Welcome to Analyst and Investor Day

Emil D. Kakkis, M.D., Ph.D.
CEO, President and Founder
April 17, 2019

Legal Warning

Cautionary note regarding forward-looking statements: This presentation contains forward-looking statements, including, but not limited to, statements regarding plans with respect to commercializing our product and product candidates, our translational research program, the expected timing of release of additional data for our product candidates, plans to initiate additional studies for product candidates and timing and design of these studies, plans regarding ongoing studies for existing programs, our liquidity position as of the most recent fiscal quarter end, expectations regarding the adequacy of clinical data to support marketing applications and approvals of product candidates, our intent to file, and potential timing and success of, marketing applications and other regulatory approvals, expectations regarding timing of receiving potential approval of product candidates, expectations regarding prevalence of patients, future regulatory interactions, and the value to be generated by our pipeline. Such forward-looking statements involve substantial risks and uncertainties that could cause our clinical development programs, future results, performance or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, the uncertainties inherent in the clinical drug development process, such as the regulatory approval process, the timing of our regulatory filings and other matters that could affect sufficiency of existing cash, cash equivalents and short-term investments to fund operations, the availability or commercial potential of our product and product candidates, and our ability to integrate acquired businesses, which are more fully described in our most recent Form 10-Q or Form 10-K under the caption “Risk Factors” and elsewhere in such reports. Any forward-looking statements made by us reflect our current views with respect to future events or to our future financial performance and involve known and unknown risks, uncertainties, and other 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 these forward-looking statements. Accordingly, our actual results may materially differ from our current expectations, estimates, and projections. Given these uncertainties, you should not place undue reliance on these forward-looking statements.

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This presentation concerns commercial products as well as discussion of investigational drugs that are under preclinical and/or clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). They are currently limited by Federal law to investigational use, and no representations are made as to their safety or effectiveness for the purposes for which they are being investigated.

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Agenda for Today

1) WELCOME & OVERVIEW	**Emil Kakkis, M.D., Ph.D.**

2) COMMERCIAL AND LATE-STAGE PIPELINE UPDATE	
Global Commercial Update	**Vlad Hogenhuis, M.D.**
Crysvita U.S. Launch Progress	**Erik Harris**
Clinical Perspective: XLH	**Anthony Portale, M.D.**
Patient Perspectives: XLH	**Aly and Theresa**
LC-FAOD Program Update	**Camille Bedrosian, M.D.**
LC-FAOD Clinical Perspective	**Jerry Vockley, M.D., Ph.D.**

3) GENE THERAPY PLATFORM	
Overview	**Emil Kakkis, M.D., Ph.D.**
Program updates: OTC and GSDIa	**Eric Crombez, M.D.**
Clinical Perspective: GSDIa	**David Weinstein, M.D.**
Clinical Perspective: Wilson Disease	**Fred Askari M.D., Ph.D.**
Wilson Disease and Manufacturing	**Sam Wadsworth, Ph.D.**
Intellectual Property	**Paul Wickman, Ph.D., J.D.**

4) TRANSLATIONAL RESEARCH PIPELINE	
Early Pipeline Review	**Arjun Natesan, Ph.D.**
mRNA Platform and GSDIII	**Arjun Natesan, Ph.D.**
Novel Creatine Prodrug for CTD[1]	**Arjun Natesan, Ph.D.**
Creatine Transporter Deficiency	**Ton DeGrauw, Ph.D.**

5) SUMMARY AND CLOSE	**Shalini Sharp**

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Introductions

Emil Kakkis, M.D., Ph.D., Chief Executive Officer	
Shalini Sharp, Chief Financial Officer	
Vlad Hogenhuis, M.D., Chief Operating Officer	
Camille Bedrosian, M.D., Chief Medical Officer, Ultragenyx	
Sam Wadsworth, Ph.D., Chief Scientific Officer, Ultragenyx Gene Therapy	
Eric Crombez, M.D., Chief Medical Officer, Ultragenyx Gene Therapy	
Erik Harris, Senior Vice President, North America Commercial Operations	
Paul Wickman, Ph.D., J.D., Vice President, Intellectual Property	
Arjun Natesan, Ph.D., Vice President, Translational Research	

Frederick K. Askari M.D., Ph.D.	**Wilson Disease expert**
Ton DeGrauw, M.D., Ph.D.	**Creatine Transporter Deficiency expert**
Anthony Portale, M.D.	**XLH expert and Crysvita study investigator**
Jerry Vockley, M.D., Ph.D.	**LC-FAOD expert and UX007 study investigator**
David Weinstein, M.D., M.Sc.	**GSDIa expert and DTX401 study investigator**

Ultragenyx: Rare by Design, 9 Years from Founding

Exceptional Rare Disease Company	▪ Forging new approaches ▪ 14+ indications ▪ Multiple modalities
Gene Therapy Platform	▪ 6+ programs ▪ Clinical POC in 2 ▪ Strong manufacturing
Global Commercial	▪ 2 approved therapies ▪ 1 to be filed in 2019 ▪ N. America, S. America, Europe and Turkey

Our Culture
A Critical Part of a Next Generation Company

- **Generous** We are committed to helping
- **Courageous** We go where others won’t
- **Relentless** We won’t give up fighting for our patients
- **Dynamic** We learn and adapt
- **Possibility** We seek the undiscovered discoveries

The RARE Formula for Effective Pipeline Development

Science We Choose

Potent & Clear Disease & Drug Biology

The Need We Solve

- Serious Unmet Medical Need: Often First Drug Ever
- Disease-Modifying Therapeutic

The Development We Plan

- Fast to Clinic and Speed: Dynamic Development Model
- Creative, Adaptive Clinical and Regulatory Strategy
- Rapid Global Submissions Long-Term Follow-up in DMP

Diverse Pipeline Across Metabolic Indications

Candidate	Description	Pre-Clinical	IND	Phase 1	Phase 2	Phase 3	Approved*	Est'd Patients in Dev. World
CRYSVITA burosumab KYOWA KIRIN	Anti-FGF23 monoclonal antibody	XLH						~48,000
		TIO						~2,000 - 4,000
Mepsevii (vestronidase alfa-vjbk) injection	Enzyme replacement	MPS 7						~200
UX007	Substrate replacement	LC-FAOD						~8,000-14,000
DTX301	AAV8-OTC Gene Transfer	OTC						~10,000
DTX401	AAV8-G6Pase Gene Transfer	GSDIa						~6,000
BAYER DTX201	AAV-FVIII Gene Transfer	Hemophilia A						~144,000

Protein Biologic | Gene Therapy | Small Molecule

14+ Translational Research Programs | Advancing One into the Clinic Every 1-2 Years

* Crysvita is approved in the U.S., Canada, EU, and Brazil
* Mepsevii is approved in the U.S., EU, and Brazil

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Early Pipeline Driving Next Opportunities Across 4 Modes

Picking the best mode for each indication

	TRADITIONAL BIOLOGICS	SMALL MOLECULE	AAV GENE THERAPY	mRNA
Commercial	CRYSVITA burosumab; Mepsevii (vestronidase alfa-vjbk) injection	LC-FAOD UX007		
Clinical	TIO Crysvita		OTC DTX301; GSDIa DTX401; Hem A DTX201 (BAYER)	
Research	Undisclosed UX064; Undisclosed UX032; Undisclosed UX008	Creatine Transporter Deficiency UX068; FSHD UX018; GNE Myopathy UX001P	Wilson UX701; CDD UX055; 3 Additional Targets	GSDIII UX053; 4 Additional Targets

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Examples of Modality Selection

	DISEASE	MODALITY	RATIONALE
Mepsevii (vestronidase alfa-vjbk) injection	MPSVII	Biologic (ERT)	▪ ERT delivers many times the total body content of enzyme each dose ▪ Needs to deliver to multiple organs, including connective tissue ▪ Simple and direct strategy: missing enzyme then replace it
CRYSVITA burosumab-twza	XLH	Biologic (Ab)	▪ Can titrate dose to control phosphate ▪ Fully bioavailable subcutaneously with no neutralizing antibodies ▪ Delivery efficiently to osteocytes not possible with gene therapy
UX007	LC-FAOD	Small Molecule	▪ ERT could not deliver to mitochondria ▪ 6 different LC-FAOD mutations, making gene therapy or mRNA difficult ▪ Inexpensive to make
DTX301	OTC	Gene Therapy	▪ Potentially curative, one-time treatment ▪ Only small amount of steadily produced enzyme required to correct ▪ No need to titrate dose
UX053	GSDIII	mRNA	▪ Gene too large for gene therapy ▪ Excellent penetration of ALL liver cells reduces toxic abnl glycogen impact ▪ Can treat young pediatrics

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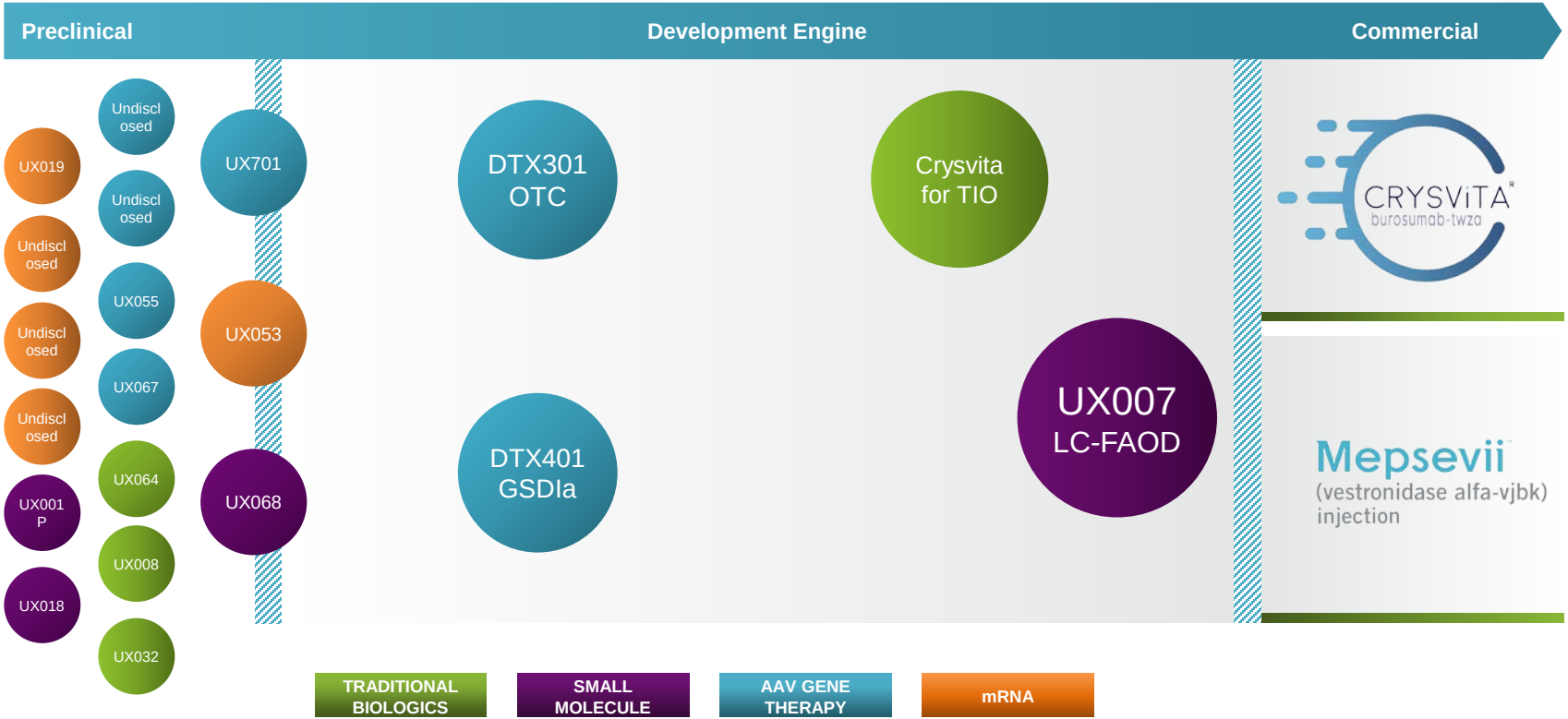
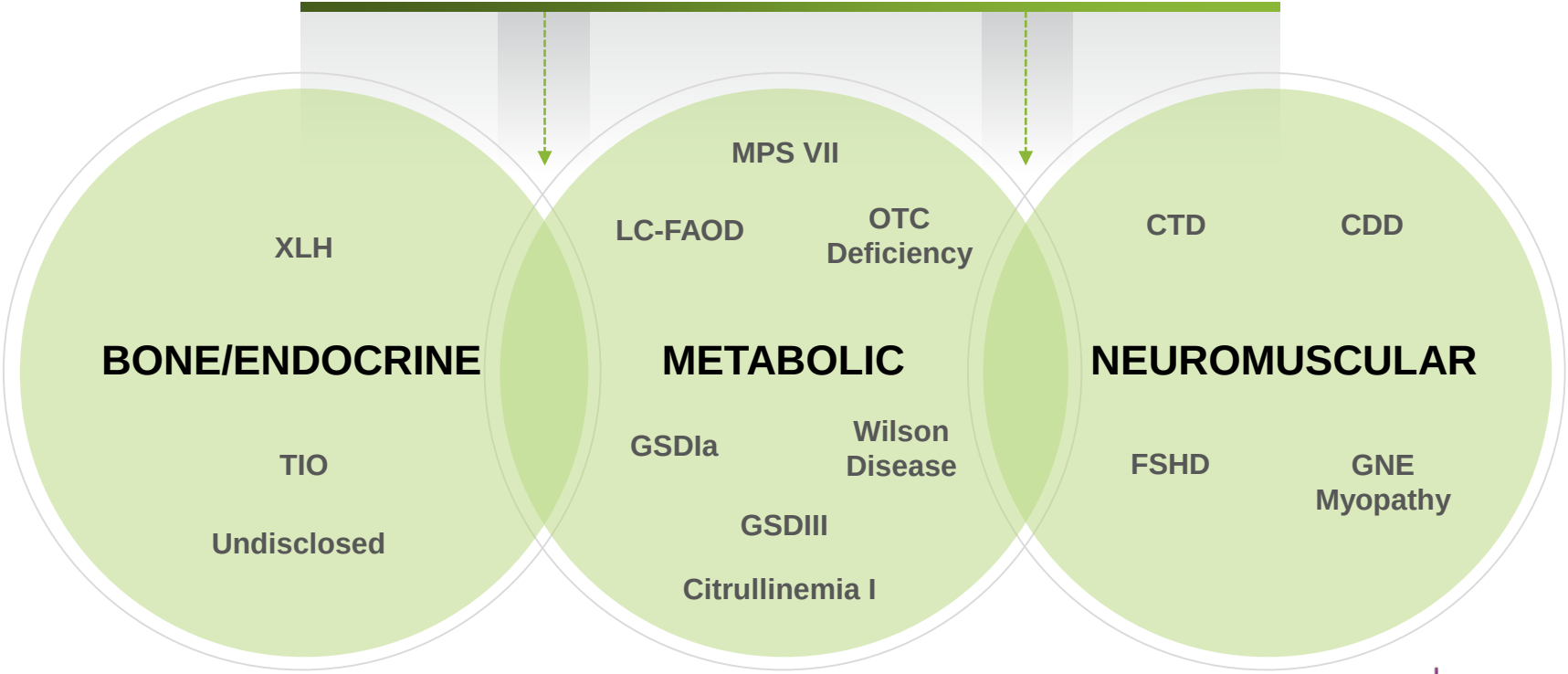
Building an Efficient, Sustainable Rare Disease Company

Early pipeline targets now lined up to refill clinical as products get approved



Current Focus on Therapeutic Areas with Rare Genetic Disease

Clinical and Commercial Synergies



Key Highlights Today

Strong global commercial progress

- U.S. launch continues to grow
- Expanding global presence rapidly and efficiently

Advancing gene therapy platform

- Platform and clinical programs: **DTX301** and **DTX401**
- Manufacturing using proprietary HeLa system
- Investing in GMP gene therapy manufacturing facility

Moving three early stage programs toward IND

- **UX701** Gene therapy for Wilson Disease
- **UX053** mRNA/LNP for Glycogen Storage Disease Type III
- **UX068** Creatine Prodrug for Creatine Transporter Deficiency

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CRYSVITA® burosumab-twza

Mepsevii™ (vestronidase alfa-vjbk) injection

Global Commercial Overview

Vlad Hogenhuis, M.D.

Chief Operating Officer

Ultragenyx is Set Up to Serve the Unique Needs of Patients with Rare Diseases

Many rare disease patients are ***lost in the system***; average time to diagnosis for a rare disease is >7 years

We help
find patients

Many patients are forced to be their own advocate, as doctors are ***unaware of their condition***

We help
take care of patients

Even if there is a treatment available, many patients are concerned about whether they qualify for it and if they can ***have access to the treatment***

We pursue broad,
swift market access

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Listening and Connecting with Patients is Central to What We Do

We Help Find Patients

Patient Diagnosis Liaison (PDL)

- Confirm physicians who may have a patient
- Assess referral patterns to understand how patients are treated

Diagnostic Testing Support

- Provide diagnosis confirmation tests and genetic counseling
- Provide gene panel tests – differential diagnosis and diagnosis confirmation

Family Tree Analysis

- Identifies suspected/high-risk family members
- Provides opportunity for a confirmatory diagnosis by a physician

We Help Take Care Of Patients

- Patients are given personal attention and the ***opportunity to receive care***
- ***In-house Patient Services*** hub allows RARE to ensure high level of patient support
- ***Personalized services*** provided by the hub to quickly get patient on the treatment:
  - Assigned case managers
  - Fast Start and Compassionate Use programs
  - Home health nurses
  - Patient assistance programs

Patient – Sites of Care Potential Locations

HOME
(Workplace, School, Dorm, Hotel, etc.)

OFFICE
(HCP Practice)

INFUSION CLINIC
(Institutional Outpatient Facility)

HOSPITAL
(In-patient/Institutionalized)

We Pursue Swift Market Access

- Synchronous global launches
- Responsible pricing for optimal patient access
- Fast Start and Compassionate Use programs

Presence in Three Major Rare Disease Markets
Less than 18 Months Post-Launch

Mepsevii
(vestronidase alfa-vjbk)
injection

	North America	Europe	Latin America
CRYSVITA	APPROVED	APPROVED	APPROVED
		NAMED PATIENT / PENDING DECISIONS	NAMED PATIENT / PENDING DECISIONS
Mepsevii	APPROVED	APPROVED	APPROVED
	PLANNED	PLANNED	NAMED PATIENT / PENDING DECISIONS

Note: Crysvita in North America is profit shared with Kyowa Kirin International (KKI); in Europe (excluding Turkey), KKI is responsible for commercialization; and in Latin America Ultragenyx is responsible for commercialization.

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Experienced Management Team Supporting Global Launches

Erik Harris – SVP
North America Commercial Ops

- Ultragenyx (2 years)
- Crescendo Bioscience:
  - U.S. Operations (6 yrs)
- Elan, Genentech, BMS (8 yrs)

KEY LAUNCHES	
Tarceva®	Tysabri®
Vectra-DA®	

Eduardo Thompson – SVP
Latin America Commercial Ops

- Ultragenyx (3.5 years)
- BioMarin:
  - LatAm Operations (10 yrs)
- Merck (6 yrs)

KEY LAUNCHES	
Naglazyme®	Vimizim®
Stocrin®	Invanz®
Maxalt®	

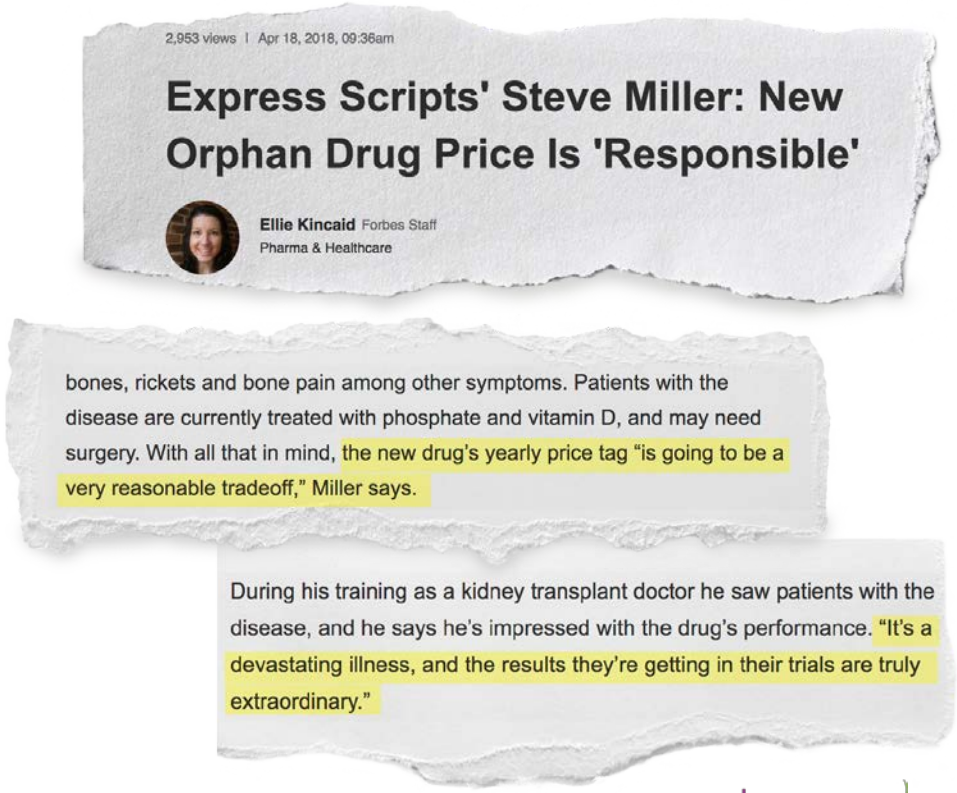
Stefano Portolano, M.D. – SVP
International Commercial Ops and Brand Strategy

- Ultragenyx (3.5 years)
- Celgene:
  - EU Commercial Ops (10 yrs)
- Genzyme (8 yrs)

KEY LAUNCHES	
Thyrogen®	Fabrazyme®
Aldurazyme®	Revlimid®
Vidaza®	Abraxane®

Access Goal: Majority of Eligible Patients with Reimbursed Access in Every Region

- Launch with a ***price band to optimize patient access across all geographies***
- ***Bridging or interim drug*** access programs prior to reimbursed coverage
  - United States: Fast start and bridge programs
  - Ex-U.S.: Compassionate use or named patient sales
- ***Responsible pricing*** to maximize timely market access



Dedicated to Providing Rare Disease Patients with Comprehensive Solutions

- Strong patient-focused culture provides for a singular focus on doing good by the patient
- Comprehensive model to serve the needs of rare disease patients
- Targeted investment to build a footprint where we can impact the most amount of lives
- Global market strategy to maximize treatment access to all patients
- Current Commercial infrastructure can be leveraged to meet the demands of future launches (e.g. UX007)

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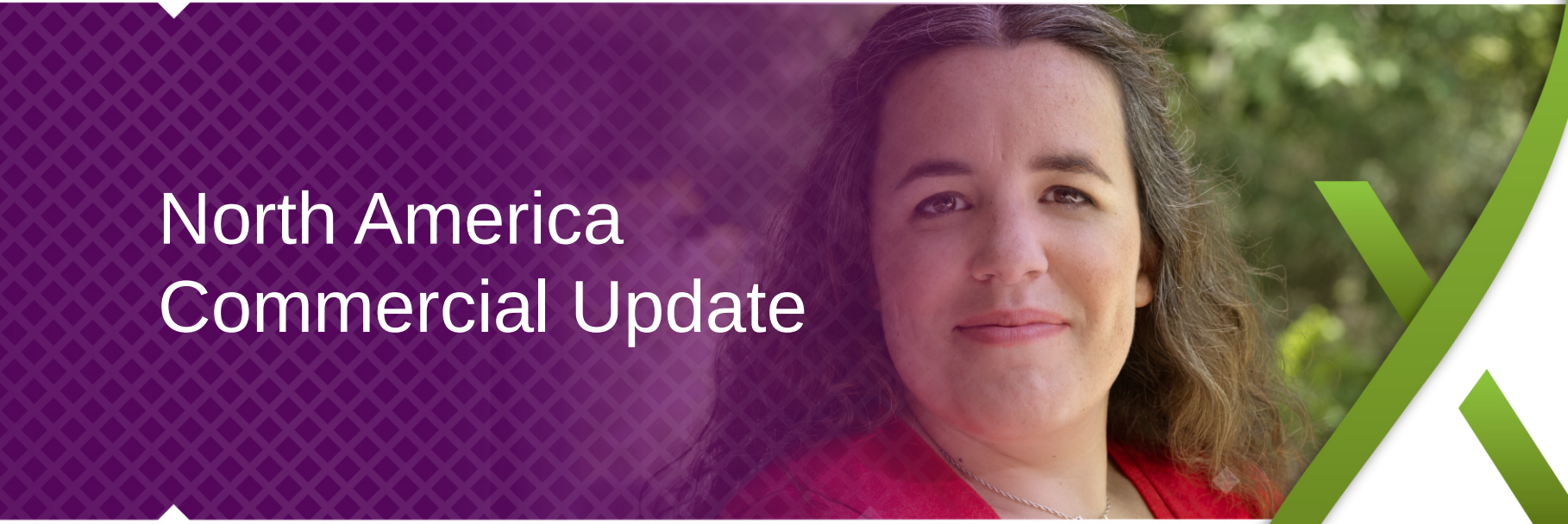
CRYSVITA® burosumab-twza

Mepsevii® (vestronidase alfa-vjbk) injection



North America Commercial Update

Erik Harris

SVP, North America Commercial Operations

Patient Experiences

"Remember when you were a little girl at school and you got to go out for recess? That's what I feel like – **I've been let out for recess!"**

– Crysvita Patient in North Carolina

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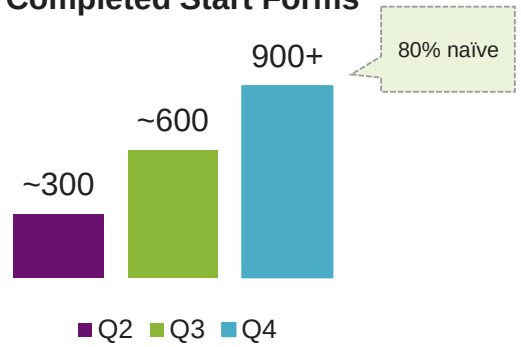
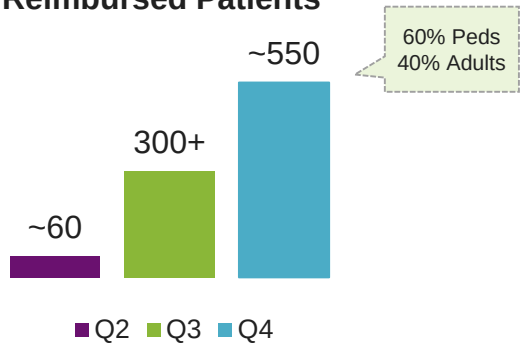
Strong U.S. Crysvita Launch
As of December 31, 2018

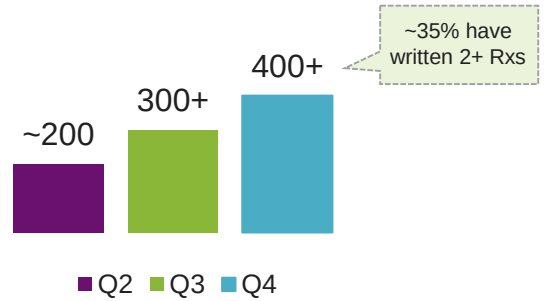
Completed Start Forms



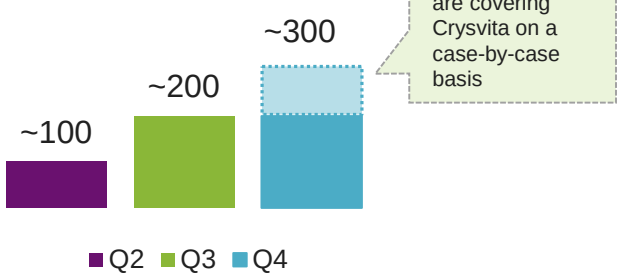
Reimbursed Patients



Unique Prescribers



Covered Lives
(in million)

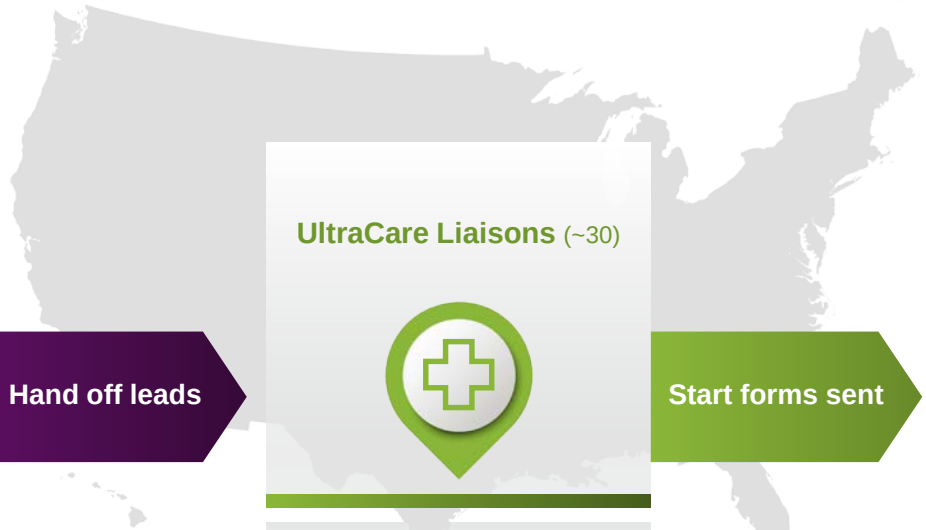


** Crysvita launched on April 27, 2018*

U.S. Patient Access Model

Unique model to support and accelerate growth

CRYSVITA® burosumab-twza



Patient Diagnosis Liaisons (~30)

Find new doctors with XLH patients

Hand off leads

UltraCare Liaisons (~30)

Assist identified XLH doctors in placing patients on therapy

Start forms sent

UltraCare Guides (~15)
Patient Access Liaisons (5)

Support treatment or reimbursement needs

Market Access Support

Medical Science Liaisons

Educate HCPs and payers throughout the process

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Accelerants of Success in 2019

Solid plans in place to continue momentum

Maximize potential with current prescribers

Expand prescriber base & generate referral pathways

Reduce time to reimbursement

Find patients with XLH

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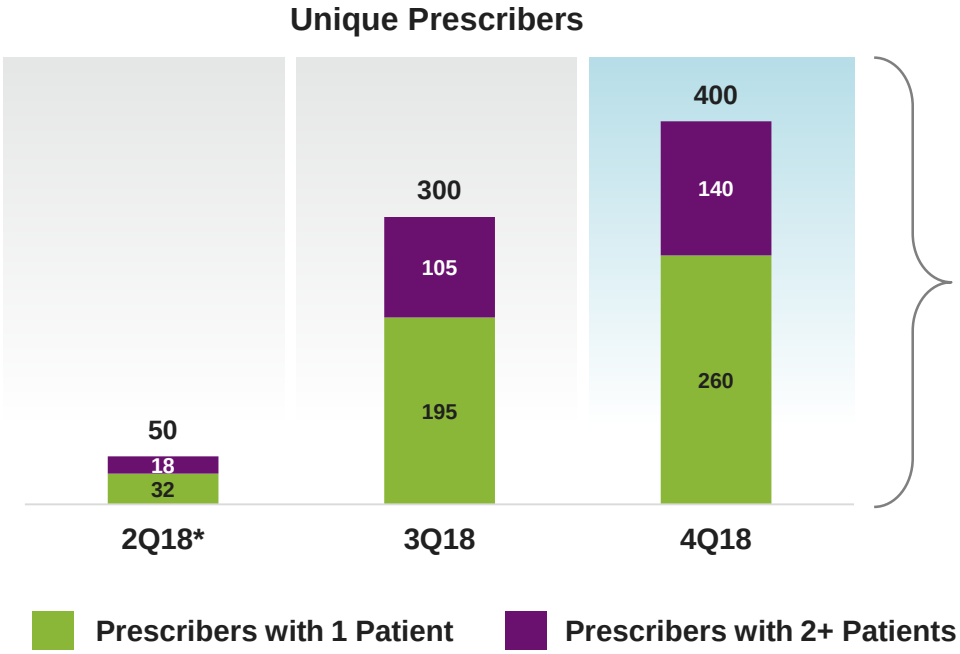
Maximize Potential with Current Prescribers

Those with 2 or more prescriptions has grown proportionally with the launch

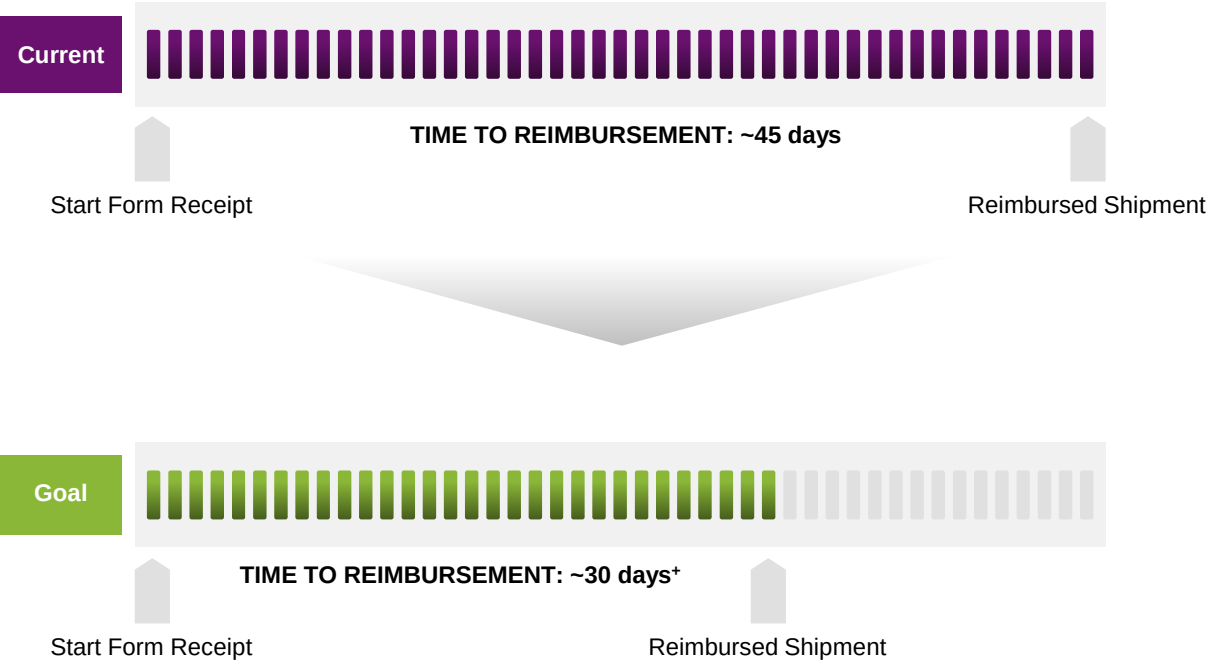


Among the ~400 prescribers in 4Q18, a large number of known pediatric and adult patients are not yet prescribed

* Crysvita launched on April 27, 2018

Reduce Time to Reimbursement

Leveraging payer-specific learnings from 2018 to expedite reimbursement



- Genetic testing (PHEX) confirmation
- Prior Authorization (PA) required for initiation and continuation

- Lack of convenient buy and bill site of care
- Incomplete PA delays payer approval process

- Program offering no-cost test to patients to expedite PA approvals recently launched
- Leveraging payer policies to expedite PA approval

- Raising awareness of J-code to streamline buy-and-bill process
- Helping ensure complete PA paper work submitted to avoid delays

** ~20% of time to complete Start Form and remaining 80% is needed for genetic test confirmation, PA approval, and finding site of care*
+ No-cost genetic test will reduce the time to reimbursement by 50% and other reduction will come from expedited PA approval since most payers now have a policy in place

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Meaningful Patient Penetration in Early Launch

Significant opportunity for continued growth

	Pediatrics	Adults
Estimated Prevalence	~3,000	~9,000
Patients with a Completed Start Form[1]	~550	~350
Patients on Reimbursed Drug[1]	~330	~220

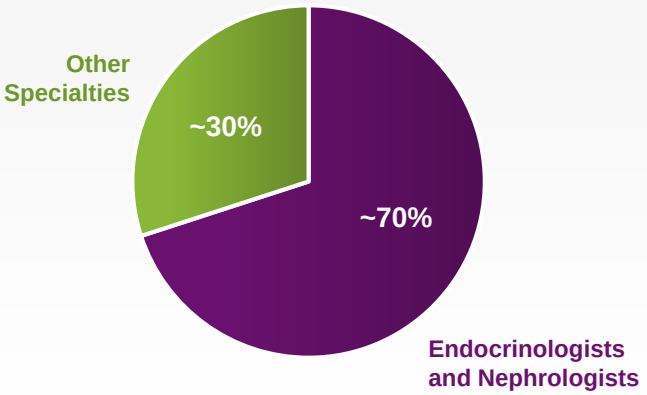
Finding adult patients remains a key priority in 2019 and beyond

[1]As of December 31, 2018

Adult Patients not Currently Treated for XLH

Focusing on other specialties where adults are treated for complications

Prescriber Mix[1]



Challenge with Finding Adult Patients

Adult patients often present to other specialties as a result of complications of XLH and not the typical endocrine/nephrologist MDs.

Action Plan

- Focus on secondary specialties (IM, FM, Genetics, Ortho, Dentistry) based on the ICD-10 and lab data
- Use pedigree analysis to find adult patients
- Raise disease awareness

Strategy is to find these adults and have them refer to offices of metabolic bone disease doctors for treatment with Crysvita

[1]As of December 31, 2018

Find New Patients

Comprehensive approach to find patients

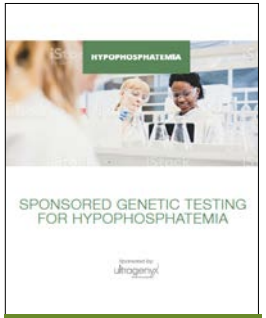
Data Mining and Predictive Analytics

ICD-9/10 E83.31; lab: serum phos; Machine learning / Artificial Intelligence: combination of all + surgeries + Rx for oral phos & calcitriol

Data used by PDL team to identify potential XLH treaters

HYPOPHOSPHATEMIA

Genetic Testing Panel



Test is used to help identify potential patients

Offered to current 900+ patients and other potential patients

Genetic Counseling

~70% of the clinical trial patients surveyed reported that they have a family member with XLH

Patients on Start Form

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Accelerants of Success in 2019

Solid plans in place to continue momentum

Maximize potential with current prescribers

Expand prescriber base & generate referral pathways

Reduce time to reimbursement

Find patients with XLH

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Real World Experience

Anthony A. Portale, MD
University of California
San Francisco

Camille Bedrosian, MD
Chief Medical Officer,
Ultragenyx (Moderator)

Aly
Patient with XLH

San Antonio, TX

Theresa
Patient with XLH

Germansville, PA

UX007 for Long Chain Fatty-Acid Oxidation Disorders (LC-FAOD)

Camille Bedrosian, M.D.
Chief Medical Officer, Ultragenyx

UX007 for LC-FAOD
NDA submission set for mid-2019

- **Key symptoms/prognosis:**
  - Hypoglycemia, muscle rupture, heart failure
  - Mortality of >50%[1]; a cause of SIDS (newborn screened in U.S.)
- **Standard of care:** Diet and MCT[2] oil
- **U.S. prevalence:** ~2,000 – 3,500

[1] J Inherit Metab Dis 2013;36:795-803
[2] Medium chain triglycerides

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UX007 Granted Fast Track and Rare Pediatric Disease Designations

Ultragenyx Announces UX007 Granted Fast Track Designation and Rare Pediatric Disease Designation by U.S. FDA for Treatment of Long-Chain Fatty Acid Oxidation Disorders

Company on Track to Submit NDA to FDA by Mid-2019

Novato, Calif. — April 16, 2019 — Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE), a biopharmaceutical company focused on the development of novel products for serious rare and ultra-rare genetic diseases, today announced that the U.S. Food and Drug Administration (FDA) has granted Fast Track designation and Rare Pediatric Disease designation to UX007 for the treatment of long-chain fatty acid oxidation disorders (LC-FAOD), a group of genetic disorders in which the body is unable to convert long-chain fatty acids into energy.

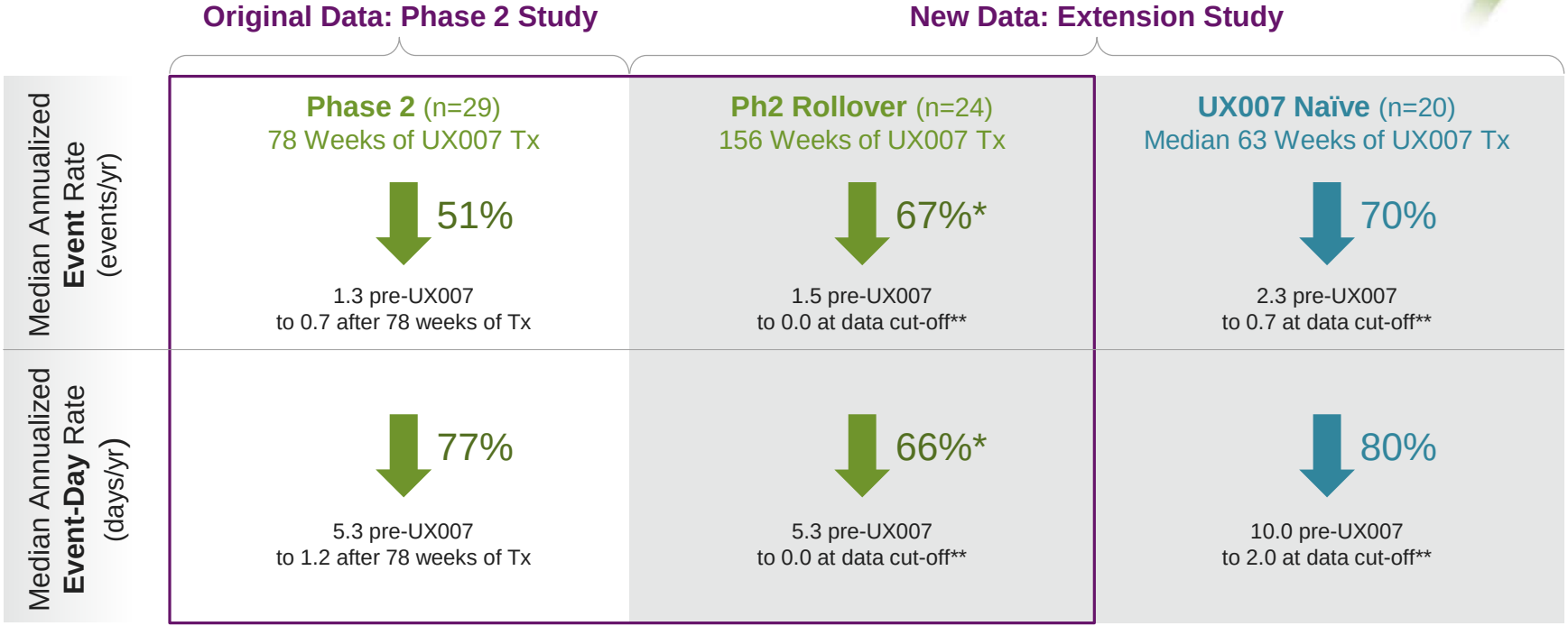
"These designations for UX007 underscore FDA's belief that new treatments are needed for patients with LC-FAOD, a severe and potentially life-threatening disease. In addition,

NDA submission will include:

- Company-sponsored Phase 2 (n=29)
- Long-term extension study (n=75)
- Retrospective medical review (n=20)
- Expanded access (n=70)
- Investigator-sponsored study (n=32)

On track to submit NDA in mid-2019

Extension Study Supports Sustained Clinically Meaningful Impact of UX007



* Percent reductions based on total UX007 treatment period (Phase 2 + Ext periods)
** 156 weeks on Tx for Ph2 rollover patients and median of 63 weeks for naïve patients

Safety profile in the long-term extension study (n=75) consistent with what has been previously observed with UX007

FAODs: The burden of illness

Jerry Vockley, M.D., Ph.D.
University of Pittsburgh
Cleveland Family Endowed Chair in Pediatric Research
Children's Hospital of Pittsburgh
Chief of Medical Genetics
Director of the Center for Rare Disease Therapy

Disclaimer

- I receive research funding from Ultragenyx for clinical trials on UX007
- I do not receive any personal consulting income from Ultragenyx

A personal history of FAODs

- FAODs with a combined incidence of ~10:000 births
- FAODs didn’t exist when I started medical school!
- Residency
  - Reye syndrome (nearly all)
  - SIDS (10-25%)
- Fellowship
  - VLCAD
  - LCHAD/TFP
- Now identified by newborn screening
- FAOD Reye syndrome and SIDS ~0

Poor outcomes

- >50% lethal pre-NBS
- Now still with significant morbidity
  - Hypoglycemia
  - Cardiomyopathy
  - Rhabdomyolysis
- Current therapies for LC FAODs are inadequate

Personal history with UX007

- First patient with cardiomyopathy ~30 years ago
- Treated first patient 15 years ago
- Assumed development of the drug 10 years ago
- Began working with Ultragenyx 5 years ago

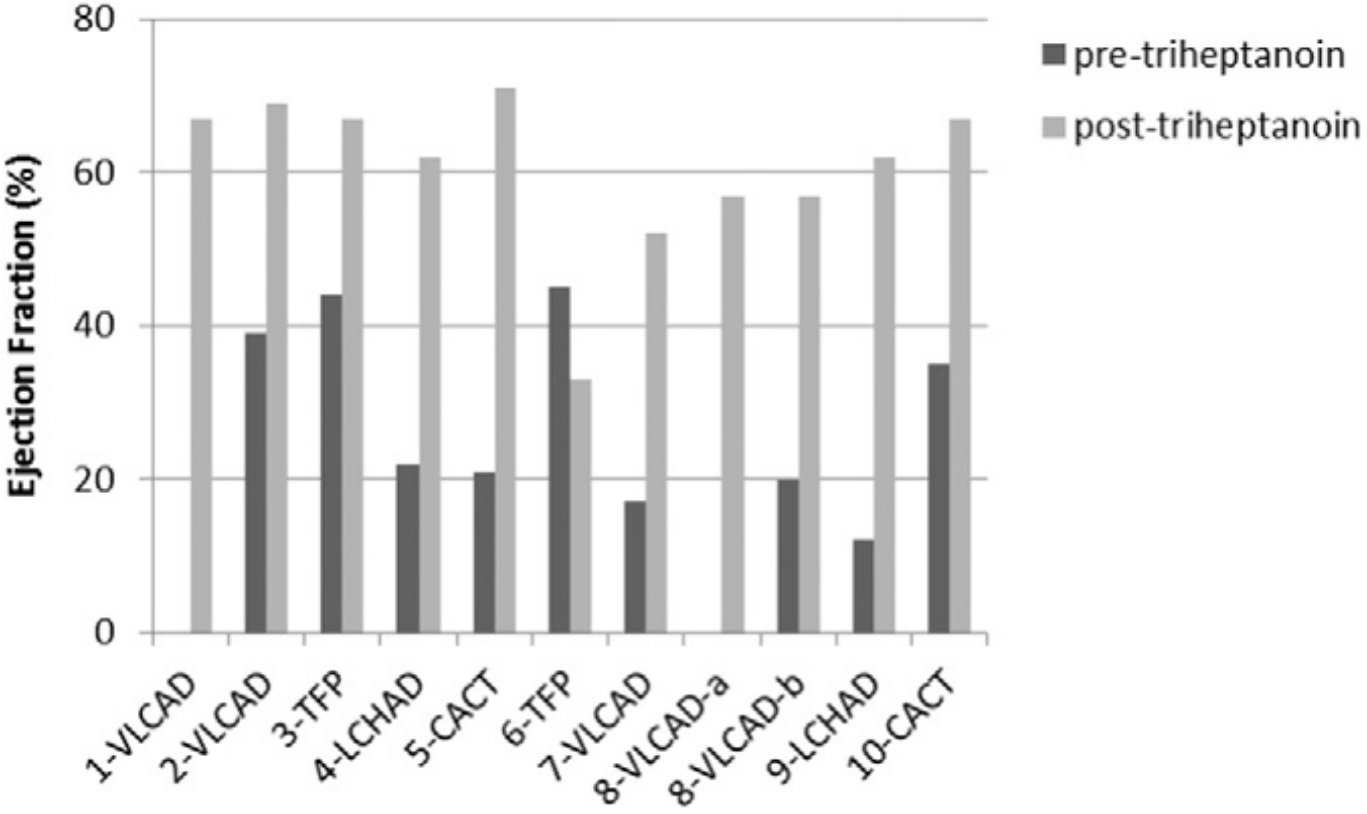
A very bad year (2014)

Clinical characteristics and interventions.

Case ID	1	2	3	4	5	6	7	8	9	10	Incidence (%)
LC-FAOD	VLCAD	VLCAD	TFP	LCHAD	CACT	TFP	VLCAD	VLCAD	LCHAD	CACT	–
Cardiac dysfunction											
Cardiomyopathy/LV dysfunction	X	X	X	X	X	X	X	X	X	X	100%
Arrest		X		X	X		X	X	X		60%
Arrhythmia				X		X	X		X		40%
Decompensation due to secondary acute infection		X	X		X					X	40%
Heart failure				X	X	X	X				40%
Pericardial effusion	X					X		X			30%
Cardiogenic shock	X							X			20%
Cardiac Interventions											
Mechanical Support (ECMO/Ventilation)		X		X		X	X	X	X		60%
Pressors		X		X	X		X	X	X		60%
Ventricular assist devices									X		10%
Pericardiocentesis						X					10%
Other (≥ 3 cases)											
Neonatal hypoglycemia	X		X		X	X	X	X			60%
Rhabdomyolysis/Elevated CK		X	X		X	X		X	X		60%
Hepatic Dysfunction					X		X	X		X	40%
Metabolic/lactic acidosis	X					X		X		X	40%
Respiratory Complications						X	X	X			30%
Hypothermia					X			X		X	30%
Death						X	X				20%

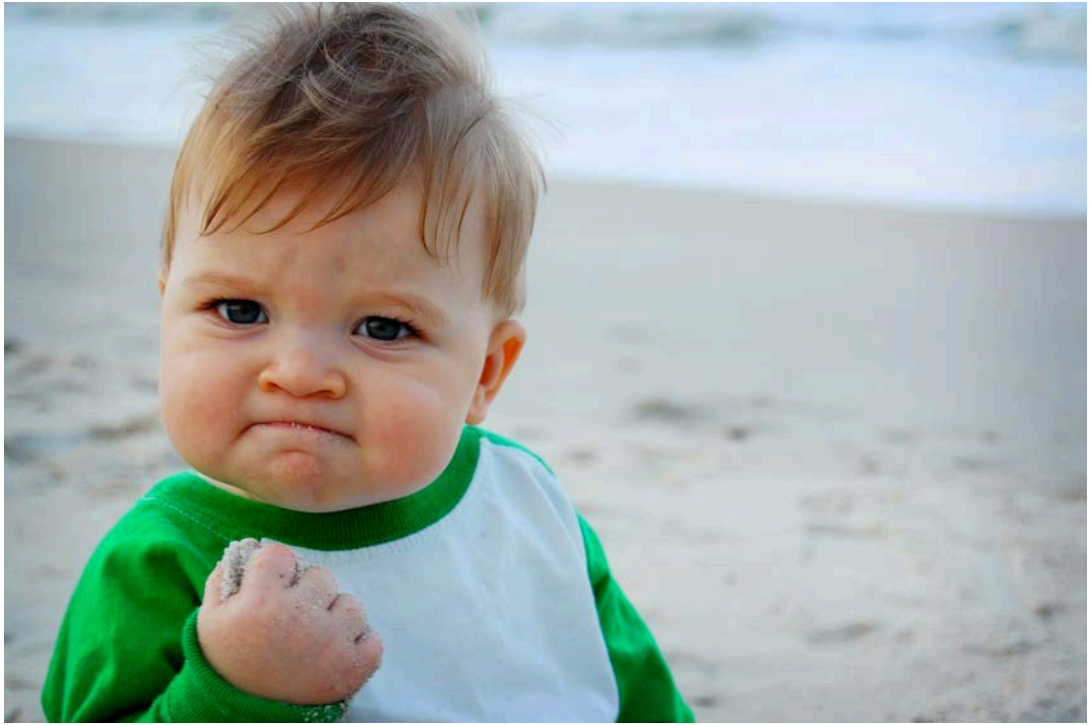
Vockley J, et al (2016). *Mol Genet Metab.* 119: 223-31. PMID 27590926.

A very good outcome



Follow-up

- The numbers show it works
- The patients (and parents) tell me it works!
  - Improved energy
  - Less pain
  - Better quality of life
  - Peace of mind



Thank you!

Q&A
Commercial and UX007

Emil D. Kakkis, M.D., Ph.D.
CEO, President and Founder

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Break

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Gene Therapy Platform

Emil D. Kakkis, M.D., Ph.D.
CEO, President and Founder

Gene Therapy Platform Supported by People, Clinical Need, and Manufacturing

People	Clear Biology + Unmet Need	Scalable Mammalian Manufacturing
▪ Dimension Therapeutics provided technology base ▪ Ultragenyx Gene Therapy has built in-house process discovery, definition, and development ▪ Internal knowledge de-risks scale up and tech transfer	▪ 2 Clinical Stage Programs – DTX301, DTX401 ▪ 1 Partnered Clinical Program – DTX201 ▪ 1 Late Stage Research – UX701 ▪ 4 Early Stage Research – UX055, UX501, UX601, UX067	▪ HEK293 ▪ HeLa producer cell line ▪ Internally controlled process development ▪ Scalable up to 2,000L

Gene Therapy Pipeline: Deep and Focused

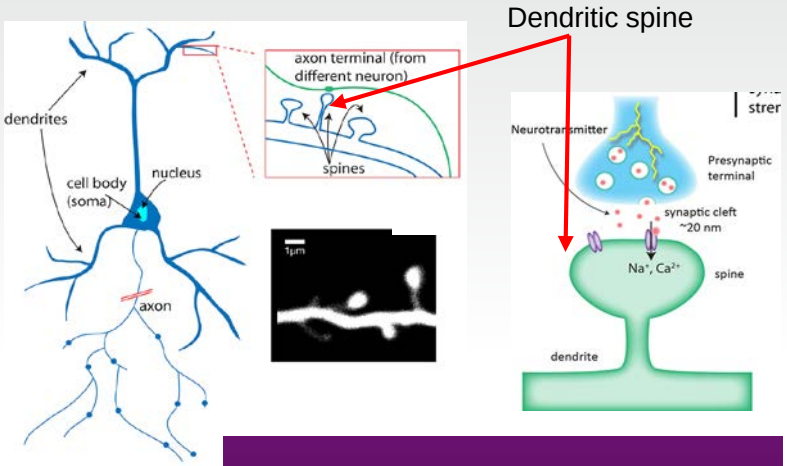
Candidate	Description	Pre-Clinical	IND	Phase 1	Phase 2	Phase 3	Est'd Patients in Dev. World
DTX301	AAV8-OTC Gene Transfer	OTC					~10,000
DTX401	AAV8-G6Pase Gene Transfer	GSDIa					~6,000
DTX201	AAV-FVIII Gene Transfer	Hemophilia A					~144,000
UX701	AAV-ATP7B Gene Transfer	Wilson Disease					>50,000
UX055	AAV9-CDKL5 Gene Transfer	CDKL5 Deficiency Disorder					~30,000
UX501	AAV8-PAH Gene Transfer	PKU					~50,000
UX601	AAV8-ASS1 Gene Transfer	Citrullinemia type I					~2,000
UX067 (Partnered)	Undisclosed						>10,000

Combination Liver Metabolic Diseases (OTC, GSDIa, PAH, ASS1 +1, Wilson) and Neurology (CDKL5)

UX055 for CDKL5 Deficiency Disorder (CDD)

Restoring functional kinase activity in neurons likely to reverse the phenotype

- **CDKL5 Deficiency Disorder (CDD)**: X-linked dominant neurodevelopmental disorder
- **Key symptoms**: Severe cognitive and developmental delays, hypotonia and movement disorders, cortical visual impairment
- **Standard of Care**: Limited Rx options, primarily focused on managing seizures
- **Prevalence**: ***~30,000*** based on genetic screening. Often misdiagnosed as atypical Rett
- **REGENXBIO Licenses** for all capsids including AAV9, expected choice for clinical use



CDKL5 is critical for dendritic spine formation and growth

Neurons are otherwise intact

CDD represents a substantial new opportunity to treat a disease whose prevalence is far greater than realized

UGT Centers of Excellence Enable Fast, Robust Transfer from Discovery to GMP Manufacturing

COE	Capabilities	Value Proposition
Producer Cell Line Development (Cambridge, MA)	Innovative Molecular Biology; Screening of **hundreds of clones** (15 ml scale)	Highest level of productivity, lowest levels of product related impurities
Process & Analytical Development (Woburn, MA)	**Platform Expertise**; Fastest product-specific parameter optimization (2L scale)	Deep process/product characterization, **immediate scalability assessments**
Pilot Plant (Woburn, MA)	**50L – 250L** vector production (non-GMP)	**Eliminates cost/time** required for Engineering Lots at CMO Transfer intact processes to CMO

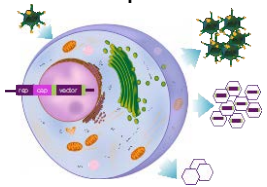
A wholly owned GMP Manufacturing Plant is in development to support, in addition to CMO's, the extensive production requirements for 4-7 gene therapy programs

Ultragenyx Gene Therapy AAV Vector Production

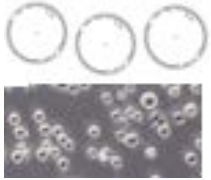
Vector Discovery to GMP Manufacturing

PD & manufacturing across 15 ml to 2,000L continuum – scaling factor > 130,000

HeLa PCL suspension/Adeno helper



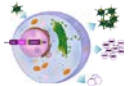
HEK293 suspension/Transfection



15mL
Ambr

50L

200L



2,000L

4 x 200L

- Cell line cloning
- Early development

- Bioprocess development
- Preclinical & tech transfer Center of Excellence
- Large scale reference tox vector manufacturing

Clinical & commercial manufacturing at partner CMOs

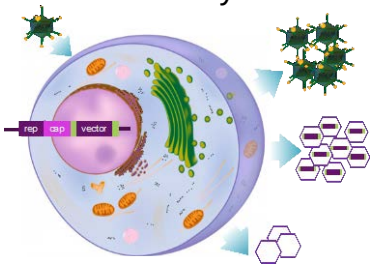
Product yield consistency maintained across scale

2,000L HeLa Producer Cell Line Production:
Largest scalable mammalian GMP production of AAV vector

- HeLa PCL for Hem A program partnered with Bayer
- Two 2,000L GMP runs completed and executed with high quality vector produced
  - Scalable, growth of PCL to 2,000 scale
  - Adenovirus helper production and removal
  - High GC load of vector as expected
- Passed through FDA review and in active IND
- Hem A patients treated, data to be reported by Bayer

2,000L

HeLa PCL System



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DTX301 Program

Ornithine Transcarbamylase (OTC) Deficiency

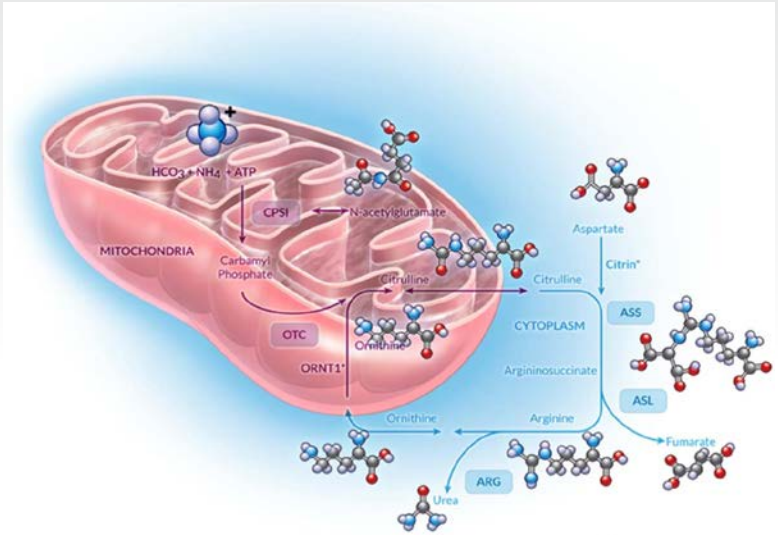
Eric Crombez, M.D.

Chief Medical Officer, Ultragenyx Gene Therapy

DTX301 AAV8 for OTC Deficiency

AAV8 gene therapy for stable expression of OTC

- **OTC Deficiency:** X-linked urea cycle disorder, genetic defect in ammonia detoxification
- **Key symptoms/prognosis:** Acute hyperammonemic episodes that can lead to hospitalization, adverse cognitive & neurological effects, death
- **Treatment limited; only curative approach is liver transplantation**
- **WW prevalence:** ~10,000, 80% late-onset



DTX301 AAV8 for OTC Study Design

Study Phase	Phase 1/2
Study Design	Open-label, multicenter, safety and dose-finding study to determine the safety, tolerability, and efficacy
Cohorts and Dosing	Single intravenous infusion ▪ Cohort 1: 2.0 × 10^12 GC/kg (3 patients) ▪ Cohort 2: 6.0 × 10^12 GC/kg (3 patients) ▪ Cohort 3: 1.0 × 10^13 GC/kg (3 patients)
Study Population	Adults with late-onset OTC deficiency
Sample Size	▪ Approximately 12 patients enrolled sequentially into cohorts ▪ 3 patients per cohort
Follow-up Period	▪ Patients will be followed for 52 weeks after dosing ▪ 4-year extension study planned to evaluate the long-term safety and efficacy of DTX301

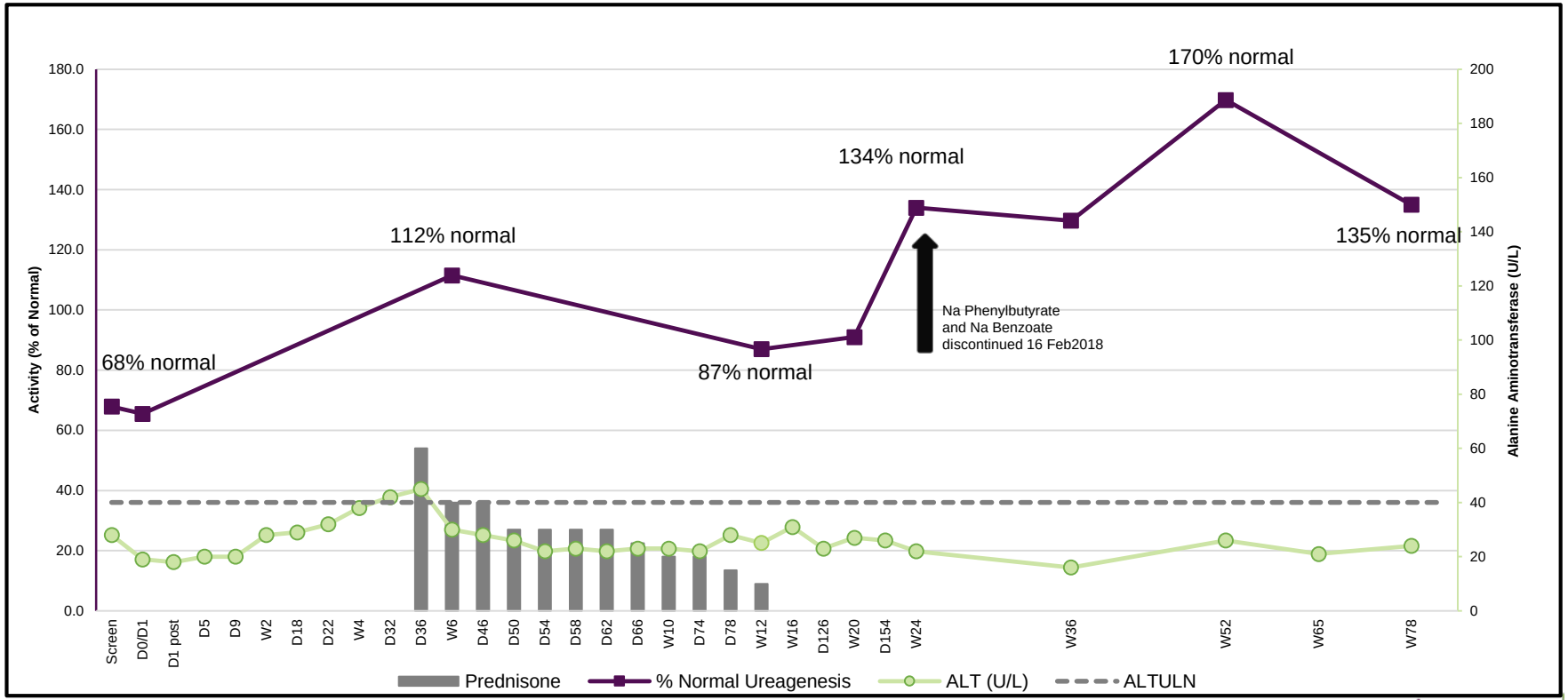
DTX301: Two Patients Continue to Demonstrate Long-term Normalization of Ureagenesis

- Sustained normalization of ureagenesis at 52-78 weeks
- Clinically and metabolically stable, while discontinuing all alternate pathway medications
- Liberalized protein-restrictive diet without hyperammonemia concerns
- One patient had proven Influenza illness without hyperammonemia episode

Cohort 3 enrollment is ongoing at 1e13 GC/kg dose
Data expected mid-2019

Cohort 1, Patient 1 – Durable Normalization of Ureagenesis

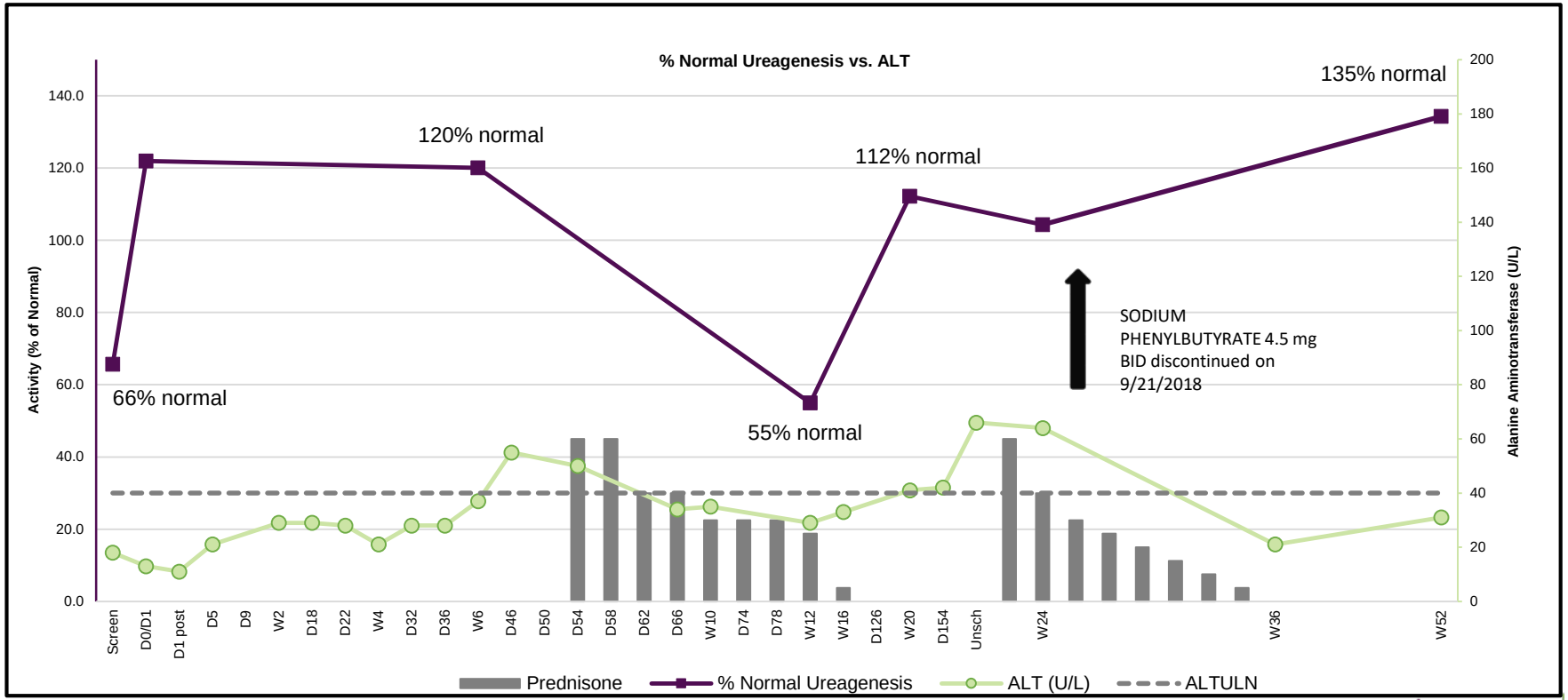
Liberalized diet and clinical stability off medications since ~Week 24



* Patient entered long-term extension study after week 52

Cohort 2, Patient 4 – Durable Normalization of Ureagenesis

Liberalized diet and clinical stability off medications since ~Week 24



Cohort 1 & 2: Favorable Initial Safety Profile

- No infusion-related adverse events
- No SAEs
- All AE severity graded as 1 or 2
- All AEs resolved and unrelated to drug except for mild, clinically asymptomatic elevated alanine aminotransferase levels (probable relatedness, resolved)

DTX401 Program
Glycogen Storage Disease Type Ia (GSDIa)

Eric Crombez, M.D.

Chief Medical Officer, Ultragenyx Gene Therapy

DTX401 AAV8 for GSDIa

- **GSDIa:** Autosomal recessive, inborn error of glucose metabolism; deficient glucose-6-phosphatase (G6Pase)

- **Key symptoms/prognosis**
  - Hypoglycemia leading to significant morbidity and mortality
  - Long-term liver and renal disease
  - Impaired growth and delayed puberty
  - Severe long-term complications (70-80% patients)

- **Treatment limited; only curative approach is liver transplantation**

- **WW prevalence:** 6,000

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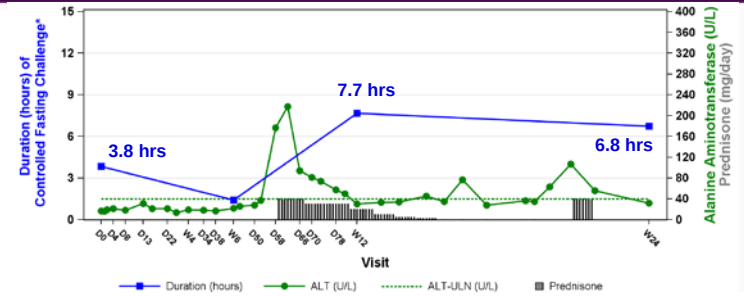
Clinical Response from All Patients in Cohort 1 at Week 24

- Time to hypoglycemia maintained or further increased
- Normal glucose levels maintained after continued reductions in use of cornstarch
- Patients continue to do well with reduced cornstarch requirements
- No treatment-related serious adverse events (SAEs)

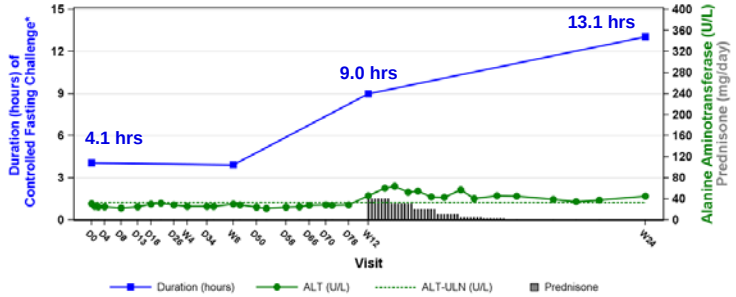
Cohort 2 enrollment is ongoing at 6e12 GC/kg dose
Data expected mid-2019

DTX401 Response in Time to Hypoglycemia Maintained or Increased While Reducing Daily Cornstarch at Week 24



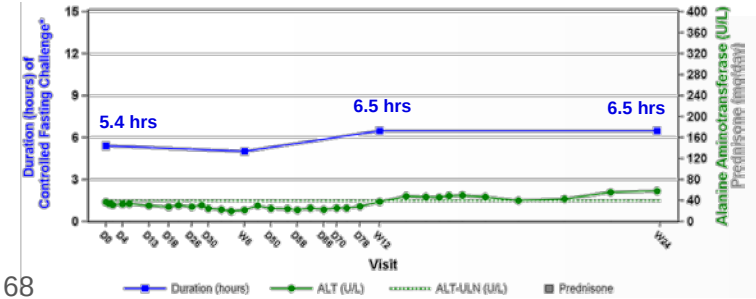
Cohort 1, Patient 1

- 79% improvement in time to hypoglycemia
- 77% reduction in daily cornstarch



Cohort 1, Patient 2

- 220% improvement in time to hypoglycemia
- 44% reduction in daily cornstarch
- 36% reduction in overnight glucose infusion rate



Cohort 1, Patient 3

- 20% improvement in time to hypoglycemia
- 73% reduction in daily cornstarch

DTX401
No Safety Issues Observed in Cohort 1

- Mild asymptomatic elevation in ALT levels due to a response to the vector administration in 2 patients
  - Successfully treated with a tapering course of steroids
- No infusion-related adverse events
- All AE severity graded as 1 or 2
- No treatment related SAEs

Positive Cohort 1 Results from the Phase 1/2 Trial with AAV8-Mediated Liver-Directed Gene Therapy in Adults with Glycogen Storage Disease Type Ia

David A. Weinstein, MD, MMSc; Ayesha Ahmad, MD; Connie Lee, PhD; Allen Poma, MD; Eric Crombez, MD

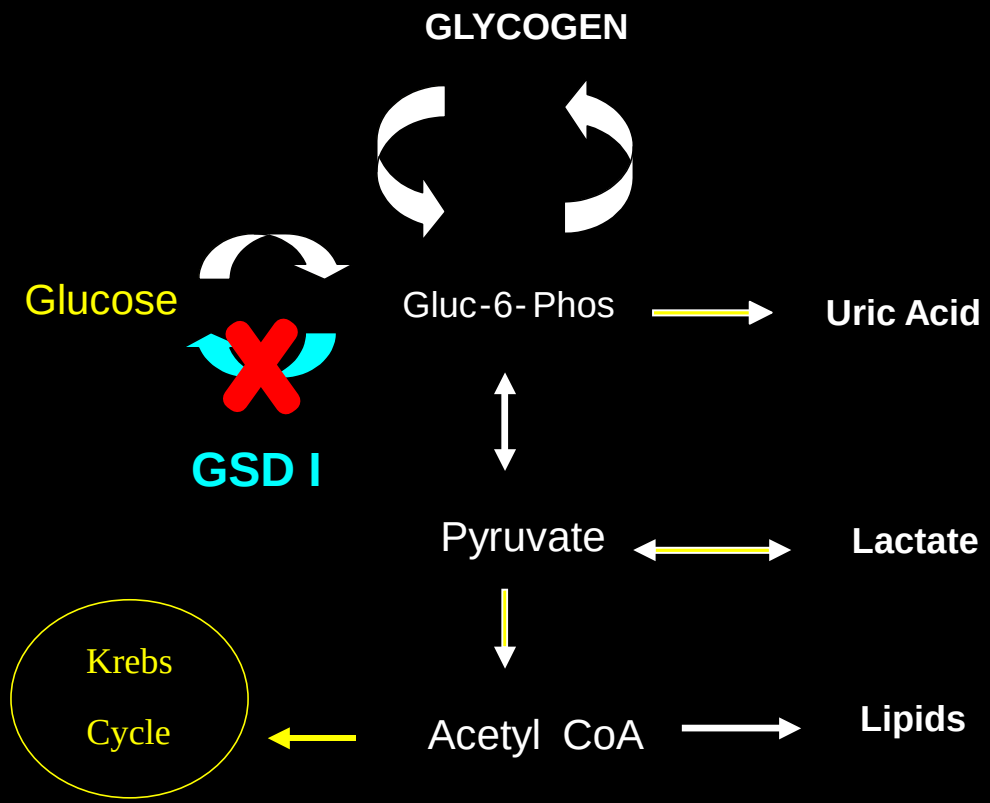
Disclosures

- **David A. Weinstein, MD, MMSc** served an investigator in this clinical trial sponsored by Ultragenyx; has received grant support from Vitaflo / Nestle (GLYDE Trial), Generation Bio, Logic Bio, and Moderna; and served as an unpaid advisory board member for Ultragenyx and Dover Lifesciences

- **Ayesha Ahmad, MD** served an investigator in this clinical trial sponsored by Ultragenyx

- **Connie Lee, PhD, Allen Poma, MD, and Eric Crombez, MD** are employees of Ultragenyx

Glycogen Storage Disease Type I



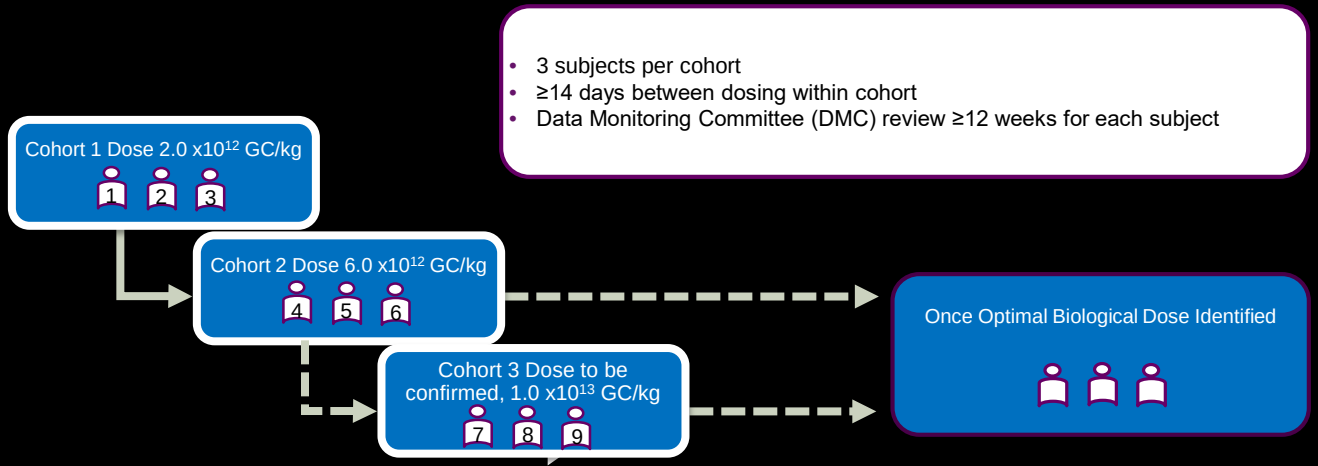
Glycogen Storage Disease
Treatment

- Cornstarch administered every 3-5 hours
- No children and less than 10% of adults can sleep through the night without awakening
- Over sleeping can result in severe hypoglycemia, seizures, and even death

DTX401

DTX401 is a non-replicating, recombinant adeno-associated virus serotype 8 (AAV8) vector that expresses the human G6PC gene under the transcriptional control of a liver specific promoter

GSDIa Phase 1/2 Gene Therapy Study: A Global Multi-center Open-label Dose Escalation Trial



- Primary objective: safety and tolerability of DTX401
- Key secondary objectives: change from baseline in time to 1st hypoglycemia event (defined as glucose <60 mg/dL during a controlled fasting challenge, hypoglycemia symptoms, or 15 hours fasting without hypoglycemia)
- Exploratory objectives: total cholesterol, LDL and triglycerides, uric acid and urine albumin; weekly use of cornstarch; and health-related quality of life (HRQoL) and sleep quality assessments

Study Requirements

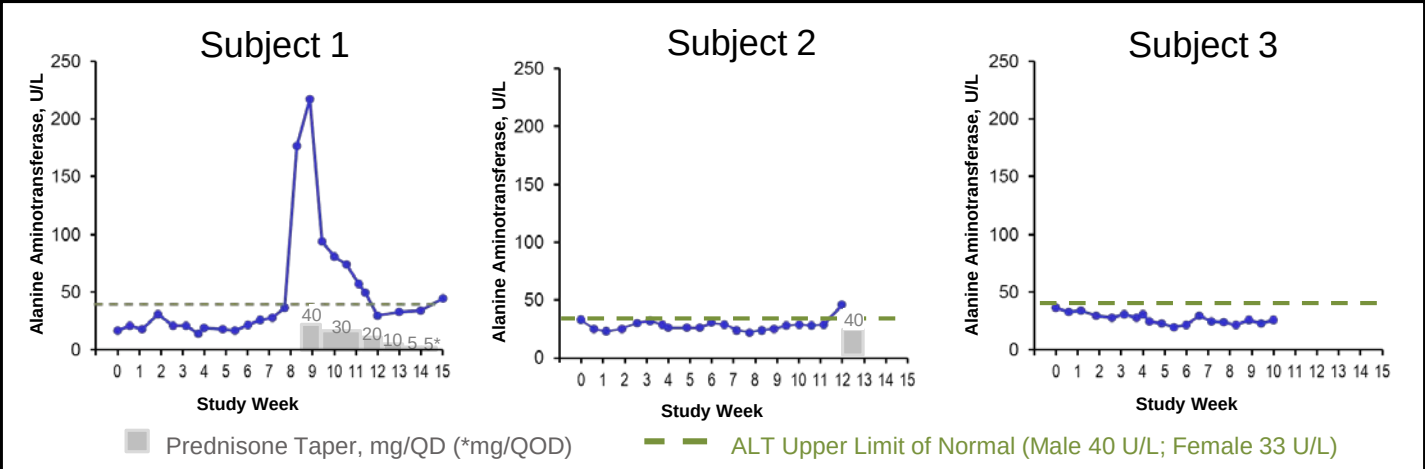
Study Visit	Day	Week	Inpatient	Outpatient	Outpatient or Home Visit* (1-1.5 hours)
1	Screening			5-6 hours	
2	0-1		48 hours		
3	4				X
4	8				X
5	13				X
6	18				X
7	22				X
8	26				X
9	28	Week 4		1.5-2 hours	
10	30				X
11	34				X
12	38				X
13	42	Week 6	24-48 hours		
14	46				X
15	50				X
16	54				X
17	58				X
18	62				X
19	66				X
20	70				X
21	74				X
22	78				X
23	84	Week 12	24-48 hours		
24	168	Week 24	24-48 hours		
25	252	Week 36		1.5-2 hours	
26	364	Week 52	24-48 hours		

Dosing Cohort #1

2 x 10^{12} GC/kg

Subject	Age	Gender	Genetics	Baseline Treatment
July 2018 1	28	Male	35X / Q347X	Cornstarch
Aug 2018 2	57	Female	Q347X / Q347X	Cornstarch + Continuous feed
Sept 2018 3	51	Male	R83C / Q347X	Cornstarch

Transaminase Elevation



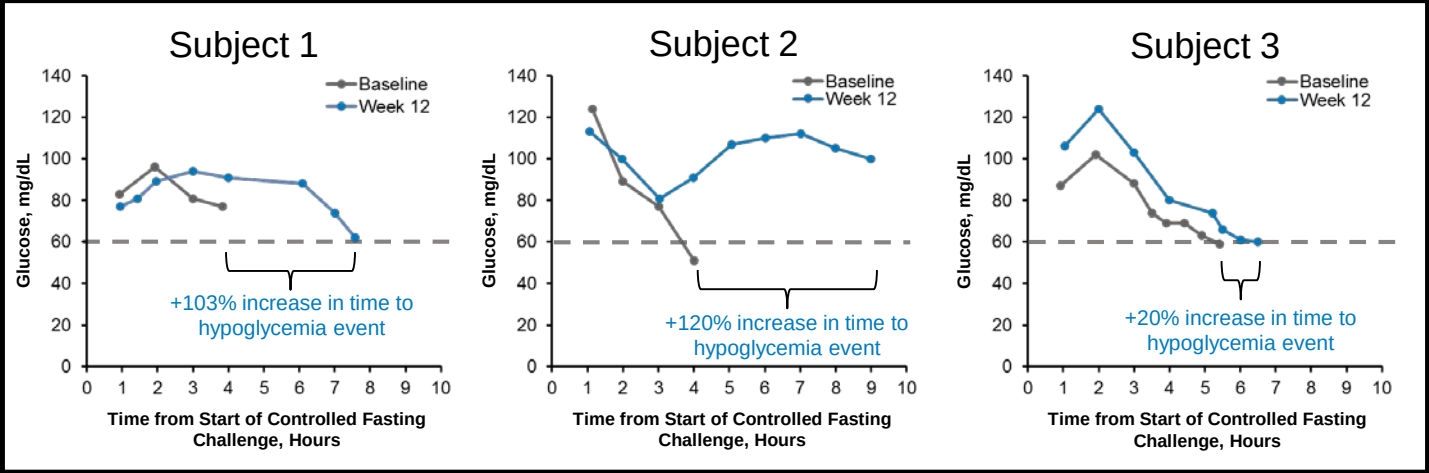
Safety Summary

- No dose limiting toxicities or infusion-related adverse events (AEs)
- 1 subject experienced metabolic instability unrelated to treatment and was hospitalized for 2 days for titration of cornstarch (serious AE)
- 8 mild adverse events

Safety Summary
Adverse Events

- Headaches (2)
- Increased Libido (2)
- Elevated AST/ALT (2)
- Hair Growth (1)
- Anxiety (1)

Fasting Study Results



All Subjects Are Requiring Less Cornstarch Therapy

	Subject 1	Subject 2	Subject 3
Baseline (g/day)	405	171	285
Present (g/day)	36	96	68
Percent Change	- 91%	- 44%	- 76%

Other Results

- Missed cornstarch has been tolerated without development of clinically significant hypoglycemia

- DTX401 therapy has resulted in significant weight loss in 2 of the 3 patients (over 20 pounds)

Summary

- DTX401 at 2.0 x10^{12} GC/kg demonstrated clinically significant increases in time to hypoglycemia during a controlled fasting challenge and reduction in daily cornstarch
- DTX401 was well tolerated with favorable safety profile
- A Data Monitoring Committee reviewed a minimum of 12 weeks of data for all subjects and recommended that it is safe to enroll subjects into Cohort 2 at a dose of 6.0 x10^{12} GC/kg

Wilson Disease Treatments and Unmet Needs

Fred Askari MD, PhD

April 17, 2019

Disclosures

- Advisory Board/Consultant Alexion, Intercept, Deep Genomics, Ultragenyx
- Research Funding Alexion, Intercept and Zydus

Fred Askari MD, PhD

- Associate Professor, University of Michigan
- Director, Wilson Disease Program
- Department of Internal Medicine, Division of Gastroenterology and Hepatology
- Academic Interests: Wilson Disease, Rare Liver Diseases

My Interest In Wilson Disease

- Post doctoral Fellowship in Liver Directed Gene Therapy
- Founded and Direct Wilson Disease Clinic at Michigan Medicine in 1997 after FDA approval of Zinc Acetate for Maintenance Treatment of Wilson Disease
- Collaborated with Dr. George Brewer on Ammonium Tetrathiomolybdate Studies for Wilson Disease
- Site PI for Wilson Therapeutics Choline TM WTX 101 studies, Alexion ALXN 1840 study-- phase II and Phase III studies.
- Evaluated and Treated over 500 patients with Wilson Disease, weekly clinic dedicated to Wilson Disease every Friday afternoon, Multidisciplinary Clinic Third Monday of every month.

Wilson Disease

- Common Orphan Genetic Disease—Incidence 1:30,000
- First Described Over 100 years ago as “hepatolenticular degeneration” by Dr. Kinnear Wilson
- Fatal if left untreated
- Copper association Described in 1940’s
- Treatments introduced: 1950’s and 1960’s BAL, Penicillamine, Trientine, 1997 Zinc Acetate Approved
- ATP7B gene identified 1993 Autosomal Recessive Inheritance

Copper

- Essential Trace Element present in food and water
- Necessary for critical life protein functions
- Copper Needs to be regulated to avoid copper deficiency or copper toxicity, both of which have serious and fatal consequences.
- People with Wilson Disease lack the ability to regulate copper function
- In Wilson Disease copper regulation is stuck open and people with Wilson Disease hold onto dietary copper when they do not need it

COPPER BACKGROUND – WILSON DISEASE

Copper Accumulates and Causes Brain and Liver Toxicity

- Due to a Failure of Biliary Excretion
- Three FDA Approved Treatments for Wilson Disease
- Earlier Anticopper Drug Penicillamine is Quite Toxic, Trientine Moderately Toxic
- Gene Codes for a Copper Binding ATPase
- Mayo Clinic Treatment Study Showed 30% Mortatlity over 10 years

ATP7B—Liver Copper Regulator

- Two Functions: Associates Copper and Ceruloplasmin, Facilitates Elimination
- Ceruloplasmin safely transports copper in blood
- If there is excess copper, ATP7B directs excess copper to be excreted in Bile
- If ATP7B is not working properly, copper is not associated with Ceruloplasmin
  - Copper not bound to Ceruloplasmin moves throughout the body in a toxic free form
  - Copper is not properly excreted from the body so it accumulates in the liver and brain

Wilson Disease—Diverse symptoms: Fatal if left untreated

- Typically presents age 5-50 at first diagnosis, Approximate Median age 20, although can present earlier and later
- 1:30,000 incidence
- US/EU Wilson disease population over 20,000 patients
- Presents with Liver, Neurologic and Psychiatric Symptoms
- Fatigue, Jaundice, Fluid Retention, Bleeding, Confusion, Abnormal Lab Tests
- Tremor, Abnormal Muscle Tone, Trouble Walking, Trouble Swallowing
- Depression, Anxiety, Mania, OCD, Frontal Release/Loss of Executive Function

Existing Therapies--Chelators

- Dosed orally away from food several times daily, take up to six months to control copper after initiation
- Penicillamine—Only FDA approved therapy for initial Treatment, but toxic, renal toxicity, allergic reactions, bone marrow suppression, drug induced lupus like syndrome
    - Drug induced neurologic worsening
    - 25% discontinuation rate
    - Binds Vitamin B6 and induces B6 deficiency
- Trientine—Approved as rescue treatment for those who fail penicillamine; still has trouble with neurologic worsening and discontinuation from renal toxicity, bone marrow suppression, allergic reactions
    - Binds Iron so Iron Deficiency is a concern
    - 25% discontinuation rate

Existing Therapies--Zinc

- Only approved as a maintenance therapy
- Dosed orally away from food three times daily
- Slower to regulate copper excess, may take up to a year to control copper
- 8% treatment failure rate per FDA filing
- Main issue is GI upset

Existing Therapies: Liver Transplantation

- Transfers normal gene for Wilson disease
- Reserved for acute liver failure or people with chronic liver disease leading to liver failure not amenable to medical therapy with copper reduction
- Shortage of donor organs
- Lifelong immunosuppression
- Survival over 90% at one year, 70% at five years

Adherence To Treatment is a major issue

- Trientine needs refrigeration
- Inconvenient—Dosed multiple times daily away from food, some GI intolerance
- Patients may lack organization to time meals and medications, and if they are on multiple other medications these also must be dosed away from Wilson Treatments
- Medication Access can be challenging for some

Unmet Needs

- Less Toxic Treatment--control copper without disturbing side effects
- More Effective Treatment—Prevent Disease Progression, ameliorate disease symptoms if they have already occurred
- Reduce Risk of Drug Induced Neurologic Worsening
- Treatment which is less disruptive to life, increased compliance leads to improved outcomes and less treatment failures

Summary

- Wilson Disease Hepatic, Neurologic, and Psychiatric Symptoms present in a variety of ways
- Early diagnosis is associated with a better outcome
- Symptom Management
- Lifelong treatment and monitoring are needed

Gene Therapy for Wilson Disease

- Disease lends itself to gene correction
- Reconstitution recapitulates normal copper transport bound to ceruloplasmin, current drug treatments reduce toxic free copper but do not replicate normal physiologic transport.
- Reconstitution recapitulates physiologic copper regulation
- Increased adherence which is one of the biggest challenges even for those with current well controlled disease
- Disease corrected by liver transplant

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Wilson Disease

AAV-ATP7B Gene Transfer

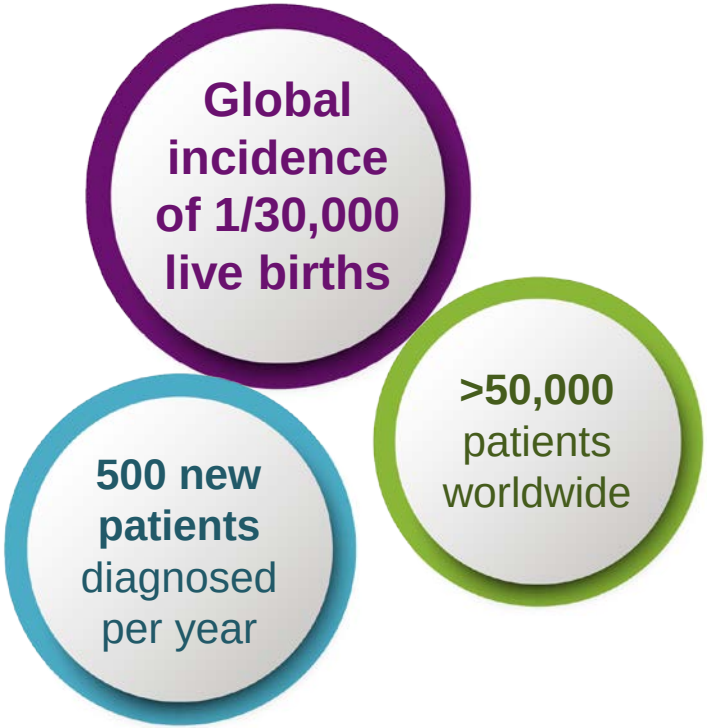
Sam Wadsworth, Ph.D.

Chief Scientific Officer, Ultragenyx Gene Therapy

Wilson Disease: Defect in Copper Metabolism

Failure to excrete and secrete Copper leads to liver and brain toxicity

- Genetic defect in P-type ATPase (ATP7B)
  - Autosomal recessive inborn error of metabolism
    - >600 unique mutations
  - Defective secretion and excretion of copper
    - Elevated blood Cu toxic to tissues including the brain
    - Ceruloplasmin Cu loading delivers Cu to the body
    - Biliary excretion of copper;
  - Cu ion required for numerous cellular functions
- High unmet medical need
  - Liver disease due to copper toxicity
  - Brain disease results as free copper leaking from the liver gets to the brain
- Underdiagnosed in timely fashion as the disease can present in complex ways



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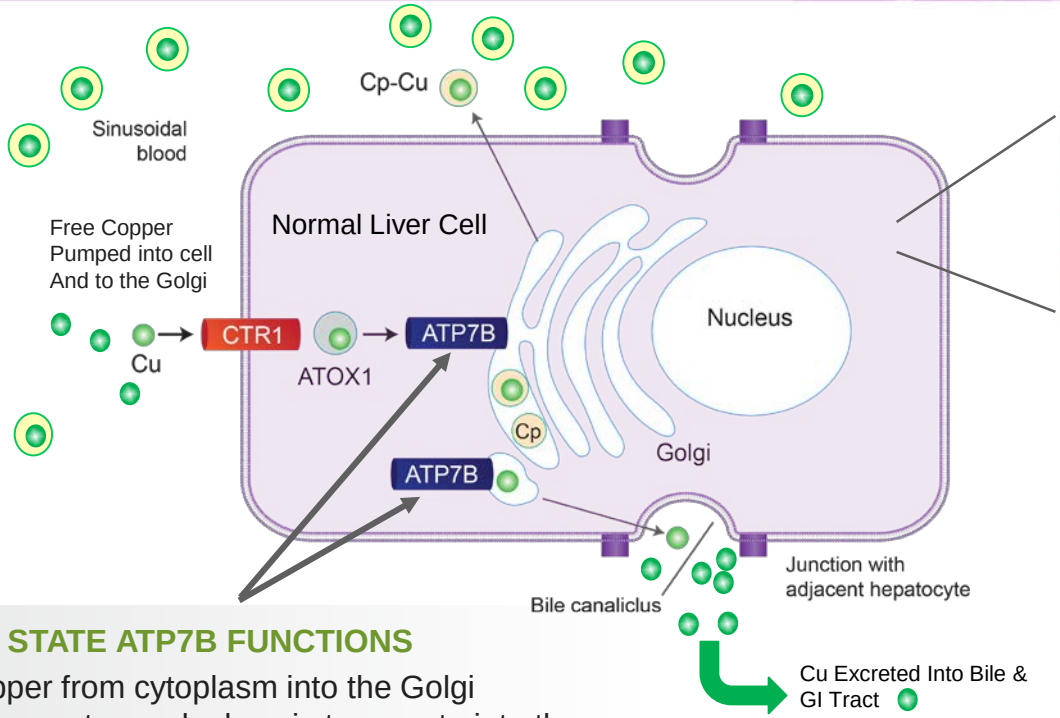
Copper is Key Necessary Cofactor for Many Enzymes

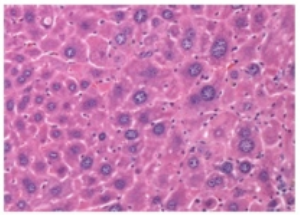
Normal copper concentration control via a Normal ATP7B



Free Cu

Cu-Cp
Cu loaded onto Ceruloplasmin

Normal liver



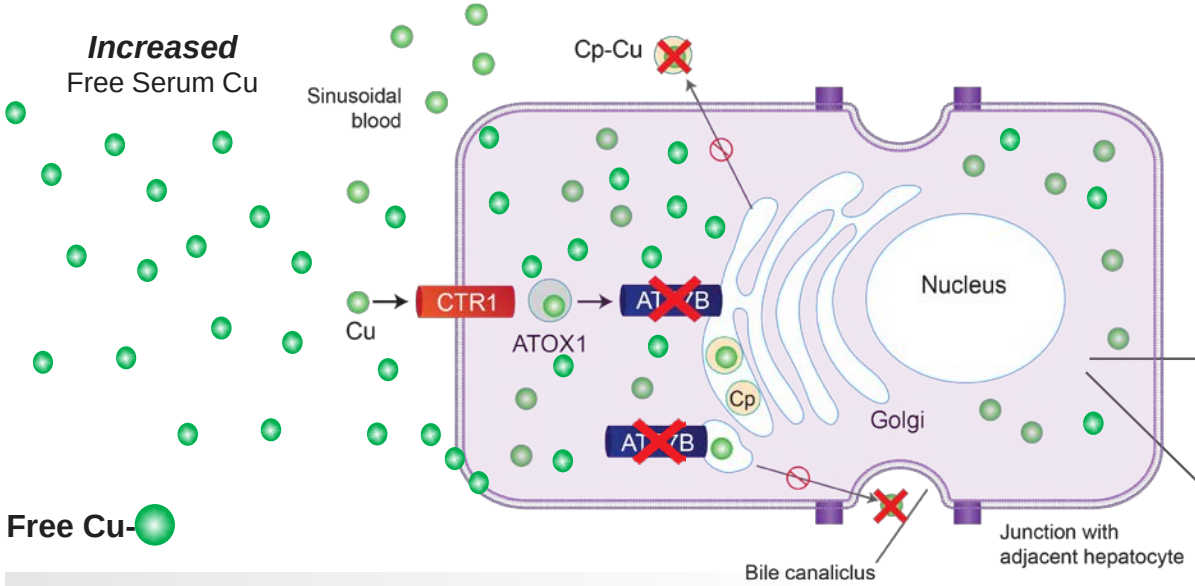
IN HEALTHY STATE ATP7B FUNCTIONS

- Pumps copper from cytoplasm into the Golgi
- Loads copper onto ceruloplasmin to secrete into the serum
- Excretes excess copper into the bile to exit the body
- Potentially toxic intracellular copper is kept in check

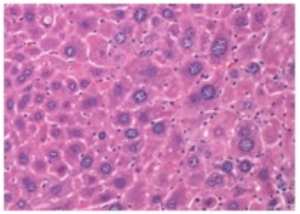
COPPER NEEDED FOR MANY ENZYMES

- Cytochrome c oxidase – part of the mitochondrial electron transport chain
- Superoxide disumutase – quenches superoxides generated in respiration

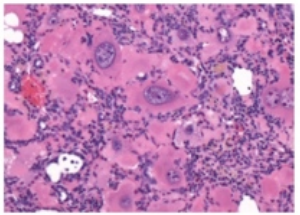
Wilson Disease with Defect in ATP7B Function



Normal liver



Wilson disease liver



Liver injury and fibrosis
Nuclear enlargement
Disorganization
Hepatocellular necrosis

IN DISEASE STATE

- Copper continues to be transported into the cell and accumulates
- Copper secretion and excretion pathways are compromised
- Intracellular free copper leads to hepatocyte toxicity
- Copper leaks out in to the blood causing multi-organ pathology

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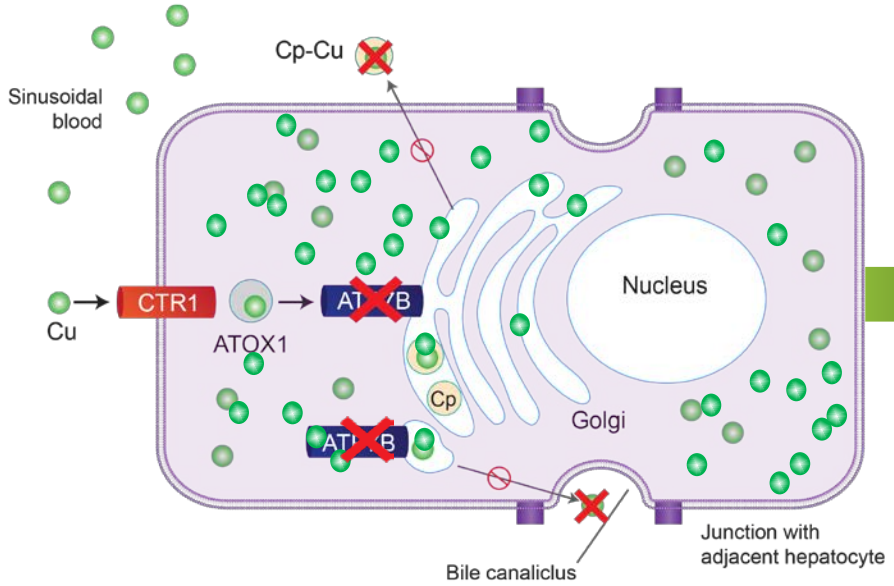
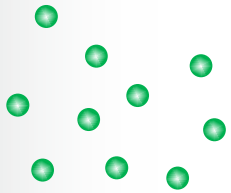
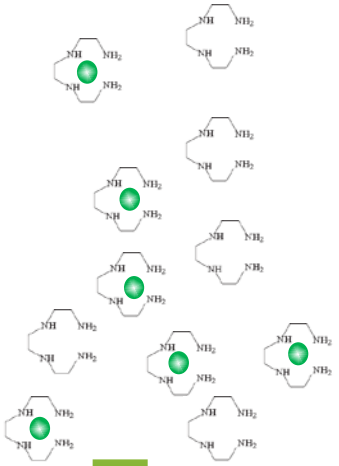
Chelators try to Leach Free Copper From the Liver to Excrete in the Urine



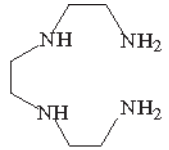
Free Serum Cu



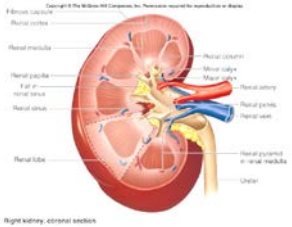
Some overfilled liver Cu *leaches* partially out into the serum in free form



Chelator



Trientine



Excretion in the Urine

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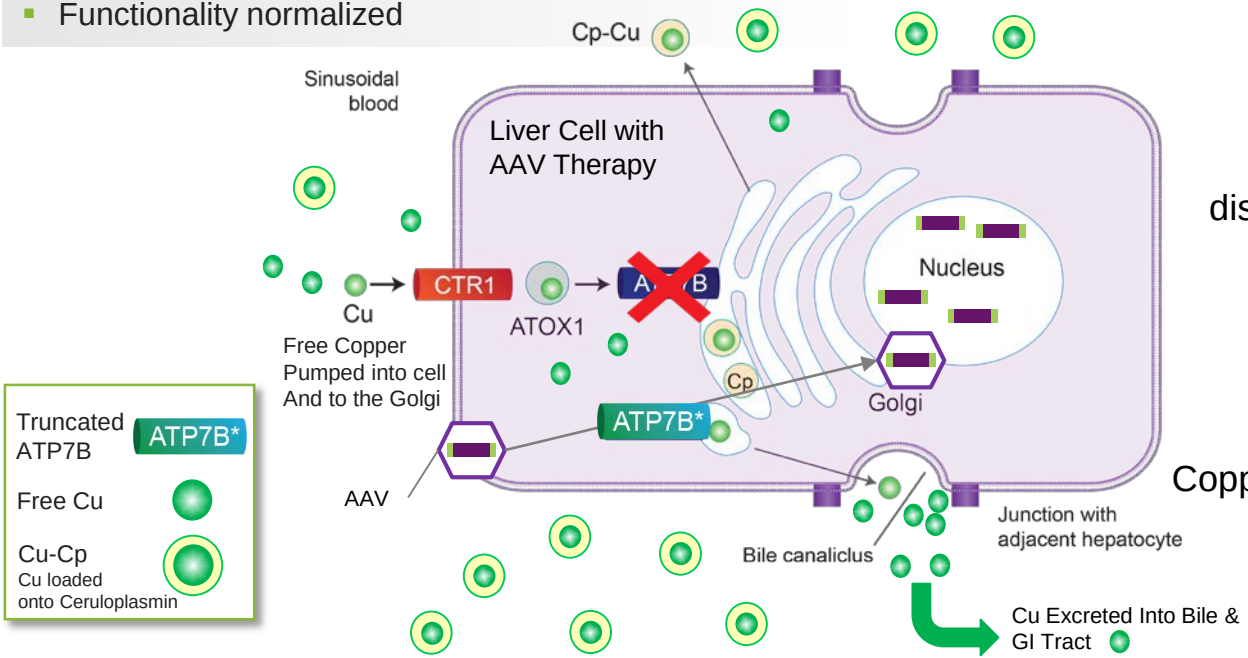
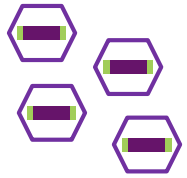
AAV Therapy Pumps Copper from the Liver into Blood and Bile

With AAV Therapy

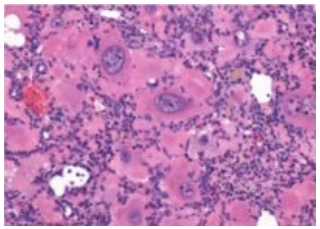
- ATP7B* is formed and pumps copper from cytoplasm into the Golgi
- Loads copper onto ceruloplasmin to secrete into the serum
- Excretes excess copper into the bile to exit the body
- Functionality normalized



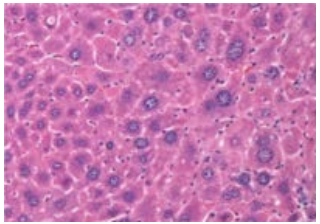


AAV ATP7B*

Wilson disease liver



Copper toxicity treated



After AAV GT with ATP7B*

Gene Therapy with ATP7B Addresses the Underlying Disease

Replaces the defective transporter to actively pump out the copper

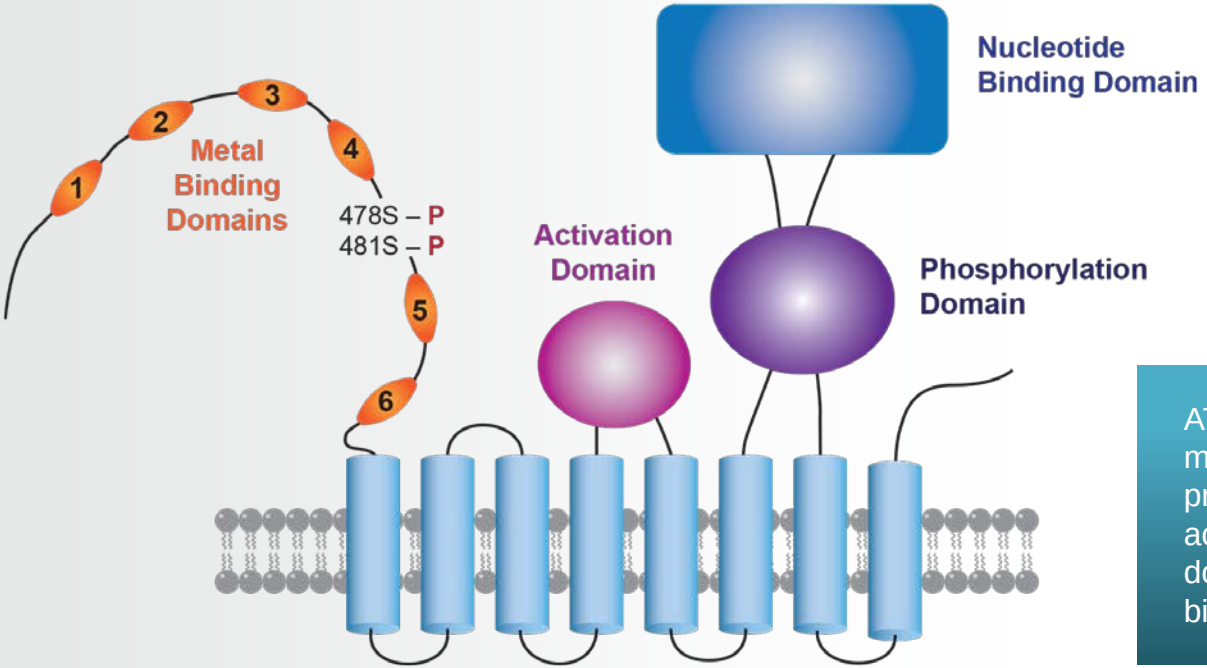
Current Chelation Therapy

- Passively binds to free serum Cu that leaches from injured overfilled liver
- Targets excess free Cu
- Chronic or oral therapy

ATP7B* Gene Therapy

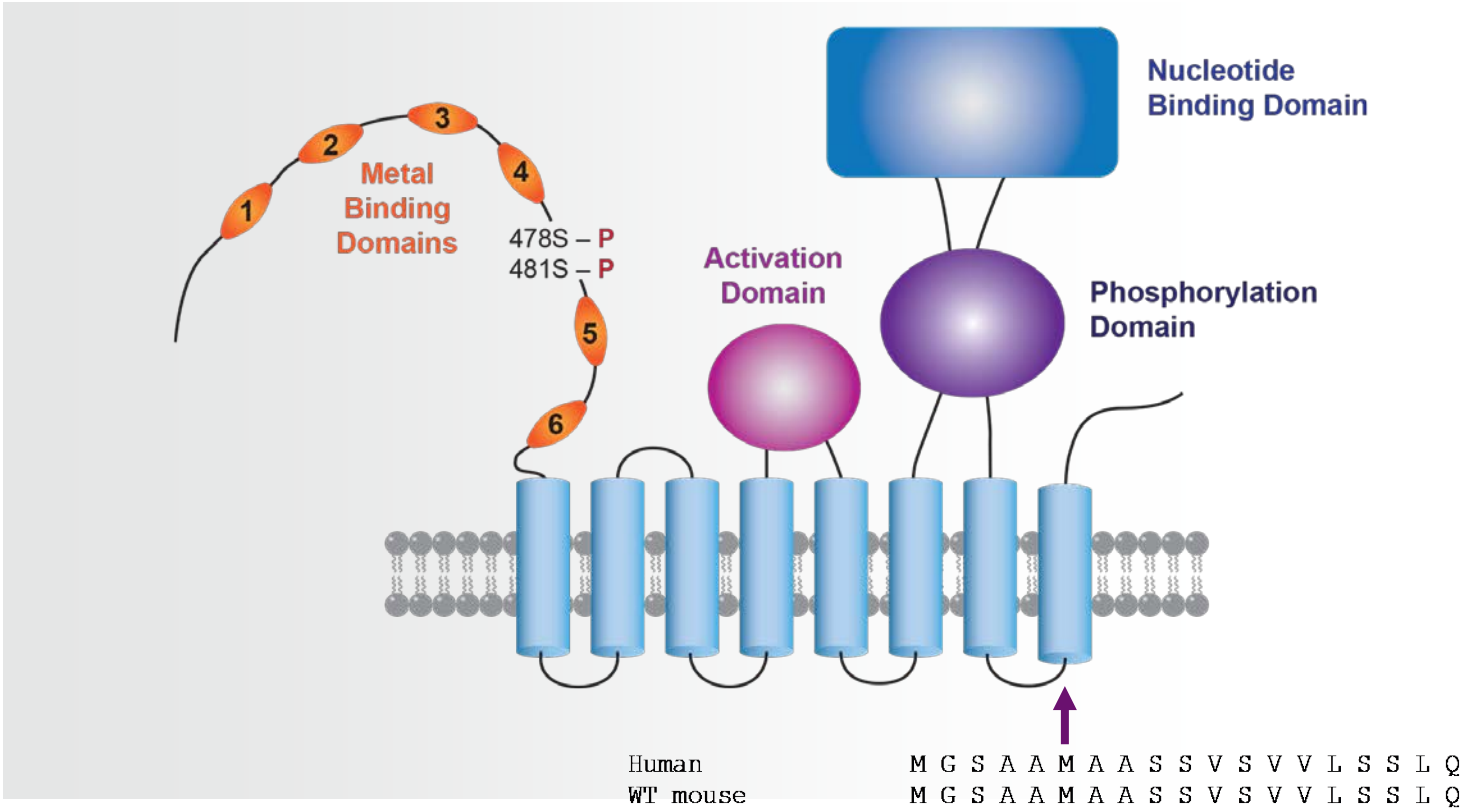
- Active ATP-dependent pumps Cu from the cytoplasm through endogenous function of ATP7B*
- Reduces intrahepatocyte liver Cu, targeting the source of disease
- Single dose

ATP7B Protein – Structure of an ATP-dependent Copper Pump

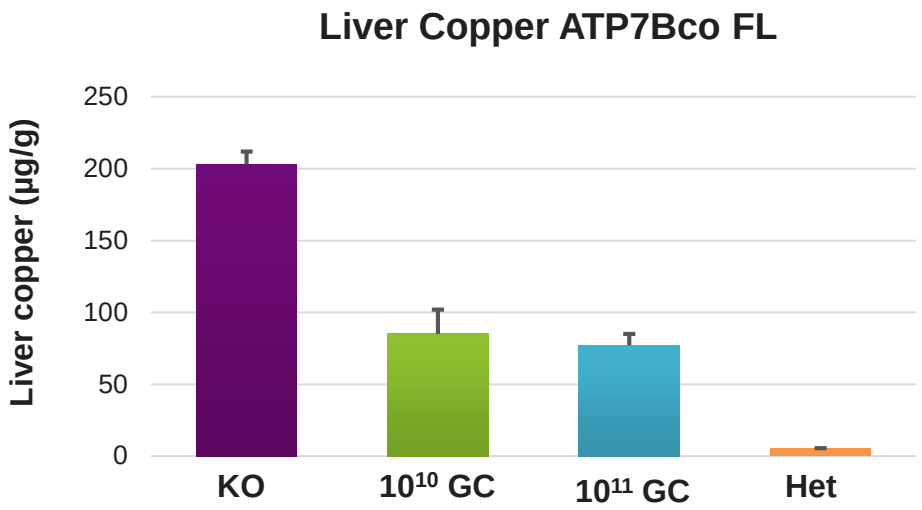


ATP7B is a multi-membrane spanning protein of 1465 amino acids with regulatory domains and six copper binding domains

The “Toxic milk” Wilson Disease Mouse Strain Bears a Naturally-occurring Missense Mutation in ATP7B



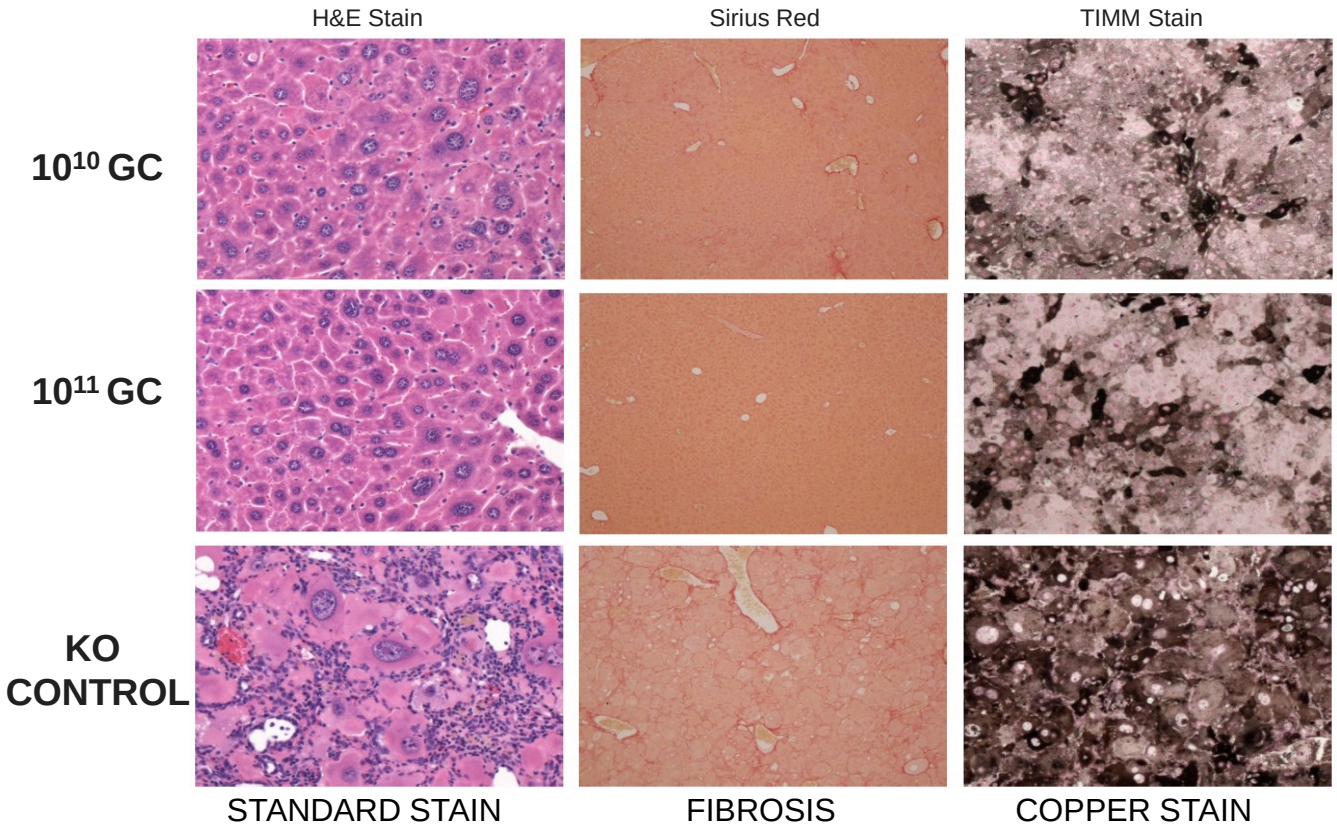
Proof of Concept Study in the Wilson Mouse Model



Study Design

- Vector: AAV8 full-length ATP7B
- At T_0 mice = 50 days old
- Duration of study: 200 days

Wilson Liver Pathology, Fibrosis and Copper Timm's Stain All Improved After Intravenous AAV GT ATP7B

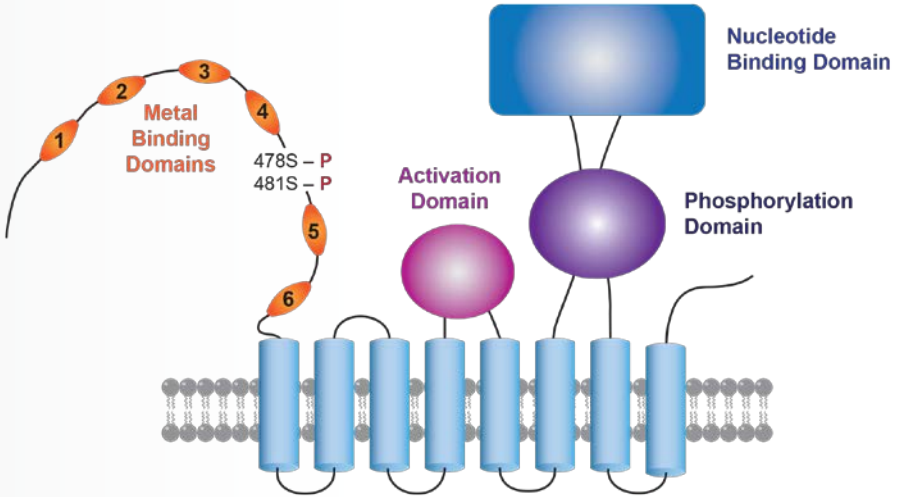


Study Design

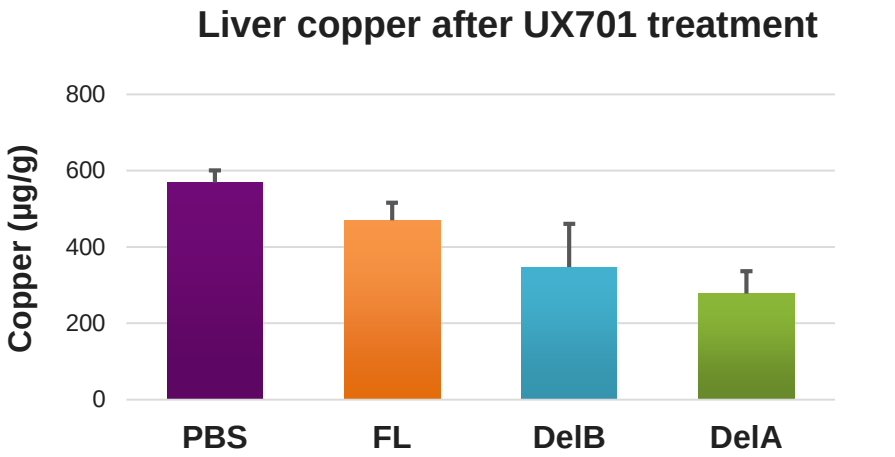
- AAV8 full-length ATP7B
- At T_0 mice = 50 days old
- Study Duration: 200 days

Engineering the Wilson Disease AAV Vector Genome

- Use of the full-length ATP7B coding sequence would exceed the normal AAV vector genome size
- MBD 6 is the only essential domain to allow copper binding and transport
- Deletion of some of the metal binding domains can provide a functional copper transporter and reduce the vector genome size



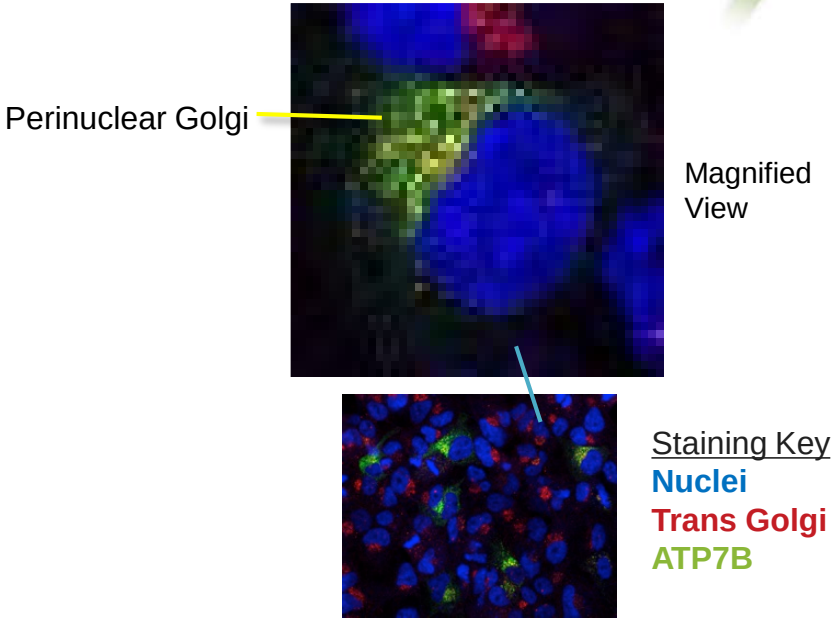
ATP7B Copper-binding Domain Variants are Active and Retain Required Intracellular Localization



DelA Modified Transporter decreases liver copper well in 4 weeks in adult mice

Study Design

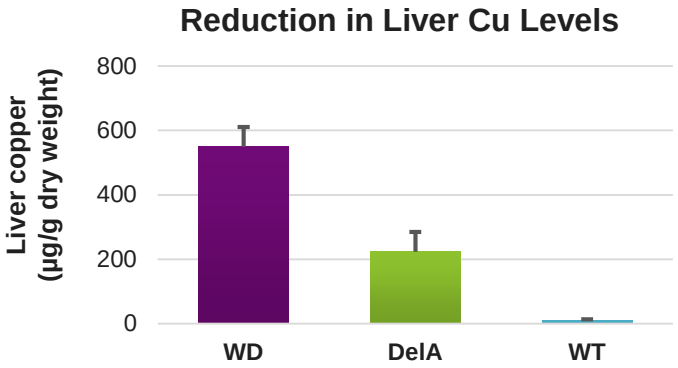
- Vector: Full-length ATP7B, DelB or DelA
- Dose: 1e13GC/kg
- At T_0 mice = 6 - 8 weeks old
- Duration of study: 4 weeks

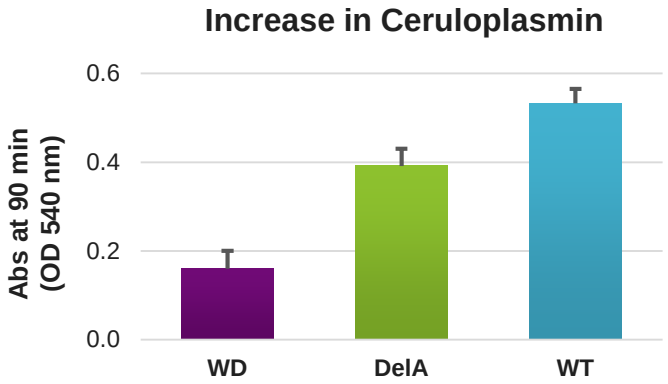


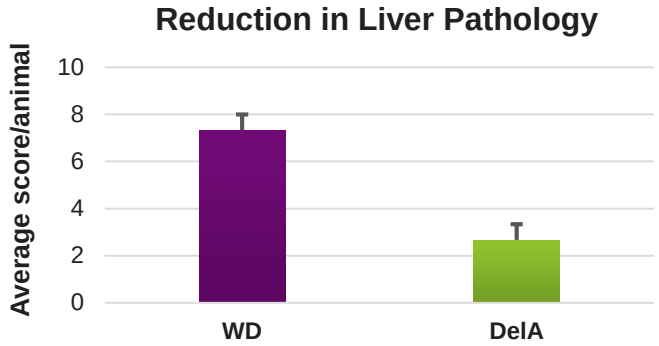
DelA ATP7B protein properly localizes to the Golgi complex in human hepatocyte cell lines

ATP7B Deletion A – Key Therapeutic Properties

Rapid reduction in free liver copper, increased copper ceruloplasmin and reduced liver pathology







Study Design

- Vector: DelA
- At T_0 mice = 6 - 8 weeks old
- Duration of study: 4 weeks

Options for Wilson Disease Capsid Choice

- License for Wilson disease provides access to full spectrum of REGENXBIO capsids including AAV8 and AAV9
- Liver gene transfer is primary target – restoration of function to hepatocytes will benefit other organs as well
- Fully scalable manufacturing will be key – larger population rare disease
- Lead candidate identified and proceeding into development
- Development proceeding on panel of reserve vectors including novel capsids to bypass pre-existing antibodies

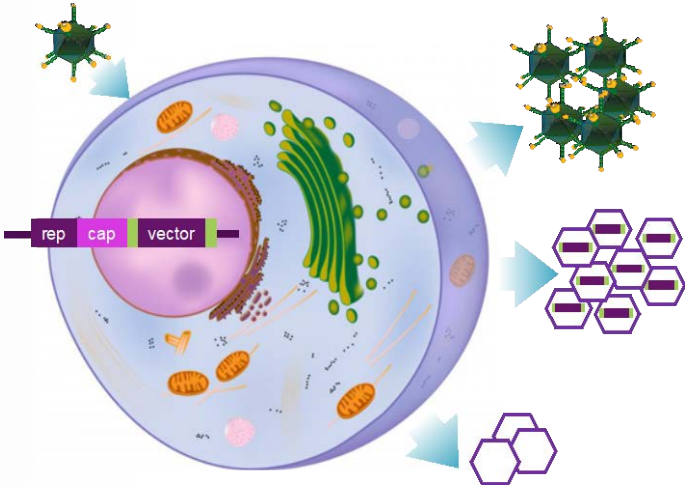
Manufacturing Wilson product using proprietary HeLa PCL system

Manufacturing Wilson Gene Therapy Using Proprietary HeLa PCL System

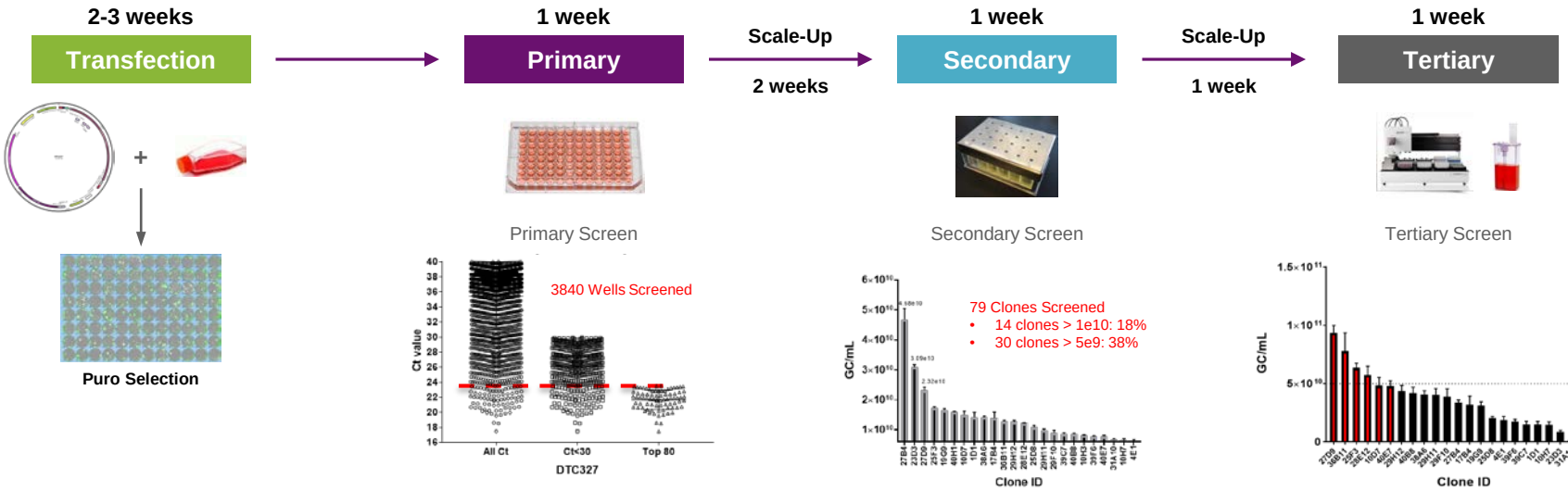
Sam Wadsworth, Ph.D.
Chief Scientific Officer, Ultragenyx Gene Therapy

Key Demonstrated Benefits of Clonal HeLa Producer Cell Line Platform for Product Manufacturing

- Reproducible, scalable system, akin to vaccine manufacturing
- Single-use bioreactor manufacturing achieved at 2,000L, in use in hemophilia A clinical trial
- High vector yield, ~1e11GC/ml readily achieved
- High proportion vector genome-containing particles, i.e. full particles
- HeLa AAV vector employed in clinical trials involving >500 hundred subjects with no safety issues



AAV Wilson Disease Producer Cell Line Generation



VECTOR CRITICAL QUALITY ATTRIBUTES

- Vector genome – sequence verified, intact genome
- Vector capsid – correct VP content and ratios
- High yield - ~1e11 GC/ml
- Cell line genetic stability as required for 2,000L scale

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IP Portfolio Overview
HeLa Manufacturing Platform

Paul Wickman, Ph.D., J.D.
Vice President, Intellectual Property

Harnessing Mammalian Biology to Scale

Two platforms at Ultragenyx Gene Therapy for commercial scale production of AAV

HEK293 Transient Transfection

- Well-known, established
- Significant use in clinical trials
- Scalable up to 200-500L
- Single MCB source
- Plasmid costs are high
- Low % of full capsids
- Requires substantial purification

Viable for smaller commercial indications

HeLa Producer Cells

- Well-known, but less established
- Some use in clinical trials
- Now scalable up to 2,000L
- New MCB for every program
- Reduces plasmid costs
- Much higher % of full capsids
- Clonal, stable, high productivity

Enables AAV production for large indications

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Significant Investment in Optimizing HeLa Platform

Dramatically improving speed, cost, titers, and product quality

- **HeLa:** First AAV-producing PCLs in mid-1990s[1]
- **Dimension Therapeutics / UGT:** Committed substantial resources to maximize scalability, reliability, and quality of HeLa-based process
  - **Result:** Next Generation HeLa 2.0 Platform
- **HeLa 2.0:**
  - Shortened timelines for PCL generation by increasing throughput, incorporating automation, and improved screening processes
  - Bolstered titers and product quality
- **Commercial and Clinical Benefits:**
  - Accelerated development, reduced COGs, improved AAV quality
- **Implemented at 2,000L Scale for DTX201: Hemophilia A GT Program Partnered with Bayer**

Vector Candidate Selection

- Develop and test multiple transgenes
- Optimize combination of enhancers, promoters, and transgenes

Vector Construction

- Optimization of PCL vector design & integrity

PCL Generation

- Cell substrate optimization
- Improved transfection efficiency
- Optimization of screening to achieve rapid, high-throughput clone selection
- Developed GMP cell banking process

Upstream Process Development

- Media development and optimization
- Optimization of infection and culture operating conditions

Downstream Process Development

- Developed and optimized purification steps to maximize AAV titer & quality
- Optimized removal of contaminants such as DNA, proteins, and empty capsids

[1]Clark *et al.,*1995, *Hum. Gene Ther.* 6:1329–1341

Ultragenyx Gene Therapy HeLa 2.0 Platform

Exclusive and proprietary technologies across multiple process steps

Cell Substrate

Multiple commercial licenses secured

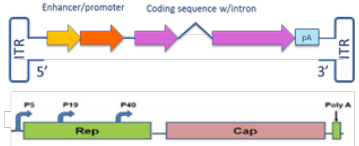
Patent application filed

Multiple TS: Transfection methods, reagents, conditions, DNA/lipid ratios, etc.

Transfection Process

Clone Selection

Molecular Components



2 patent applications filed

Multiple TS: Subcloning methods, screening techniques, culture conditions, monoclonality validation, cell banking, etc.

3 patent applications filed & 4th in prep

Upstream Operations

- Media formulation
- Passage stability
- Bioreactor operations

Multiple TS: Optimized growth and production media, reactor pH, temp, and DO_2

Downstream Operations

- Chromatographic scale up
- ICH viral clearance

Patent application filed

Analytical

- Quality/purity/potency

Multiple TS: Optimal affinity resins, improved reagents and conditions for max AAV capture and contaminant removal

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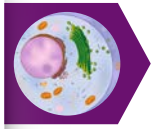
Strong Manufacturing Capabilities and Robust IP Protection

HeLa 2.0 adds substantial value and enables partnering opportunities for large indications

HeLa 2.0 Platform



- Shortens time to development of high-producing PCLs & reduces COGS
- Enables rapid large scale production of full AAV particles
- ✓ Successful 2,000L commercial scale manufacturing achieved

Robust IP Estate

- Global protection for key process improvements enabling production at scale
- 7 patent families filed and 8th application in prep (expiration dates of 2037-2040)
- Trade secrets across multiple process steps + world class in-house expertise

Partnering

- UGT's manufacturing capabilities validated through Bayer Hem A collaboration
- Ultragenyx to strategically pursue additional gene therapy partnerships
- Implementation and monetization of platform IP to drive growth

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IP Portfolio Overview
Commercial and Late-Stage Programs

Paul Wickman, Ph.D., J.D.
Vice President, Intellectual Property

Crysvita® Exclusivity Summary

XLH Orphan Exclusivity: 2025

Biologics Exclusivity: 2030

Crysvita CoM Patent: 2032*

Q2W Dosing (Pending): 2035

2018 2020 2022 2024 2026 2028 2030 2032 2034 2036

XLH Orphan Exclusivity: 2028

D&M Exclusivity: 2030

Crysvita CoM Patent: 2033*

Q2W Dosing (Pending): 2035

*Includes projected US PTE and EU SPC awards

Mepsevii™ Exclusivity Summary

Mepsevii™
(vestronidase alfa-vjbk)
injection, for intravenous use

MPS7 Orphan Exclusivity
2024

Biologics Exclusivity
2029

Mepsevii CoM Patent
2035

2018 2020 2022 2024 2026 2028 2030 2032 2034 2036

2028
MPS7 Orphan + D&M Exclusivity

2035
Mepsevii CoM Patent

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UX007 Exclusivity Summary

NCE Exclusivity ~2025

LC-FAOD Orphan Exclusivity ~2027

UX007 CoM Patent ~2029/30*

Ultrapure UX007 (Pending) 2034

2018 2020 2022 2024 2026 2028 2030 2032 2034 2036

Est. LC-FAOD Orphan Exclusivity (10 yrs post-approval)

Est. D&M Excl. (12 yrs post-approval with PIP)

2034 Ultrapure UX007 (Pending)

*Includes projected U.S. PTE award

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Q&A
Gene Therapy and Intellectual Property

Emil D. Kakkis, M.D., Ph.D.
CEO, President and Founder

ultragenyx pharmaceutical

Translational Research

Creating and Advancing A Pipeline of Rare Disease Therapeutics

Arjun Natesan, Ph.D.

Vice President, Translational Research

We Have Developed Deep Expertise in 3 Therapeutic Areas

While continuing to be opportunistic to grow the pipeline

Disease	Early Preclinical Pipeline	Late Preclinical Pipeline (IND Filing 2020)
Metabolic Diseases		
Glycogen Storage Disorder Type III (UX053)		
Wilson Disease (UX701)		
Undisclosed UX008		
Undisclosed UX019		
Undisclosed UX067		
CNS/Neuromuscular Diseases		
Creatine Transporter Deficiency (UX068)		
Undisclosed UX001P		
Undisclosed UX018		
Undisclosed UX055		
Endocrine/Bone Diseases		
Undisclosed UX032		
Undisclosed UX064		

Criteria for Sourcing New Projects

1. Substantial unmet need in well-defined genetic disease
2. Strong, clear biology
3. Disease-specific treatment of underlying disease preferred
4. Clinical therapeutic fit and tractability
5. Commercial fit

Translational Research Portfolio by Modality

Flexibility to use the best approach to address disease unmet need

Biology for each Disease Dictates Choice of Modality

	TRADITIONAL BIOLOGICS	SMALL MOLECULE	AAV GENE THERAPY	mRNA
IND 2020 Late Preclinical		Creatine Trans Deficiency UX068	Wilson UX701	GSDIII UX053
Early Preclinical	Undisclosed UX064	FSHD UX018	CDD UX055	Undisclosed UX019
	Undisclosed UX008	GNEM UX001P	Undisclosed UX067	3 Additional Targets
	Undisclosed UX032		2 Additional Targets	

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mRNA Platform and UX053 for Glycogen Storage Disease III

Arjun Natesan, Ph.D.
Vice President, Translational Research

Why mRNA?
Unique properties to tackle diseases untreatable with other modalities

mRNA overcomes limitations of other replacement modalities

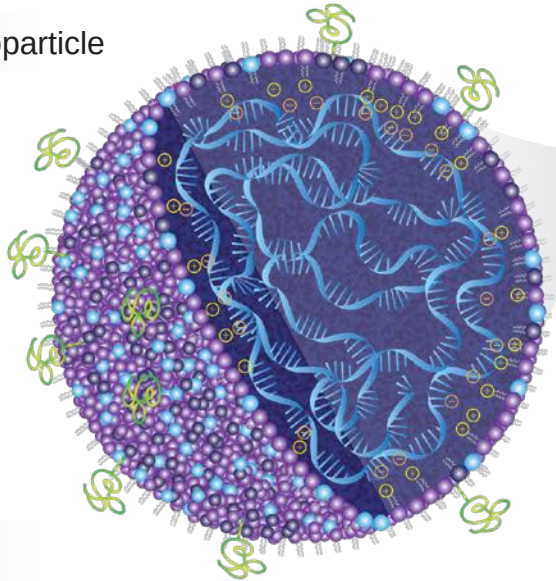
- Replace protein in any cellular compartment (not only lysosome)
- Transient expression, therefore can titrate dose (maximize safety and efficacy)
- Broad and high level cellular expression within the target tissue
- No limitations regarding protein size, and provides native post-translational modifications

For certain diseases, mRNA is the best option to successfully develop a therapeutic

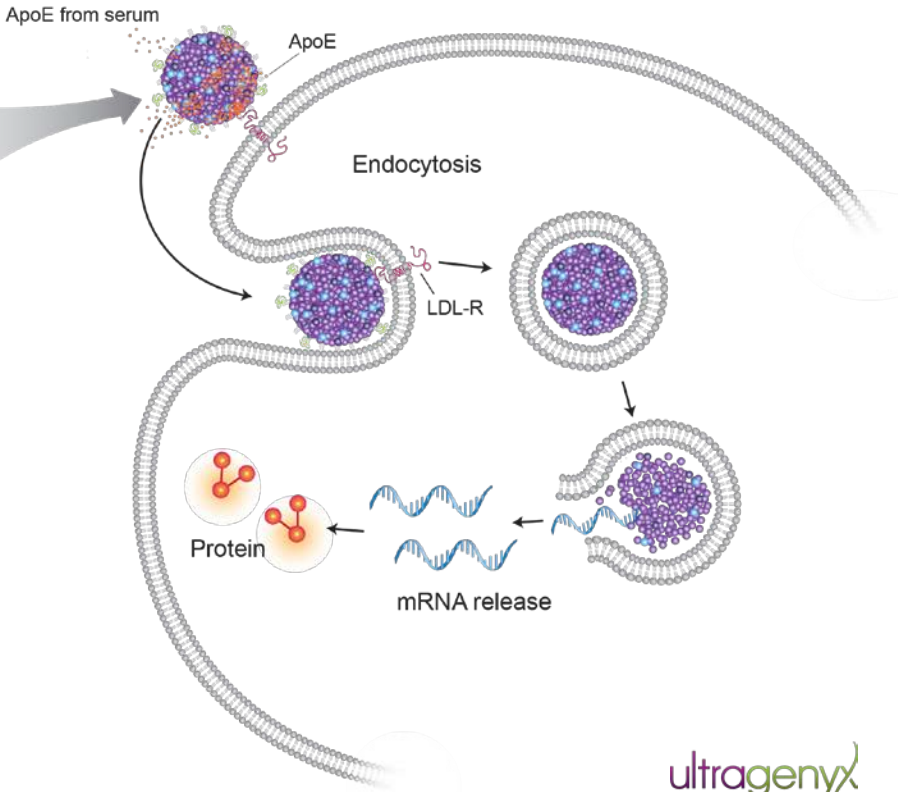
mRNA Modality

mRNA delivered in a lipid nanoparticle to express a functional protein

Lipid Nanoparticle



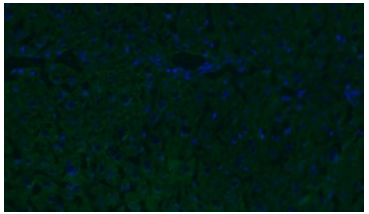
- DSPC
- PEG
- Aminolipid
- Cholesterol



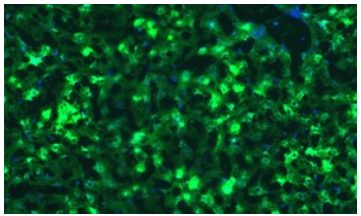
mRNA Platform for Liver Disease

mRNA delivered throughout the liver, except Kupffer cells

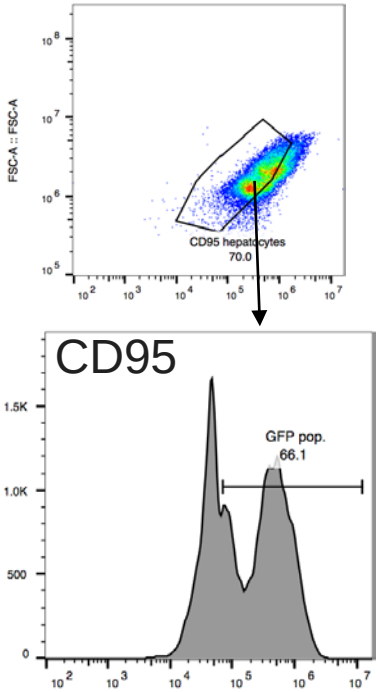
24 hours after 1 dose, >60% of the hepatocytes express substantial protein from the delivered mRNA



Mock No Treatment

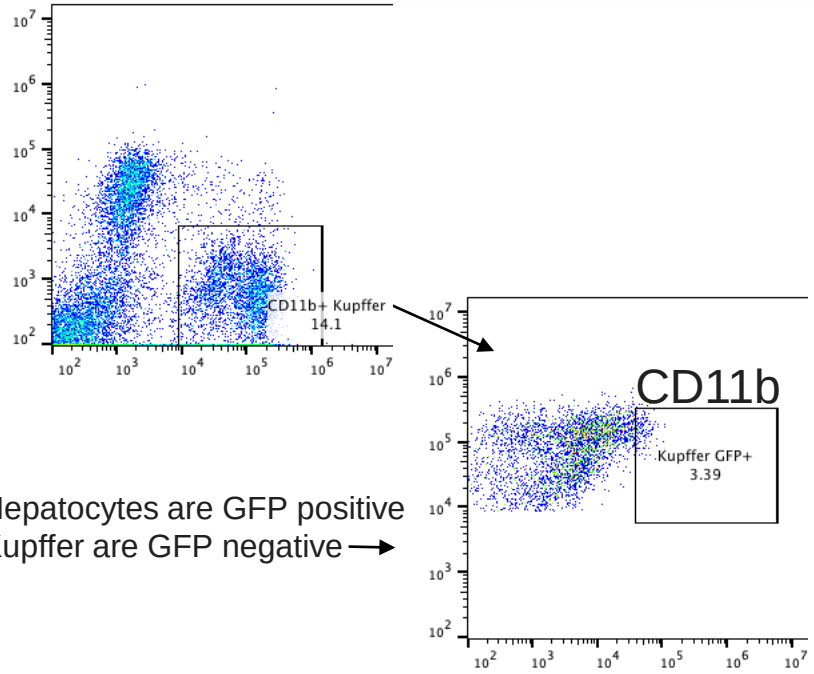


GFP mRNA in LUNAR LNP



Hepatocytes are GFP positive
Kupffer are GFP negative

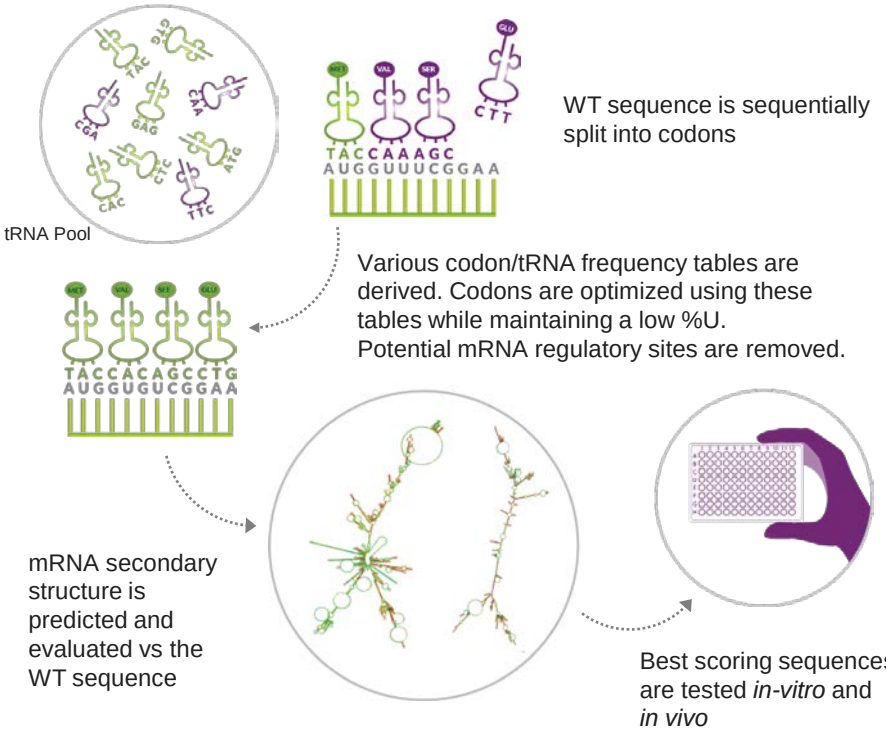
Kupffer cells (liver macrophages) do not express the protein, likely minimizing any immune response



Sequence Selection: Codon Optimization and *in vitro* Testing

Algorithm to select very potent mRNA and test in primary human hepatocytes

RARE Codon Optimization Strategy



Optimizing Sequence Selection

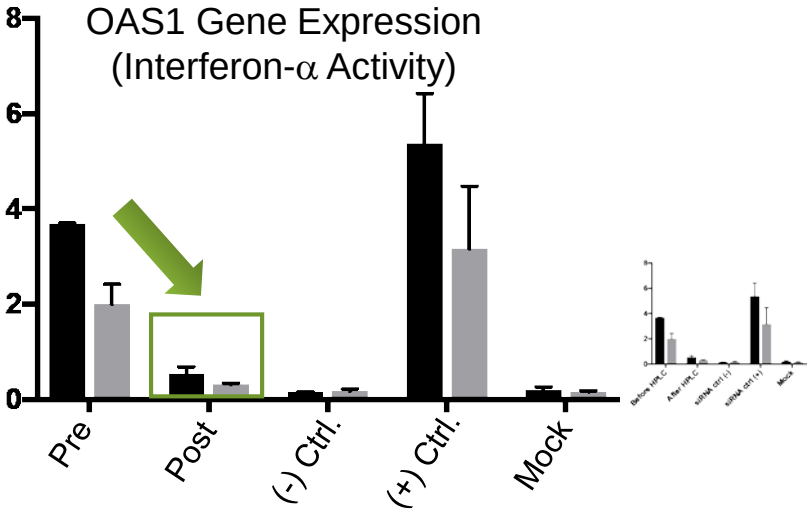
Sequence can be tuned for desired combination of characteristics

Optimization of Safety to Avoid Immune Response Risk

Sequence selection and process purification to minimize innate immunity

Human Cell-Based Assay

Positive and negative control validate in NHP



Gene regulation panel:
(PPIB and HPHT controls)
OAS1, OAS2, MX1, IRF9, IFITM1, IL6, STAT1, IFNA1, IFNB1, FGG, IGFBP5, ISG20, PDK1, RAP2B, LAMA4

Cytokine panel:
IL6, TNFα, IFNα, MIP1α

- Test of innate immune stimulation to select the most potent and least immunogenic sequence
- Residual innate immunogenicity is removed by our large-scale manufacturing process

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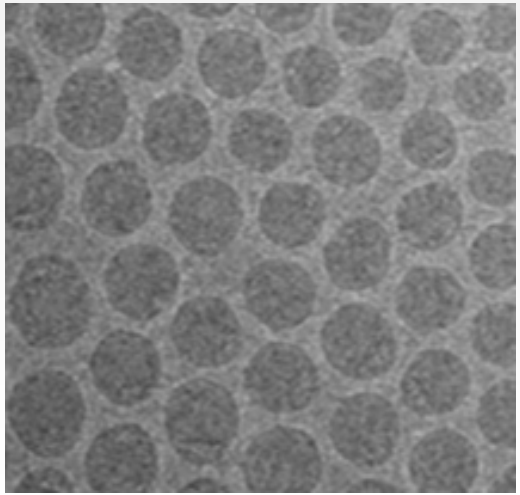
Scalable and Consistent Manufacture of mRNA-LNP

Size and polydispersity consistent in a tight range

Electron Micrograph of LNP



PDI <0.3 indicates a homogeneous monodisperse population of particles

Batch	Size (nm)	PDI	% Encapsulation rate
JV18_00016	88	0.16	96
JV18_00017	91	0.18	92
JV18_00018	94	0.17	91
JV18_00019	95	0.20	93
YB18_00096	88	0.17	94
YB18_00097	95	0.14	93
YB18_00098	84	0.13	94
YB18_00096*	86	0.14	94
YB18_00097*	92	0.10	94
YB18_00098*	84	0.09	94
Mean + Std. Dev.	89 ± 4	0.15 ± 0.03	94 ± 1.4

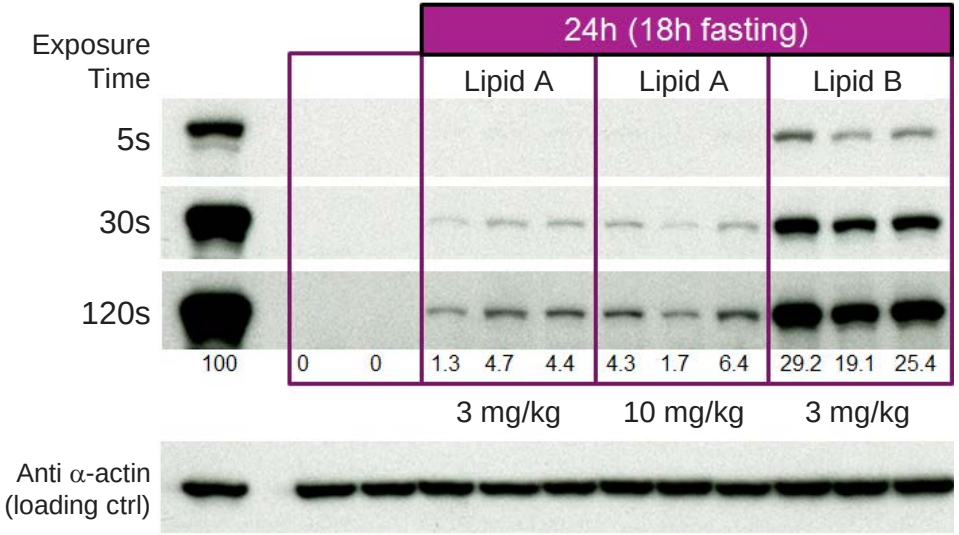
Consistent manufacturing process, polydispersity index <0.2, tight size range and high encapsulation efficiency, and good in-use and long-term particle stability.

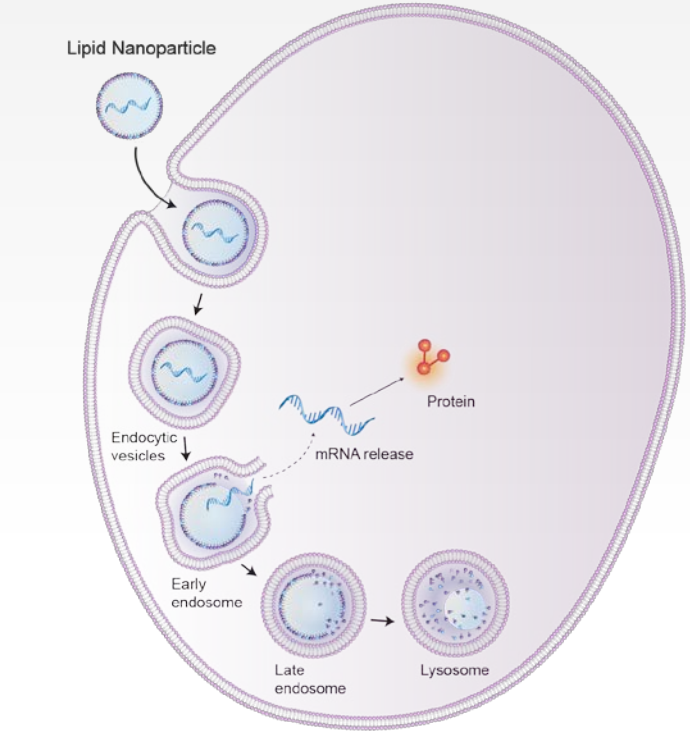
(Danaei et al, 2018)

Novel Cationic Lipid Selected to Maximize Potency

LNP potency likely enhanced due to rapid endosomal release

Western Blot to Measure Protein Level

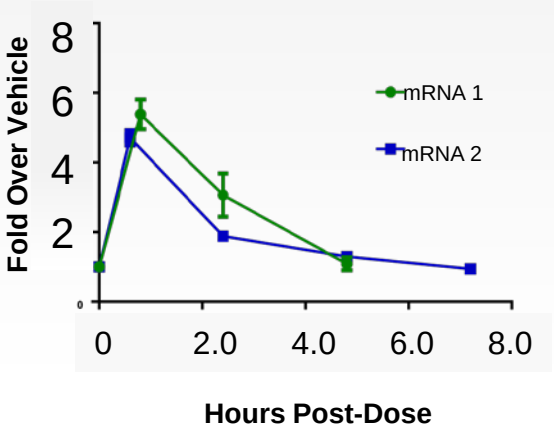




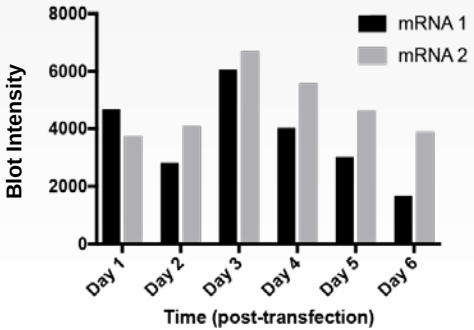
Multiple lipids (component of the LNP) were screened for potency. Selected lipid (lipid B) shows very high potency, likely due to rapid endosomal escape.

High Protein Levels Are Achieved Above Wild-Type Level Upon mRNA Administration for Multiple Targets

Protein Expression (target 1) relative to WT *in vivo*



Protein Expression (target 3) in primary human hepatocytes



Note: Baseline protein expression in primary human hepatocytes is undetectable

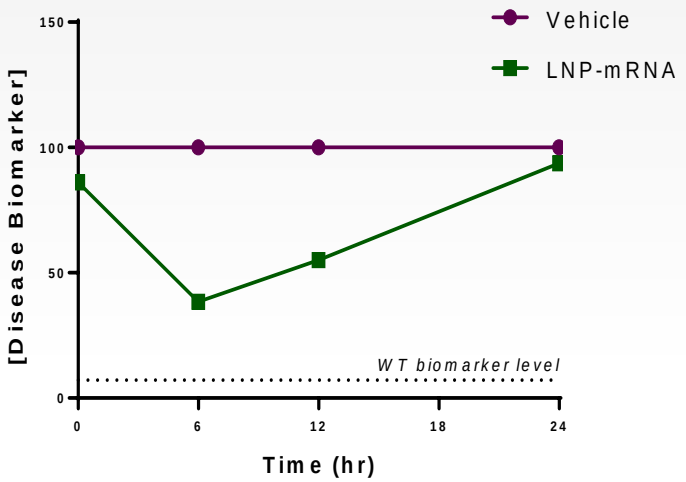
Protein Generated from mRNA Administration

- Target 1 - >500% protein expression over WT *in vitro* and *in vivo*
- Target 2 (AGL) – 100-150% WT expression *in vitro* and *in vivo*
- Target 3 - *>500%* expression over WT *in vitro*

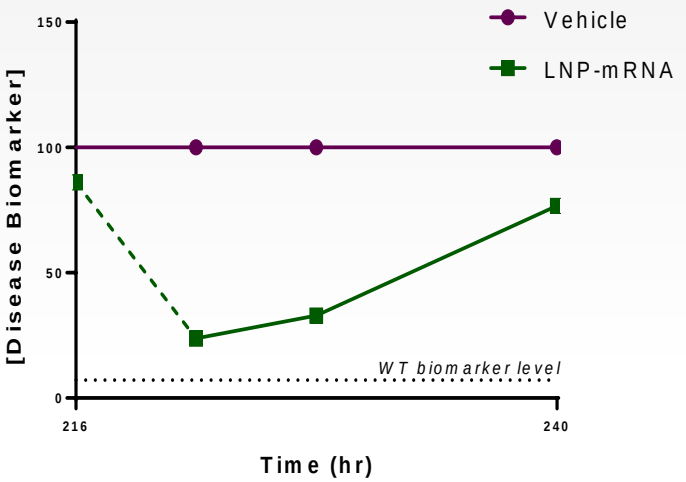
mRNA Administration *In vivo* Stimulates Robust PD Response

Magnitude of PD response is maintained or increased with repeat dosing

Dose 1 Post-Injection



Dose 4 Post-Injection



Effect on PD biomarker increases over multiple doses

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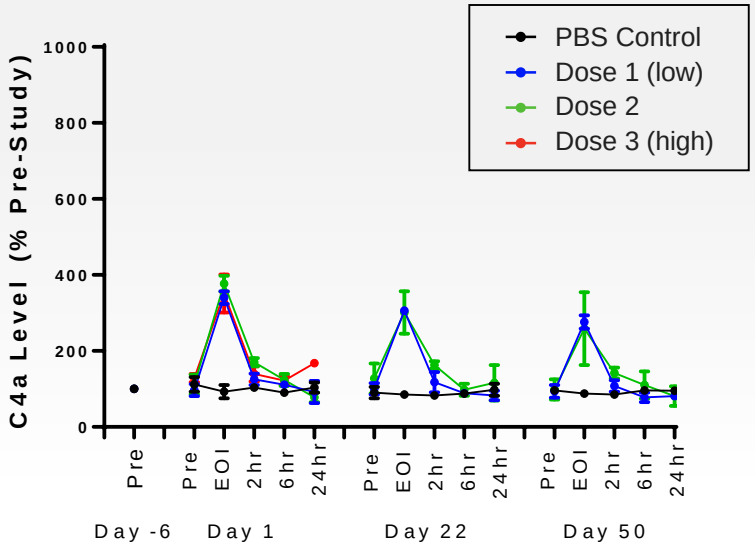
Lipid Nanoparticle Selection – NHP Safety Profile

Selected LNP show no cumulative toxicity

Nonhuman primates dosed weekly for 8 weeks



Complement Activation

C4a – transient, no accumulation

C3a, BB and sc5b-9 all look similar

- Transient increases in liver transaminases upon dosing, no evidence of cumulative toxicity
- Complement activation is transient and remained at baseline between infusions
- No symptoms observed at 3mg/kg or below indicating complement activation did not increase over time

Conclusion

- Safety of repeat intravenous doses of the lead LNP candidate was comprehensively evaluated up to a maximum tolerated dose
- Data provides early indication that there is an achievable therapeutic window

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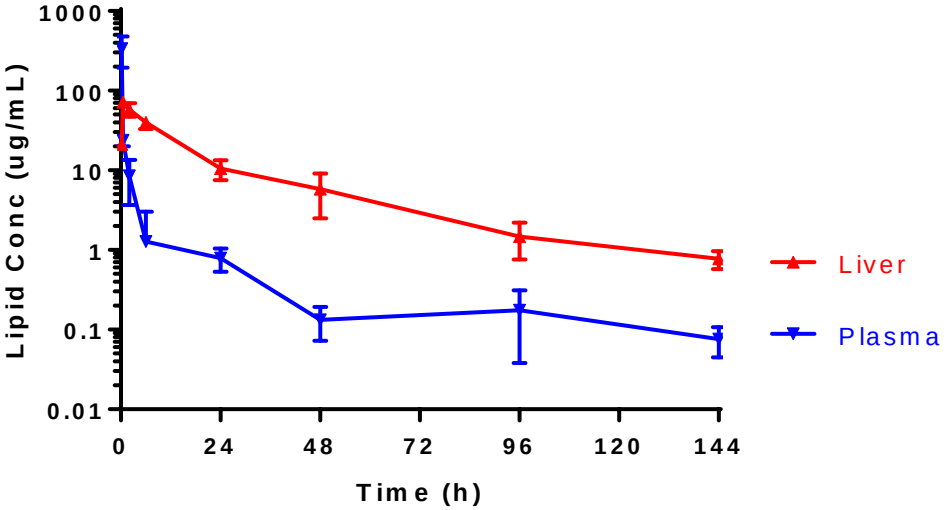
LNP Components are Biodegradable and Short Lived

ADME characteristics likely explain safety



- Aminolipid Analysis
  - Liver half-life: ~35 hours
- ~99.5% metabolized from rat liver after 6 days with single dose
- ~0.5% of dose remaining

mRNA Targets – Replacement Strategy

Not readily treated by other methods

mRNA Programs	Addressable Patients (WW)
UX053/GSDIII	~10,000
UX019	>50,000
Target-3	~5,000
Target-4	~50,000
Target-5	~6,000

Multiple therapeutics fill the mRNA pipeline

Continued success with GSDIII Program unlocks mRNA platform

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UX053 for Glycogen Storage Disease III

Lead mRNA preclinical program; ~10,000 patients worldwide

Genetics

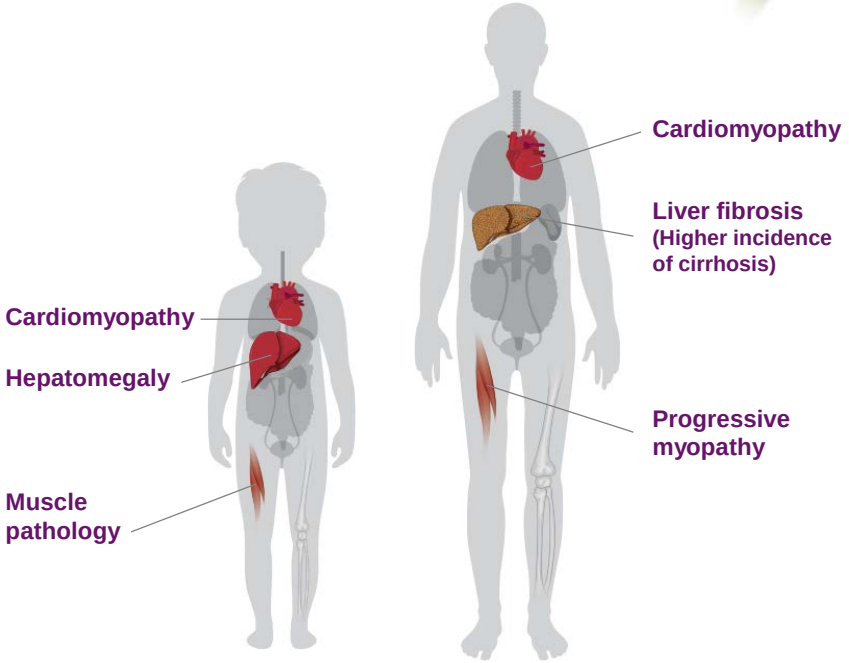
Autosomal recessive mutation in the AGL gene leading to glycogen accumulation in the liver and muscle

Clinical Presentation (based on literature)

- Beginning in infancy:
  - Hypoglycemia, hyperlipidemia, increased LFTs, hepatomegaly
- Later in Life
  - Fibrosis and cirrhosis
  - Cardiomyopathy, hypotonia, myopathy

Current Management

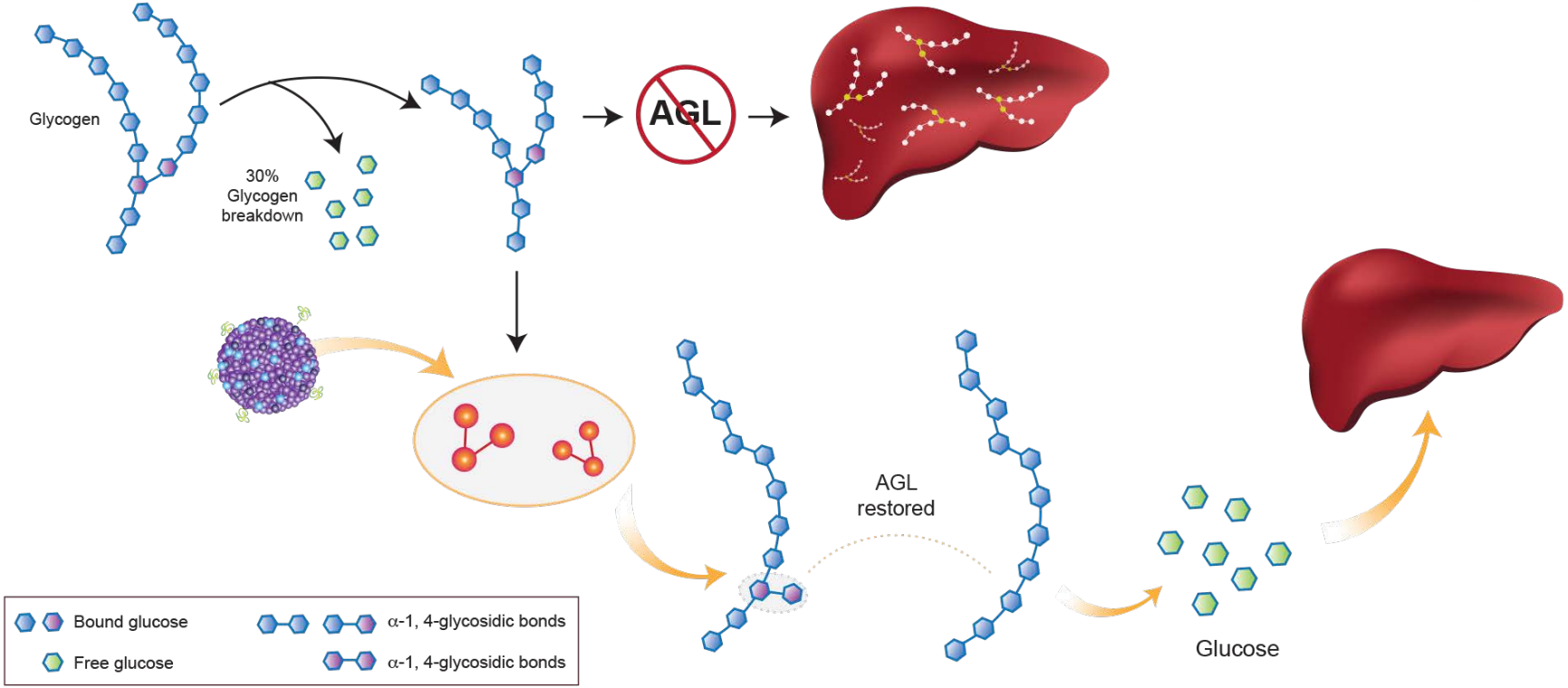
- High protein, cornstarch, fructose / galactose
- Hypoglycemia prevention
- Liver transplant



IND-Enabling Studies Underway
IND Filing Expected 2020

UX053 Mechanism of Action

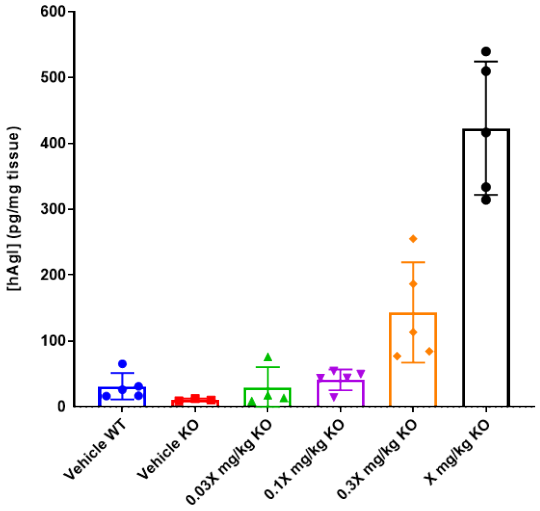
mRNA for glycogen debrancher (AGL) delivered to liver to restore glycogen breakdown to glucose



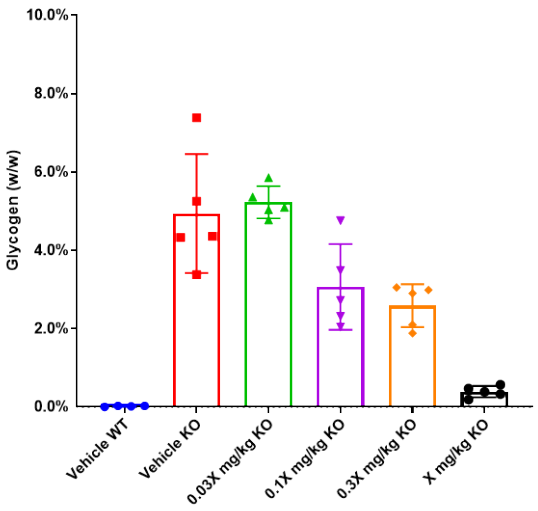
Dose-Response for AGL mRNA-LNP in GSDIII Mouse Model

Reduction in liver glycogen, and an increase in blood glucose

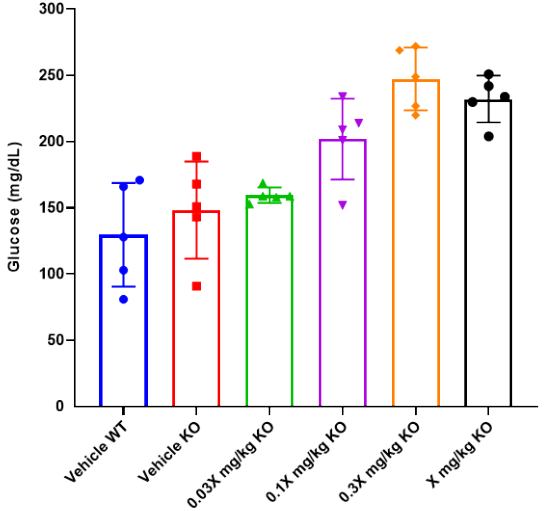
Liver human AGL Protein (hGDE) 24 hours Post-Dose



Liver Glycogen Content 24 hours Post-Dose



Serum Glucose 24 hours Post-Dose



X= dose undisclosed

Dose-response after a single dose of AGL-mRNA to reduce liver glycogen and stimulate increase in serum glucose (24 hours post-dose shown)

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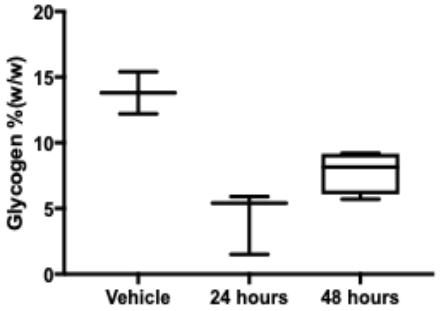
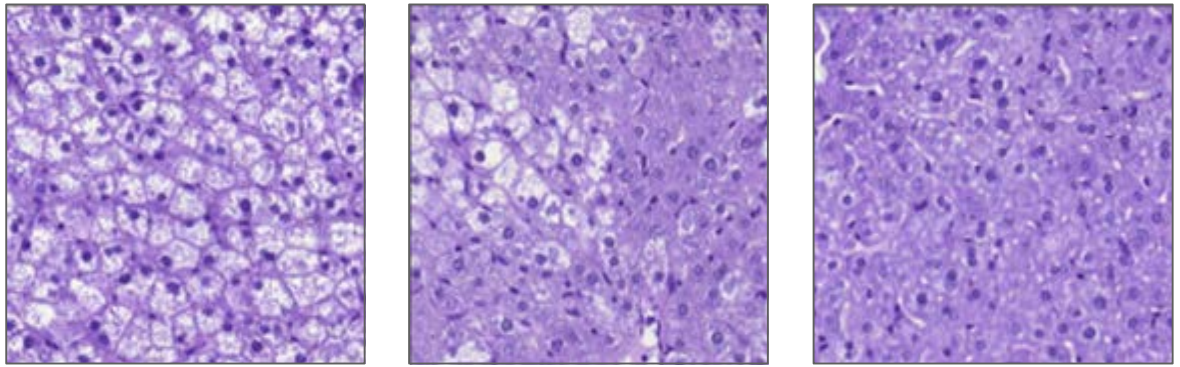
AGL mRNA-LNP Reduces Liver Glycogen in Single Dose

Levels approach normal and are maintained for 48 hours in mouse model

Liver Glycogen
GSDIII Fasted Mice



Vehicle | AGLmRNA/24 hours | AGLmRNA/48 hours



Protein levels:

WT | Vehicle | AGLmRNA/24 hours | AGLmRNA/48 hours

Glycogen levels are reduced and hepatocyte hypertrophy is completely resolved after a single dose, and maintained for 48 hours. PD Response correlates with liver delivered protein levels.

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UX053 for Glycogen Storage Disease III
Path to IND – filing in 2020

IND-Enabling Nonclinical Studies

- Dose-range finding and GLP repeat dose toxicology studies in rat and non-human primates to support Phase 1 clinical trial in GSDIII patients
- Genotoxicity battery, *in vitro* and *in vivo* PK studies, and assay development for clinical biomarker and immunogenicity underway
- Continued dose-range finding & additional mechanistic studies in dog model of disease

CMC

- Continued process development and scale-up
- GMP runs scheduled

Clinical

- Clinical protocol development and pre-IND meeting planning underway

IND Filing 2020

UX068

Double-Trigger Prodrug for Creatine Transporter Deficiency

Arjun Natesan, Ph.D.
Vice President, Translational Research

UX068 for Creatine Transporter Deficiency

Lead small molecule preclinical program; >50,000 patients worldwide

Genetics

X-linked recessive disorder due to mutations in SLC6A8

- Leading cause of X-linked intellectual disability in males
- Females can have mild to severe phenotype

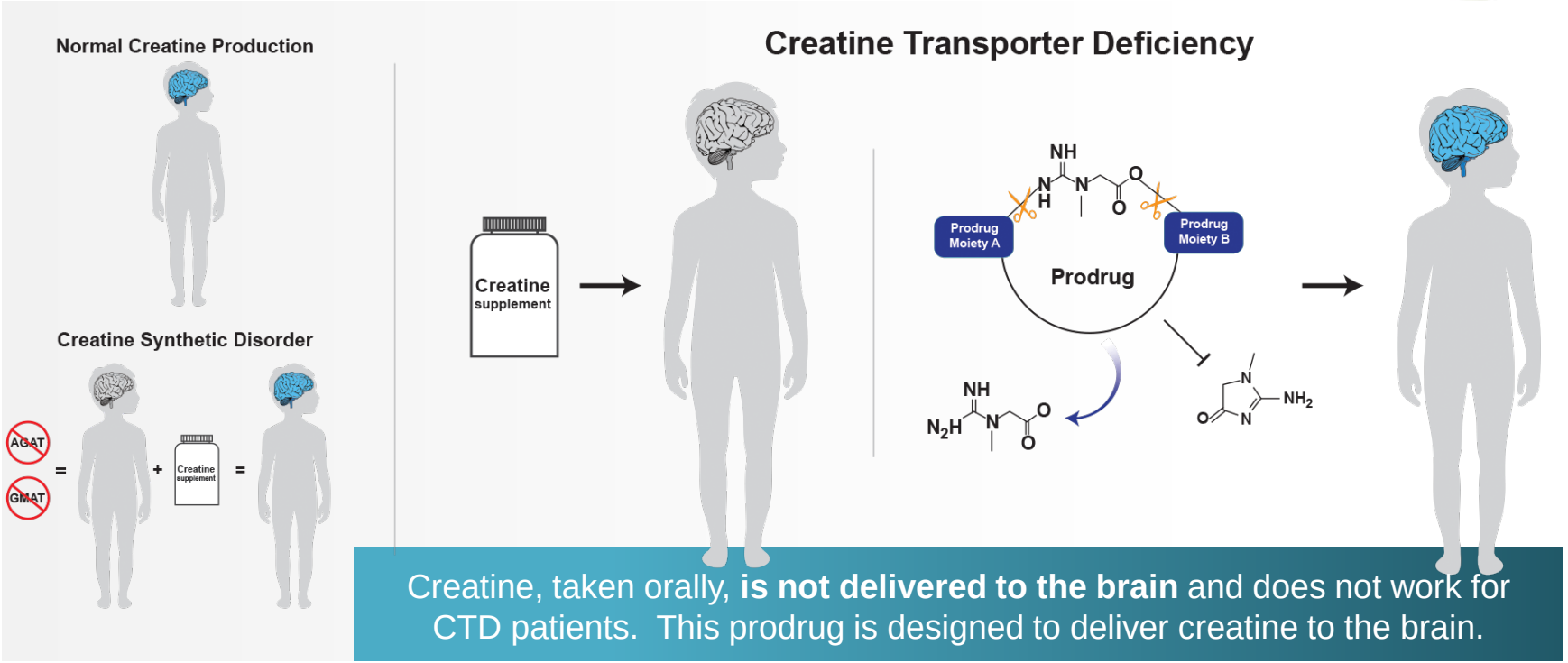
Clinical Presentation (based on literature)

- Neurological deficits
  - Autism, speech/language developmental delays, behavioral problems,
  - Cognitive / developmental impairment
  - Motor skill delays, extrapyramidal symptoms
  - Seizures
  - Brain Cr levels range from undetectable to ~20 % of normal (5 mM) as determined by brain MRS
- Non-CNS deficits
  - Muscle hypotonia and hypotrophy

Current Management

High unmet need, no SOC, supportive care, AEDs effective for seizures

UX068 Creatine Prodrug for Creatine Transporter Deficiency



Creatine, taken orally, **is not delivered to the brain** and does not work for CTD patients. This prodrug is designed to deliver creatine to the brain.

IND-Enabling Studies Underway | IND Filing Expected 2020

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Patients with Other Creatine Deficiencies Benefit After Receiving Creatine

Clinical POC established for creatine delivery to the brain

Summary of representative retrospective studies with supplements

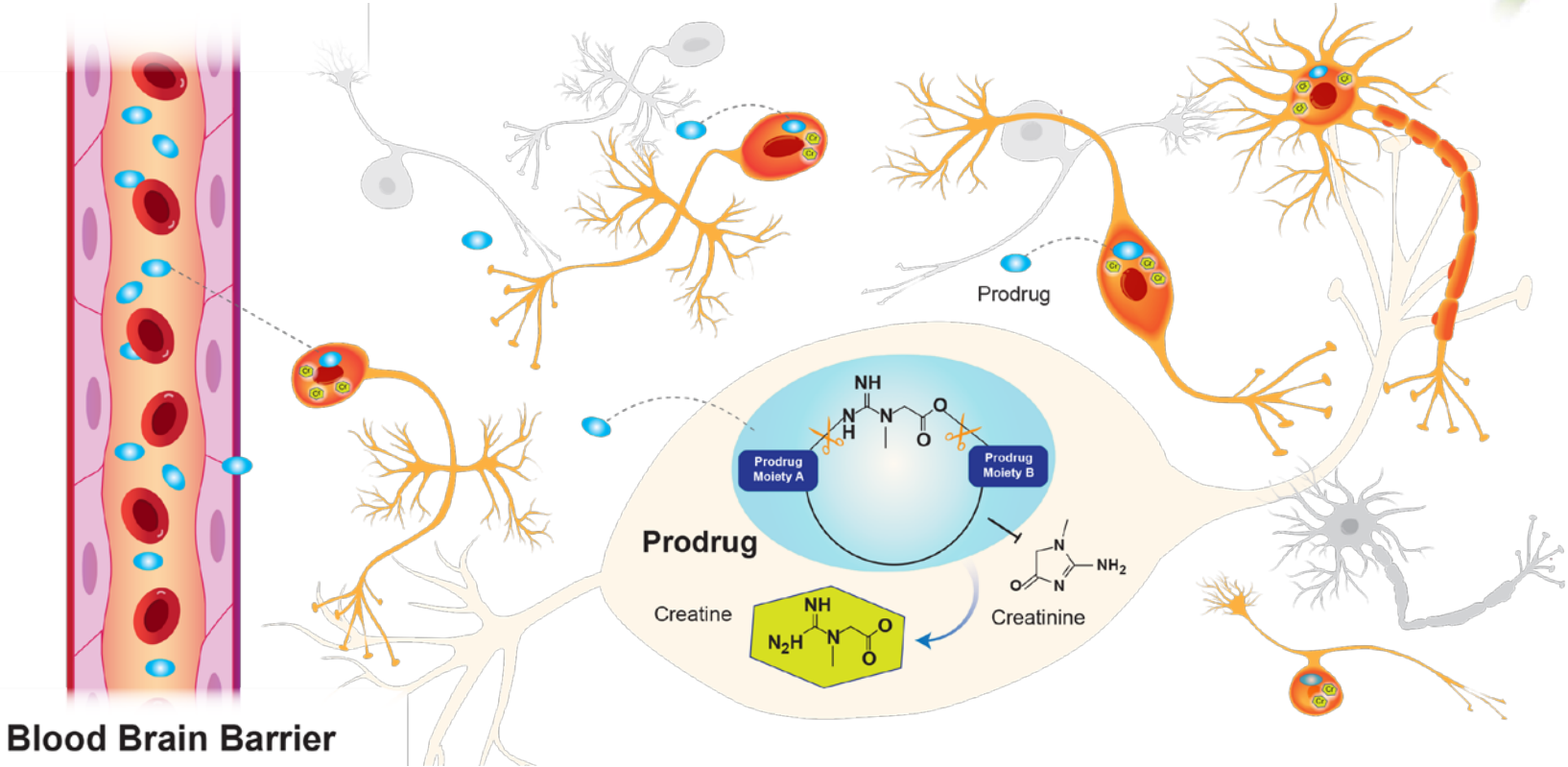
Creatine Synthetic Disorder	# patients	Age range of diagnosis	Brain creatine % of normal, pre-treatment	Brain creatine % on normal, post-treatment
AGAT[1]	16	3 weeks – 25 years	Markedly reduced or not detected	60-90
GAMT[2]	22	10 months – 25 years	Markedly reduced or not detected	50-90

- Treatment causes reduction in seizure frequency, improved intellectual ability, and improved global development and motor abilities
- Patients receiving early treatment (<1yr) showed normal development
- Early intervention may be curative, however later intervention should still offer benefit

[1]Sockler-Ipsiroglu et al. (2015), Molecular Genetics and Metabolism
[2]Khaikin et al. (2018), European Journal of Paediatric Neurology

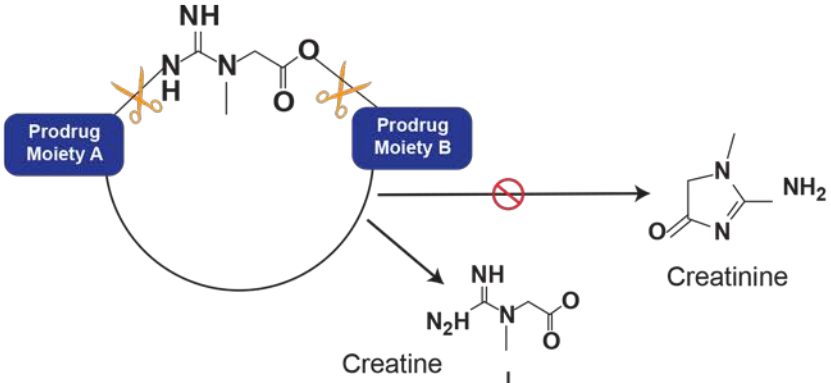
UX068 Mechanism of Action

Prodrug traverses the BBB and cell membrane and releases creatine to neurons



UX068 Mechanism of Action

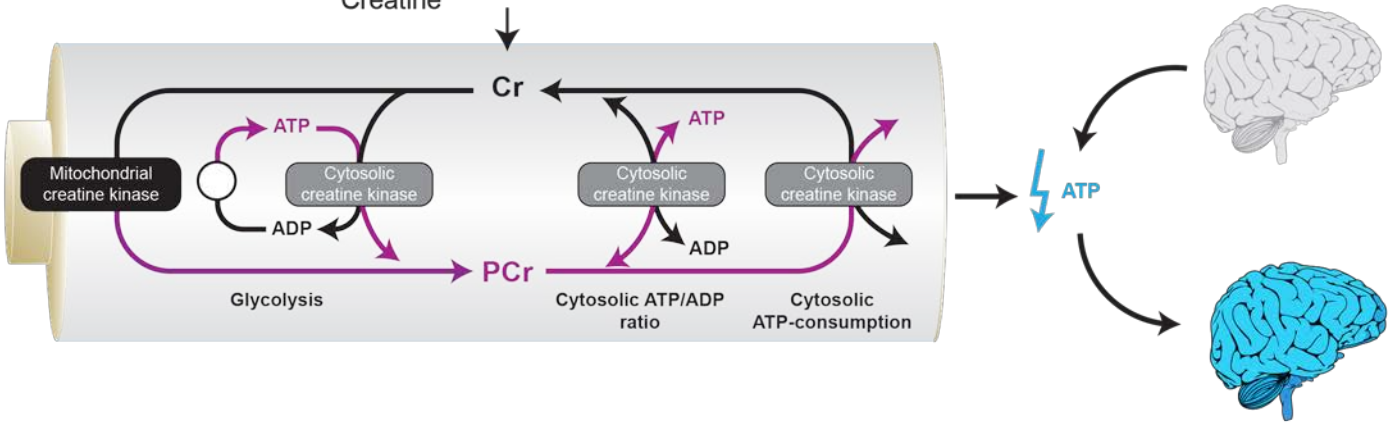
Double-trigger prodrug cleavage enzymes required to release creatine in neurons



350 Compounds, 5 Different Scaffolds

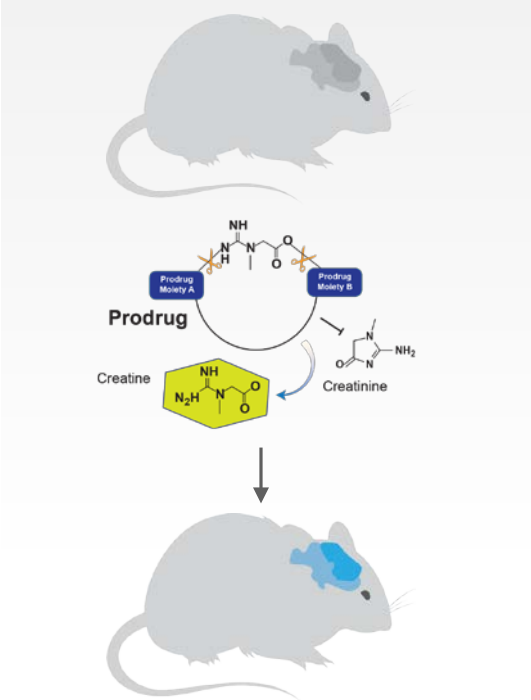
- Maximize neuronal delivery and uptake
- Enzyme affinity tuned to maximize creatine release

Lead Compound; Macrocycle Scaffold



UX068 Compound Selection for Screening

SAR focus dependent on carbon ring-size and sub-moiety branching complexity



Ring Size	Increasing Macrocycle Ring Size ➔➔➔						
⬇⬇⬇ Increasing Branching Complexity	–	++	+++	+++	++++	+++++	+++++
			++++	++	++++	++++	
			++	++	+++	+++	
			+				
	–				+		

\+ = Product-derived creatine found in brain

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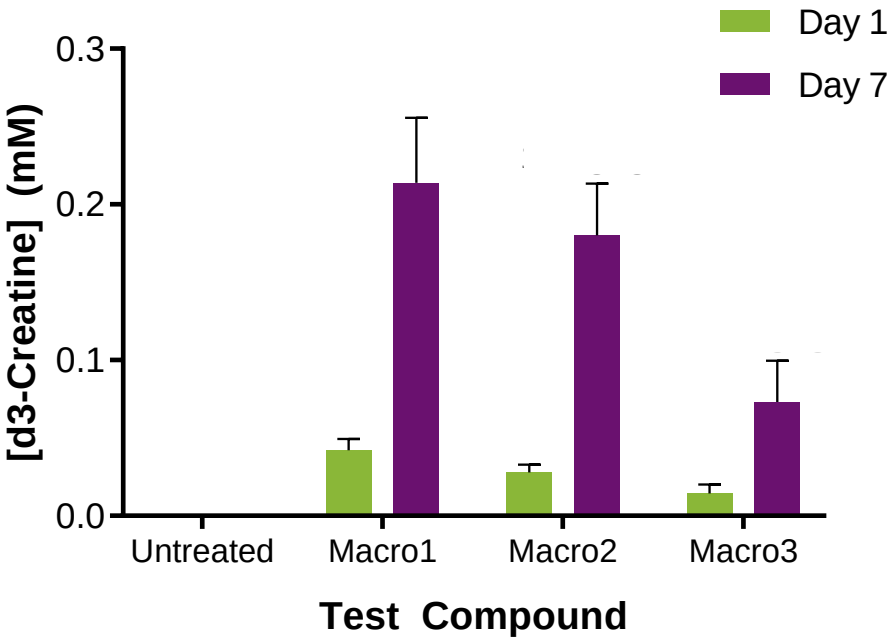
Proof-of-Concept: Rapid Creatine Accumulation in the Brain

Repeated daily IV-administration leads to creatine accumulation in nonhuman primate brains



- Multiple compounds from macrocycle scaffold deliver creatine to the brain
- Creatine accumulates linearly in the brain upon repeat daily dosing with minimal efflux

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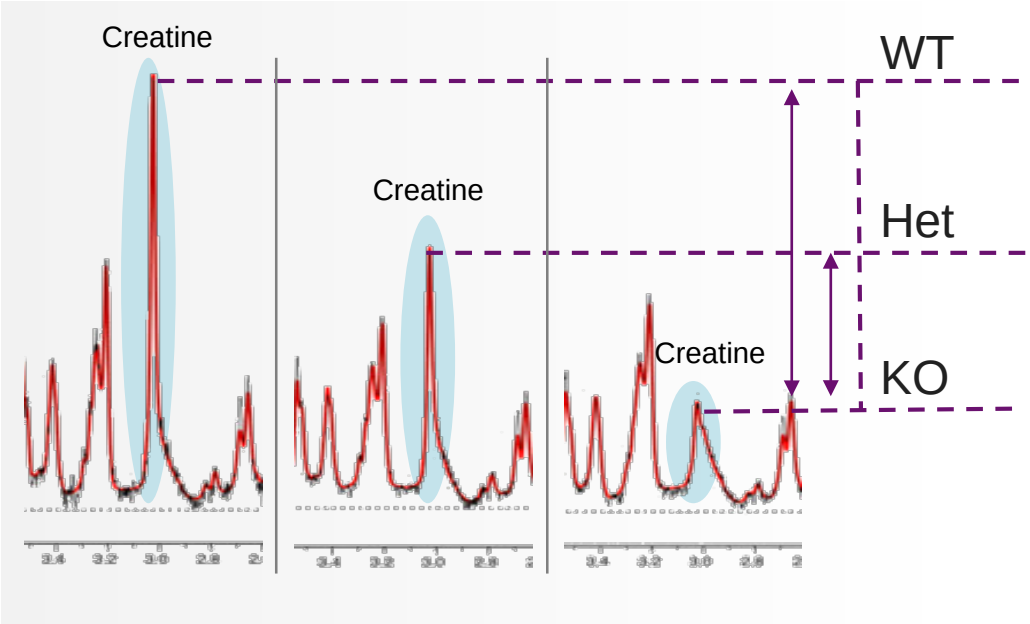
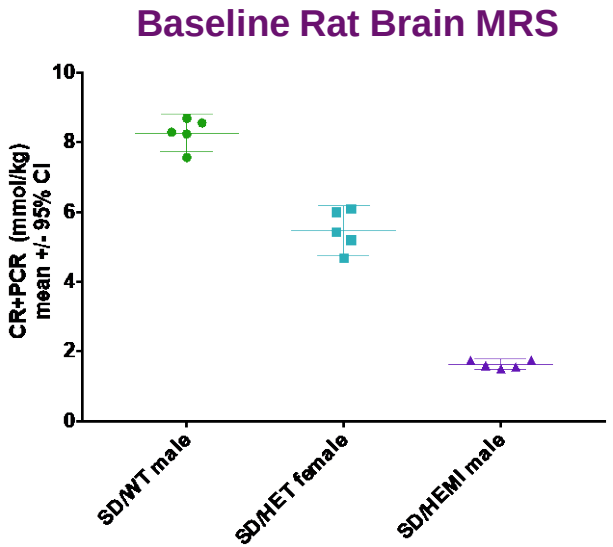
UGX-developed Rat KO Model using CRISPR-technology

MR Spectroscopy, a clinically relevant biomarker, is used to characterize creatine in this animal model





MR Spectroscopy discriminates total brain creatine by genetic phenotype

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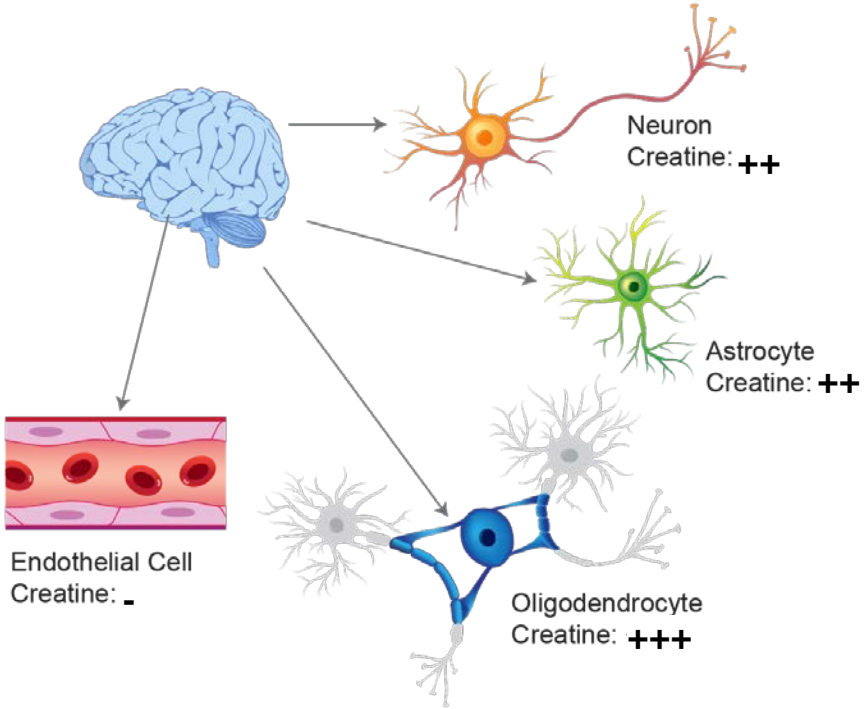
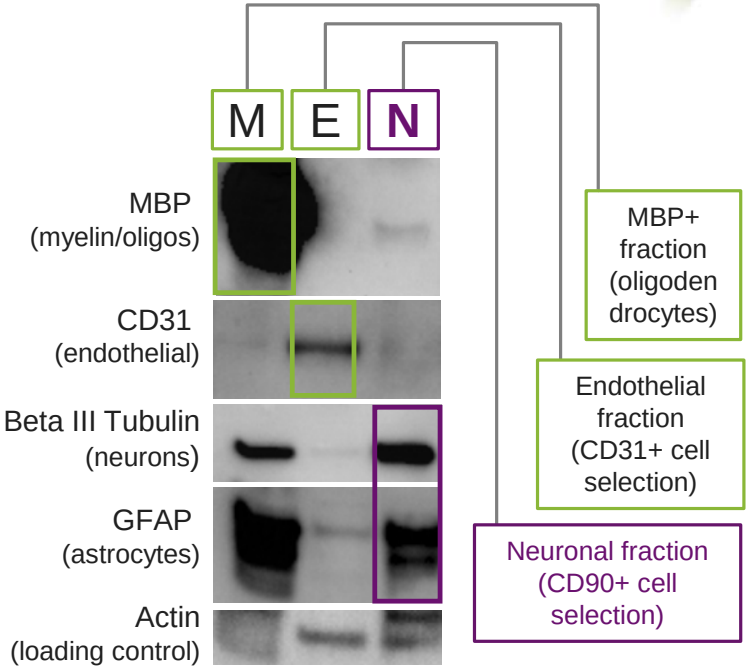
Prodrug Delivered Creatine is Released in Brain Cells

Cell sorting provides evidence of neuronal d3-creatine localization



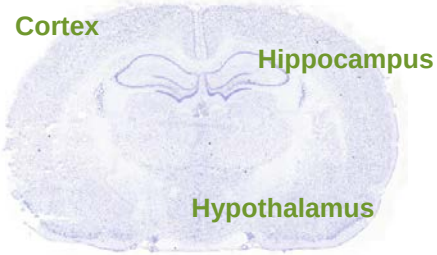
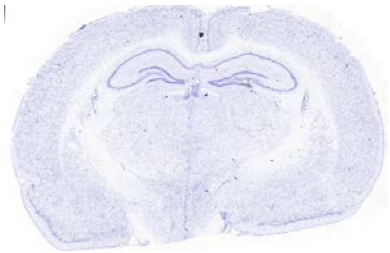
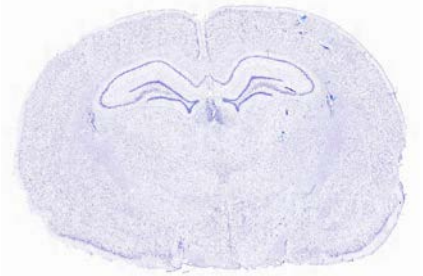
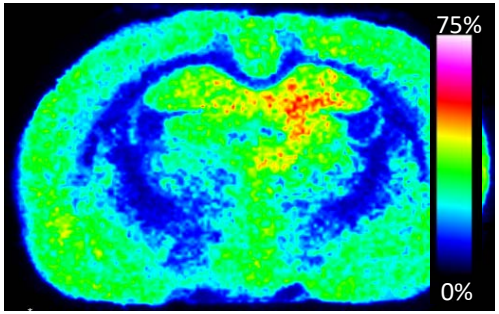
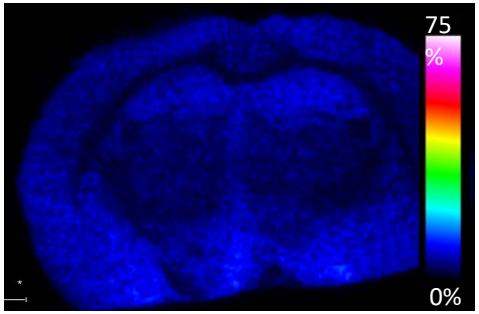
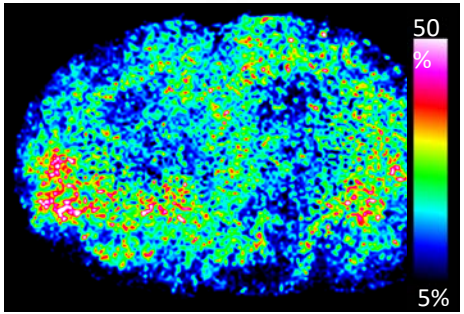


***Ex vivo* cell sorting from rat brain shows that d3-creatine can be measured in cell fractions that contain only neuron and glia**

Widespread Prodrug-derived Brain Creatine Distribution

Creatine is delivered throughout the brain, including cortex and hippocampus

Imaging Mass-Spec for d3-Creatine (prodrug derived)

	Wild Type Rat Endogenous creatine	CrT KO rat Endogenous creatine	CrT KO rat Prodrug derived d3-Creatine
Nissl staining			
d3-Cr imaging Mass Spec			

40 mg/kg dosed over 8 hours to SLC6A8 KO-rat, brains harvested after 24 hours

UX068 for Creatine Transporter Deficiency
Path to IND – Filing 2020

IND-Enabling Nonclinical Studies

- Toxicology studies in rodent and non-rodent to support Phase 1 clinical trial
- Genotoxicity, safety pharmacology, and DMPK/ADME
- Optimization of dose regimen (exploration of loading dose + maintenance dosing)

CMC

- Scalable process development ongoing
- Formulation optimization

Clinical

- Development and standardization of an imaging biomarker (MRS) for nonclinical and clinical use underway
- Patient survey & natural history study
- Clinical protocol development, pre-IND meeting planning underway

IND Filing 2020

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Translational Research Overview – up to 3 INDs in 2020

Tailored approach for each Disease Target

UX053	mRNA to treat glycogen storage disease III ~10,000 patients	IND Filing in 2020
UX068	Double-trigger prodrug to treat creatine transporter deficiency, >50,000 patients	IND Filing in 2020
UX701	Gene therapy to treat Wilson disease, >50,000 patients	IND Filing in 2020
	Continue to Grow and Advance the Pipeline	~1 IND per year to fuel a development portfolio of 5-7 clinical programs

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CREATINE TRANSPORTER DEFICIENCY

TON DEGRAUW, MD, PhD
EMORY UNIVERSITY
APRIL 2019

EMORY
UNIVERSITY
SCHOOL OF
MEDICINE

INTELLECTUAL DISABILITY

MILD:	IQ 50-69
MODERATE:	IQ 35-49
SEVERE:	IQ 20-34
PROFOUND:	IQ <20

U.S. population: 2.3% with I.Q. <70,
0.5% with I.Q. <35

MALES TO FEMALES: 1.4-1.6

INTELLECTUAL DISABILITY ETIOLOGY

- ENVIRONMENTAL, TERATOGENIC: 5-13%
- PERINATAL: 2-10%
- CULTURO-FAMILIAL: 6%
- **GENETIC: 60-70%**

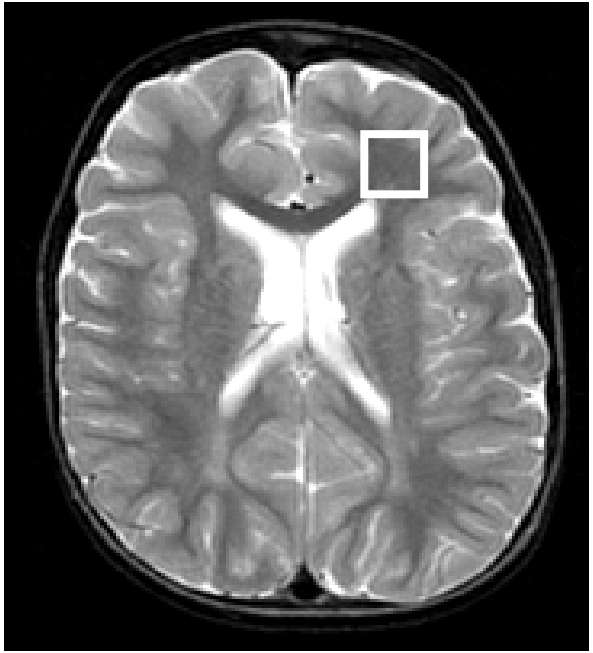
BASEL-VANAGAITE, L.,2008

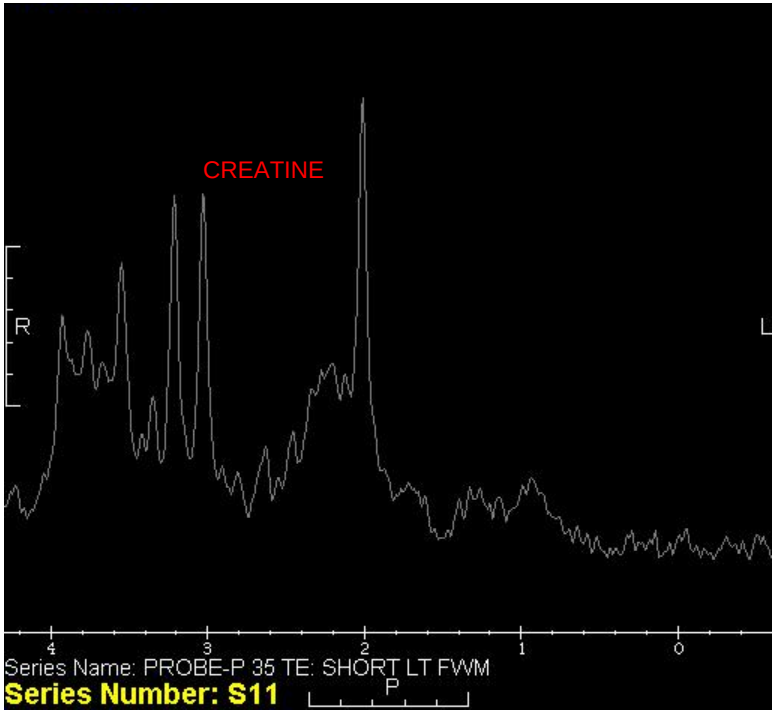
EMORY UNIVERSITY SCHOOL OF MEDICINE

CASE 1

- **CAUCASIAN MALE, 7 YRS OLD, UNRELATED PARENTS**
- **PREGNANCY, NEONATAL PERIOD NORMAL**
- **8 MONTHS: HYPOTONIA, MILD DEV. DELAY**
- **24 MONTHS: PARTIAL STATUS EPILEPTICUS, NO SPEECH.**
  - **EEG: EPILEPTIFORM DISCHARGES. CHROMOSOMES: NORMAL**
- **7 YEARS: NO SPEECH, NO SOCIAL FUNCTION, REPETITIVE BEHAVIORS**
  - **MRI: NORMAL, MRS ABNORMAL**

Standard Proton MRS





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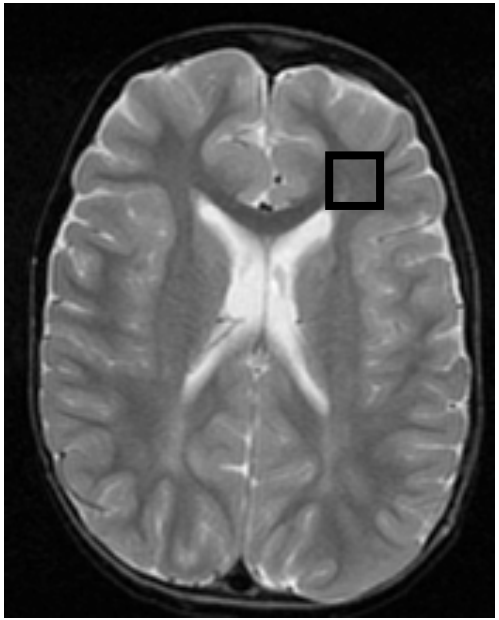
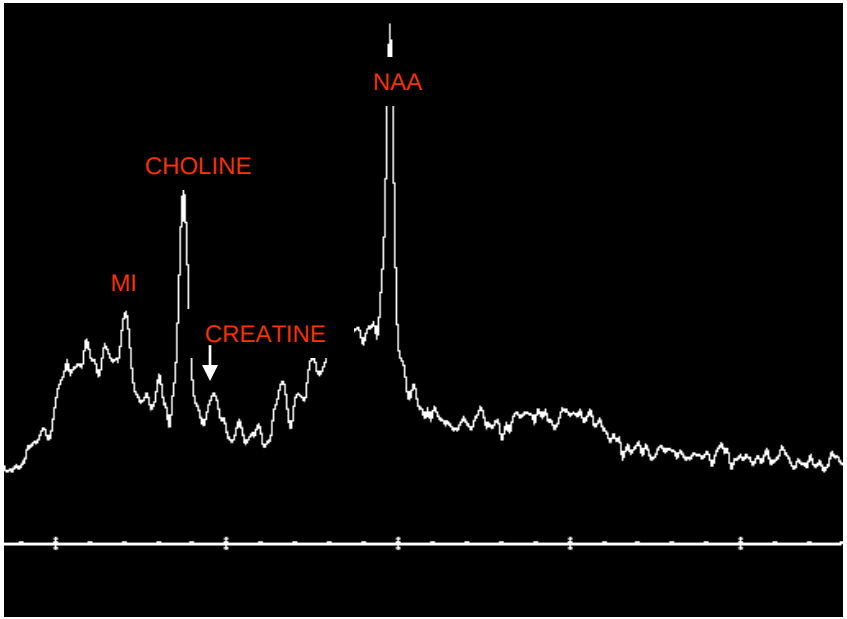
MEDICINE

Proton MRS - Short Echo
CASE 1





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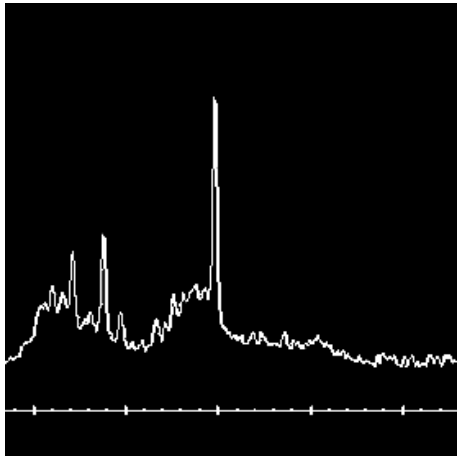
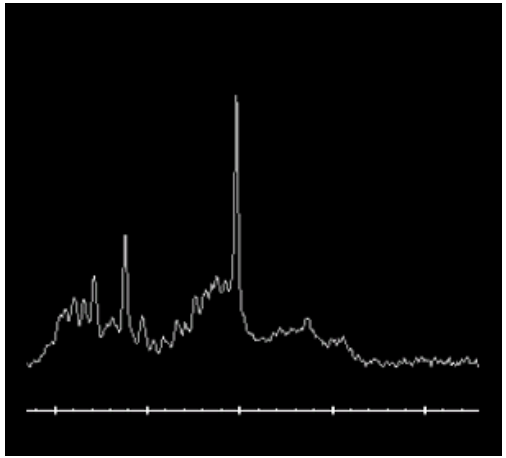
CREATINE TRANSPORTER DEFICIENCY

PATIENT: CH, 2YRS OLD



PRE-TREATMENT



POST-TREATMENT

750MG/KG/DAY

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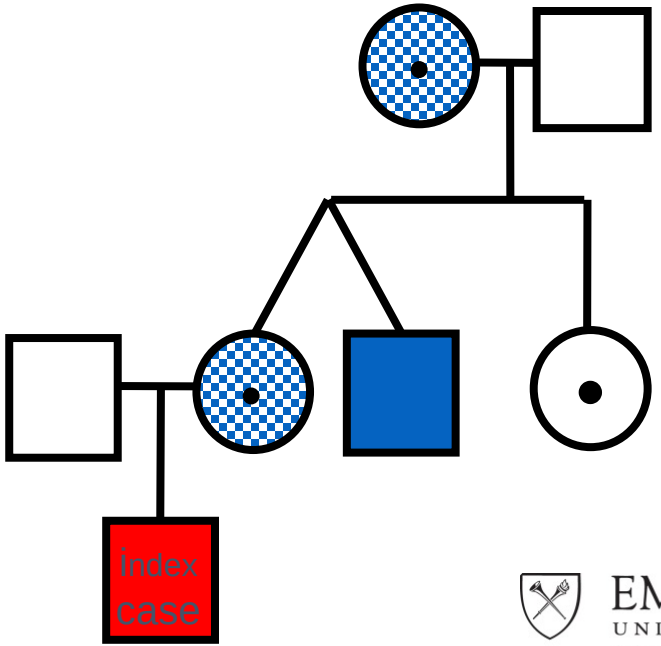
Creatine transporter deficiency?

- **creatine in blood and urine ↑**
- **MRS of brain: no creatine signal**
- **no effect of creatine supplementation**
- **X-linked disease?**
- **creatine transporter (*SLC6A8/CRTR*) Xq28**



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CREATINE TRANSPORTER DEFICIENCY

- X-LINKED DISORDER WITH SYMPTOMATIC FEMALE CARRIERS

- PHENOTYPE:
  - COGNITIVE DYSFUNCTION, LANGUAGE MORE AFFECTED
  - PARTIAL EPILEPSY, EASILY CONTROLLED
  - SOMETIMES MOVEMENT DISORDER
  - NO OTHER ORGAN INVOLVEMENT
  - HETEROZYGOUS FEMALES: LEARNING DISABILITY

- LABS: SERUM CR NL OR↑, CRN NL OR↓, **URINE CR/CRN ↑↑**, GAA NL OR ↑
  - GAMT DEFICIENCY: SERUM CR↓, CRN↓, GAA↑, URINE GAA↑
  - AGAT DEFICIENCY: SERUM CR↓, CRN↓, GAA↓, URINE GAA↓

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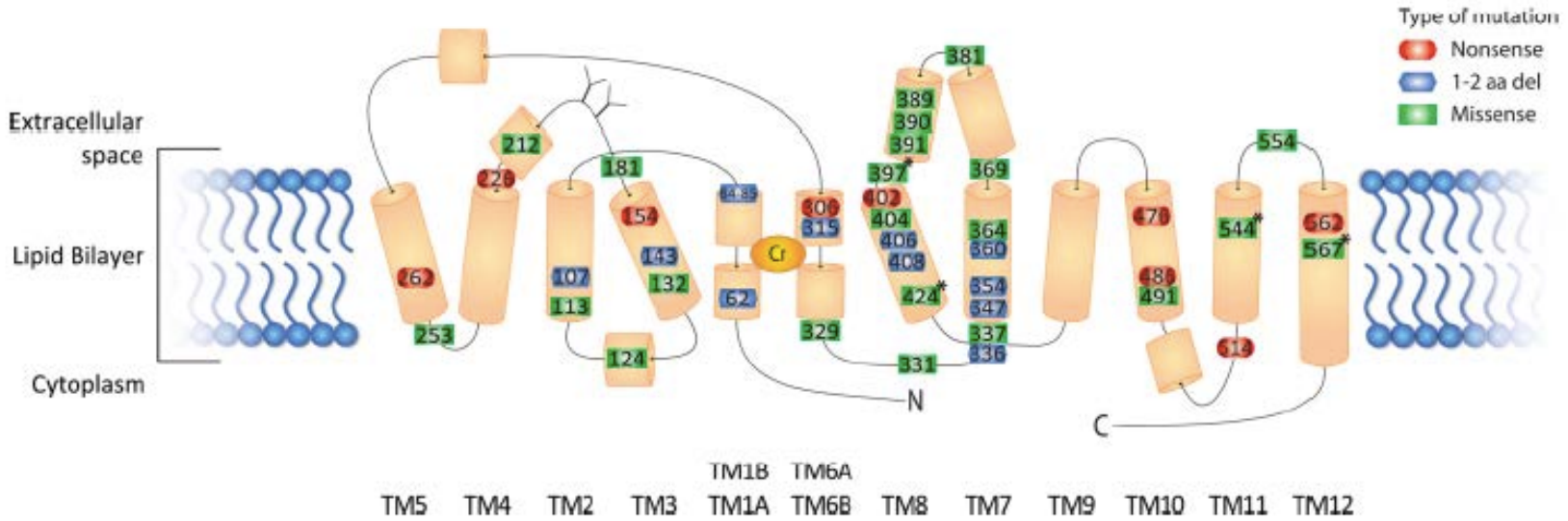
MUTATIONS IN 85 MALE PATIENTS WITH CTD



VAN DE KAMP ETAL, 2013

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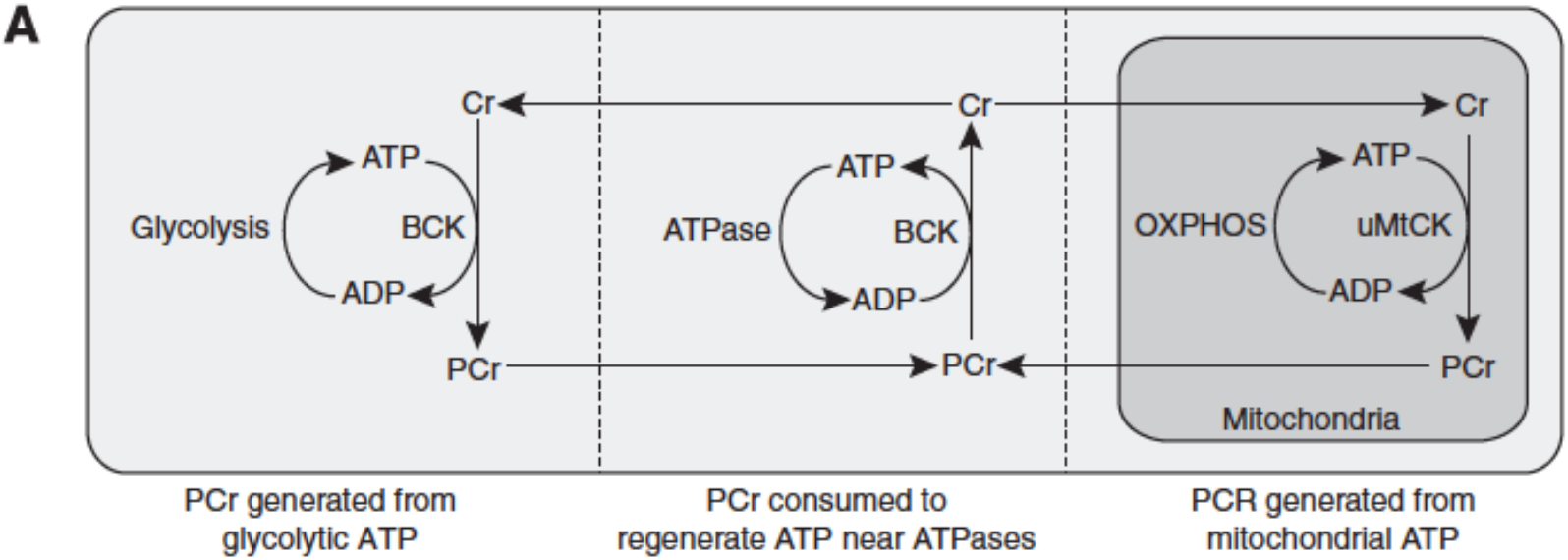
CREATINE PHYSIOLOGY



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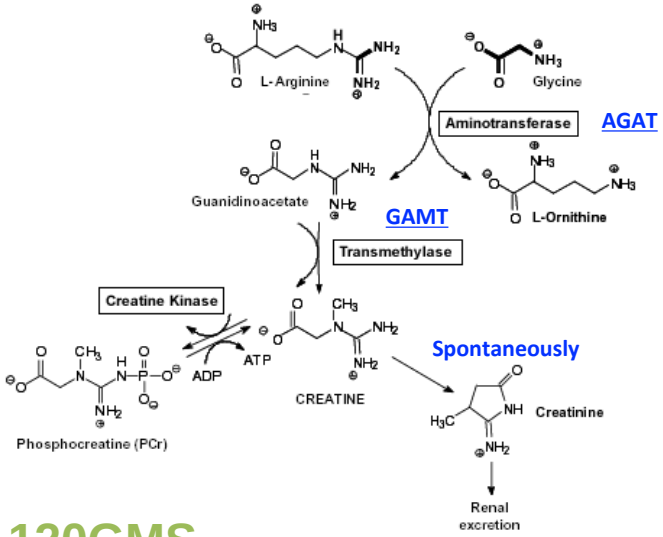
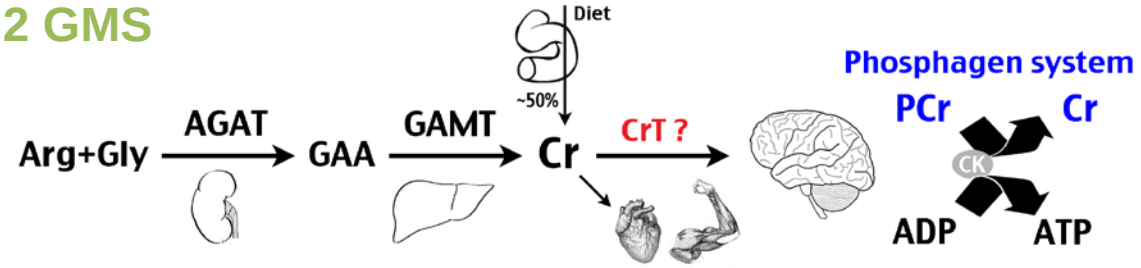
CREATINE METABOLISM



TOTAL CR POOL: 120GMS

DAILY NEED: 2 GMS



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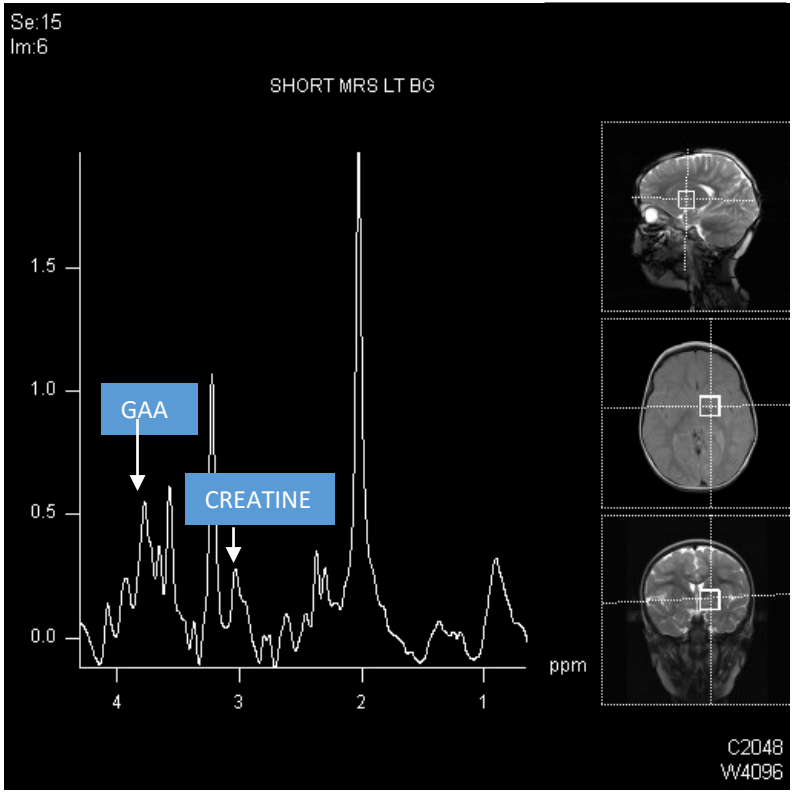
CASE 2

- 18months old girl
- Motor and speech language delay
- Exam: hypotonia, unable to stand, vocalizes, but she does not communicate

- Older sister, 4yrs old with same problem plus seizures and Autism

CASE 2



CREATINE DEFICIENCY

<u>GAMT</u> DEFICIENCY

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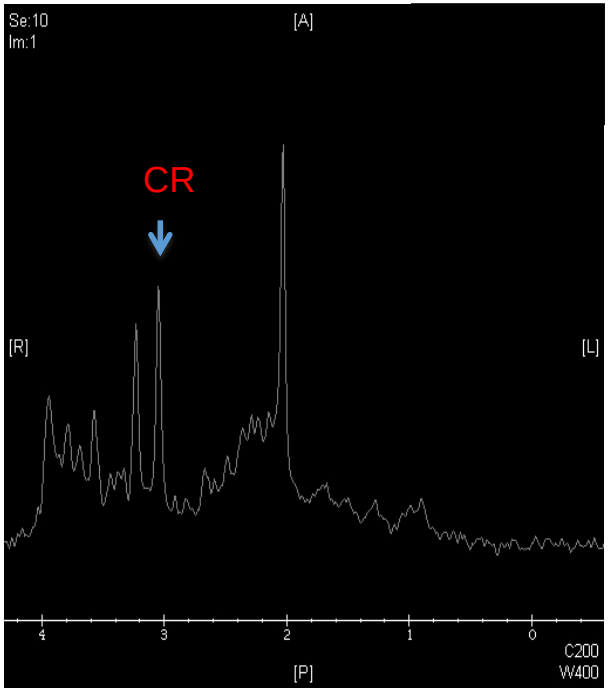
GAMT DEFICIENCY



- 6 months of creatine treatment: normal creatine peak in CNS

- **18Mo follow-up: speaks single words, walks without support**
- **5Yr follow-up: in regular first grade and older sister in regular 4th grade**

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CREATINE TRANSPORTER DEFICIENCY

EPIDEMIOLOGY

- 188 BOYS WITH M.R. AND NORMAL CHROMOSOME STUDIES (INCLUDING FRAGILE X): 2.7% WITH CREATINE DEFICIENCY SYNDROME [1]
- 2.3% OF 157 MALES WITH MENTAL RETARDATION WERE FOUND TO HAVE CrT DEFICIENCY BASED UPON Cr/Crn IN URINE [2]
- 2% OF MALES WITH X-LINKED M.R. HAVE CrT DEFICIENCY [3]

Lyon-Francais, 2006, 2. Mercimek-Mahmutoglu, 2009, 3. Puusepp, 2009

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SUMMARY
CRT DEFICIENCY

PHENOTYPE CAN BE RESCUED WITH CREATINE SUPPLEMENTATION

- AGAT DEFICIENCY: NORMAL PHENOTYPE IF TREATMENT STARTS EARLY IN LIFE
- GAMT DEFICIENCY: PHENOTYPE SIGNIFICANTLY IMPROVED, IF TREATMENT STARTS EARLY IN LIFE
- CRT DEFICIENCY: NO RESPONSE TO CREATINE, MOST COMMON TYPE OF CREATINE DEFICIENCY

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Q&A
Translational Research

Emil D. Kakkis, M.D., Ph.D.
CEO, President and Founder

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Closing Remarks

Shalini Sharp, CFO

Key Highlights You Heard Today

Strong global commercial progress

- U.S. launch continues to progress
- Expanding global presence rapidly and efficiently

Advancing gene therapy platform

- Platform and clinical programs: **DTX301** and **DTX401**
- Manufacturing using proprietary HeLa system
- Investing in GMP gene therapy manufacturing facility

Moving three early stage programs toward IND

- **UX701** Gene therapy for Wilson Disease
- **UX053** mRNA/LNP for Glycogen Storage Disease Type III
- **UX068** Creatine Prodrug for Creatine Transporter Deficiency

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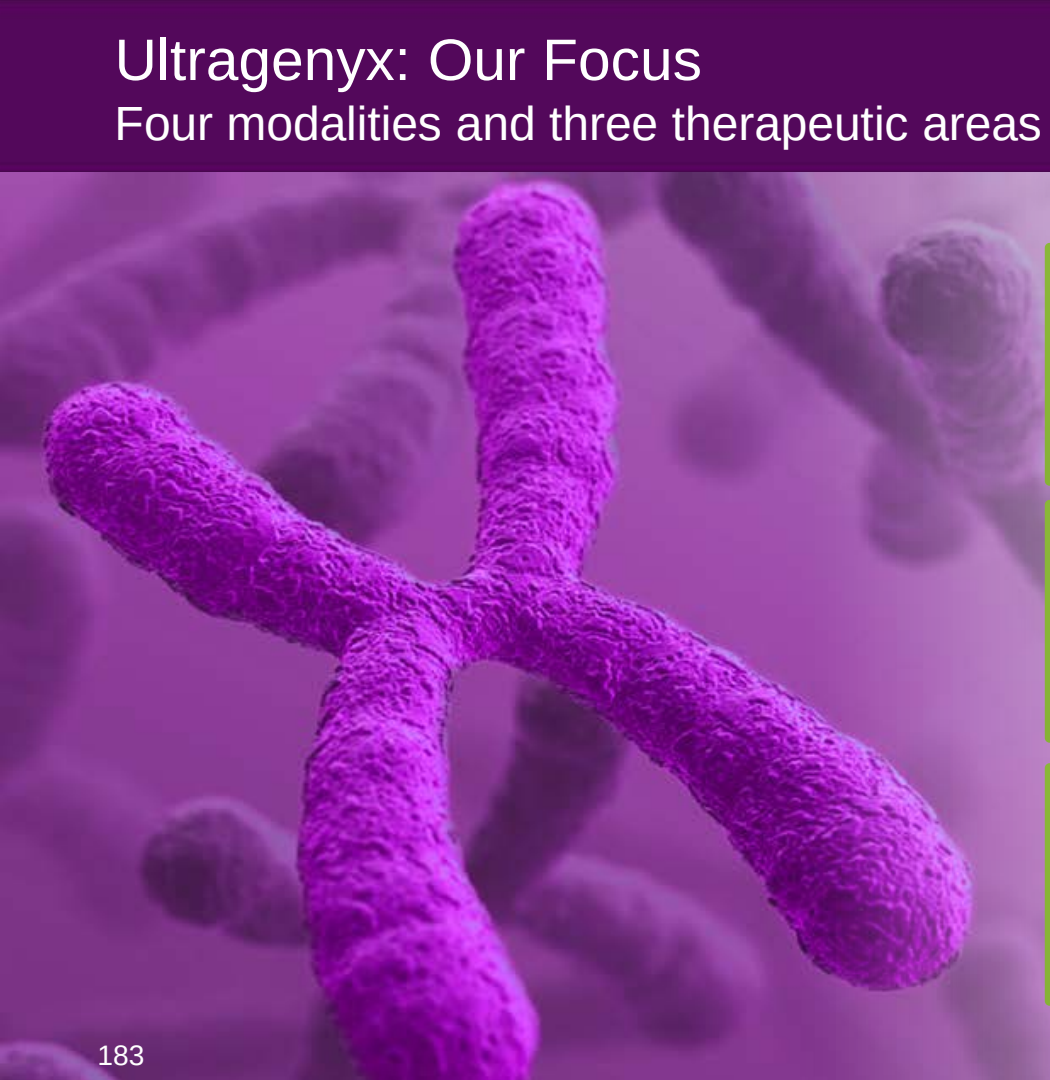
Ultragenyx: Our Focus

Four modalities and three therapeutic areas



Clear Biology

- ✓ Known method of action
- ✓ Favorable probability of success

Disease Modifying

- ✓ Create meaningful value for patients
- ✓ Goal to optimize global access

Accelerated Development

- ✓ Innovative clinical trials, statistics, and registrational pathways
- ✓ Rapid manufacturing process development

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Our Focus has Created a Robust Development Engine

Global commercial infrastructure generates value from a deep pipeline

Advancing Translational Research Pipeline	Dynamic Development Model	Global Commercial Presence
TRANSLATIONAL RESEARCH	**CLINICAL DEVLOPMENT**	**COMMERCIAL EXECUTION**
14+ Programs	*Two Phase 2 Programs with Three INDs planned for 2020*	*Two Approved with a third NDA Submission in mid-2019*

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We are Capitalized to Deliver Value From this Pipeline

As of Dec 31, 2018

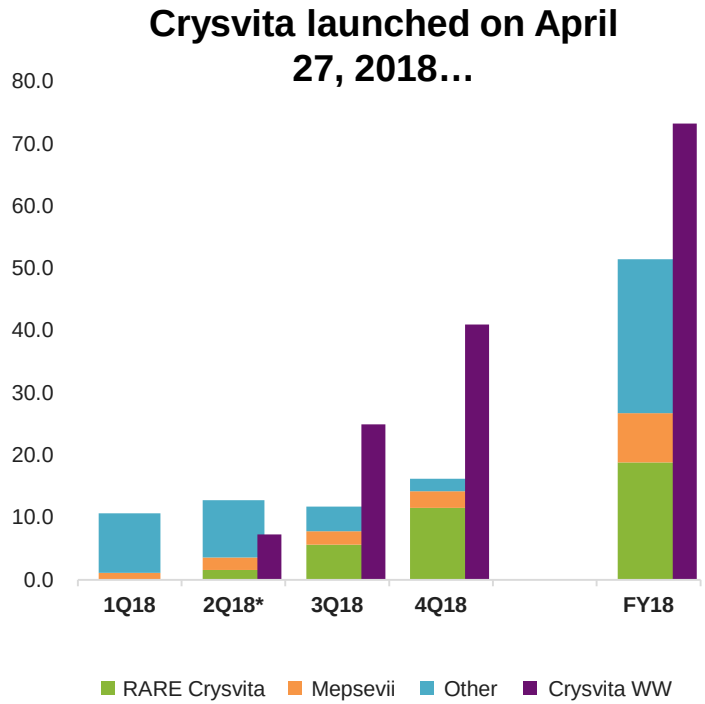
- **Total Revenue: $51.5 million**
- **Total RARE Crysvita Revenue[1]: $18.9 million**
- **Cash[2]: $459.7 million**
  - **Incremental ~$330M in net proceeds raised in March 2019**
- **Cash Used in Operations:**

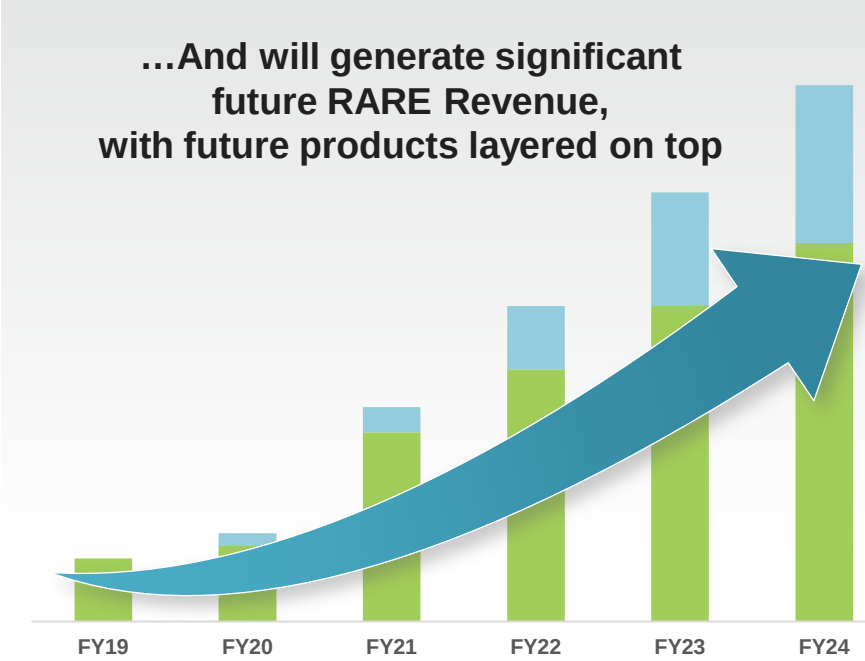
  $290.6 million
- **No Debt**

[1]Launched on April 27, 2018
[2]Cash, cash equivalents, and investments as of Dec 31, 2018. Excludes funds from secondary offering in March 2019.

Launch Success Should Lead to Revenue Growth

And meaningful offset to cash expenditures with product after product





Illustrative, not to scale

2019 Will Fuel Continued Value Expansion

2010 – 2018

- 2 Commercially approved products in 3 major geographic regions
- 34 active or completed clinical studies
- 14+ programs in the development pipeline

2019

- Continue successful global launches of Crysvita and Mepsevii
- Submit UX007 NDA
- DTX301 and DTX401 data readouts
- Begin building our AAV GMP manufacturing facility
- Prepare for up to 3 INDs to be filed in 2020
- Active on BD front

2020+

- Ph 3 gene therapy studies
- Launch UX007 for LC-FAOD if approved
- Initiate clinical trials for Wilson, GSDIII, and CTD programs
- Incorporate other BD deals into the pipeline

Thank You

- To our patients for giving us our reason for being
- To the IR team: Danielle, Josh, and Michele for their hard work
- To our guest speakers for making the effort to come and teach us
- To the Ultragenyx team for their excellence in execution
- To all of you for coming and listening to our story today