

CYPRIMUM
THERAPEUTICS

Corporate Presentation
December 2021

► Forward Looking Statements

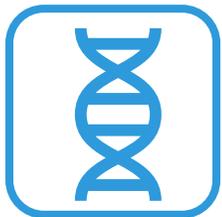
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► Company Highlights

- **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.

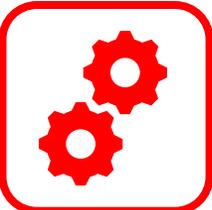


- **CUTX-101 (Copper Histidinate Injections)** ODD FT RPD BTD OMP
 - Rolling NDA submission to the FDA initiated in December 2021 – NDA submission expected to complete in mid-2022.
 - Potential to be the first FDA-approved treatment for Menkes Disease
 - Reported positive topline clinical efficacy data, 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
	Brain Development	
	Catecholamine production	Dopamine β -hydroxylase
	Mitochondrial respiration	Cytochrome C oxidase
	Iron and copper transport	Ceruloplasmin
	Peptide amidation	Peptidylglycine α -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

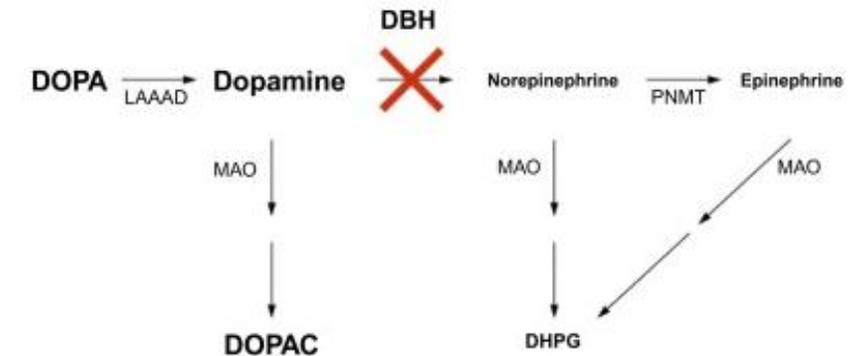
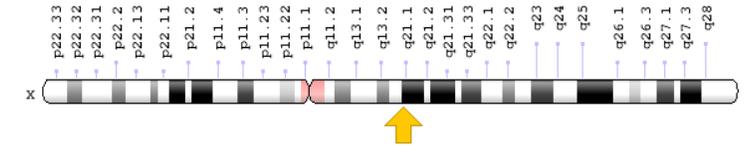
- First described by Dr. John Menkes in 1962
- X-linked recessive disease: affecting mostly boys
- Minimum birth prevalence for Menkes disease believed to be 1 in 34,810 live male births, but could potentially be as high as 1 in 8,664 live male births, higher than previously recognized
- Disorder of 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

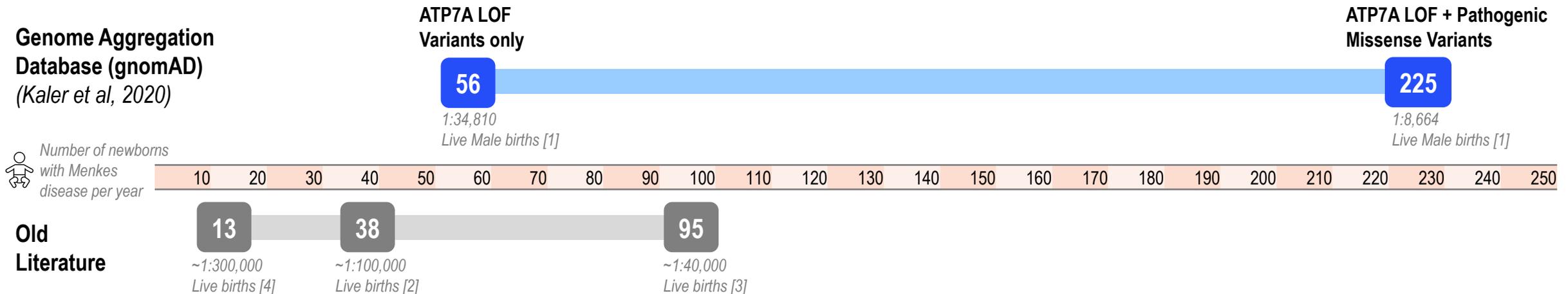
- Low serum copper and ceruloplasmin levels
- Abnormal catecholamine levels
- ATP7A gene sequencing confirmation



▶ 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:

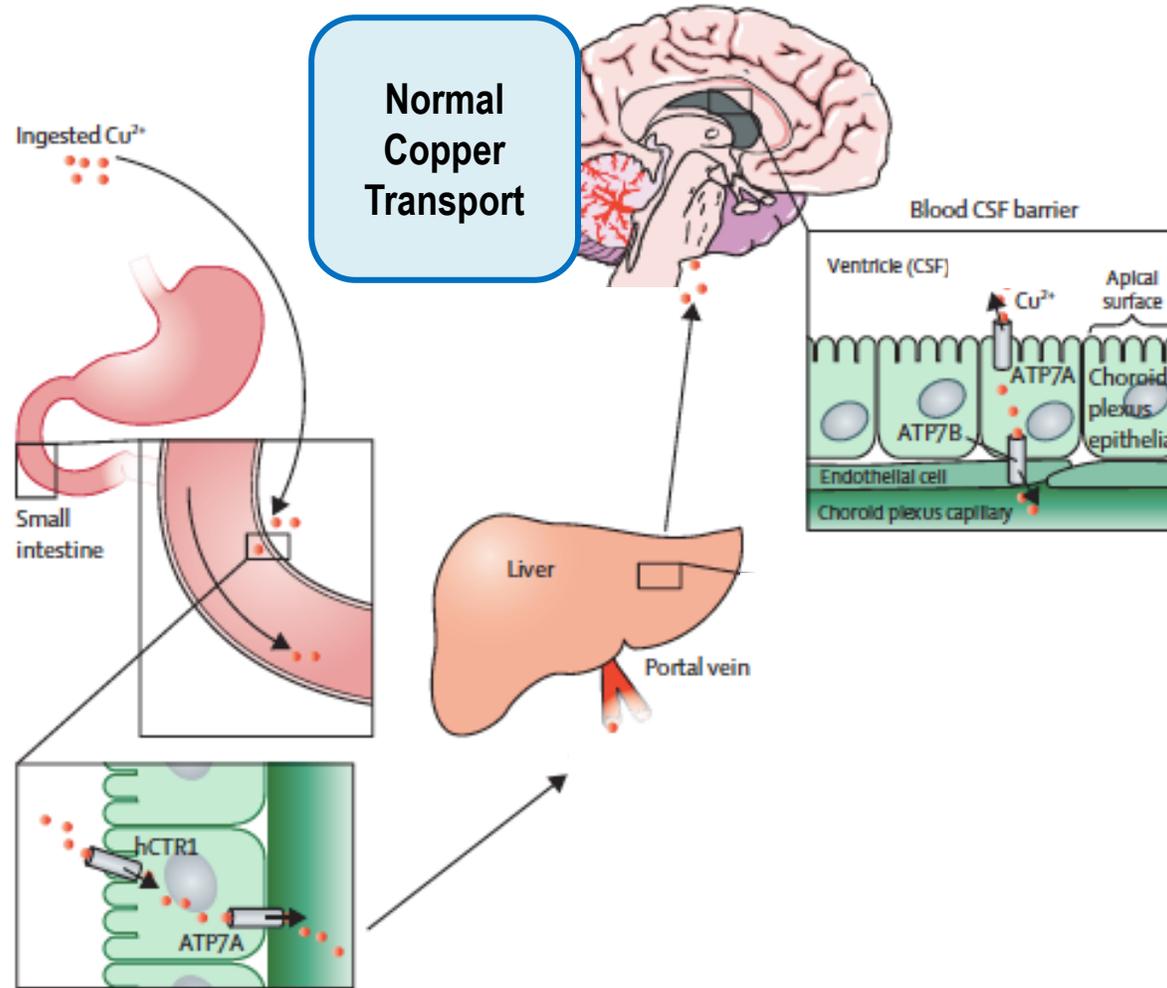
[1] Kaler, et al, 2020

[2] Burton et al, 2017

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

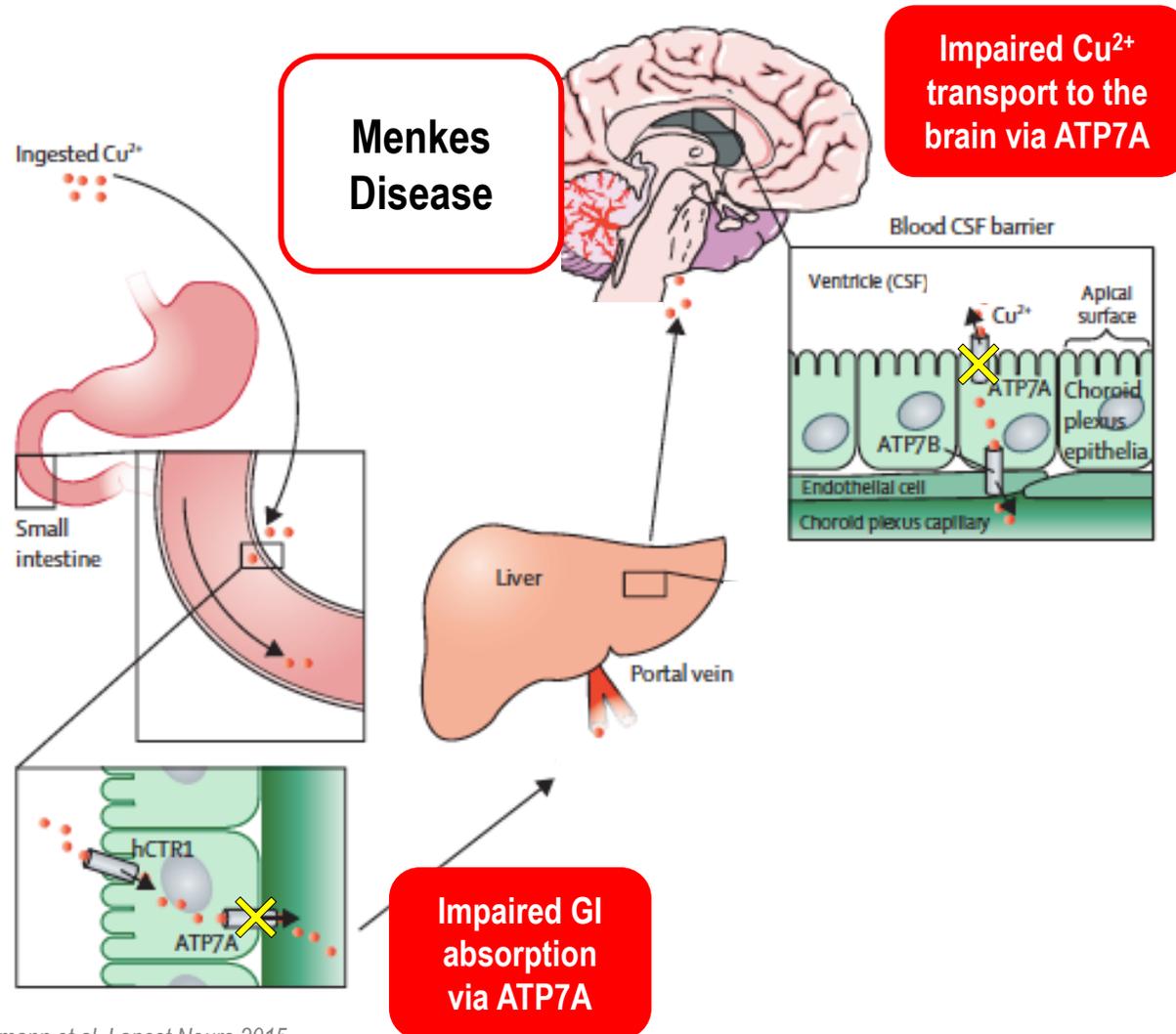
[4] <https://rarediseases.org/rare-diseases/pompe-disease/>

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



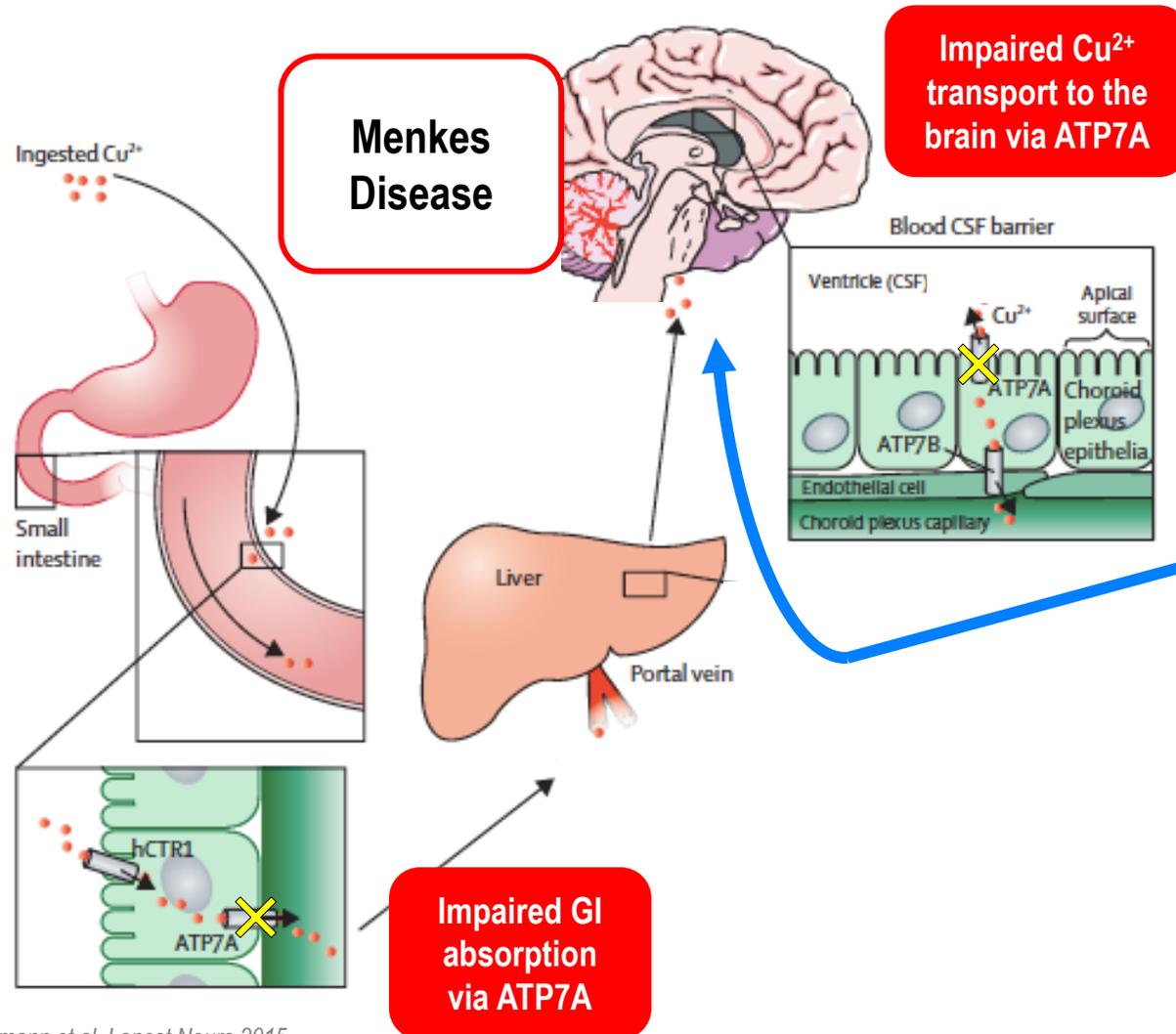
Adapted from: Bandmann et al, Lancet Neuro 2015

▶ Copper Transport is impaired in Menkes Disease



Adapted from: Bandmann et al, Lancet Neuro 2015

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



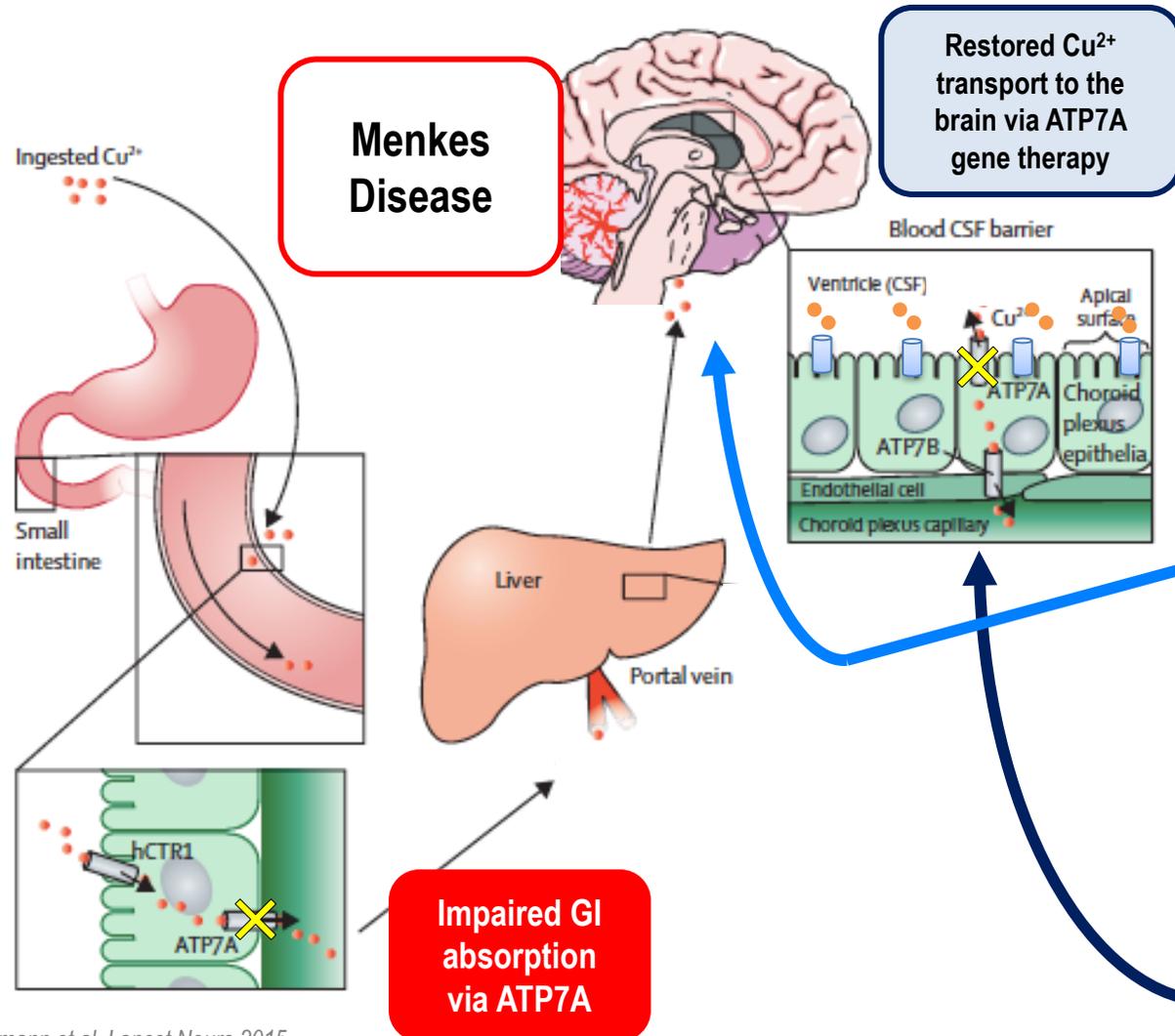
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CUTX-101 Copper Histidinate

- SC injection to replenish CuHis
- Bypass GI absorption of 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 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 ₂)	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 ²⁺ ions bound to albumin)	N/A
Chemistry	Coordination complex (not free Cu ²⁺ ions)	Inorganic salt (reactive free Cu ²⁺ ions)	Inorganic salts
Clinical experience in Menkes patients	20+ years experience at NIH; 130+ patients treated	Minimal	Minimal

► Partnership with NICHD/NIH

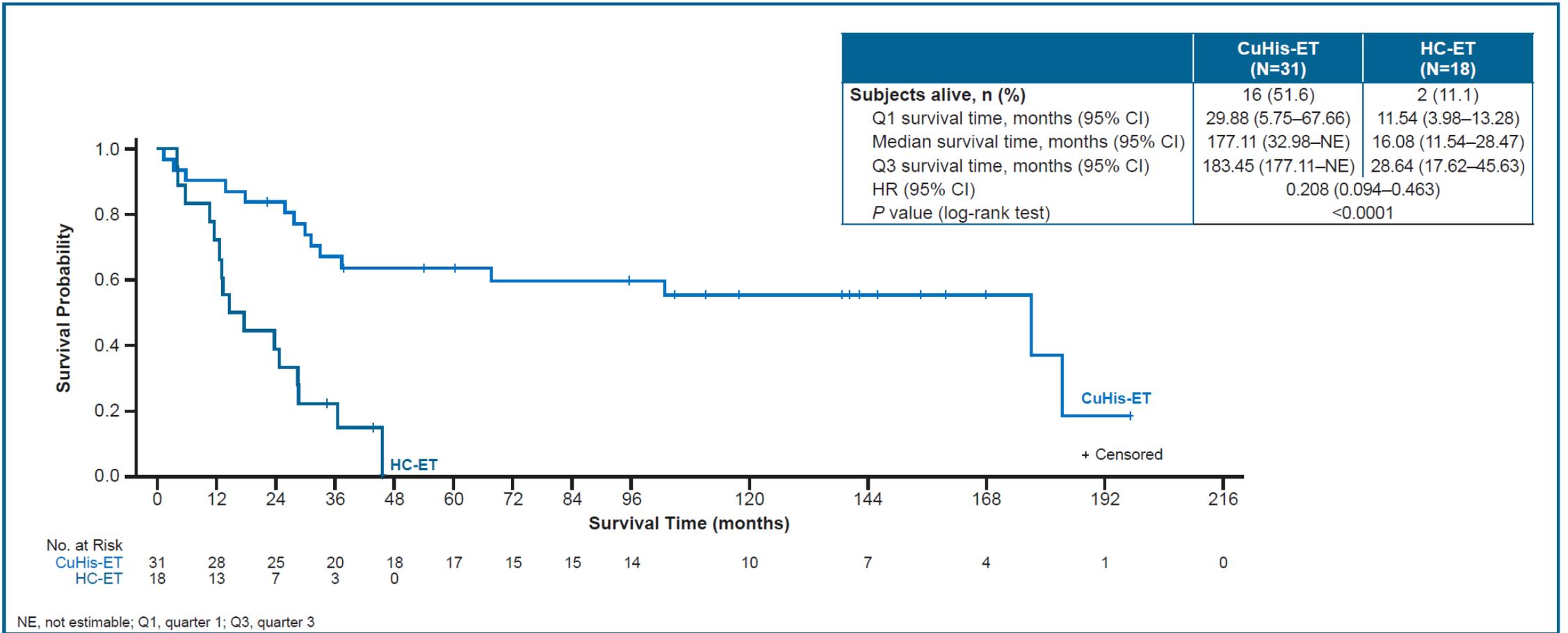
- **Menkes disease program originated at *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD):**
 - Led by Stephen G. Kaler, MD, Senior Investigator and Former Head, Section on Translational Neuroscience, Molecular Medicine Branch, NICHD
 - Currently with Center for 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	
Statistical Analysis Plan (SAP)	Agreed upon with the FDA for Integrated Summary of Effectiveness (ISE) section of the NDA
Primary Efficacy Endpoint	Overall survival (OS) measured from birth
Treatment Cohorts (as defined in SAP)	Early Treatment (ET): received CUTX-101 beginning within 4 weeks of age (adjusted for prematurity) (n=31) Historical Control (HC): did not receive copper therapy (n=18)
Overall Survival (OS) Results	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).
Median survival	Early Treatment (ET): 14.8 years (177.1 months) Historical Control (HC): 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



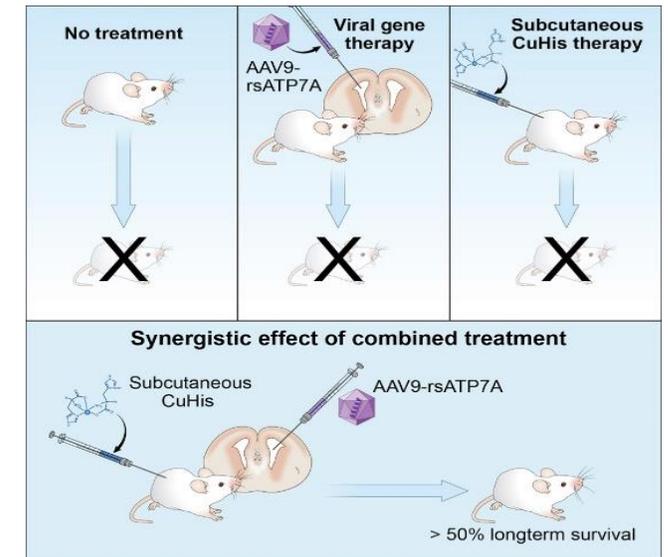
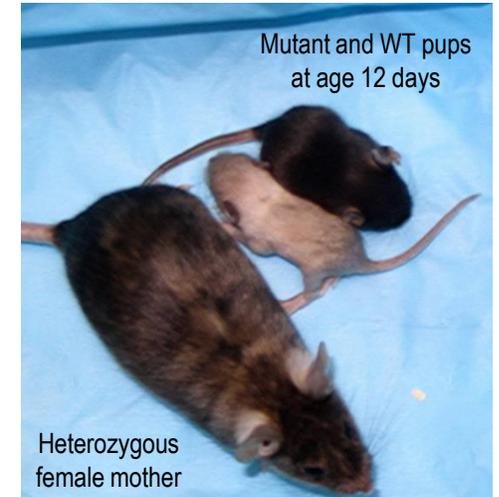
▶ Development and Asset Purchase Agreement signed with Sentynl Therapeutics

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*^{mo-br} 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



Source: Stephen G. Kaler, MD; Haddad et al, 2018

Thank you!

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