Newsletter Issue No. 2

1.1.2018 – 30.06.2023
Duration

6.25 M €
Funding

11 Partners from 6 countries
Consortium

Editorial

We are delighted to share our second CureCN newsletter with you.

With this issue, we are providing you with an update of our project and partners and give some insights into our work into the past three years of the project. CureCN is a 5.5-year research project (2018-2023) funded by the European Commission under the Horizon 2020 programme with a total budget of € 6.25 million and coordinated by Genethon (France). The 11 partners from 6 European countries are joining forces from academia, hospitals, healthcare companies and patient organisations and aim to develop a curative treatment for the Crigler-Najjar syndrome (CN).

During the past three years of this project, we have greatly advanced our project goals. We have, for examples, initiated a clinical trial and had the opportunity to present results on safety and preliminary efficacy of the gene therapy product at the International Liver Congress and at the congress of the European Society for Gene and Cell Therapy. We conducted fundamental research to address challenges of a gene transfer strategy to be able to treat the Crigler-Najjar Syndrome in the widest population. This second issue of our newsletter will give you more information about the project and on the progress we have made so far and some of our next steps.

Thank you for your interest and support – and enjoy reading this newsletter!
We also invite you to check out our website at https://curecn.eu/.

Best regards,

The CureCN Coordination Team

Gérald Perret

Giuseppe Ronzitti

About CureCN

The European research project CureCN aims to develop a curative gene therapy against the ultra-rare Crigler-Najjar syndrome (CN). Crigler-Najjar is a life-threatening liver disease which affects one in a million individuals at birth. The goal of the CureCN consortium is thus to prove the safety and

efficacy of an adeno-associated virus (AVV) gene therapy in a clinical trial and make it available to patients.

Partners in CureCN have been chosen for their complementary scientific excellence, technical expertise, and experience in translational research. Joining forces, they take on the mission to find a curative treatment for CN syndrome. The project's major goals are:

- Developing a curative AAV gene therapy and validating a technology transposable to many other inherited liver-related disorders
- Proving the safety and efficacy of the vector-mediated gene transfer with AAV in a clinical trial
- Providing a treatment suitable for young individuals affected by CN syndrome as well as for older patients who potentially carry pre-existing immunity to AAV
- Verifying a way to eradicate pre-existing immunity to AAV
- Accelerating the orphan drug development towards a marketing authorisation for the treatment

One important goal of CureCN is to establish the first global Crigler-Najjar patient natural history registry, to better understand outcomes and natural history of the disease.

CureCN also strives to provide better information for patients, families, healthcare providers and the general public about CN syndrome and existing treatments.

> Learn more about the project

> Discover our consortium

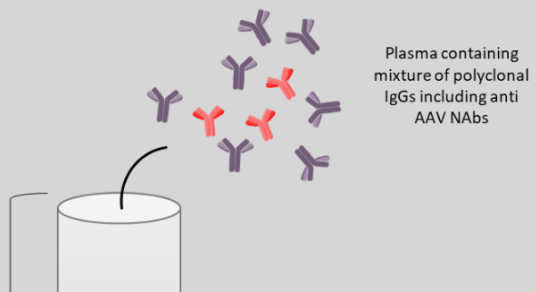
Update about the trial

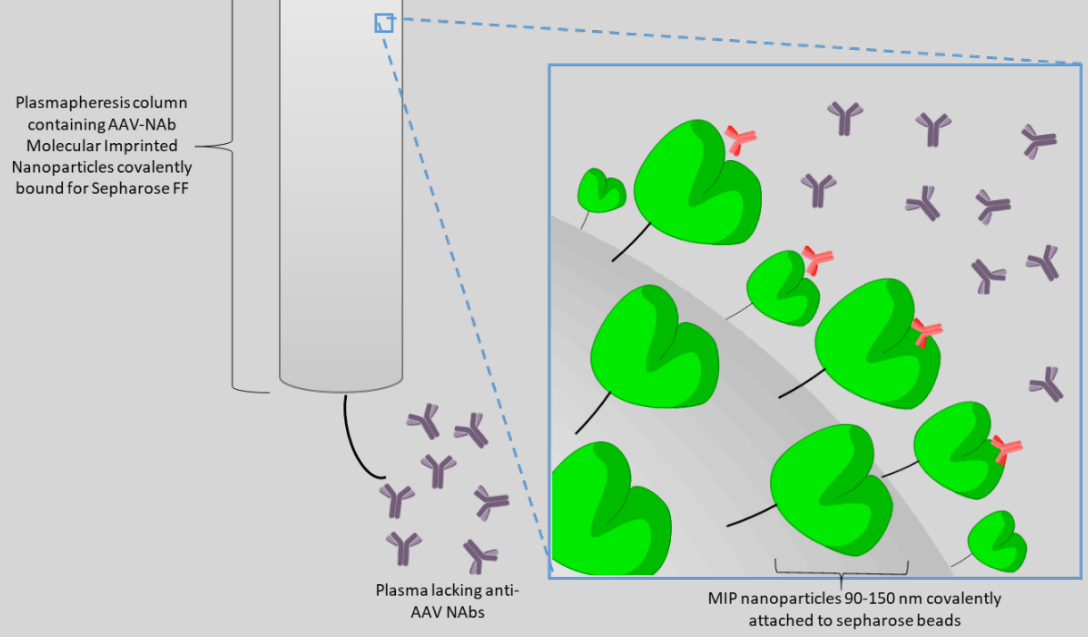
The CureCN European trial aims to assess the product's safety, identify the optimal dose, and evaluate the therapeutic efficacy of the drug candidate. Patients in Cohort 2 of the CureCN trial, treated in Bergamo, experienced a deep and sustained reduction of serum bilirubin. This allowed to stop phototherapy successfully, and patients did not experience any significant adverse event so far. All are currently off phototherapy, and one has reached 48 weeks of follow up. This data has been presented at the International Liver Congress and at the congress of the European Society for Gene and Cell Therapy. If these results will be confirmed in all the patients in this cohort, and after discussion with the Data Safety Monitoring Board, we will start to enrol more patients.

Update from the University of Leicester

AAV-mediated gene therapies can have life changing effects for patients. However, a limiting factor is that many individuals are exposed to naturally occurring AAV and their immune system has developed Neutralizing Antibodies (NAbs) to AAV. The presence of this pre-existing immunity reduces the efficacy of the gene therapy and limits the pool of patients that can be treated, and may hinder re-administration in the future, if required. Techniques to overcome this include immune suppression and broad range plasmapheresis (a plasma exchange process), both coming with increased susceptibility to infection.

At the University of Leicester, we have been using our expertise in design and preparation of molecularly imprinted polymers which will be used as recognition elements in a novel, polymer-based anti-AAV Ig-specific plasmapheresis resin to selectively remove NAbs from the bloodstream of seropositive subjects. We have identified epitopes of the hypervariable region of these NAbs and utilised these to generate high affinity molecularly imprinted nanoparticles, demonstrated their affinity to the epitopes and bound particles to media generating a first prototype NAb specific affinity column which is currently being tested for specificity, capacity and ligand stability.



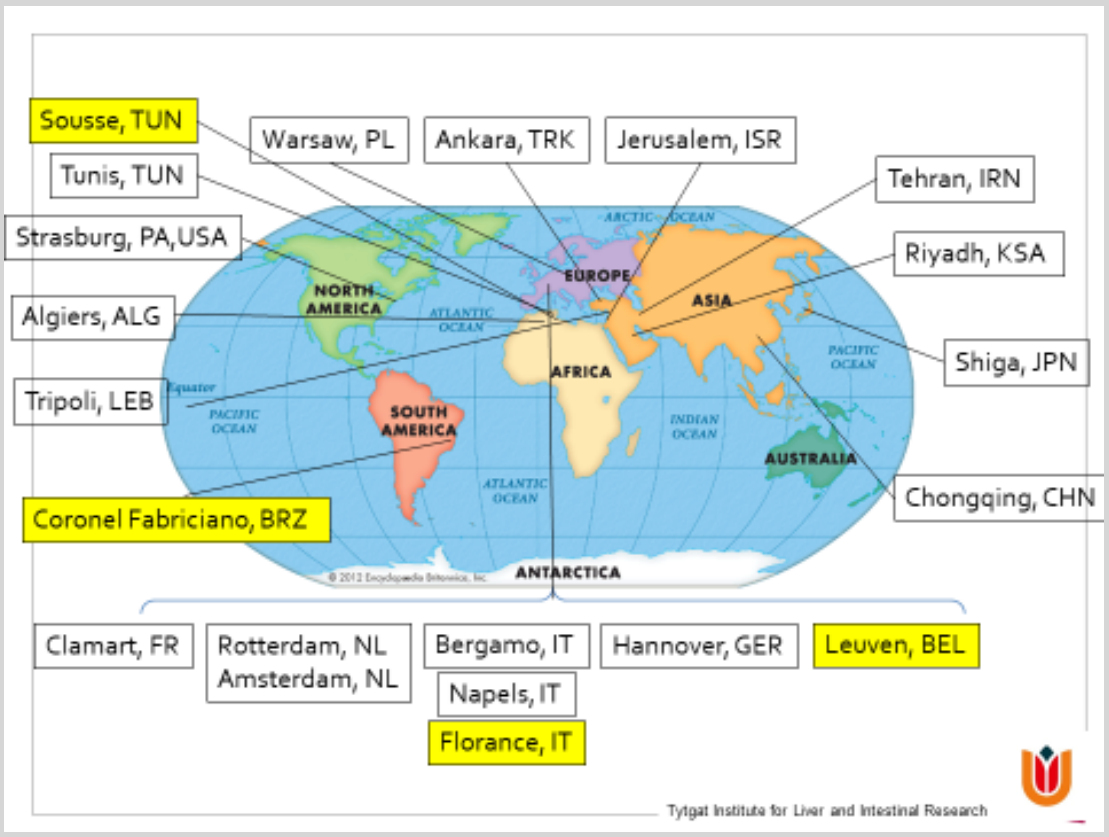


Update from Academisch Medisch Centrum Bij de Universiteit van Amsterdam

Currently, gene therapy with AAV vectors can only be done once time due to the induction of antibodies that make re-treatment ineffective. Thus, in case of a sub-optimal treatment or loss of correction overtime, re-dosing of the vector is not yet possible. Since AAV expression may significantly decrease when the liver grows, this is also an issue for the use of this therapy in young children.
Therefore, we have been investigating if applying immune suppression at the time of the first treatment can be used to prevent the induction of antibodies; thereby allowing effective re-treatment. This indeed seems to be a feasible result that we published end of last year in a paper entitled "Efficacy of AAV8-hUGT1A1 and immunosuppressive regimens in neonatal, suckling and juvenile rats to model treatment in pediatric Crigler-Najjar patients". Xiaoxia Shi was the first author of this paper in Mol.Ther/Methods Clin.Dev. 2020. This paper is part of her thesis "New Avenues In Gene Therapy for inherited liver disease" that she defended on 01 April, 2021.
We are still working on this approach since the results were promising but there are some drawbacks of the immunosuppressive regimen applied in that study, which we hope to overcome using delivery of this drug in nano particles.

Update about the world-wide Crigler-Najjar registry

The CureCN consortium has set up a world-wide registry for Crigler-Najjar patients. The data of over 200 patients have been included in this registry already, but we are interested in further expanding it. For more information about this initiative and how to participate, you can send an email to: p.j.bosma@amsterdamumc.nl



Contact us

If you have any questions regarding the CureCN project or suggestions for our newsletter, feel free to get in touch! We are looking forward to receiving your feedback.

Coordination
Genethon, France
Gérald Perret
email

Management
EURICE – European Research and Project Office GmbH, Germany
Laura Schweigert
email

www.curecn.eu

The CureCN project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 755225.