

CYPRIMUM
THERAPEUTICS

A subsidiary company of



Corporate Presentation

May 2019

► 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.
- In March 2017, Cyprium acquired the World-Wide development and commercial rights to the Menkes program at NIH/NICHD through CRADA and licensing agreements with NICHD.



- **CUTX-101 (Copper Histidinate Injections):**

- Reported compelling Phase 1/2 data; Phase 3 study completed enrollment
- Orphan Drug and Fast Track Designations granted by FDA
- Natural History Study of untreated Menkes patients ongoing
- Meetings with FDA to discuss regulatory pathway
- Eligible for the Rare Pediatric Disease Priority Review Voucher
- **NDA filing in 1H20 – would be the first FDA-approved treatment for Menkes Disease**



- **AAV-ATP7A Gene Therapy:**

- Preclinical and already has Orphan Drug Designation from FDA
- **Expects to nominate candidate for clinical development in 1H20**

► Copper 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

▶ Menkes Disease

Menkes Disease

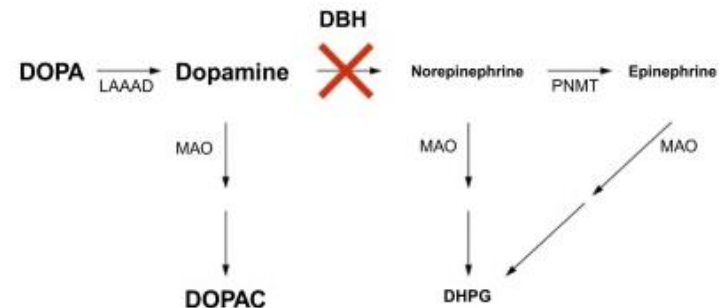
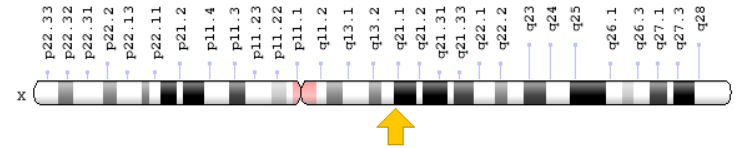
- First described by Dr. John Menkes in 1962
- X-linked recessive disease: affecting mostly boys
- 1: 50,000 - 100,000 live births per year
- Disorder of copper metabolism
- Mutations in the Copper transporter ATP7A
- **If untreated, premature death ~ 3 years**

Distinctive clinical phenotypes

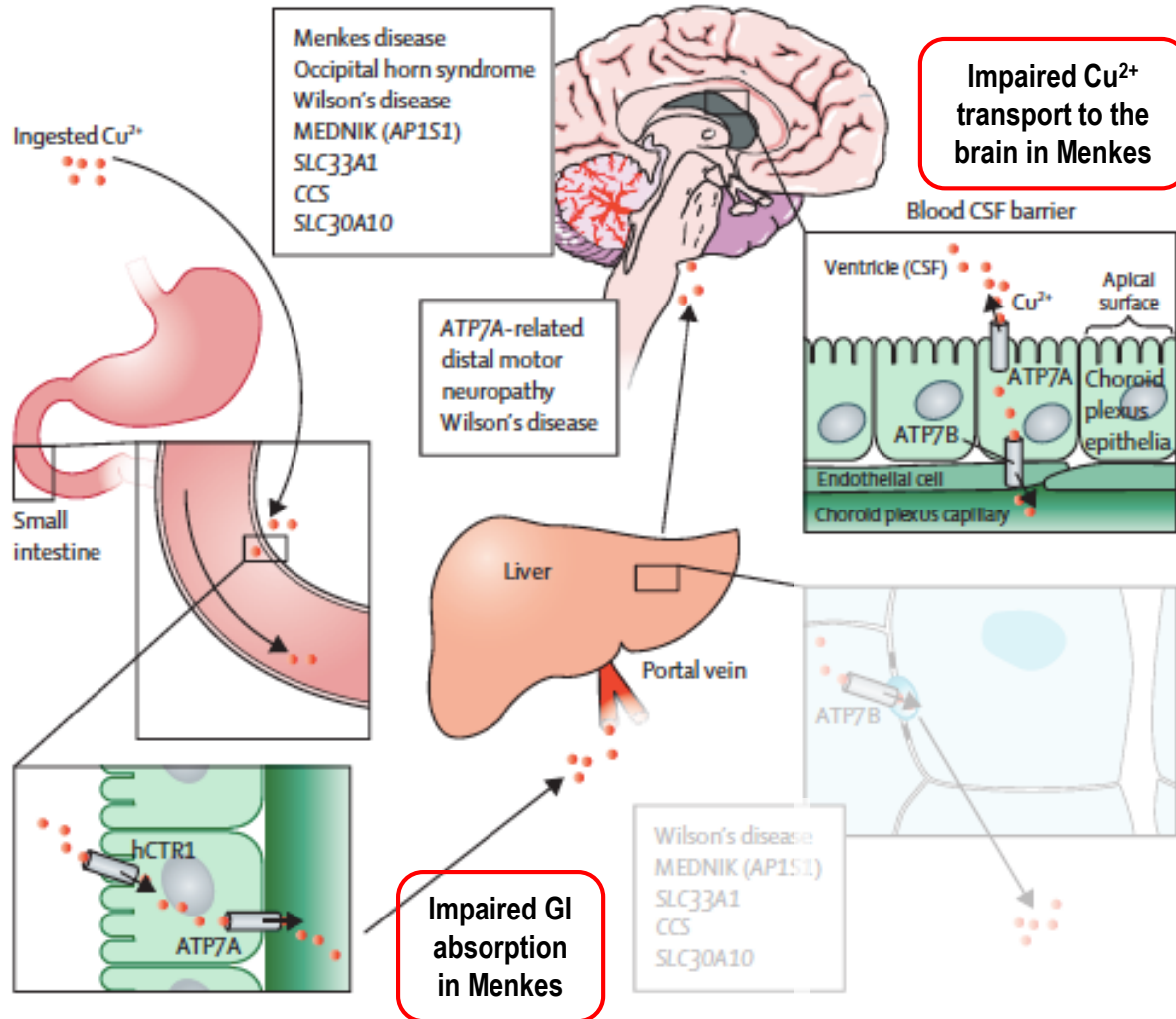
- Sparse, depigmented hair (“kinky hair”)
- Neuro symptoms: Seizures, Hypotonia, and Developmental delays
- Failure to thrive
- Connective tissue problems

Distinctive biochemical phenotypes

- Low copper in blood and brain
- Abnormal catecholamine levels

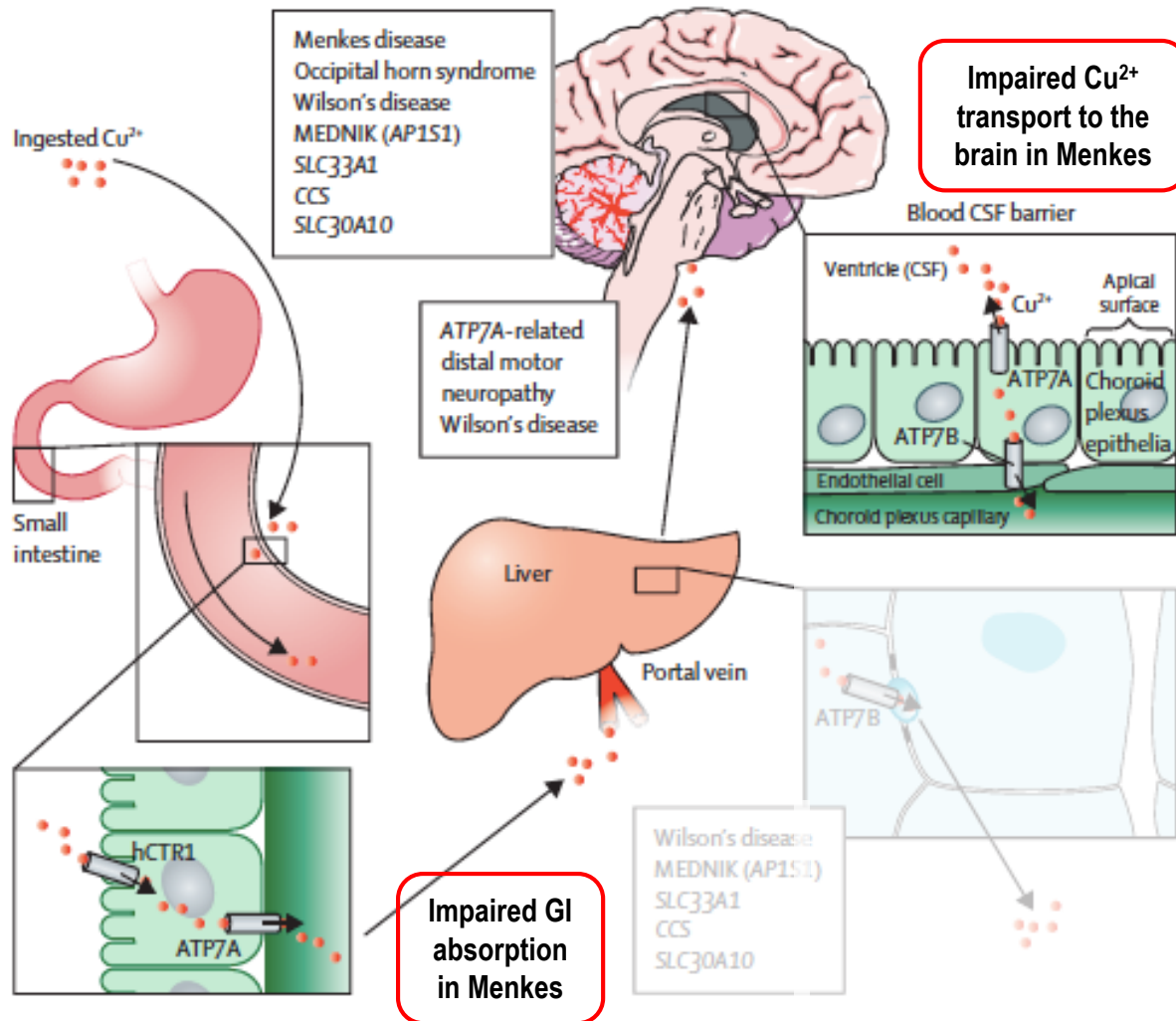


ATP7A Critical for Copper Transport to the Brain & GI



Bandmann et al, Lancet Neuro 2015

► Therapeutic Strategy for Menkes Disease



1

CUTX-101 Copper Histidinate

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

Phase 1/2 efficacy data published;
Phase 3 Study ongoing;
Natural History Study ongoing

2

AAV-ATP7A Gene Therapy

- Codon-optimized reduced-sized ATP7A to be delivered via AAV vector (Preclinical)
- May restore Cu^{2+} transport
- Will require Cu^{2+} injections

Preclinical

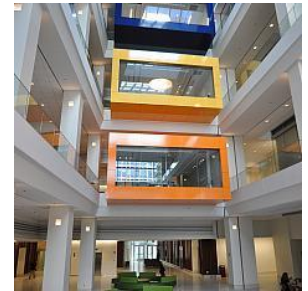
▶ CUTX-101 is Optimized for Menkes Patients

	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; 100+ patients treated	Minimal	Minimal

Product label; Deschamps et al 2005

► Partnership with NICHD/NIH

- **Menkes disease program at Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD):**
 - Led by Stephen G. Kaler, MD, Senior Investigator and Head, Section on Translational Neuroscience, Molecular Medicine Branch, NICHD
- **Cooperative Research And Development Agreement (CRADA)**
 - Executed and announced in March 2017
 - Research Plan describes the responsibilities of both parties
 - NIH granted Cyprium Authorization to file NDA for CUTX-101
 - Dr. Kaler remains the PI of Menkes clinical study at NICHD
 - Cyprium continues GMP manufacturing of CUTX-101
 - Cyprium provides research support to Dr. Kaler's lab based on milestones
- **Licensing Agreement for AAV-ATP7A Gene Therapy**
 - 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



Clinical Studies of CUTX-101 in Menkes Patients (Dosing up to 3 Years)

- Phase 1/2 Study (NCT00001262)
- Status: Completed

- Phase 3 Study (NCT00811785)
- Status: Completed enrollment (Parallel with NDA filing)

Classic Menkes Disease Dx

- Neurochemical levels
- ATP7A mutation analysis

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Classic Menkes Disease Dx

- Neurochemical levels
- ATP7A mutation analysis



Group I: Late Treatment

CuHis treatment begins:

- After 1 month of age
- After onset of symptoms

22

Group II: Early Treatment

CuHis treatment begins:

- Within 1 month of age
- Before onset of symptoms

35

Group I: Late Treatment

CuHis treatment begins:

- After 1 month of age
- After onset of symptoms

Group II: Early Treatment

CuHis treatment begins:

- Within 1 month of age
- Before onset of symptoms

CUTX-101 Injections

Age < 1 Yr
250ug SC BID

Age > 1 Yr
250ug SC QD

Both Groups Have Same Dosing Schedule

CUTX-101 Injections

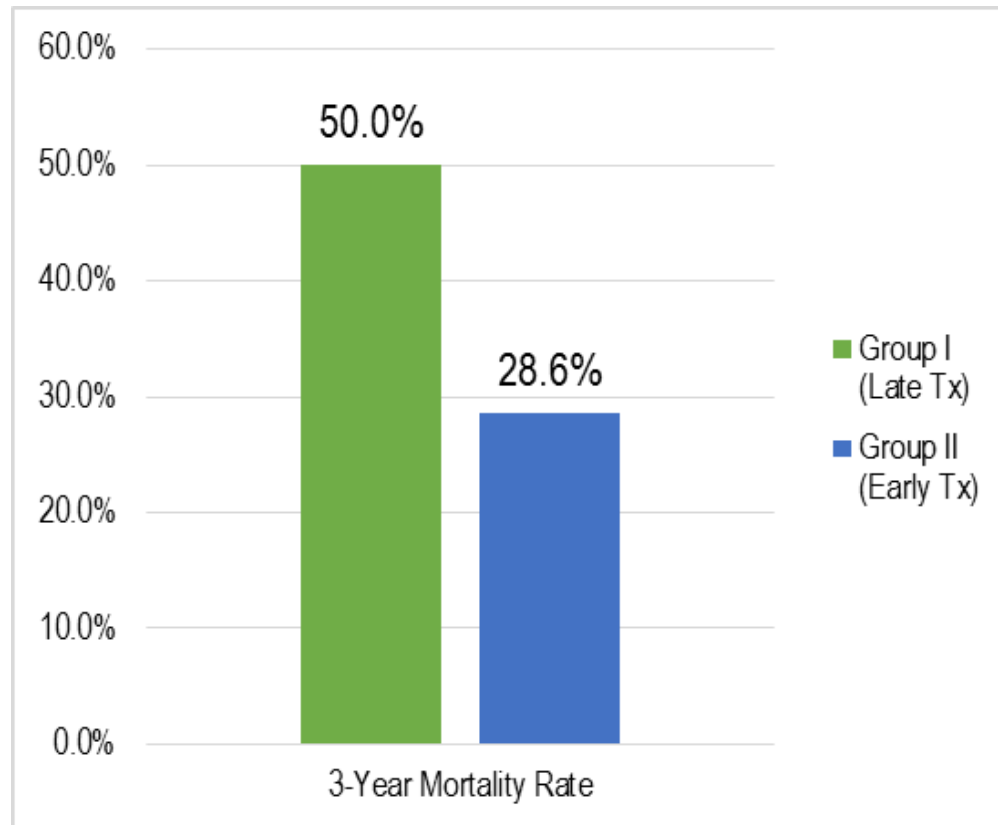
Age < 1 Yr
250ug SC BID

Age > 1 Yr
250ug SC QD

Both Groups Have Same Dosing Schedule

Early Treatment of CUTX-101 Improved 3-Year Mortality Rate

- Menkes patients who received early treatment of CUTX-101 had a lower 3-Year Mortality rate compared to late treatment.



► Clinical Summary for CUTX-101

- Early treatment with CUTX-101 significantly improved Denver Developmental Screening Test in all 4 scales (gross motor, fine motor/adaptive, personal-social, and language).
- Menkes patients who received early treatment of CUTX-101 had a lower 3-Year mortality rate (28.6%) compared to late treatment (50%). Importantly, 3-Year mortality rate for Menkes patients treated with CUTX-101 was significantly lower than untreated historical control (preliminary data not yet reported).
- CUTX-101 appears to be safe and well tolerated. Low incidence of renal tubular dysfunction was observed, which was reversible upon drug discontinuation.
- NICHD is conducting a natural history study of Menkes disease patients who have not been treated with copper supplements. Data from this natural history study may serve as a historical control to demonstrate the efficacy of CUTX-101.

▶ CUTX-101: Current Status & Next Steps

Regulatory:

- FDA has been very helpful in providing guidance for regulatory pathway towards NDA submission for CUTX-101. FDA recommended Cyprium/NICHD to continue frequent communications.
- FDA acknowledged Cyprium would submit NDA based on data from NICHD studies and historical control, using survival as primary endpoint.
- FDA granted Fast Track Designation
- IND transferred to Cyprium in January 2019
- Additional regulatory activities in US and other territories

Clinical:

- In parallel with filing, continue Phase 3 Study of CUTX-101 in Menkes patients (NICHD) (NCT00811785)
- Continue Natural History Study of Untreated Menkes Patients (NICHD)

CMC:

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

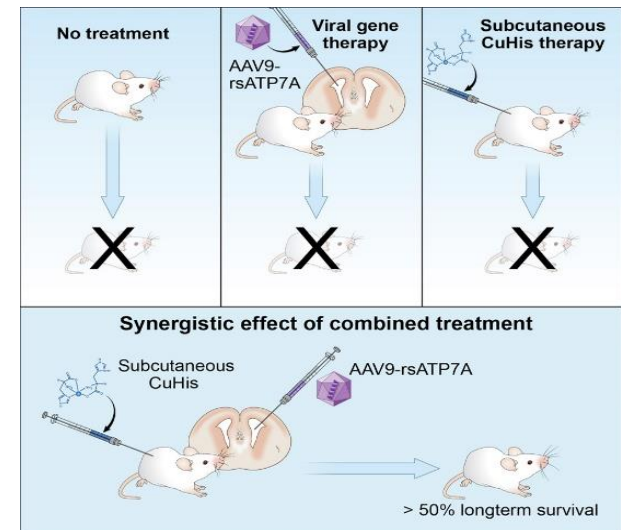
Others:

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



▶ 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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