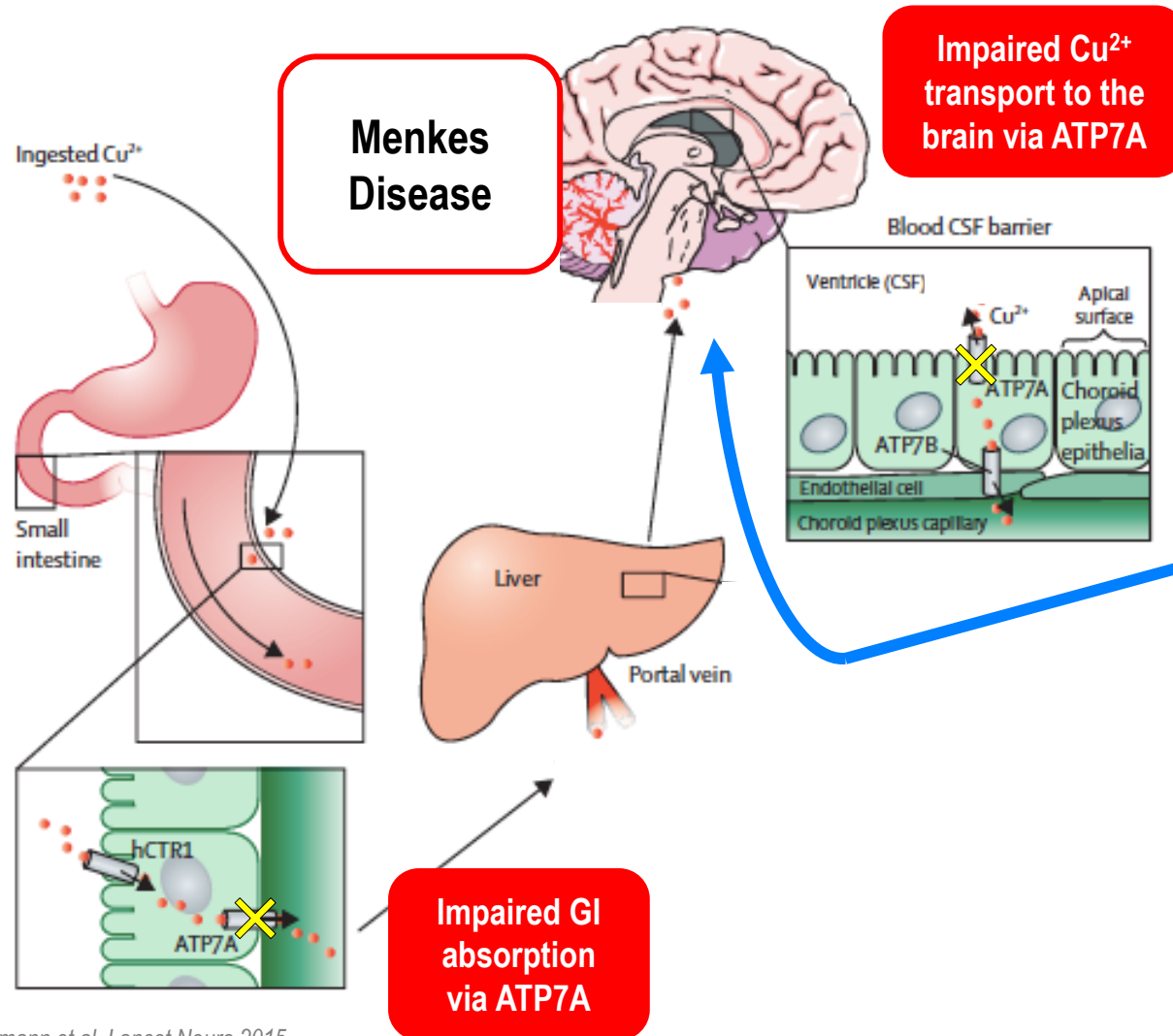


# ▶ Copper Transport is impaired in Menkes Disease



Adapted from: Bandmann et al, Lancet Neuro 2015

# Therapeutic Strategy for Menkes Disease: CUTX-101 (Copper Histidinate)



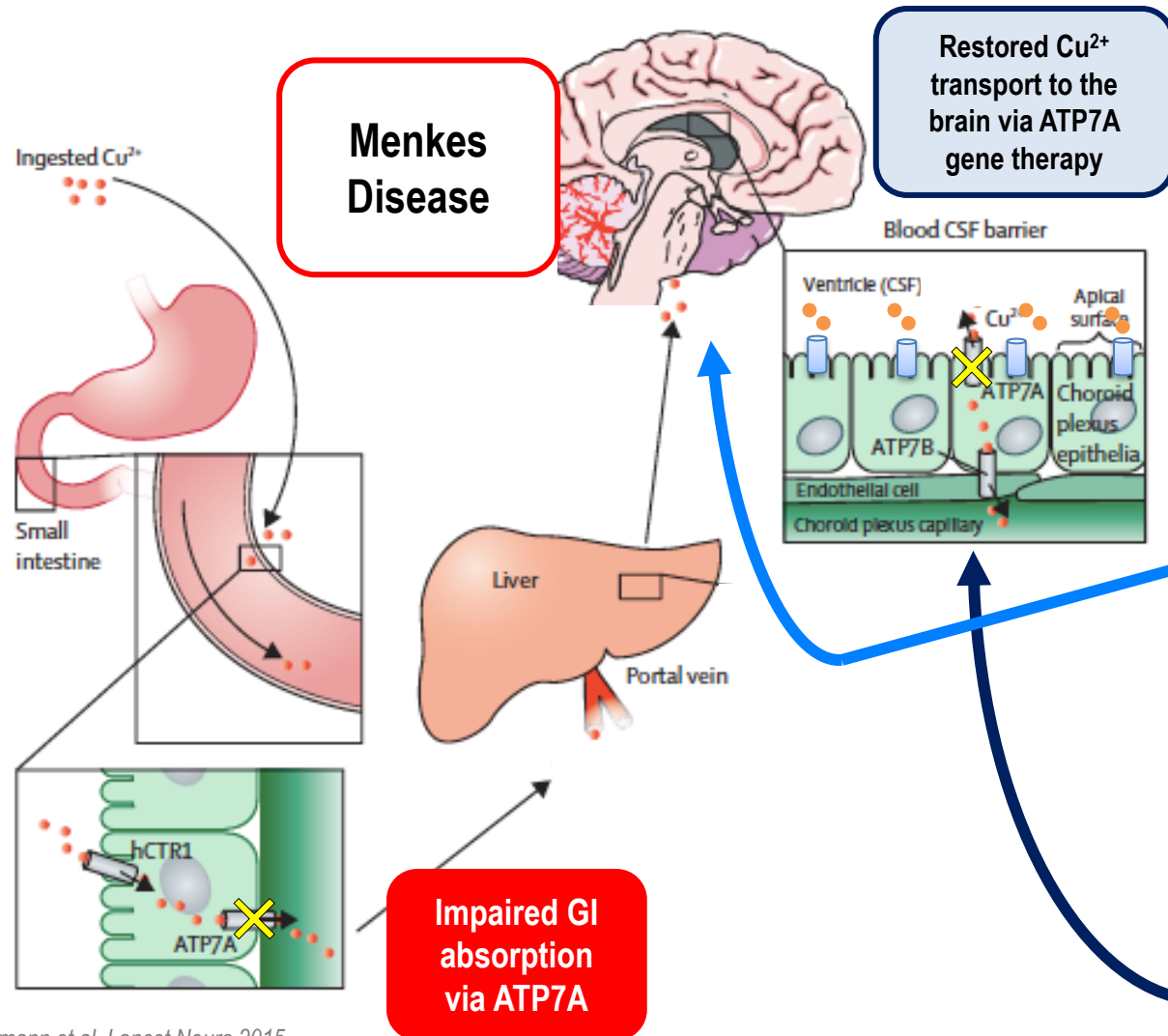
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## CUTX-101 Copper Histidinate

- SC injection to replenish CuHis
- Bypass GI absorption of  $\text{Cu}^{2+}$  (impaired in Menkes patients)
- Better tolerability (pH 7.4)
- May not be sufficient alone in some Menkes patients

- ◆ Reported positive topline clinical efficacy data
- ◆ Rolling NDA Submission initiated in December 2021
- ◆ Expanded Access protocol ongoing

# Therapeutic Strategy for Menkes Disease: CUTX-101 (Copper Histidinate) + AAV-ATP7A Gene Therapy



1

## CUTX-101 Copper Histidinate

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2

## AAV-ATP7A Gene Therapy

- Codon-optimized reduced-sized ATP7A to be delivered via AAV vector (Preclinical)
- May restore  $\text{Cu}^{2+}$  transport
- Will need CUTX-101 injections

Preclinical

Adapted from: Bandmann et al, Lancet Neuro 2015

## ▶ CUTX-101 is Optimized for Menkes Disease Patients

	CUTX-101 (Copper Histidinate)	Cupric Chloride (CuCl <sub>2</sub> )	Oral Cu supplements
Route of Administration	Subcutaneous (SC)	IV (additive to TPN)	Oral
pH	7.4 (physiologic)	2.0 (highly acidic)	N/A
Tolerability	Good	Poor (if injected SC)	N/A
GI absorption in Menkes patients	Bypassed	Bypassed	Very low
Bioavailability to cells	High	Low (Cu <sup>2+</sup> ions bound to albumin)	N/A
Chemistry	Coordination complex (not free Cu <sup>2+</sup> ions)	Inorganic salt (reactive free Cu <sup>2+</sup> ions)	Inorganic salts
Clinical experience in Menkes patients	20+ years experience at NIH; 130+ patients treated	Minimal	Minimal

## ► Partnership with NICHD/NIH

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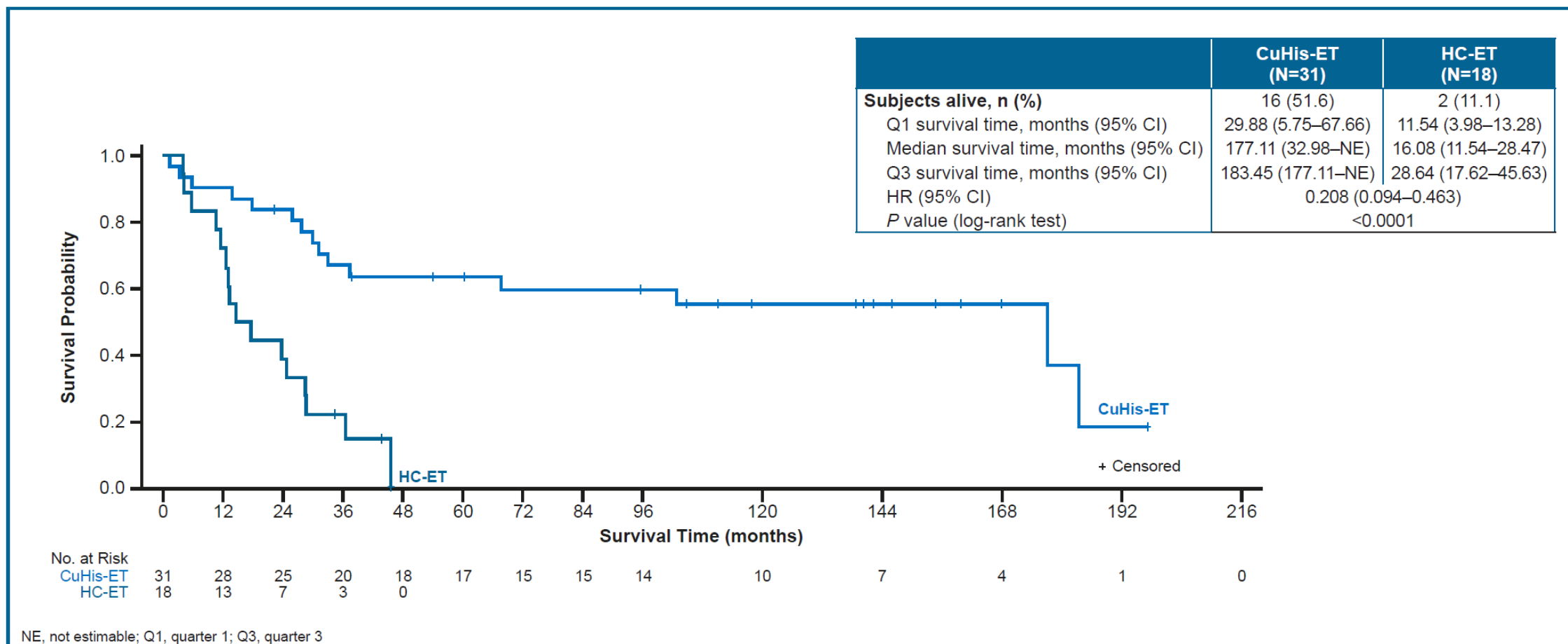
- **Menkes disease program originated at *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD):**
  - Led by Stephen G. Kaler, MD, Senior Investigator and Former Head, Section on Translational Neuroscience, Molecular Medicine Branch, NICHD
    - Currently with Center for Gene Therapy at Nationwide Children's Hospital (Columbus, OH)
- **CRADA and Data Transfer Agreement with NICHD**
  - Cyprium continues GMP manufacturing of CUTX-101
  - IND transferred to Cyprium in Jan 2019
  - NICHD leadership supportive of NDA and has completed data transfer to Cyprium for NDA submission
- **Licensing Agreement for AAV-ATP7A Gene Therapy with NICHD**
  - Executed and announced in March 2017
  - Cyprium obtained Worldwide exclusive rights to develop and commercialize codon-optimized AAV-ATP7A Gene Therapy program for the treatment of Menkes disease and related disorders

## ► Positive Topline Clinical Efficacy Data for CUTX-101

Summary	
<b>Statistical Analysis Plan (SAP)</b>	Agreed upon with the FDA for Integrated Summary of Effectiveness (ISE) section of the NDA
<b>Primary Efficacy Endpoint</b>	Overall survival (OS) measured from birth
<b>Treatment Cohorts (as defined in SAP)</b>	<b>Early Treatment (ET):</b> received CUTX-101 beginning within 4 weeks of age (adjusted for prematurity) (n=31) <b>Historical Control (HC):</b> did not receive copper therapy (n=18)
<b>Overall Survival (OS) Results</b>	Statistically significant improvement in overall survival for Menkes disease subjects who received early treatment (ET) with CUTX-101, compared to an untreated historical control (HC) cohort, with a nearly 80% reduction in the risk of death (Hazard Ratio = 0.21, p<0.0001).
<b>Median survival</b>	<b>Early Treatment (ET):</b> 14.8 years (177.1 months) <b>Historical Control (HC):</b> 1.3 years (15.9 months)

- The topline primary efficacy data and other relevant briefing materials were presented to the FDA at a pre-NDA meeting. Other pre-specified secondary and sensitivity analyses will be included in the NDA submission. Additional data and analyses will be disclosed in peer-reviewed publications and at future medical or scientific conferences.

# Kaplan-Meier Overall Survival Curves for Early Treatment Cohorts



- Data presented as a virtual poster at the 2021 American Academy of Pediatrics (AAP) National Conference & Exhibition: Kaler SG, et al, Copper Histidinate Treatment for Menkes Disease (Kinky Hair Syndrome)

# ▶ CUTX-101: Current Status & Next Steps

## Regulatory:

- **Rolling NDA submission initiated in December 2021 – NDA submission expected to complete in mid-2022.**
  - **Potential to be the first FDA-approved treatment for Menkes Disease**
- FDA has been very helpful in providing guidance for regulatory pathway towards NDA submission for CUTX-101. FDA recommended Cyprium to continue frequent communications (Fast Track Designation, Breakthrough Therapy Designation).
- NDA is based on data from NIH studies and historical control, using overall survival as the primary endpoint.
- **FDA granted Breakthrough Therapy Designation in December 2020**
- **EMA COMP granted Orphan Medicinal Product Designation in 2020**
- Additional regulatory activities in US and other territories

## Clinical:

- Cyprium's Intermediate-Size Expanded Access Protocol CYP-001 (NCT04074512)
  - Provides CUTX-101 for newly diagnosed Menkes disease patients and patients from NIH study

## CMC:

- Continues GMP manufacturing of CUTX-101
- Additional CMC and product development activities

## Others:

- Additional PK and nonclinical studies to be completed based on FDA communications





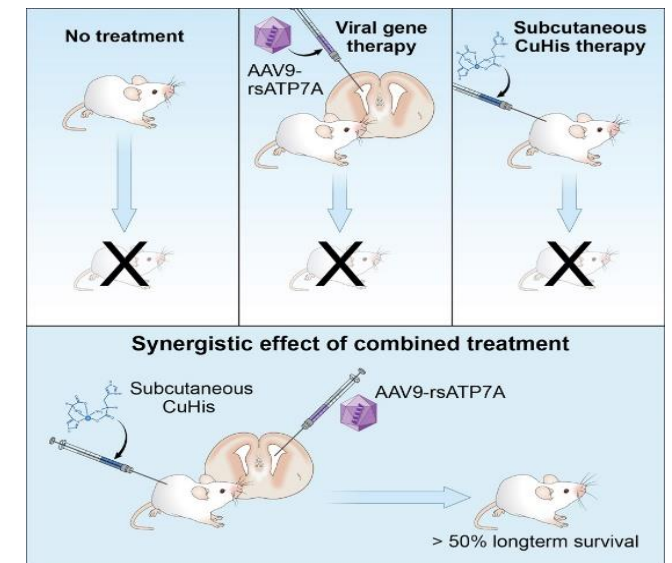
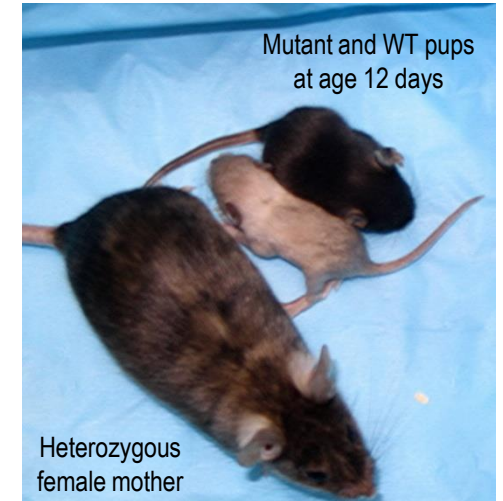
# ▶ Development and Asset Purchase Agreement signed with Sentynl Therapeutics

## Development and Asset Purchase Agreement signed with Sentynl Therapeutics in February 2021

- Sentynl to acquire CUTX-101 for up to \$20M in upfront and regulatory milestone payments through NDA approval
- Cyprium eligible to receive sales milestones totaling up to \$255M
- Royalties on CUTX-101 net sales are also payable:
  - 6% due on portion of annual net sales up to \$75M
  - 17.5% due on portion of annual net sales between \$75M and \$100M
  - 25% due on portion of annual net sales over \$100M.
- Cyprium will retain 100% ownership over any FDA PRV that may be issued at NDA approval for CUTX-101. Data suggests PRVs may be worth ~\$75M to ~\$110M, each

# ▶ AAV-ATP7A Gene Therapy for Menkes Disease

- *Mottled – brindled* mouse model recapitulates the disease phenotype
  - *Atp7a*<sup>mo-br</sup> phenotype
  - A 6 bp in-frame deletion in exon 11 of *Atp7a*
  - Depigmented coat color and curly whiskers
  - Premature death (~13 days of age)
  - Poor growth; Neurological symptoms
  - Low brain copper; Abnormal catecholamine levels
- NICHD has developed several constructs for reduced size, codon-optimized AAV-ATP7A gene therapy
- AAV-ATP7A + SC CuHis administration led to:
  - Improvements in muscle strength, balance and coordination in preclinical model
  - Improved biochemical phenotype (Cu and catecholamine)
  - Improved survival



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# Thank you!

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