# Neuronal Ceroid Lipofuscinose
# Eksperimentell behandling
## 9. mars 2021

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# Neuronal Ceroid Lipofuscinose

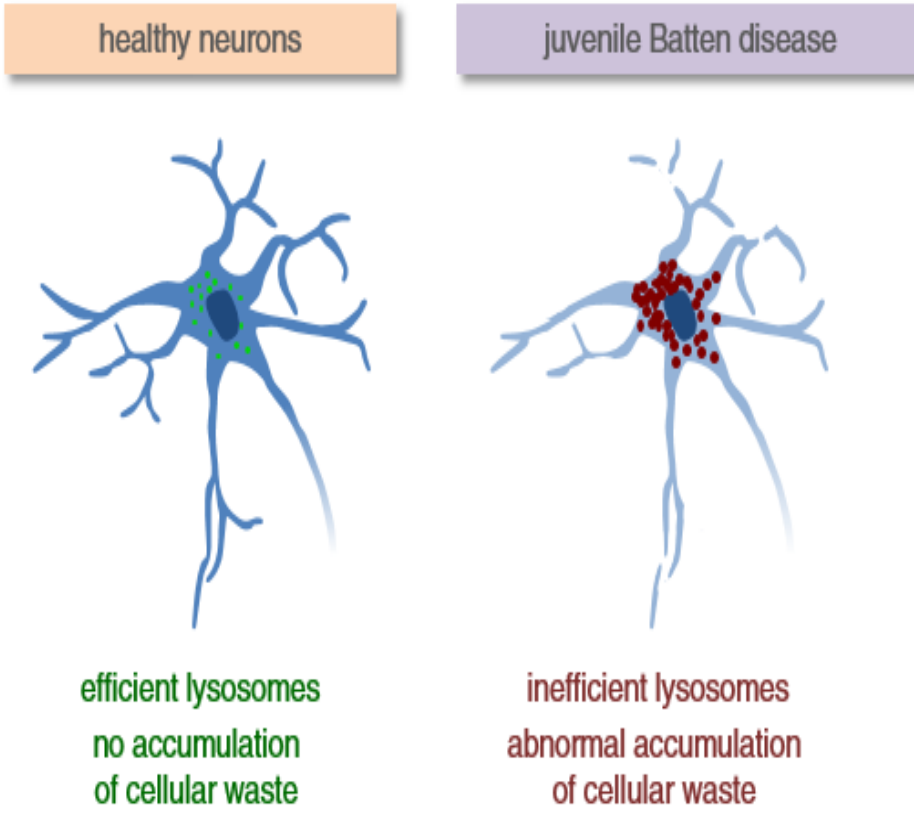
- Hyppigste arvelige, medfødte stoffskiftesykdom som primært rammer sentralnervesystemet
- Lysosomal avleiringssykdom
  - gulfargede fettforbindelser som autofluoriserer
    - ceroid og lipofuscin
- NCL betegner flere ulike genetiske lysosomale avleiringssykdommer
- Autosomalt rescessivt arvelig
- Monogen arv
- Felles:
  - Synstap
  - Epilepsi
  - Demensutvikling
  - avleiring av autofluoriserende lipofuscin i cellene.

- Sykdomsmekanismene komplekse og ikke helt ut forstått
  - Endringer i intracellulær trafficking
  - Autofagi
  - Fettstoffskiftet
  - Immunsystemet
    - Nevroinflammasjon

## *Sykdomsutvikling (på cellenivå i hjernen)*

- Akkumulering av avfallstoffer i cellene
  - Økt produksjon
  - Redusert nedbryting

- ***Tap av nerveceller***




*Picture from: https://medicalxpress.com/news/2017-02-reveals-strategy-potentially-juvenile-batten.html*

*Magnar Bjørås,*
*UIO/NTNU*

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- Første sykdoms-gen identifisert i 1995
- April 2015
  - 14  gen beskrevet
  - Nesten 450 forskjellige mutasjoner
- Alle genene beskrevet i NCL Mutation Base
  - (http://www.ucl.ac.uk/ncl)
- Alle NCL-genene ligger på autosomer
- En bestem genotype knyttet til de fleste NCL-genene med totalt tap av genfunksjon, med mildere mutasjoner som gir sykdom med mer protrahert forløp.
- Allikevel ikke totalt overlapp mellom genotype og phenotype

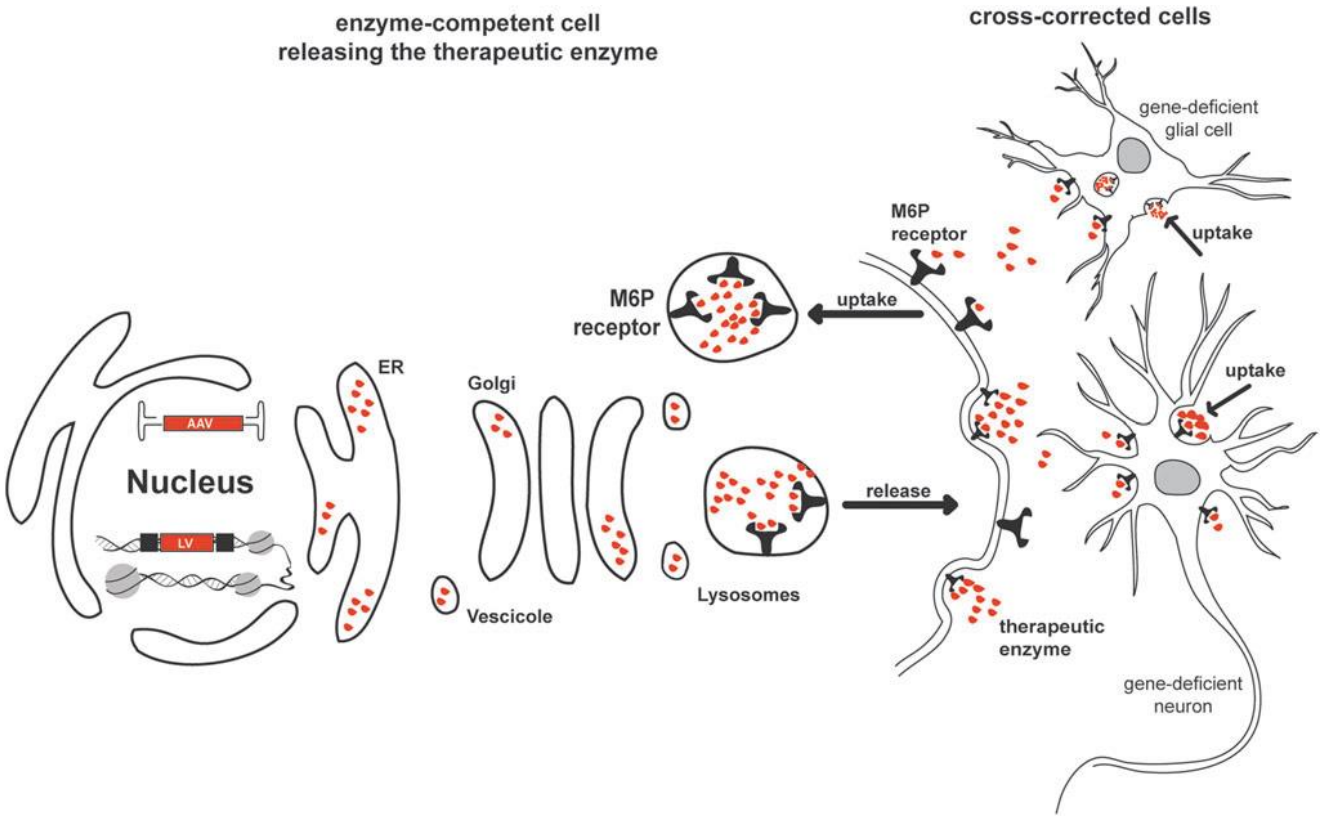
# To «grupper»

- Mutasjonen fører til
-
  - enzym i cellemembranen virker dårlig
  - løselig enzym blir affisert. Løselige lysosomale enzymer blir utskilt til rommet mellom cellene, og kan bli tatt opp igjen av samme celle eller andre celler.
    - Disse er mer tilgjengelig for behandling (cross-correction)

- Løselig enzym
  - CLN1, CLN2, CLN4, CLN5, CLN10, CLN11, CLN13, CLN14

- Protein som sitter i membranen (transmembran)
  - **CLN3**, CLN6, CLN7, CLN8, CLN12

# Cross-correction




*Polett & Biffi; Hum Gen Ther 30,10*

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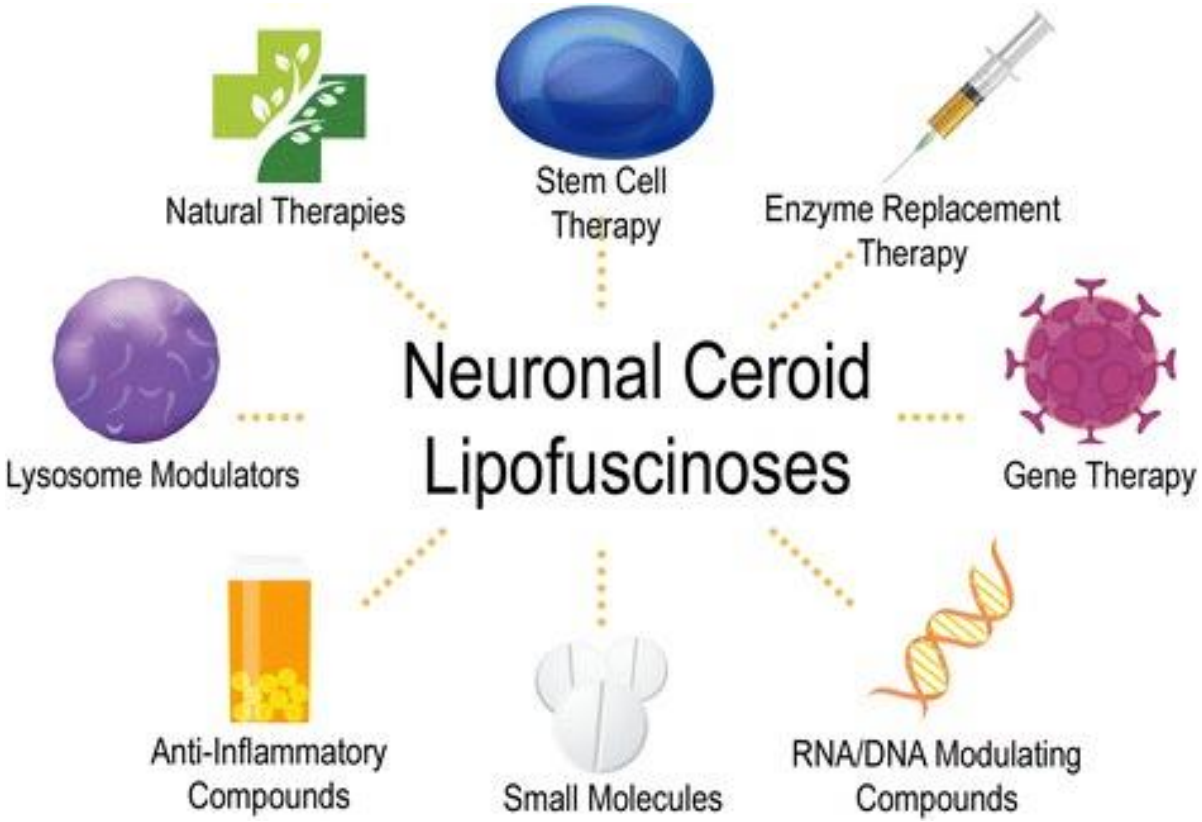


*Orphanet J Rare Dis.* 2016; 11: 40.

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# Årsaksrettete behandlinger

- Stamcellebehandling
- ERT
  - Enzyme Replacement Therapy
- **Genterapi**
- RNA/DNA modullering
- Behandling med små molekyler
- Anti-inflammatorisk behandling

# Stamcellebehandling

- Teoretisk kan stamcelle-behandling virke på to (tre) måter
  - ved at stamcellene produserer enzymet som mangler og at dette tas opp av andre celler (cross-correction)
  - ved at stamcellen differensierer og erstatter personens egne (syke) celler.
  - Redusere inflammasjonen

# Cellebehandling

- Benmargstransplantasjon/navlesnorceller
  - Flere dyremodeller har vist varierende effekt
  - En klinisk studie på CLN1 (3 pas): noe forsinket sykdomsutvikling
- Nevrale stamceller
  - 1 fase 1 studie på seks pas med CLN1 og CLN2
    - Behandlingen sikker og gjennomførbar
    - Ingen effekt på sykdomsutviklingen
    - Donorcellene i liten grad «slått seg til»

# Stamcellebehandling

- Mesenchymale stamceller
  - Forsøkt i dyremodell uten sikker effekt

- Neurale celler
  - To musemodeller (CLN8 og CLN6)
  - Embryonale stamceller differensiert til nerveceller
  - Noe effekt i CLN8-modellen (øye)
    - Neurotrope faktorer

# Stamcellebehandling

- Pågående studie Duke University; North Carolina
  - Umbilical Cord Blood Transplantation
- *UCB Transplant of Inherited Metabolic Diseases With Administration of Intrathecal UCB Derived Oligodendrocyte-Like Cells (DUOC-01)* https://www.clinicaltrials.gov/ct2/show/NCT02254863?cond=Batten+Disease&draw=5&rank=31
- Foreløpige resultater sier at to pasienter (NCL3) har normal nevrokognisjon, ingen kramper og trenger kun tilrettelegging for dårlig syn på skolen
  - Stem Cells Transl Med. 2019 Sep; 8(Suppl Suppl 1): S12
  - (**https://www.facebook.com/groups/714949675303536**)

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# ERT – Enzyme Replacement Therapy

- Tilførsel av enzym har vist seg å ha effekt ved andre lysosomale avleiringssykdommer.
- Utfordringer
  - Enzym kan vanskelig komme inn i hjernen på grunn av blod-hjerne-barriæren.
  - Nødvendig å tilføre enzymet i cerebrospinalvæsken, enten direkte inn i sideventriklene (Ommaya) eller intrathecalt (ved stikk i ryggen).
  - Å få laget et helt ”rent” enzym
  - At kroppen lager antistoff mot enzymet og anafylaktiske (allergiske) reaksjoner
  - Toleranseutvikling (medikamentet slutter å virke etter en tid).
  - Enzymet må tilføres jevnlig, noe som medfører store kostnader.

# Cerliponase alfa

- ERT
- 300 mg hver 14.dag
- Administreres i Ommaya reservoar over 4 timer
- Studie
  - 23 pasienter hvorav 20 responderte
  - 3 infeksjoner, ellers få bivirkninger
  - Oppfølgingstid 4 år

- Forsinker/stopper utviklingen av sykdommen

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Study of Intraventricular Cerliponase Alfa for CLN2 Disease

Angela Schulz, M.D., Temitayo Ajayi, M.D., Nicola Specchio, M.D., Ph.D., Emily de Los Reyes, M.D., Paul Gissen, M.B., Ch.B., Ph.D., Douglas Ballon, Ph.D., Jonathan P. Dyke, Ph.D., Heather Cahan, M.D., Peter Slasor, Sc.D., David Jacoby, M.D., Ph.D., and Alfried Kohlschütter, M.D., for the CLN2 Study Group*

From the Department of Pediatrics, University Medical Center Hamburg–Eppendorf, Hamburg, Germany (A.S., A.K.); BioMarin Pharmaceutical, Novato, CA (T.A., H.C., P.S., D.J.J.); the Department of Neuroscience, Bambino Gesù Children's Hospital, IRCCS, Rome (N.S.); Nationwide Children's Hospital and Ohio State University, Columbus (E.L.R.); UCL Great Ormond Street Institute of Child Health, London (P.G.); and the Citigroup Biomedical Imaging Center, Departments of Radiology and Genetic Medicine, Weill Cornell Medical College, New York (D.B., J.P.D.). Address reprint requests to Dr. Schulz at the Department of Pediatrics, University Medical Center Hamburg–Eppendorf, Martinistrasse 52, Hamburg 20246, Germany, or at an.schulz@uke.de.

*A list of investigators in the CLN2 Study Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on April 24, 2018, and updated on May 17, 2018, at NEJM.org.

N Engl J Med 2018;378:1898-907.
DOI: 10.1056/NEJMoa1712649


ABSTRACT

BACKGROUND

Recombinant human tripeptidyl peptidase 1 (cerliponase alfa) is an enzyme-replacement therapy that has been developed to treat neuronal ceroid lipofuscinosis type 2 (CLN2) disease, a rare lysosomal disorder that causes progressive dementia in children.

METHODS

In a multicenter, open-label study, we evaluated the effect of intraventricular infusion of cerliponase alfa every 2 weeks in children with CLN2 disease who were between the ages of 3 and 16 years. Treatment was initiated at a dose of 30 mg, 100 mg, or 300 mg; all the patients then received the 300-mg dose for at least 96 weeks. The primary outcome was the time until a 2-point decline in the score on the motor and language domains of the CLN2 Clinical Rating Scale (which ranges from 0 to 6, with 0 representing no function and 3 representing normal function in each of the two domains), which was compared with the time until a 2-point decline in 42 historical controls. We also compared the rate of decline in the motor–language score between the two groups, using data from baseline to the last assessment with a score of more than 0, divided by the length of follow-up (in units of 48 weeks).

RESULTS

Twenty-four patients were enrolled, 23 of whom constituted the efficacy population. The median time until a 2-point decline in the motor–language score was not reached for treated patients and was 345 days for historical controls. The mean (±SD) unadjusted rate of decline in the motor–language score per 48-week period was 0.27±0.35 points in treated patients and 2.12±0.98 points in 42 historical controls (mean difference, 1.85; P<0.001). Common adverse events included convulsions, pyrexia, vomiting, hypersensitivity reactions, and failure of the intraventricular device. In 2 patients, infections developed in the intraventricular device that was used to administer the infusion, which required antibiotic treatment and device replacement.

CONCLUSIONS

Intraventricular infusion of cerliponase alfa in patients with CLN2 disease resulted in less decline in motor and language function than that in historical controls. Serious adverse events included failure of the intraventricular device and device-related infections. (Funded by BioMarin Pharmaceutical and others; CLN2 ClinicalTrials.gov numbers, NCT01907087 and NCT02485899.)

# På bakgrunn av historiske data

- Godkjent av FDA/EMA i mai 2017
- Ingen restriksjoner på hvem som kan få medisinen
- Pris?
  - ” Brineura will carry a list price of $27,000 per carton, with patients requiring one carton every other week, according to BioMarin execs. That's a total of $702,000 per year before any discounts. “
- Foreløpig ikke godkjent til bruk i Norge

# Tilbud om behandling

- Viktig å stille diagnosen tidlig!!
- Ved andre krampeanfall har barnet allerede utviklet ataksi

- Bør alle barn med forsinket språkutvikling utredes?
- Alle barn med debut av epilepsi i 2-4 års alder?
- Inn i Screeningprogrammet?

- Hvordan få behandlingen godkjent?

# Langtidsprognose

- Lysosomal avleiringssykdom
- Når barna lever lengre, vil de da få symptomer fra andre organsystem?
- Vil de ha behov for i.v. behandling i tillegg?

# Hva er genterapi?

***Behandler sykdommer ved å***

- ***Korrigere (redigere) en gen-defekt (eks behandling av genetiske sykdommer)***
- ***Modifisere gen-uttrykk (eks. kreftbehandling)***

## Strategier for genterapi

- ***Øke ekspresjon av genprodukter (proteiner) i celler hvor mangel på produksjon av spesifikke proteiner forårsaker sykdom***
- ***Målrettet dreping av sykdomsfremkallende celler (f.eks. ved immunterapi)***
- ***Målrettet redigering av sykdomsfremkallende mutasjoner i gener (f. eks. ved CRISPR som er et høypresisjonsverktøy for genredigering)***
- ***Målrettet hemming av sykdomsfremkallende gener (f. eks. i kreftceller)***

# Typer genterapibehandling

## Ex vivo genterapi

***Tar celler ut av kroppen for redigering og overfører deretter de redigerte cellene tilbake til pasienten***

## In vivo genterapi

- ***Introdusere et gen i ved hjelp av et virus med redusert virulens (svekket virus) som vektor.***
- ***Eneste mulighet for pasienter når man ikke kan ta celler ut av kroppen for redigering og deretter føre de friske cellene tilbake til pasienten***

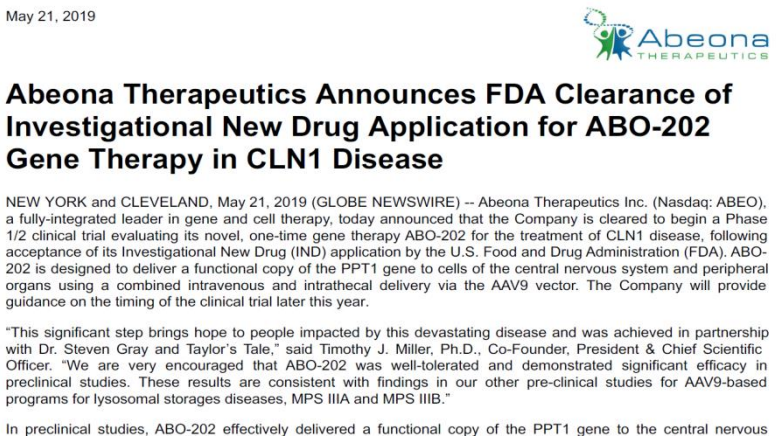
# *Virus i genterapi*

- ***Virus kan brukes for å transportere friske gener inn i menneskeceller med defekte gener***
- ***Virus brukt i genterapi er konstruert slik at de er ufarlige for menneske celler men tas effektivt opp i menneskeceller***
- ***Adeno assosiert virus (AAV) er det mest brukte viruset i genterapi***
- ***AAV forårsaker ikke sykdom***
- ***AAV tas opp i celler som ikke deler seg (eks. hjerneceller)***

***AAV med friskt gen overføres til menneske celle***

# Genterapi – v/NCL løselig enzym

- CLN1
  - Musestudier med forskjellige vektorer:
    - AAV2, AAV5 og AAV9
    - Evt i kombinasjon med andre terapiformer
    - Kombinert intrathecal og intraventrikulær injeksjon mest lovende
    - Langsommere progresjon av sykdommen



May 21, 2019

Abeona THERAPEUTICS

**Abeona Therapeutics Announces FDA Clearance of Investigational New Drug Application for ABO-202 Gene Therapy in CLN1 Disease**

NEW YORK and CLEVELAND, May 21, 2019 (GLOBE NEWSWIRE) -- Abeona Therapeutics Inc. (Nasdaq: ABEO), a fully-integrated leader in gene and cell therapy, today announced that the Company is cleared to begin a Phase 1/2 clinical trial evaluating its novel, one-time gene therapy ABO-202 for the treatment of CLN1 disease, following acceptance of its Investigational New Drug (IND) application by the U.S. Food and Drug Administration (FDA). ABO-202 is designed to deliver a functional copy of the PPT1 gene to cells of the central nervous system and peripheral organs using a combined intravenous and intrathecal delivery via the AAV9 vector. The Company will provide guidance on the timing of the clinical trial later this year.

"This significant step brings hope to people impacted by this devastating disease and was achieved in partnership with Dr. Steven Gray and Taylor's Tale," said Timothy J. Miller, Ph.D., Co-Founder, President & Chief Scientific Officer. "We are very encouraged that ABO-202 was well-tolerated and demonstrated significant efficacy in preclinical studies. These results are consistent with findings in our other pre-clinical studies for AAV9-based programs for lysosomal storages diseases, MPS IIIA and MPS IIIB."

In preclinical studies, ABO-202 effectively delivered a functional copy of the PPT1 gene to the central nervous

*ABEONA THERAPEUTICS AND TAYSHA GENE THERAPIES HAVE ENTERED INTO AGREEMENTS CONCERNING ABO-202, AN INVESTIGATIVE GENE THERAPY FOR INFANTILE BATTEN DISEASE. A GOAL IS TO ADVANCE THE GENE THERAPY INTO A PHASE 1/2 CLINICAL TRIAL IN PATIENTS.*

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- CLN2
  - Ti pasienter fikk AAV2-TPP1
  - 12 injeksjoner corticalt
  - Noe effekt av behandlingen
  - AAV2 neppe beste vektor (Worgall et al., 2008).
  - Andre vektorer utprøvd i dyremodeller
  - To studier registrert i Clinical Trials; avsluttet men ingen resultater publisert
- CLN5
  - AAV9-CLN5 forsøkt i sauemodell med svært lovende resultat
- CLN10 og 11
  - Dyremodeller
  - CLN11: sterk immunrespons

# Genterapi - membranprotein

- Cross-correction  neppe mulig

- Krever at et stort antall celler i CNS må transduseres

NIH U.S. National Library of Medicine
ClinicalTrials.gov

- Gene Therapy for Children With CLN6 Batten Disease

| | |
|---|---|
| Study Type : | Interventional (Clinical Trial) |
| Actual Enrollment : | 13 participants |
| Intervention Model: | Single Group Assignment |
| Masking: | None (Open Label) |
| Primary Purpose: | Treatment |
| Official Title: | Phase I/IIa Gene Transfer Clinical Trial for Variant Late Infantile Neuronal Ceroid Lipofuscinosis, Delivering the CLN6 Gene by Self-Complementary AAV9 |
| Actual Study Start Date : | March 2016 |
| Estimated Primary Completion Date : | October 2021 |
| Estimated Study Completion Date : | December 2021 |

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# Amicus Therapeutics, Inc. (NASDAQ:FOLD)

- Initiated the phase 1/2 clinical trial of AAV9-CLN3 (adeno associated virus serotype 9-CLN3).
- Goal: evaluation of effectiveness and safety in children suffering from CLN3 Batten Disease.

Onboarding CLN3 children of 3 and 10 years old for clinical study in two groups:

- First group**:** administration of a **lower dose** of AAV9-CLN3 → After evaluating the outcome of the children in the first group:
- Second group: **higher dosage** of AAV9-CLN3.

The current study will last for **three years**.

The company has not observed any serious side effects during the administration of the drug in the first month. *Published on January 4th, 2019*

Initial data from the Phase 1/2 CLN3 study expected in early 2021

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LB-10

# An Open-Label, Phase 1/2a, AAV9-*CLN3* Gene Transfer Clinical Trial for Juvenile Neuronal Ceroid Lipofuscinosis

de los Reyes E,[1] Aylward S,[1] Islam M,[1] Meyer K,[1] Stefanelli E,[2] Jiang H,[2] Weimer J,[2,3] Goldman M[2]

[1]Nationwide Children's Hospital, Columbus, OH, USA; [2]Amicus Therapeutics, Inc., Cranbury, NJ, USA; [3]Pediatrics and Rare Diseases Group, Sanford Research, Sioux Falls, SD, USA

## BACKGROUND

- Pathogenic variants in *CLN3* cause juvenile *CLN3* Batten disease or classic juvenile neuronal ceroid lipofuscinosis (JNCL), a severe neurodegenerative disorder with childhood onset (between 4 and 7 years of age) that leads to blindness, motor impairment, learning difficulties, epilepsy, and ultimately premature death between 20 and 30 years of age[1]
- Currently, there is no therapy for JNCL
- Because pathogenic *CLN3* variants predominantly cause a loss or reduced level of functional protein, a promising therapeutic approach is gene transfer of corrected *CLN3*, leading to production of functional protein[2]

## OBJECTIVE

- To report preliminary results from the first clinical gene therapy study (AT-GTX-502; NCT03770572) of classic JNCL currently underway to evaluate the safety and efficacy of *CLN3* gene transfer via an adenovirus-associated virus serotype 9 vector, an investigational therapy

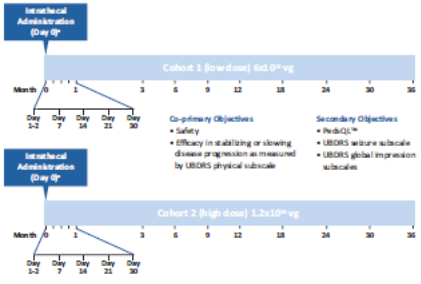
## METHODS

- This open-label, dose-escalation, phase 1/2a study included a low-dose and a high-dose cohort (**Figure 1**)
  - The high-dose cohort was dosed ≥6 weeks later than the low-dose cohort to allow a safety review of the low-dose cohort
- Safety assessments included dose-limiting toxicity, adverse events (AEs), vital signs, physical and neurological examination, blood and urine laboratory parameters, electrocardiography, immunologic assessments, and viral shedding
- The Unified Batten Disease Rating Scale (UBDRS) was developed specifically for monitoring disease progression of JNCL and includes physical, behavioral, seizure, and capability subscales.[3] The primary efficacy assessment for this study was the UBDRS physical subscale (**Table 1**)
- The preliminary results are reported as descriptive data; no statistical analysis was conducted for this interim analysis
- The data cutoff date was August 11, 2020

**Figure 1. Study Design**

**Screening**
(Up to Day −30)

- Diagnosis of juvenile *CLN3* Batten disease as determined by genotyping
- Aged ≥3 to <11 years
- UBDRS physical score ≤7
- Able to walk independently for ≥50 ft




PedsQL™=Pediatric Quality of Life Inventory; UBDRS=Unified Batten Disease Rating Scale; vg=vector genomes.
aPatients were administered prophylactic steroids starting on Day −1.

**Table 1. UBDRS Physical Subscale**

| Category | Item | | Scoring |
|---|---|---|---|
| Vision | • Visual acuity | | • Each item scored 0-4<br>0 = normal (or abnormality absent)<br>4 = severely impaired<br>• Bilateral items scored separately (28 items total)<br>• Maximum total score = 112<br>• Higher score indicates greater physical impairment |
| Motor | • Gait<br>• Hand tapping (bilateral)<br>• Heel stomping (bilateral) | • Retropulsion pull test<br>• Finger-to-nose dysmetria | |
| Speech | • Speech clarity | • Abnormal repetitive speech sounds | |
| Bulbar function | • Tongue protrusion | | |
| Tone | • Tone of neck<br>• Tone of arms (bilateral)<br>• Tone of legs (bilateral) | • Upper extremity maximal dystonia (bilateral)<br>• Arm strength (bilateral)<br>• Leg strength (bilateral) | |
| Abnormal movement | • Appendicular chorea<br>• Rest tremor<br>• Action tremor<br>• Myoclonus | • Normal spontaneous movement<br>• Motor tics or stereotypies | |

## RESULTS

### Baseline Characteristics

- Four subjects were enrolled in the study and received a single intrathecal injection of AT-GTX-502: 3 received $6\times10^{13}$ vector genomes (vg) (low dose) and 1 received $1.2\times10^{14}$ vg (high dose), based on quantitative polymerase chain reaction
- Demographic and baseline characteristics are shown in **Table 2**

**Table 2. Demographics and Baseline Characteristics**

| Dose | Subject | Sex | Genotype | Race | Age at Enrollment, months | Age at Symptom Onset, months | Duration in Study, months |
|---|---|---|---|---|---|---|---|
| Low | 1 | M | 1-kb deletion in *CLN3* (homozygous)a | White | 114 | 72 | 20.7 |
| Low | 2 | F | 1-kb deletion in *CLN3* (homozygous)a | White | 71 | 36 | 15.6 |
| Low | 3 | M | 1-kb deletion in *CLN3* (homozygous)a | White | 105 | 36 | 16.8 |
| High | 4 | M | 1-kb deletion in *CLN3* (homozygous)a | White | 120 | 79 | 8.7 |

aA 1.02-kb genomic deletion in *CLN3* is the most common variant in JNCL; the deletion covers 2 exons and the flanking intronic sequence and leads to the deletion of 217 base pairs of coding sequence, resulting in a truncated protein.[4]

### Safety

- AEs that occurred in ≥1 subjects are reported in **Table 3**
- Most AEs were mild or moderate and unrelated to AT-GTX-502
- Four AEs were considered related to AT-GTX-502; all were hepatic enzyme increases that resolved without sequelae
- There were 2 serious AEs, 1 of which was deemed AT-GTX-502-related (elevated alanine aminotransferase, grade 3) and resolved with steroid treatment after 3 months
  - The other serious AE was a grade 2 seizure, which was considered not related to treatment, but rather disease related
- There were no discontinuations in follow-up because of AEs
- There were no grade 4 or 5 (death) AEs

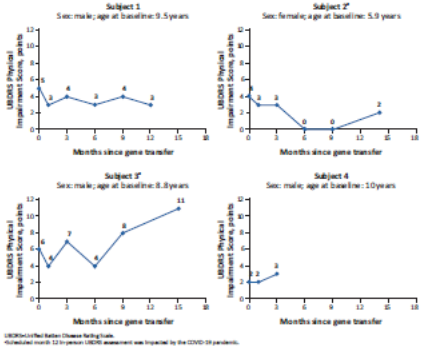
**Table 3. Adverse Events Occurring in ≥1 Patient**

| Adverse Event (preferred term) | Patients, n | Events, n |
|---|---|---|
| Vomiting | 4 | 9 |
| Headache | 4 | 6 |
| Nausea | 3 | 3 |
| Respiratory disorder | 2 | 4 |
| Back pain | 2 | 2 |
| Cough | 2 | 2 |
| Hepatic enzyme increased | 2 | 2 |
| Sinus bradycardia | 2 | 2 |

### Preliminary Efficacy

- UBDRS physical impairment scores have been recorded up to month 15 for 3 subjects in the low-dose cohort (**Figure 2**)
  - The only subject in the high-dose cohort had UBDRS evaluations up to month 3

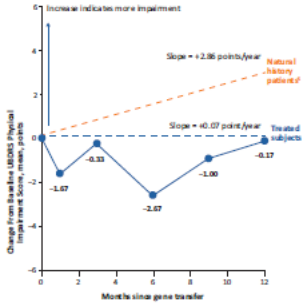
**Figure 2. UBDRS Physical Impairment Score Over Time**




UBDRS=Unified Batten Disease Rating Scale.
*Scheduled month 12 in-person UBDRS assessment was impacted by the COVID-19 pandemic.

- Mean (SD) yearly rate of change in UBDRS Physical Impairment score in the 3 subjects in the low-dose cohort was 0.07 (3.33) (**Figure 3**)
- In comparison, a historical natural history study of 82 patients with JNCL predicted an average increase of 2.86 points per year (95% CI, 2.27-3.45)[5]

**Figure 3. Mean Change From Baseline in UBDRS Physical Impairment Score in 3 Subjects in the Low-Dose Cohort Compared With Patients in the Natural History Study**




UBDRS=Unified Batten Disease Rating Scale.
The solid blue line shows the mean change from baseline in UBDRS Physical Impairment score in treated subjects. The dotted regression lines show the slopes of change from baseline for patients in the natural history study (orange) and treated subjects (blue), respectively.

## CONCLUSIONS

- The mean yearly rate of change in UBDRS Physical Impairment score in the 3 subjects with *CLN3* Batten disease receiving $6\times10^{13}$ vg of AT-GTX-502 was substantially lower than that expected for untreated patients based on historical natural history studies (0.07 vs 2.86 points/year), suggesting potentially early signs of disease stabilization
- Preliminary results suggest that AT-GTX-502 was generally well tolerated and support further evaluation

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5. Kwon JM et al. *Neurology*. 2011;77:1801-1807.

### Acknowledgments

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### Disclosures

ER has received consulting fees and grants from Amicus Therapeutics and BioMarin. SA has received research/salary support from Amicus Therapeutics and BioMarin. MI has received research/salary support from Amicus Therapeutics and holds stock/stock options in Abbott Laboratories, AbbVie, Eli Lilly, and Pfizer. KM and spouse have served on advisory boards and conducted contracted research for and received consulting fees from Alcyone; KM has also received royalties from Amicus Therapeutics; KM's spouse has conducted contracted research and received royalties from Audentes. ES, HJ, JW, and MG are employees of and hold stock/stock options in Amicus Therapeutics.

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*Safety analyses included data from four children, three who received the low dose and one treated at high dose. These analyses indicated AT-GTX-502 was safe and well-tolerated, with most common side effects either mild or moderate in severity and not related to treatment. Four reported side effects — all cases of elevated levels of liver enzymes — were deemed to be related to treatment, but all were resolved.

*Analyses of preliminary efficacy were based on data from three children in the low-dose at 15 months post-treatment, and the one high dose child who had been monitored for three months. These analyses showed that those given AT-GTX-502 at low dose had a mean change in the UBDRS Physical Impairment score of 0.07 at one year post-treatment, much lower than the expected annual increase of 2.86 points, based on published data of the disease's natural history in the absence of treatment. This suggests that AT-GTX-502 may help to slow disease progression.

*This Phase 1/2 trial is due to conclude in September 2023.

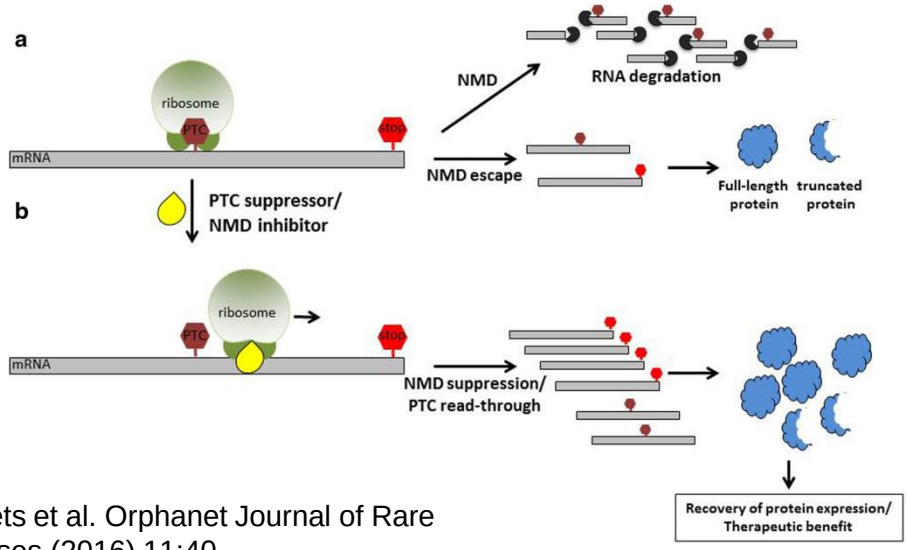
# Amicus Therapeutics, Inc. (NASDAQ:FOLD)

- Next Phase: 2021
- Include About 30 children
- Aiming to include OUS as a node to this study
- **Ongoing dicussions with Amicus**
- **Key points:**
  - ➢ **Natural history**
  - ➢ **Monitoring**
    - ✓ **Biomarkers**
    - ✓ **Cognitive tests**
    - ✓ **etc**

- CLN4
  - Annerledes enn de andre sykdommene
  - Dominant arvelig
  - Sannsynligvis «for mye protein»
  - Mulig behandling:
    - Slå ut genet

# RNA/DNA modullering

- RNA modullering
  - Antisense oligonucleotids (ASO) (CLN7; klinisk studie)
  - Non-sense suppresjon
  - Non-sense mediated decay inhibitors (NMD)




Geraets et al. Orphanet Journal of Rare Diseases (2016) 11:40

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- Behandling med små molekyler
  - Trehalose
    - Aktivator av TFEB; reduserer opphopning av lipofuscin i celle- og muse modell
    - Pre-klinisk studie mtp toxisitet;
      - I.v trehalose + p.o miglustat
    - Klinisk studie planlegges
  - PPAR-α agonist
    - **Polaryx** – **PLX-200 (**Gemfibrozil)
      (https://www.clinicaltrials.gov/ct2/show/NCT04637282?term=Polaryx&draw=2&rank=1)
      - Starter rekruttering i år; kun fra USA

# Anti-inflammatorisk behandling

- En studie på mykofenolat (CLN3)
  - Ingen klinisk effekt
- En studie på en kombinasjon av cystagon og N-acetylcystein
  - Liten eller ingen effekt

# Kombinasjonsbehandling

- Mange forskjellige behandlingsformer lovende effekter i pre-kliniske og kliniske studier
- Mulig at kombinasjon av to eller flere behandlingsformer enda mer effektivt
  - ERT og genterapi?
  - Genterapi og små-molekyler
  - Immunsuppresjon og stamcellebehandling?

# Utfordringer

- Cellebehandling
  - Behov for immunterapi
  - Cellen spres ikke tilstrekkelig
  - Generelt kun aktuelt for løselige enzymer
- ERT
  - Livslang behandling
  - Fare for infeksjon
  - Kun aktuelt for løselig enzym
  - Kun «lokal» effekt?

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# Utfordringer

- Genterapi
  - Antistoff mot vektor?
  - Immunterapi ved injeksjon?
  - «passe mengde enzym»
  - Er sykdommen selvgående når den først er startet?
  - Autoimmun komponent?
  - Systemisk/lokal effekt?

## CLN3 prosjekt

**Fagenhet for Laboratoriemedisin, NTNU**
**Klinikk for laboratoriemedisin, OUS**
**Barneklinikken, OUS**

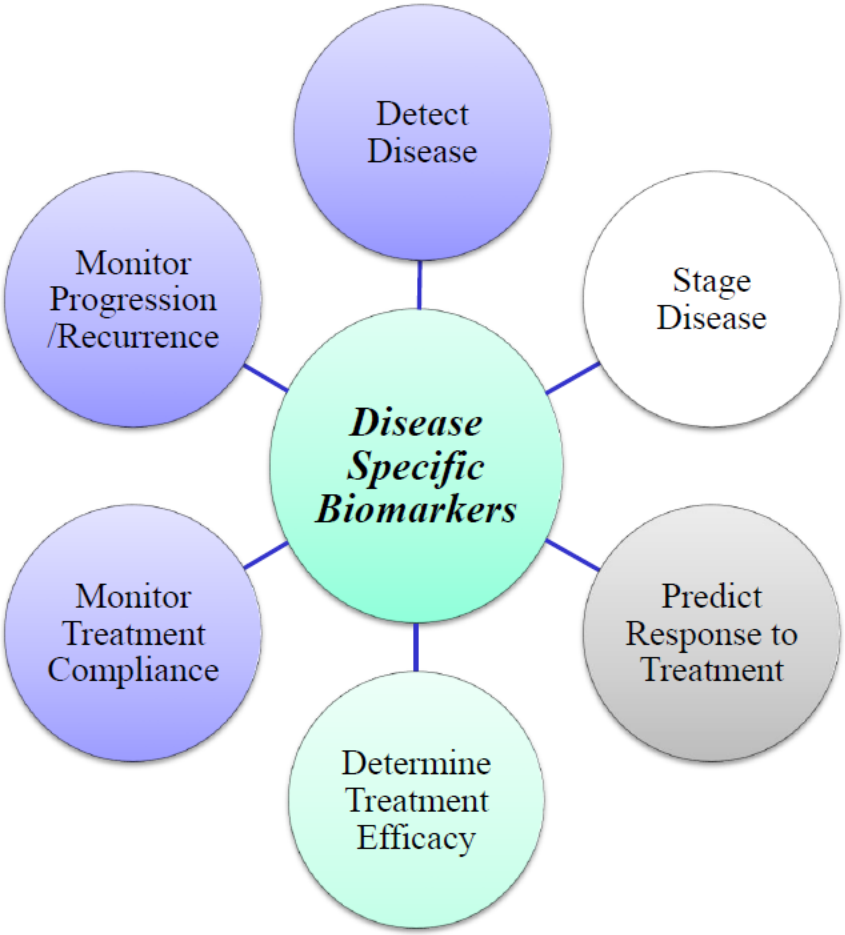
**Bjørås group:**

***Wei Wang***
***Ping JI***
***Borghild H Farsund***
***Erlend Ravlo***
***Mirta de Souza***

***Ingrid Helland, OUS***

**Takk for utmerket samarbeid med foreldre og barn i NCL foreningen!**


# *Biomarker: Indicator of specific biological or disease state*

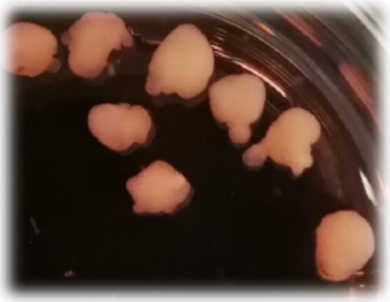



"A biomarker is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or a response to an exposure or intervention."

# Kan vi lage menneske hjerner i laboratoriet?

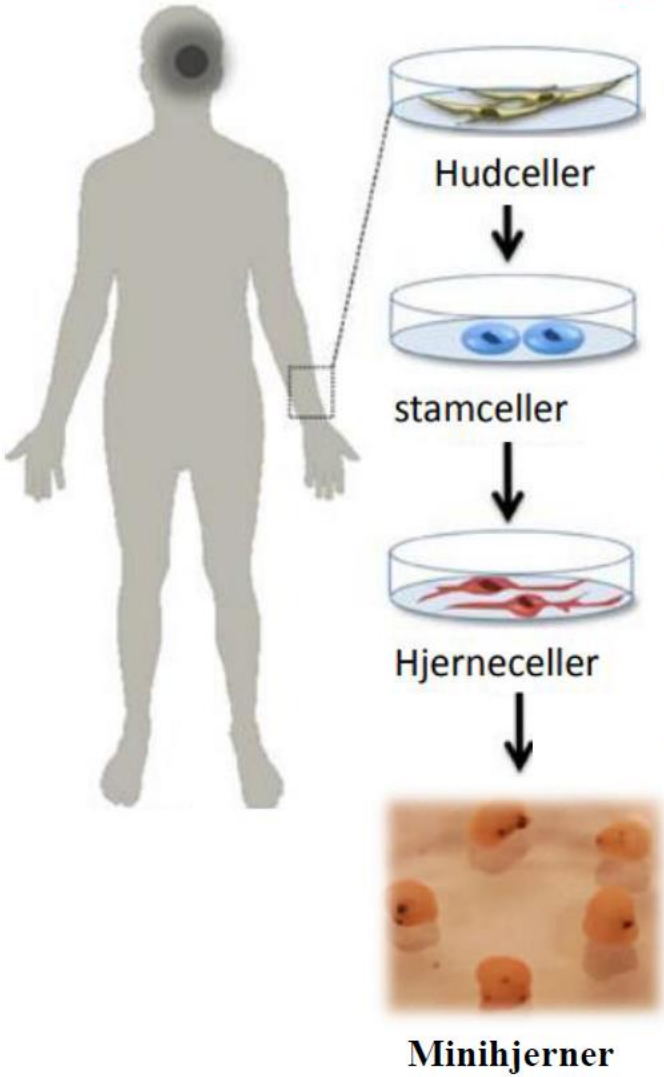
*Fiction or reality*

**Vi kan lage minihjerner i laboratoriet**
**– *såkalte hjerneorganoider***



*Minihjerner generert ved Laboratoriesenteret, NTNU*

# Hvordan lager vi minihjerner?




*1. Lager stamceller fra hudceller (30 dager)*

*2. Lager hjerneceller fra stamceller (11 dager)*
*- såkalte induserte Pluripotente Stamceller (iPSC)*

*3. Lager minihjerner fra hjerneceller (20 dager -1 år)*

*Magnar Bjørås, UIO/NTNU*

# Hva kan minihjerner og andre miniorganer brukes til?

- Enestående verktøy for å studere detaljene under sykdomsutvikling på cellenivå og helt ned på molekylnivå
  - viktig for identifisering av nye target/målproteiner for utvikling av ny behandling
- Identifisere og utvikle nye medikamenter mot sykdom
- Cellebasert terapi/regenerativ terapi (transplantasjon av minihjerner/miniorganer)

# Takk for oppmerksomheten

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