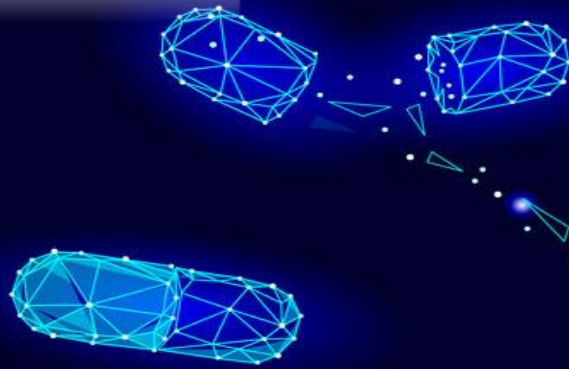




UNIVERSITY of CALIFORNIA, SAN DIEGO
SCHOOL OF MEDICINE



HEMATOPOIETIC STEM CELL GENE THERAPY FOR CYSTINOSIS: UPDATE OF THE PHASE 1/2 CLINICAL TRIAL

Stephanie Cherqui, Ph.D
Professor
Department of Pediatrics
Division of Genetics

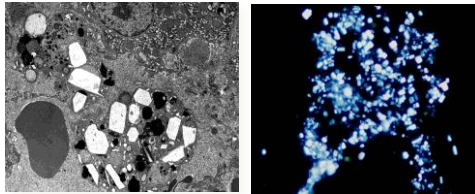
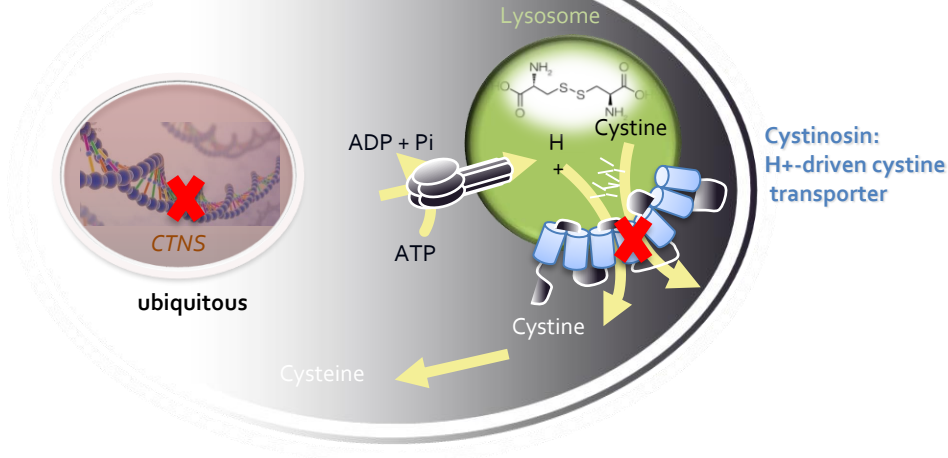


DISCLOSURE

- I am cofounder, shareholder and a member of both the scientific board and board of directors of Papillon Therapeutics Inc.
- I am a Consultant for AVROBIO, Inc.
- I am a member of the Cystinosis Research Foundation Scientific Review Board and Board of Trustees

CYSTINOSIS, A LYSOSOMAL STORAGE DISORDER

- Autosomal recessive
- Incidence 1/100,000 – 1/200,000



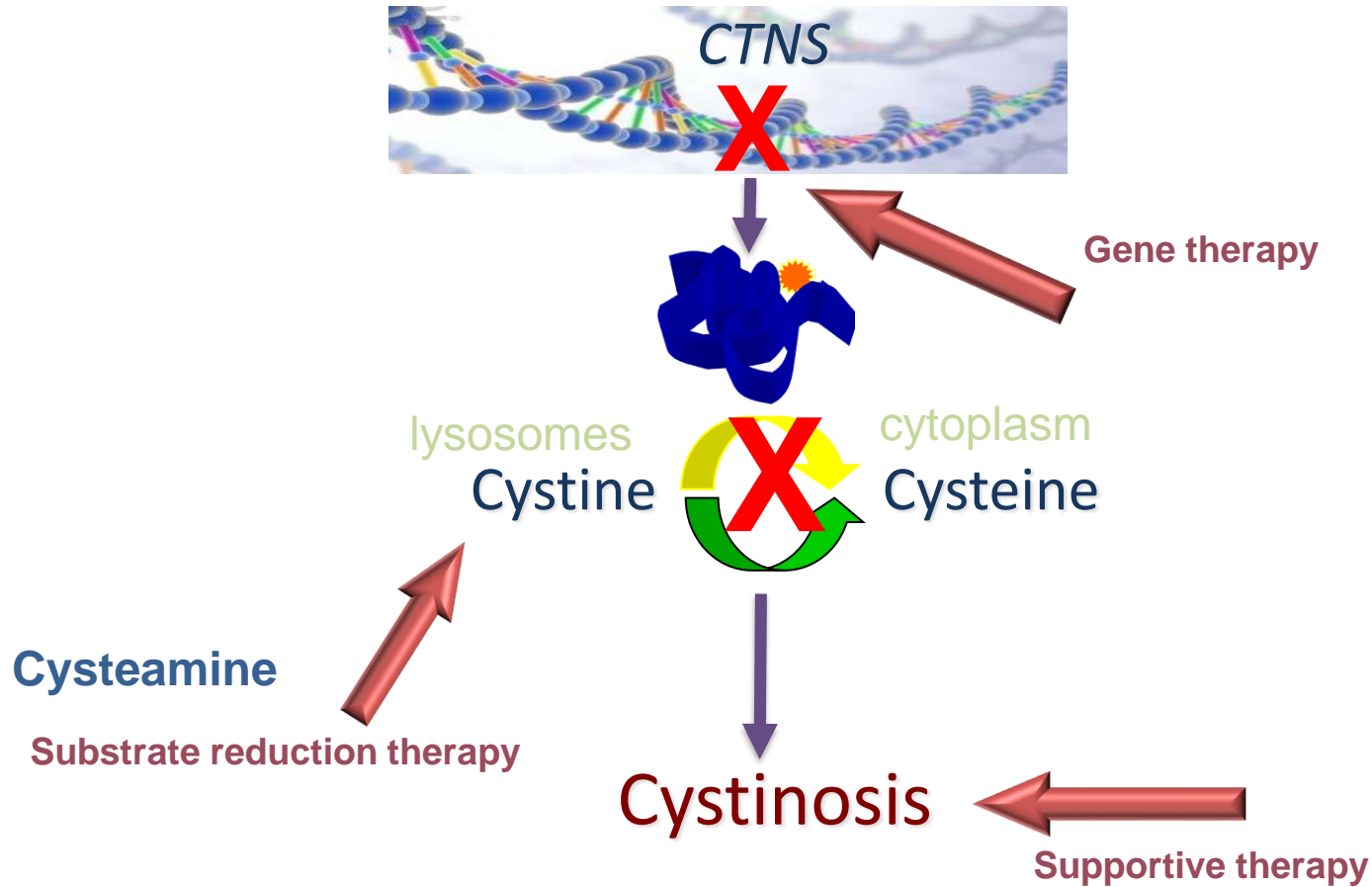
Multisystemic degenerative disease

Diagram illustrating the clinical manifestations of cystinosis, shown as a human silhouette with arrows pointing to various symptoms:

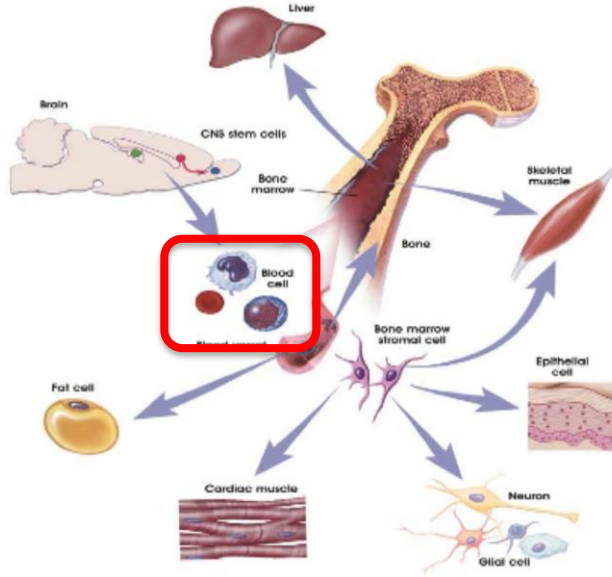
- Neurological defects
- Hypothyroidism
- Elevated cystine in white blood cells
- Fanconi syndrome
- Kidney failure
- Failure to thrive
- Corneal cystine crystals
- Excessive thirst
- Dehydration
- Myopathy
- Excessive urination
- Rickets



CURRENT TREATMENT FOR CYSTINOSIS



Adult bone marrow stem cells



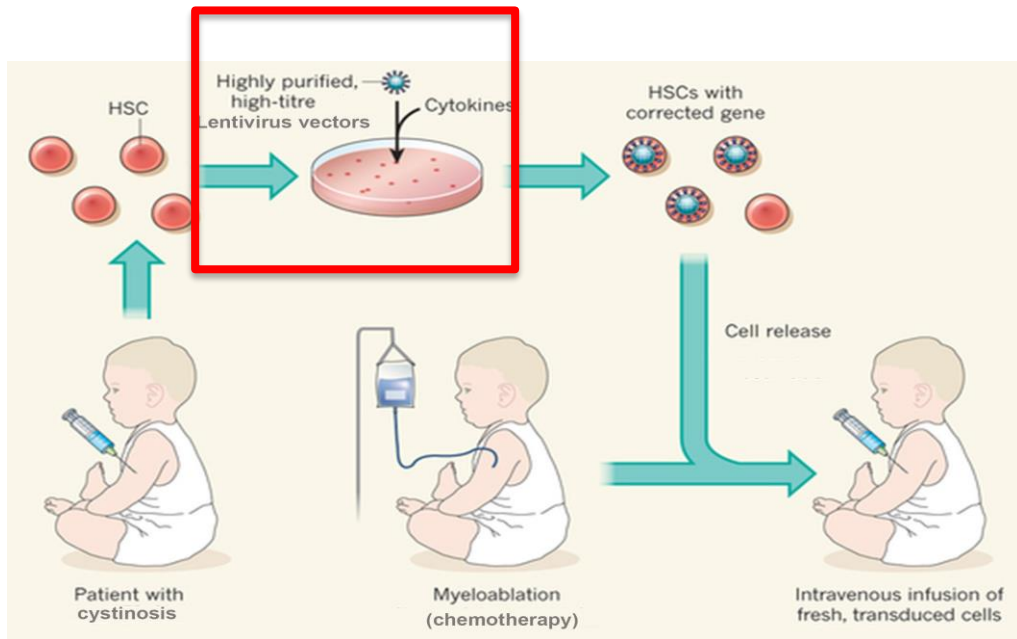
➤ Adult bone marrow stem cells

- Pluripotent
- Safe
- Currently used in clinical applications

➤ Three types of BMSC:

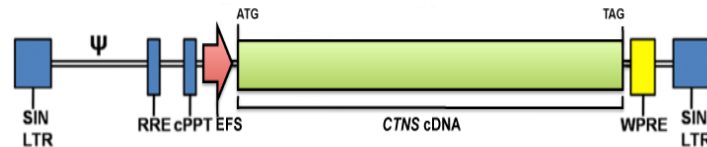
- Whole bone marrow cells (BMC)
- Hematopoietic stem cells (HSC)
- Mesenchymal stem cells (MSC)

CLINICAL TRANSLATION: AUTOLOGOUS GENE-MODIFIED HSC TRANSPLANTATION



Adapted from Leboulch, Nature 2013

CCL-EFS-CTNS-WPRE

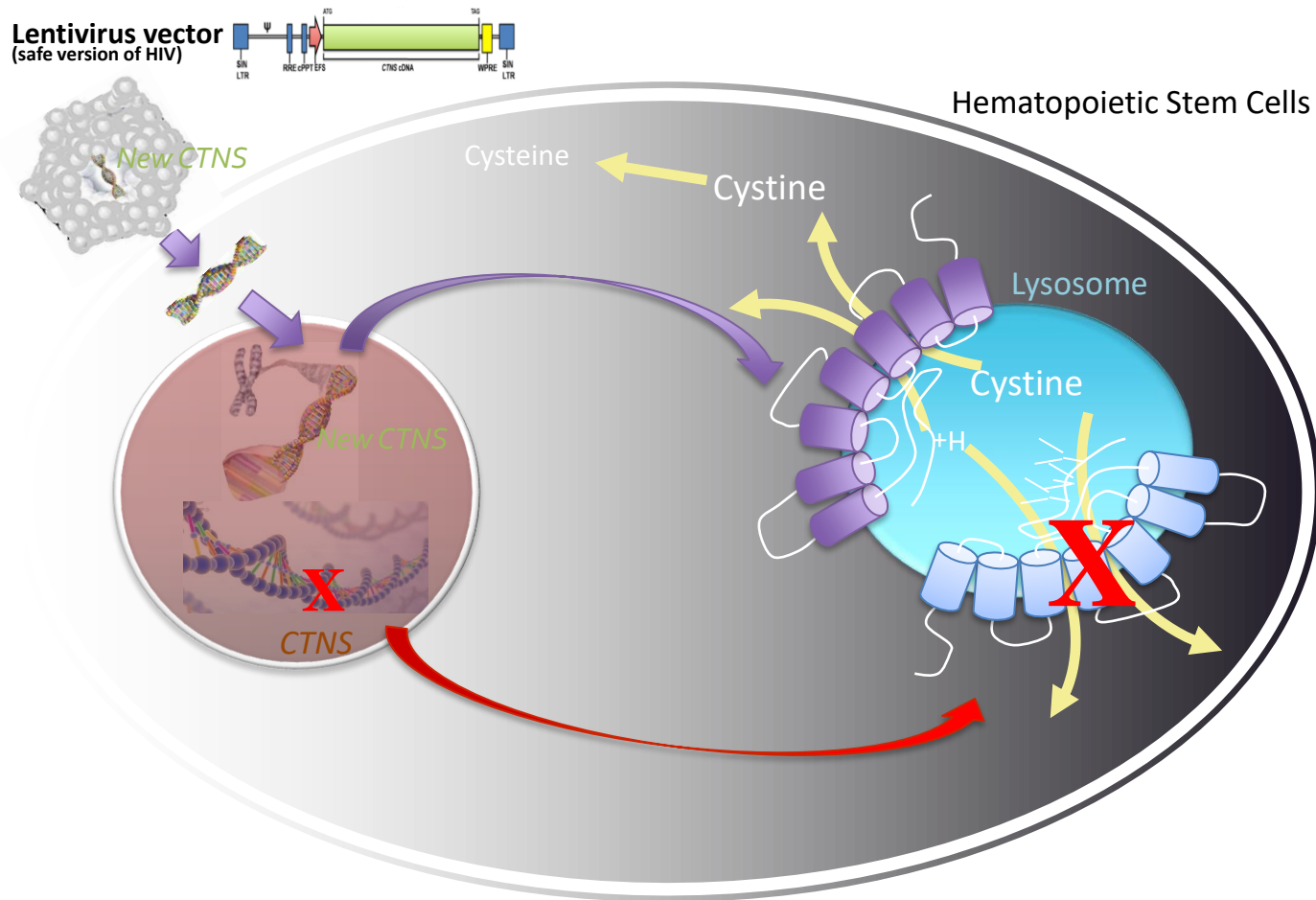


Lentivirus vector (engineered version of HIV)

Provided by Dr. Donald Kohn (UCLA)

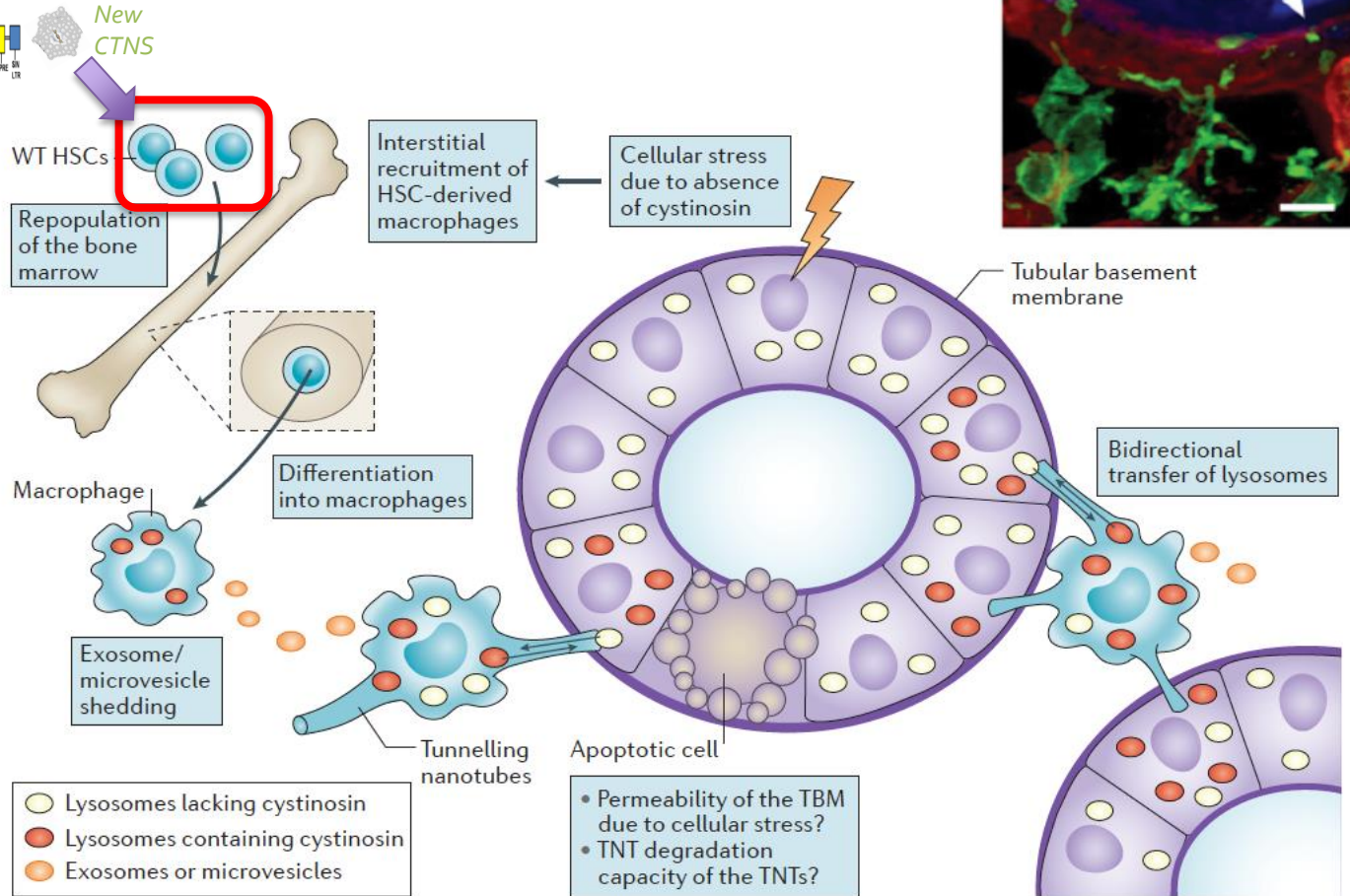
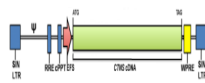
Drug Product: CD34+ HSCs from patients, *ex vivo* gene-corrected using pCCL-CTNS

Ex vivo gene modification of the autologous stem cells



HEMATOPOIETIC STEM CELL TRANSPLANTATION: MECHANISM OF ACTION

Lentivirus vector
(safe version of HIV)



PHASE 1/2 AUTOLOGOUS STEM CELL GENE THERAPY CLINICAL TRIAL FOR CYSTINOSIS

Trial started on July 8th, 2019 at UC San Diego Health Center
ClinicalTrials.gov Identifier # NCT03897361

Study Design: One arm, open label, single treatment safety and efficacy study - **6 patients**

- **Primary Endpoints**

- To assess the clinical tolerability and safety of treatment with CTNS-RD-04;

- **Secondary Endpoints;** To evaluate the impact of treatment with CTNS-RD-04 on:

- To assess the effect of treatment with CTNS-RD-04 on white blood cell cystine levels
 - Clinical outcomes (especially kidney, eye and endocrine function)
 - Cystine level in tissues (rectal and skin biopsies)
 - Cystine crystal density (skin and eye)

Inclusion Criteria: 6 patients (3 cohorts of 2 patients)

- Male or female subject is ≥ 18 years of age.
- Subject is diagnosed with infantile cystinosis.
- Subject is free of acute illness.
- Subject is at least one-year status post-kidney transplant.
- Subject has adequate organ function.
- Subject is willing and able to comply with the study restrictions and requirements.
- Subject is willing to provide written informed consent prior to participation in the study.



UC San Diego Health

THE CYSTINOSIS STEM CELL AND GENE THERAPY CONSORTIUM

Stephanie Cherqui, Ph.D - Hematopoietic Stem Cell Gene Therapy, UCSD – Principal Investigator

Bruce Barshop, M.D., Ph.D – Director of the UCSD Biochemical Genetics lab – Principal Investigator

Edward D. Ball, M.D – Director of Bone Marrow Transplantation at UCSD – Principal Investigator

Natalie Afshari, M.D – Ophthalmology, UCSD

Nadine Benador, M.D – Nephrology, UCSD

Anna DiNardo, M.D – Dermatology, UCSD

Magdalene Dohil, M.D – Dermatology, UCSD

Ranjan Dohil, M.D – Gastroenterology, UCSD

Robert Mak, M.D – Nephrology/Muscle, UCSD

Susan Phillips, M.D – Endocrinology, UCSD

Kathleen Rickert, M.D – Orthopedy, UCSD

Doris A. Trauner, M.D – Neurology, UCSD

Donald B. Kohn, M.D – Hematopoietic Stem Cell Gene Therapy, UCLA

Paul Grimm, M.D – Nephrology, Stanford

Nancy Stack – Director of the Cystinosis Research Foundation



1- Inform Consent and Screening (2 days)

2- Baseline evaluation (8-9 days)



Kidney function

Blood, 24h urine
Iohexol clearance

Dr. Nadine Benador,
Dr. Robert Mak



Eye exam

Corneal confocal microscopy
Angiography
Electroretinogram
Optical Coherence Tomography

Dr. Natalie Afshari
Dr. Eric Nudleman



Muscle function, bone density

Walk test
Grip strength
X-ray absorptiometry (DEXA)

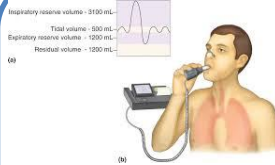
Dr. Robert Mak
Dr. Kathleen Rickert



Neurological function

Quality of Life
Neurological exam
Questionnaires

Dr. Doris Trauner



Respiration capacity

Spirometry

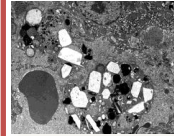


Endocrine function

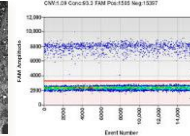
Thyroid hormones
Fasting glucose
Reproductive hormones

Rectal Biopsies

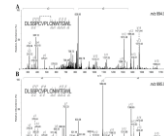
Dr. Ranjan Dohil



Histology to
quantify
cystine
crystals



Vector Copy Number
CTNS expression



Cystine measures in
blood and tissue

**Dr. Bruce
Barshop**



In vivo confocal microscopy

Skin cystine crystal
quantification

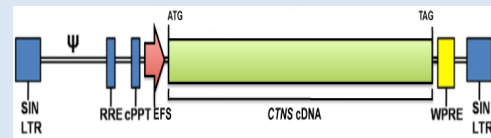
**Dr. Magdalene
Dohil**

Patients stop oral cysteamine 2 weeks prior to drug product infusion and cysteamine eye drops 1-month post-infusion



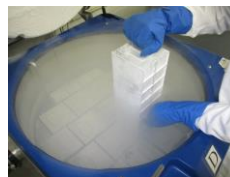
GMP Human Gene and Cell Therapy
Dr. Donald Kohn

CCL-EFS-CTNS-WPRE lentiviral vector



2- CD34⁺ cell isolation and transduction (3 days)

3- Cell characterization (UCSD/UCLA; 30-60 days)

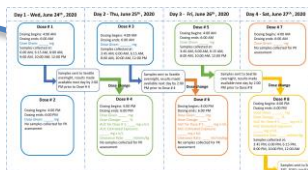


4- Gene-modified stem cells shipped back to UCSD as a cryopreserved product



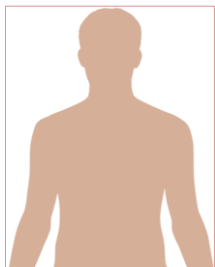
1- G-CSF/plerixaflor cell mobilization (4 days) and Apheresis

A back up apheresis product will be kept at UCSD



5- Busulfan conditioning (4 days)
Targeted Area Under the Curve (AUC) - 90 mg x h/L

6- Infusion



Adult with cystinosis



UC San Diego Health

PATIENT BASELINE CHARACTERISTICS AND MANUFACTURING PRODUCTS

	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5
Age of symptom onset/diagnosis	0 year / 8 months	0 year / 6 months	4 years	6 years	8 months
Age dosed with CTNS-RD-04	20 years Infused October 2019	46 years Infused June 2020	22 years Infused November 2020	33 years Infused November 2021	31 years Infused March 2022
Gender	Male	Male	Male	Male	Female
Mutation	<ul style="list-style-type: none"> 57-kb deletion c.696dupC, p.Val233Argfs*63 	<ul style="list-style-type: none"> 57-kb deletion c.473T>C, p.Leu158Pro 	<ul style="list-style-type: none"> c.18_21del, p.Thr7Phefs*7 c.295_298del, p.Val99Ilefs*18 	<ul style="list-style-type: none"> 57-kb deletion c.473T>C, p.Leu158Pro 	<ul style="list-style-type: none"> 57-kb deletion c.414G>A, p.Trp138*
Kidney transplant status and cysteamine dosing prior to CTNS-RD-04 dosing	<ul style="list-style-type: none"> No kidney transplant; stage 3 (moderate CKD) renal failure On oral Cysteamine On Cysteamine drops 	<ul style="list-style-type: none"> 2 renal transplants (1987 and 1999) On oral Cysteamine On Cysteamine drops 	<ul style="list-style-type: none"> 1 renal transplant (2010) On oral Cysteamine On Cysteamine drops 	<ul style="list-style-type: none"> 2 renal transplants (2008 and 2017) On oral Cysteamine Off Cysteamine drops 	<ul style="list-style-type: none"> No renal transplant; stage 3 (moderate CKD) renal failure On oral Cysteamine On Cysteamine drops
Manufactured CTNS-RD-04 product and busulfan dose	<ul style="list-style-type: none"> 7.88 x 10e6 CD34+ cells/kg VCN: 2.07 94% viability AUC Bu: 81.8 mg.h/L 	<ul style="list-style-type: none"> 5.07 x 10e6 CD34+ cells/kg VCN: 1.27 91% viability AUC Bu: 86.7 mg.h/L 	<ul style="list-style-type: none"> 9.59 x 10e6 CD34+ cells/kg VCN: 1.59 95% viability AUC Bu: 90 mg.h/L 	<ul style="list-style-type: none"> 3.63 x 10e6 CD34+ cells/kg VCN: 0.59 90% viability AUC Bu: 88.5 mg.h/L 	<ul style="list-style-type: none"> 9.12 x 10e6 CD34+ cells/kg VCN: 2.5 95% viability AUC Bu: 88.2 mg.h/L

Phase 1/2 Cystinosis Trial (5 patients)

No unexpected safety events or trends related to CTNS-RD-04 identified

Preliminary Safety Results

No SAEs or AEs related to CTNS-RD-04 drug product

No SAE reported

Preliminary AEs reported (as of May 6th, 2022)

- N=40 for subject 1; N=22 for subject 2; N=8 for subject 3; N=25 for subject 4; N=13 for subject 5
- Majority of AEs are mild or moderate
- 1 severe AEs for subject 1
 - *Appendicitis* (resolved) – unrelated to study treatment or procedures
- AEs are generally consistent with myeloablative conditioning or underlying disease:

Pre-gene therapy treatment and prior to conditioning (not all events listed)

- Diarrhea, hypokalemia, hypomagnesemia, thrombocytopenia, dizziness, dehydration, vomiting, bone pain, and headache.

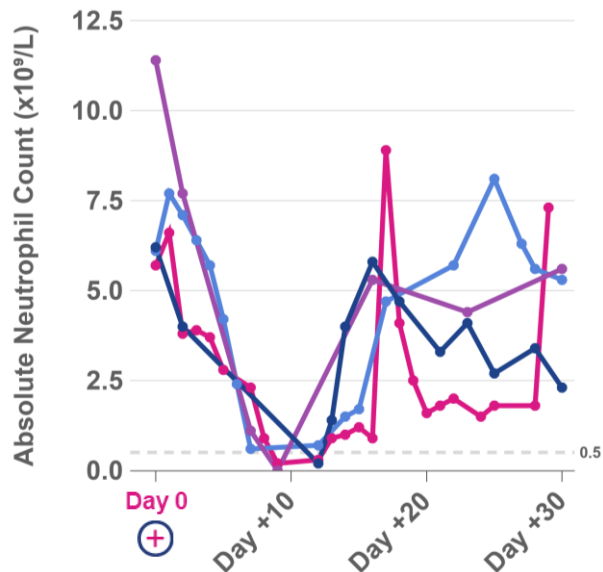
Post-treatment (not all events listed)

- Pancytopenia, deep vein thrombosis, Staphylococcus sepsis, Coronavirus infection, alopecia, rash, mucositis.
- Intermittent: diarrhea, vomiting, loss of appetite, epistaxis, blurry vision, febrile neutropenia, hypomagnesemia, and hypokalemia.

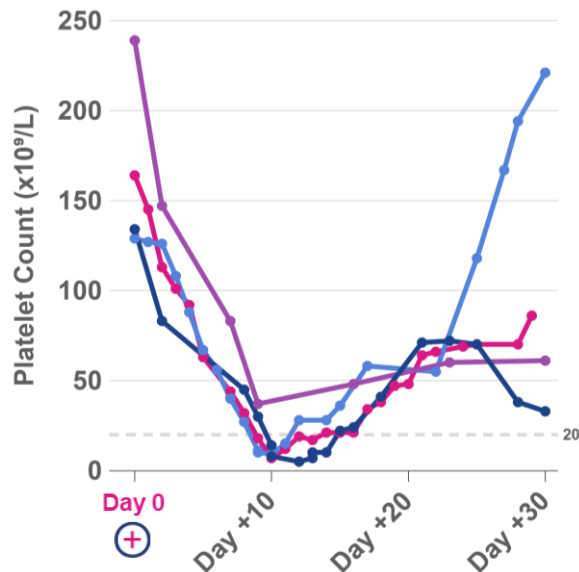
BLOOD COUNT

Busulfan is transiently myeloid depleting while sparing lymphocytes

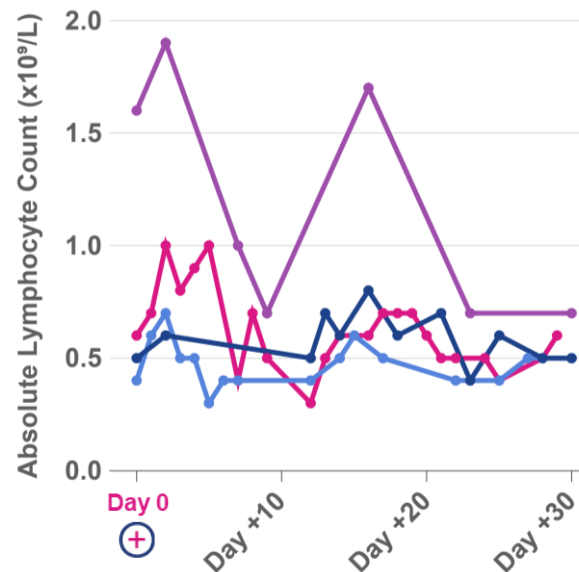
Absolute Neutrophil Count (ANC)



Platelet Count



Absolute Lymphocyte Count

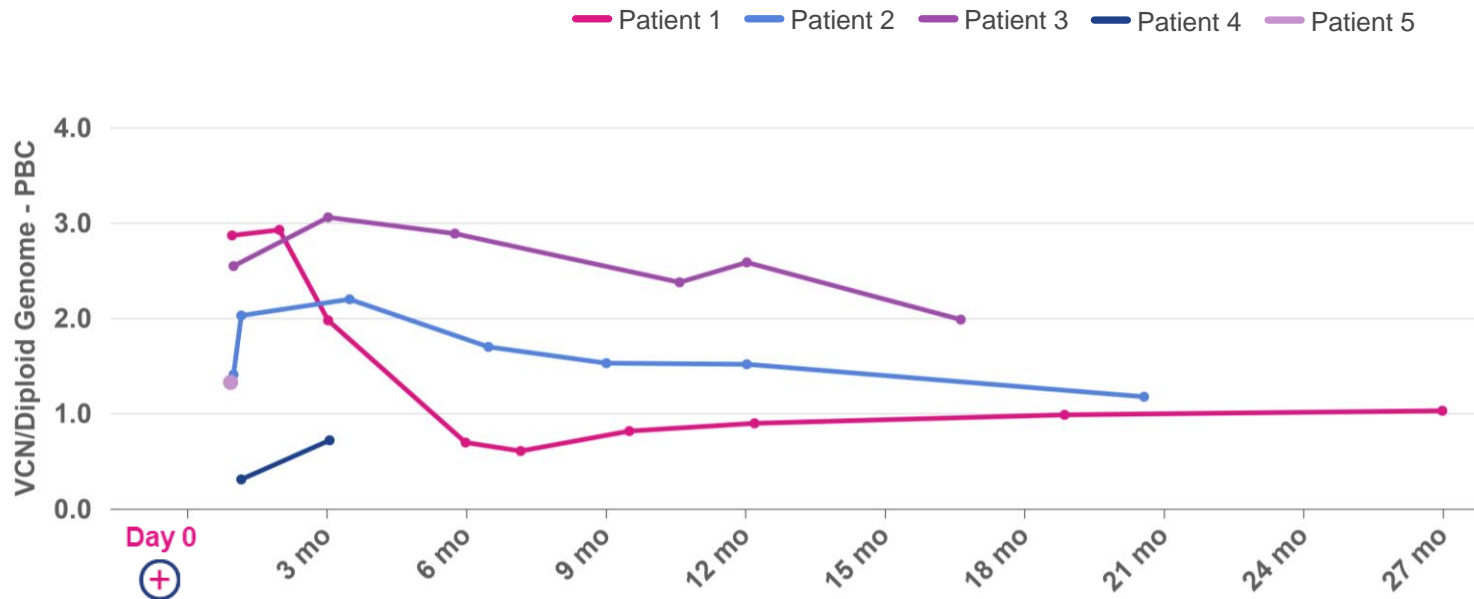


— Patient 1 — Patient 2 — Patient 3 — Patient 4

VECTOR COPY NUMBER (VCN)

Measured in the peripheral blood of patients at different time points

Drug Product VCN/dg	
Patient 1	2.1
Patient 2	1.3*
Patient 3	1.6
Patient 4	0.6
Patient 5	2.5



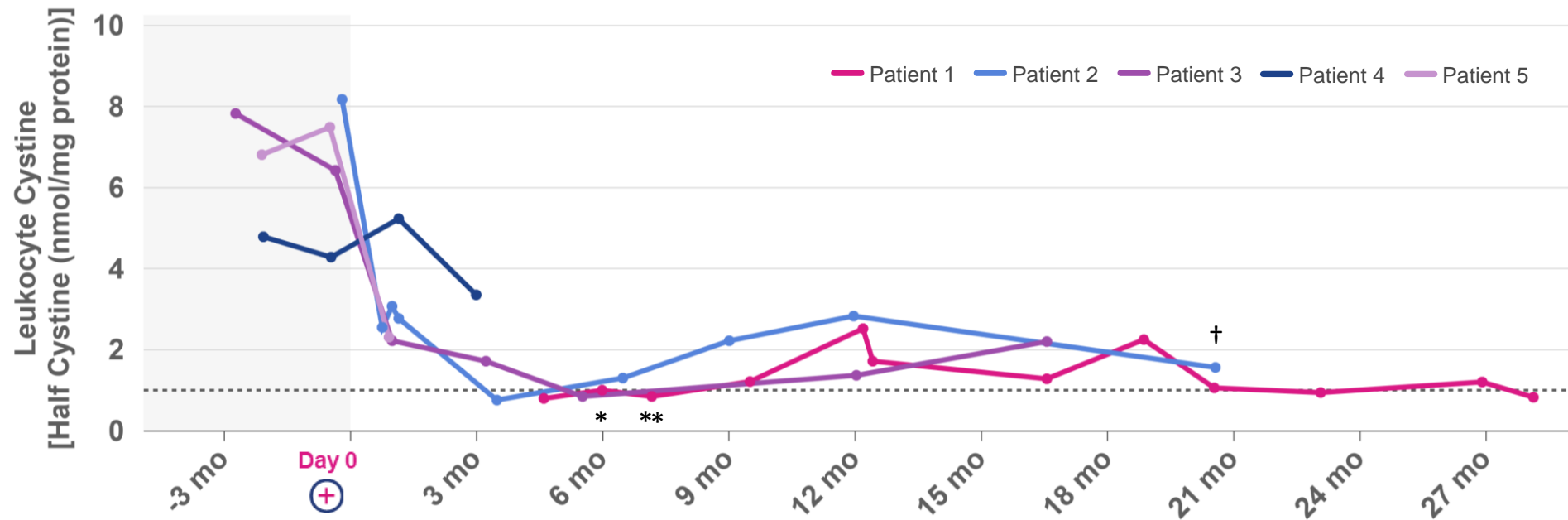
PRELIMINARY DATA

* From second apheresis

VCN: Vector Copy Number; PBCs: Peripheral Blood Cells; dg: Diploid Genome

LEUKOCYTE CYSTINE LEVELS

Leukocytes cystine levels decreased out to 28 months



PRELIMINARY DATA

Note: Therapeutic range is <1.0 Half Cystine (nmol/mg protein). Measure of 1 is level of healthy heterozygote.

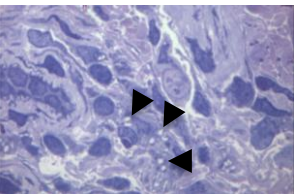
For Patient 1, Leukocyte Cystine Quantification was initiated at approximately week 20

*Patient 1: Hemolyzed sample which may potentially lead to lower results

**Patient 1: Sample processed outside of the range of the stability

†Patient 2: Sample was not collected and shipped according to study protocol

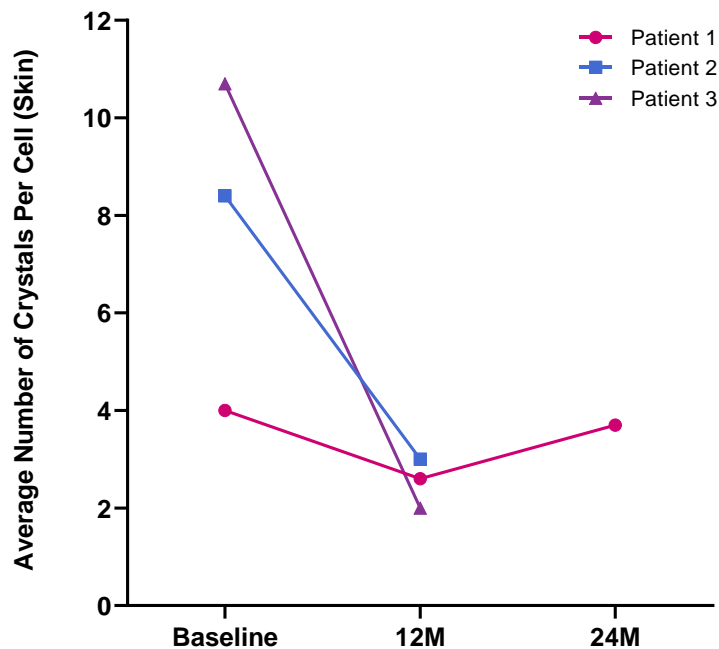
TISSUE CYSTINE CRYSTALS: BIOPSIES



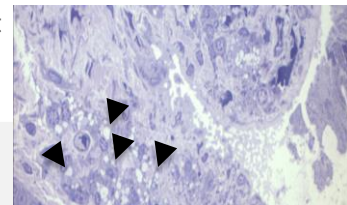
Skin biopsy image at
Baseline - Patient 1

Average intracytoplasmic crystals per cell

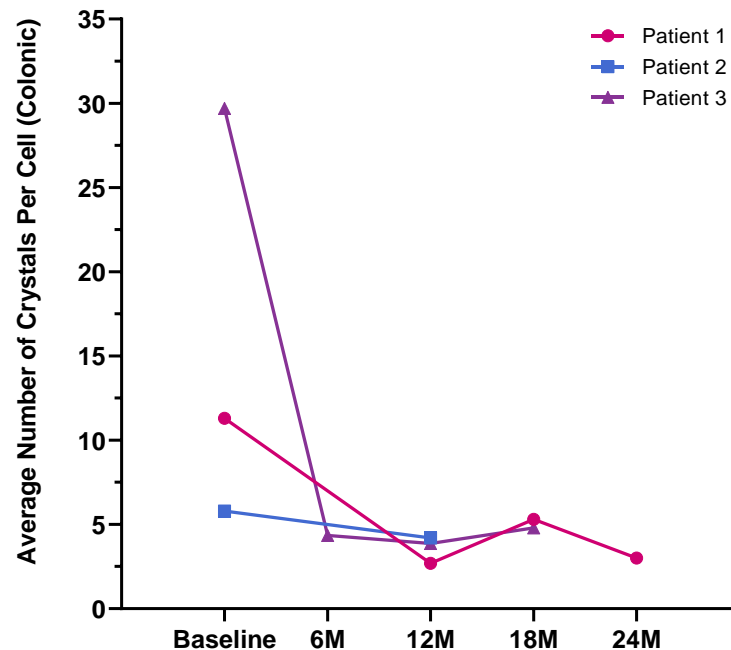
Skin Biopsy



Rectal biopsy image at
Baseline - Patient 1



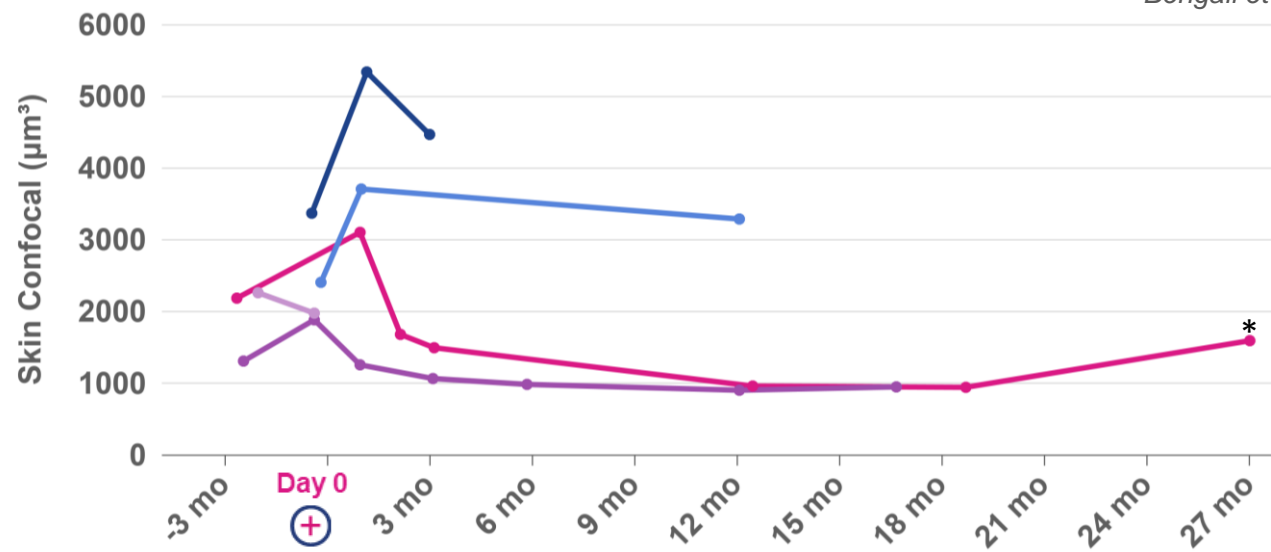
Rectal Biopsy



TISSUE CYSTINE CRYSTALS IN THE SKIN: CONFOCAL

Exploratory endpoint

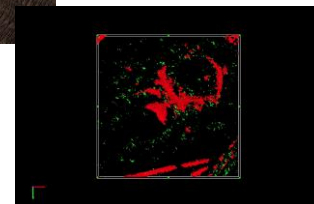
Patient 1 Patient 2 Patient 3 Patient 4 Patient 5



PRELIMINARY DATA

*Patient 1: There are some concerns with the reliability of this data point as the analysis was done slightly different due to issue with software

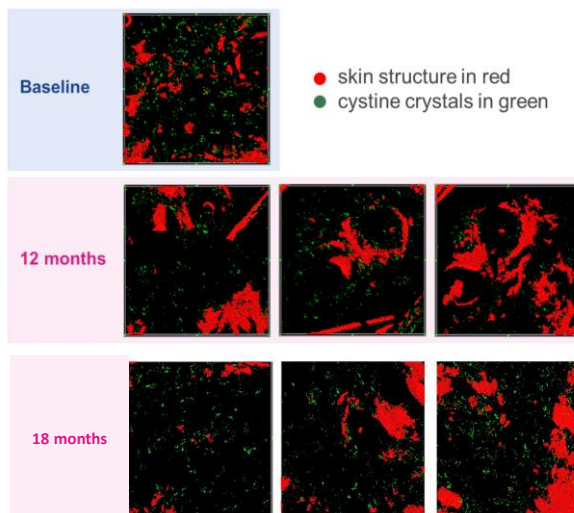
Caliber Vivascope® Skin Confocal microscope



Analysis and quantification (3D Image-Pro software)

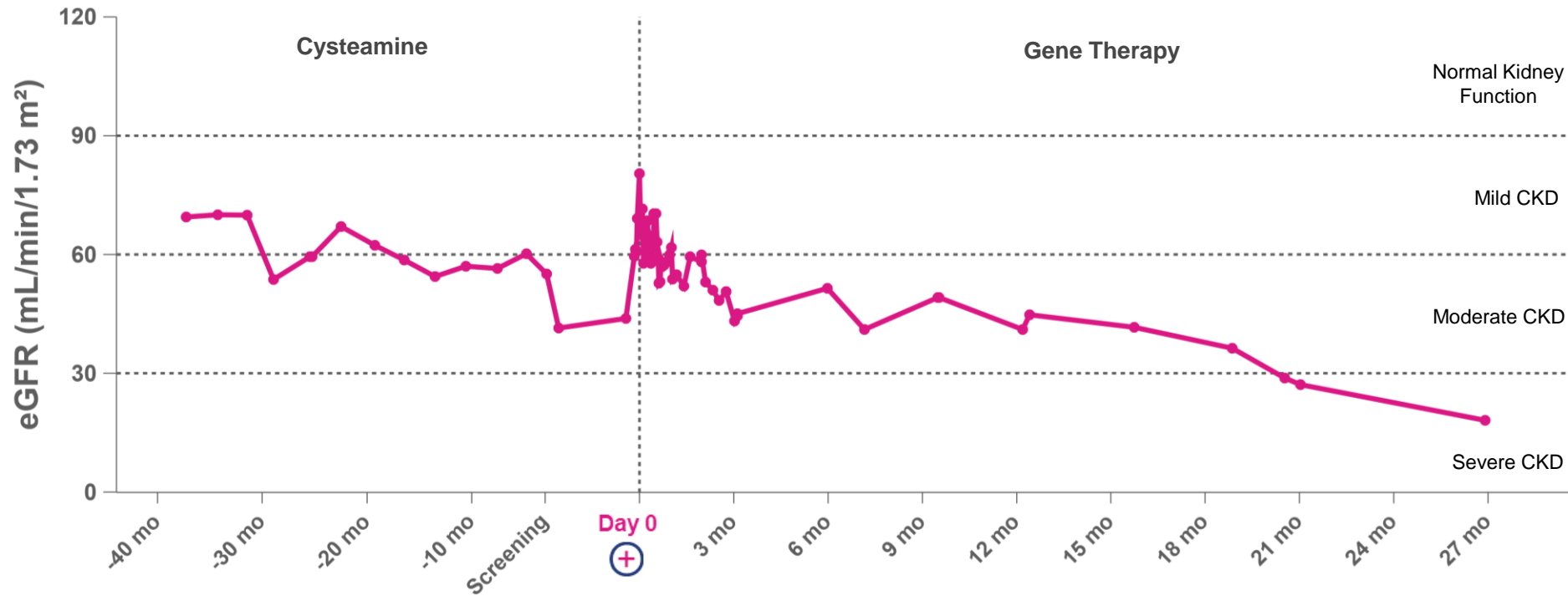
Bengali et al, PLOS ONE 2021

3D Crystal Reconstruction



PATIENT 1: KIDNEY FUNCTION

Entered trial with progressive kidney disease (eGFR of 48), decline accelerates in line with natural history

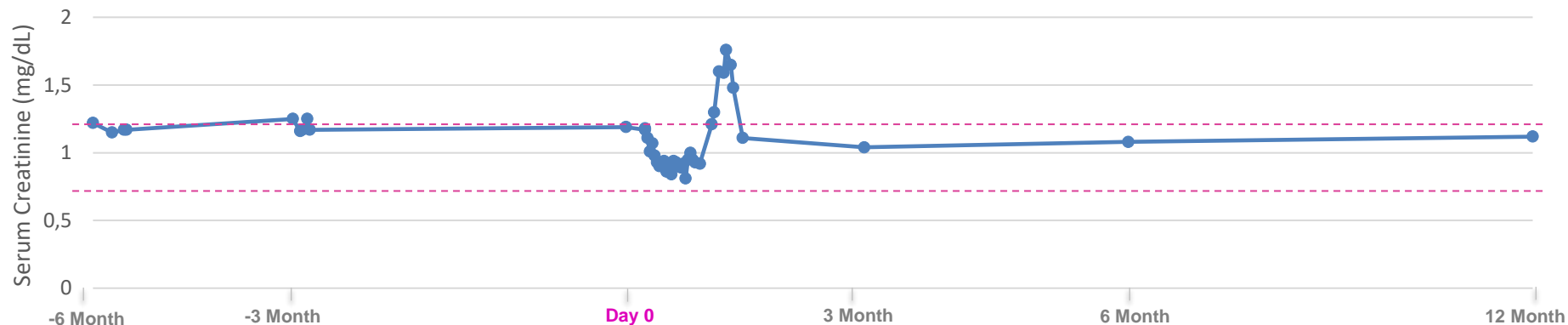


PRELIMINARY DATA

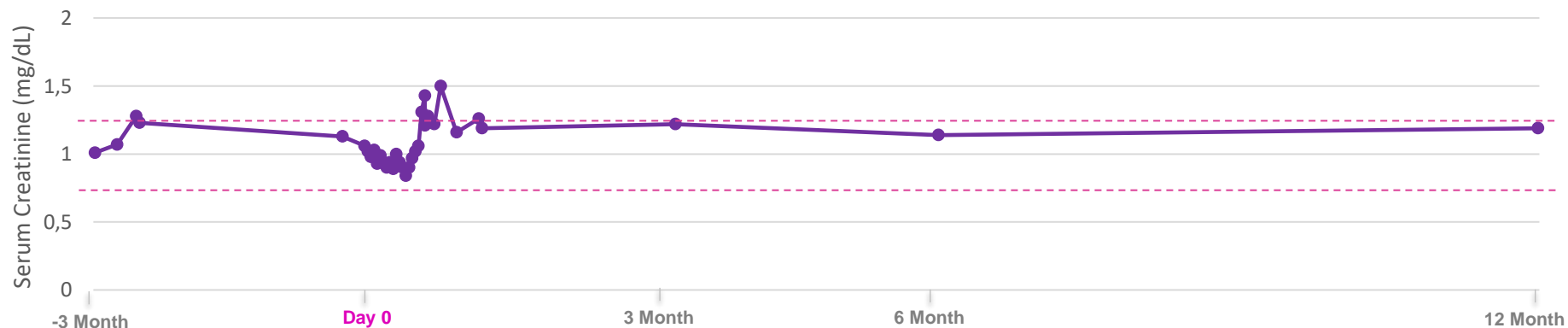
eGFR: Estimated Glomerular Filtration Rate; eGFR calculated using CKD-EPI formula;

PATIENT 2 AND 3 – KIDNEY FUNCTION

Patient 2 - Serum Creatinine (mg/dL) Normal Range: 0.7 - 1.2



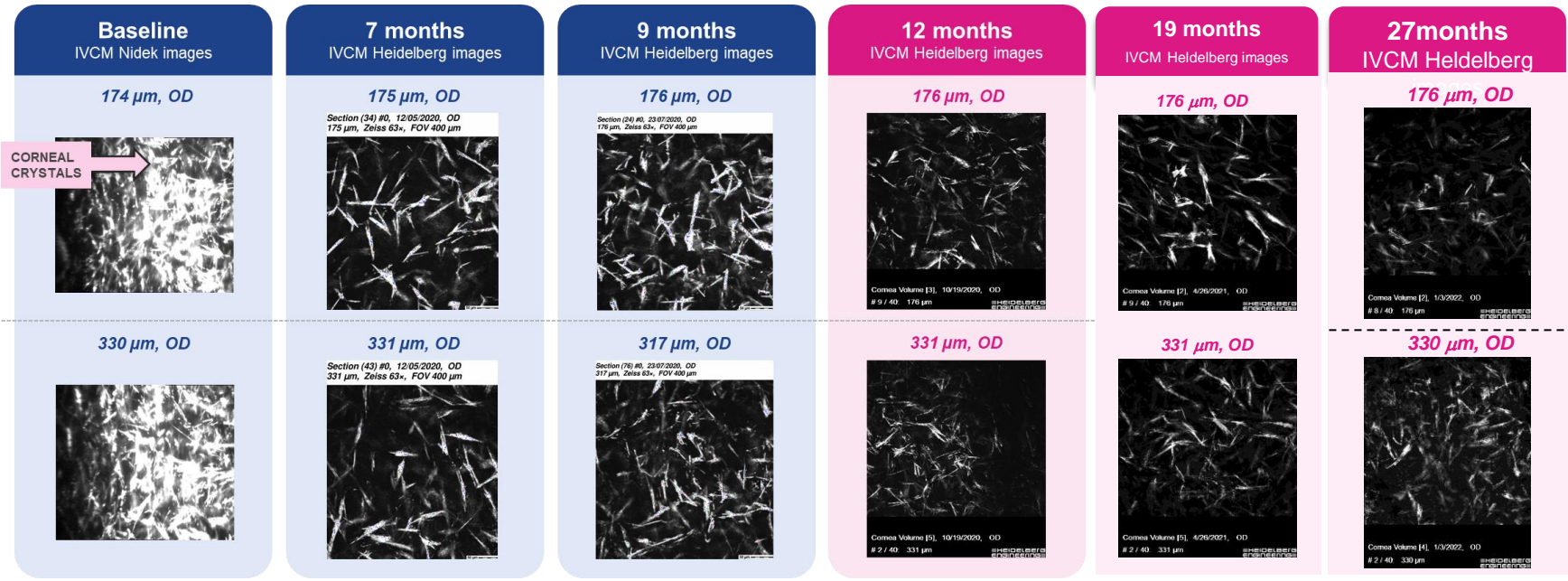
Patient 3 - Serum Creatinine (mg/dL) Normal Range 0.7 - 1.2



PATIENT 1 – TISSUE CYSTINE CRYSTALS IN THE CORNEA

Front of cornea

Back of cornea



Score range: 1-5 where 1 is no photophobia and 5 is severe

Photophobia Grade (Patient reported)	
Pre-Conditioning	3
3 Months PT	Moderate
12 Months PT	1
18 Months PT	3
24 Months PT	1

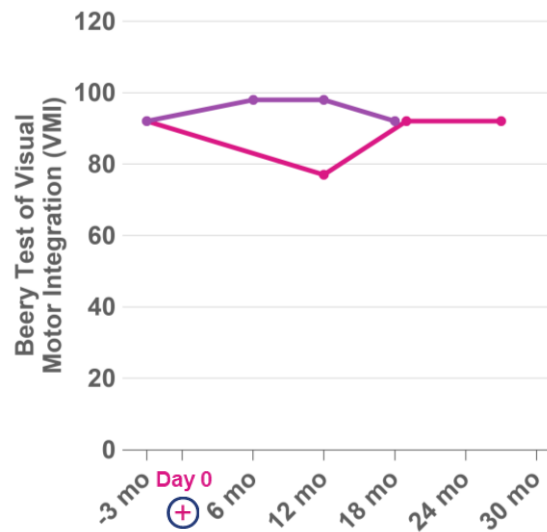
Preliminary scoring
performed by
Dr. Hong Liang,
CNRS, Paris, France

Eye layers	OD		OS	
	Baseline	12 months	Baseline	12 months
Anterior Stroma	4	3	4	1.86
Middle Stroma	4	3	4	1.71
Posterior Stroma	4	2.13	4	2

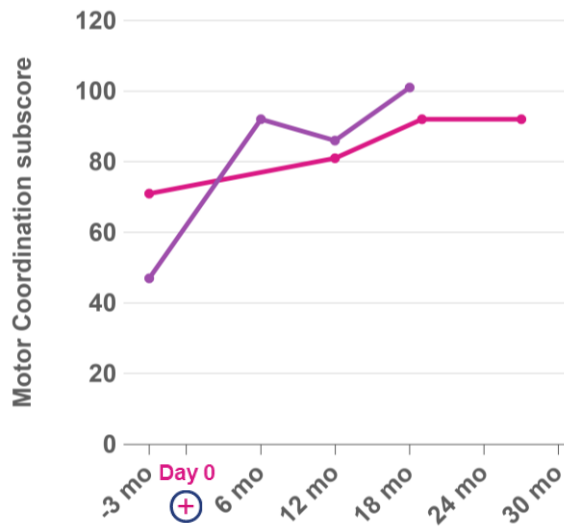
Scoring instructions: for each layer, assign a score of 0-4, where 0=no crystal; 1 <25%; 2=25-50%; 3=50-75%; 4>75%; Liang et al., IOVS 2015

Improvement in motor coordination and visual perception observed post-gene therapy

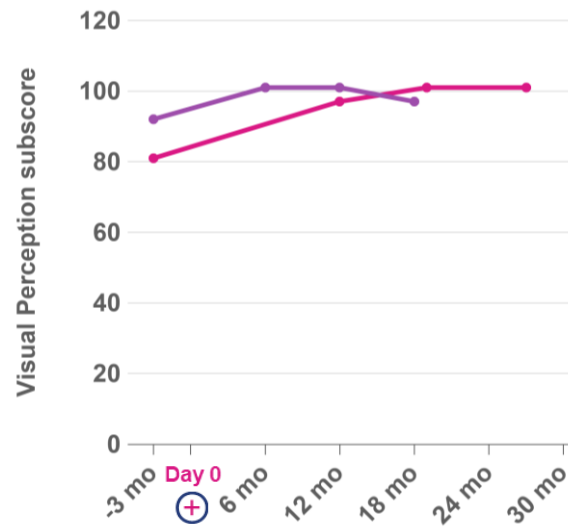
Patient 1 Patient 3

Beery Test of Visual
Motor Integration (VMI)

Motor coordination subscore



Visual perception subscore

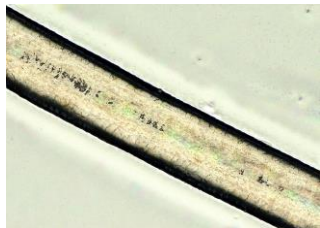


PRELIMINARY DATA

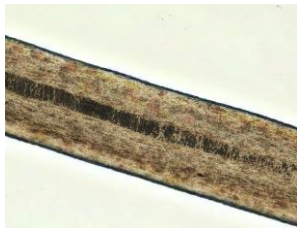
The Beery – Buktenica Developmental Test of Visual Motor Integration (Beery VMI) [6th edition] is a standardized test evaluating the ability of the brain to interpret and translate visual information into an exact motor response

EXPLORATORY ENDPOINT: HAIR, SKIN AND EYE COLOR

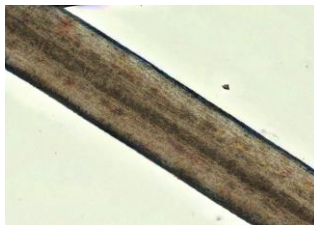
12 Months PT



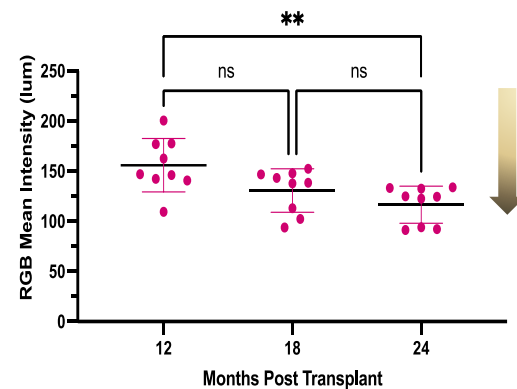
18 Months PT



24 Months PT



CT.001 Hair color – RGB intensity



Baseline



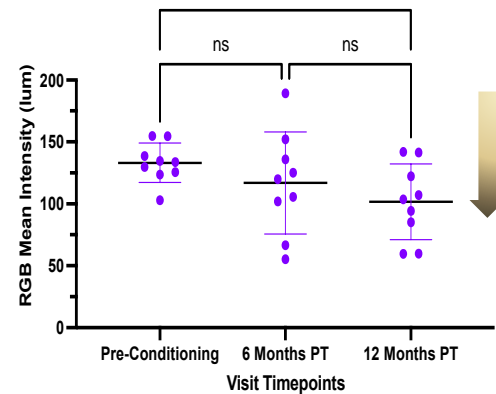
6 Months PT



12 Months PT












CT.005 Hair color – RGB intensity



PATIENTS 1- 5

All patients continue to be oral cysteamine-independent
Patient #1 out 2+ years

	PATIENT	MONTHS OFF CYSTEAMINE PILLS AND EYE DROPS POST CTNS-RD-04 INFUSION	CURRENT STATUS
cysteamine pills	PATIENT 1	 31	OFF
	PATIENT 2	 22	OFF
	PATIENT 3	 17	OFF
	PATIENT 4	 5	OFF
	PATIENT 5	 1	OFF
cysteamine eye drops	PATIENT 1	 31	OFF
	PATIENT 2	 13	ON (patient restarted July 2021)
	PATIENT 3	 17	OFF
	PATIENT 4	Was not on cysteamine eye drops prior to infusion	OFF
	PATIENT 5	 1	OFF

Note: All 5 patients remain off cysteamine pills. Patients 1 and 3 remain off cysteamine eye drops. Patient 2 elected to re-start cysteamine eyedrops; Patients 2, 3 and 5 stopped cysteamine eye drops 1-month post-transplant (per protocol); Patient 1 stopped cysteamine eye drops prior to baseline; Data as of May 6, 2022



ACKNOWLEDGEMENTS



Department of Pediatrics Division of Genetics

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Maulik Panchal
Anne Sawyers
Imama Ahmed
Priyanka Mishra
Rafael Badell Grau
Veenita Khare
Anusha Sivakumar
Thi Le
Alexander Silva

Former members

Celine Rocca
Laura Hernandez
Spencer Goodman
Tatiana Lobry
Marya Bengali
Peter Hevezi, Ph.D
Swati Naphade, PhD
Carlos Castellanos
Betty Cabrera
Frank Harrison
Joseph Rainaldi
Athena Lau
Peter Hevezi, Ph.D
Brian A. Yeagy, PhD
Robert Cano
Joseph Haquang
Meisha Khan



UNIVERSITY of CALIFORNIA, SAN DIEGO
SCHOOL OF MEDICINE



The Cystinosis Stem Cell and Gene Therapy Consortium members

Bruce Barshop, MD – Theodore Ball, MD – Natalie Afshari, MD –
Magdelene Dohil, MD – Ranjan Dohil – Nadine Benador, MD – Robert
Mak, MD – Doris Trauner, MD



UC San Diego Health

CIRM Alpha Stem Cell Clinic

UC San Diego Health

Sanford Stem Cell Clinical Center

UC San Diego Health



Medical Personnel
Patients

UCLA

Donald B. Kohn, MD

Julian Midgley, MD

Alberta Children's Hospital

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and Human Services

