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PRIX GALIEN 2012

Inserm

# AAV gene therapy for Crigler-Najjar syndrome: from the bench to the bedside

Giuseppe Ronzitti, PhD
*Principal Investigator*
*Immunology and liver gene transfer team*
*INSERM U951 and Genethon*



BIOCONVS
Bioconvergence pour la Santé
Domaine de Recherche et d'Innovation Majeur

Région îledeFrance

Italy

France

B.Sc. Biotechnology

Ph.D. Biochemistry

Post-doc in molecular neuroscience

Post-doc in gene therapy

2003

2008

2013

2015

Marie Skłodowska-Curie Fellowship

2017

Modena

Bologna

Genova

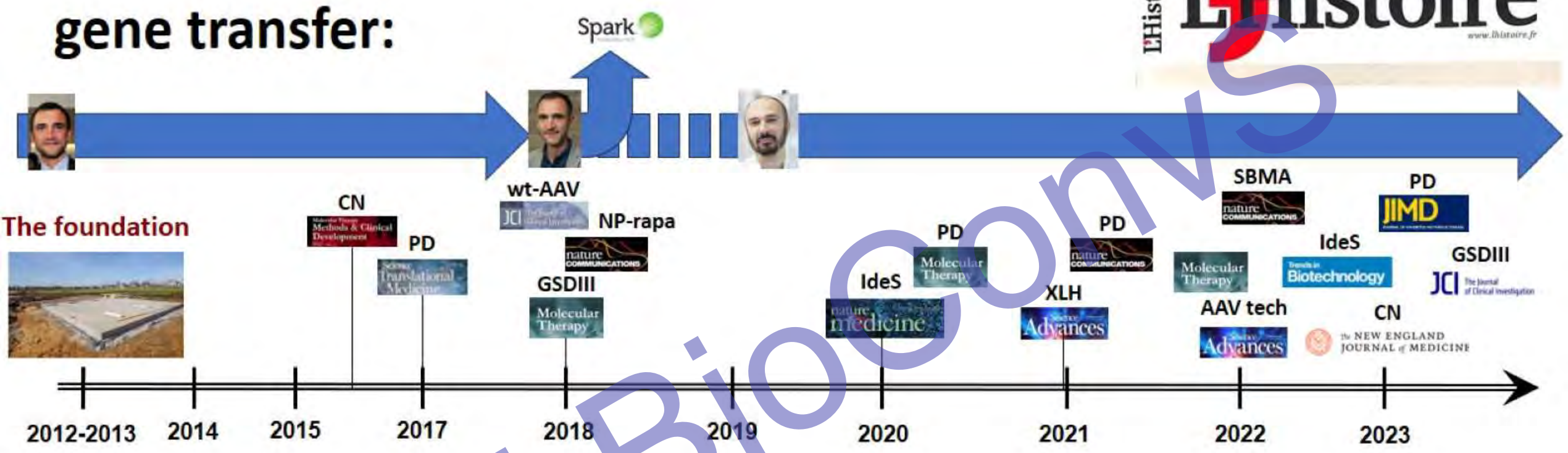
2011 Riva del Garda

# Immunology and liver gene transfer:


**The foundation**

2012-2013 2014 2015 2017 2018 2019 2020 2021 2022 2023

# Immunology and liver gene transfer:



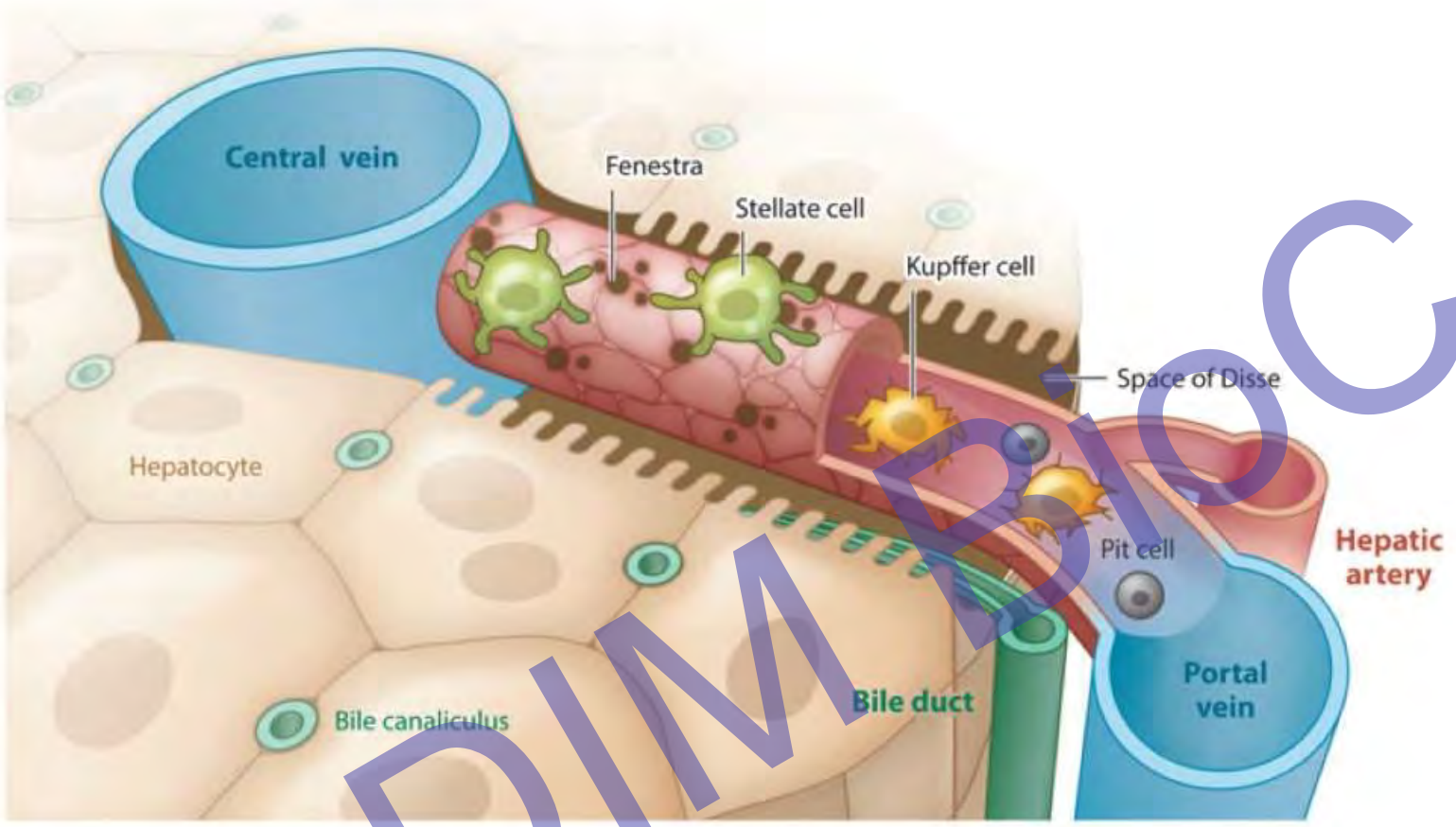

L'Histoire

CureCN + NCT03466463

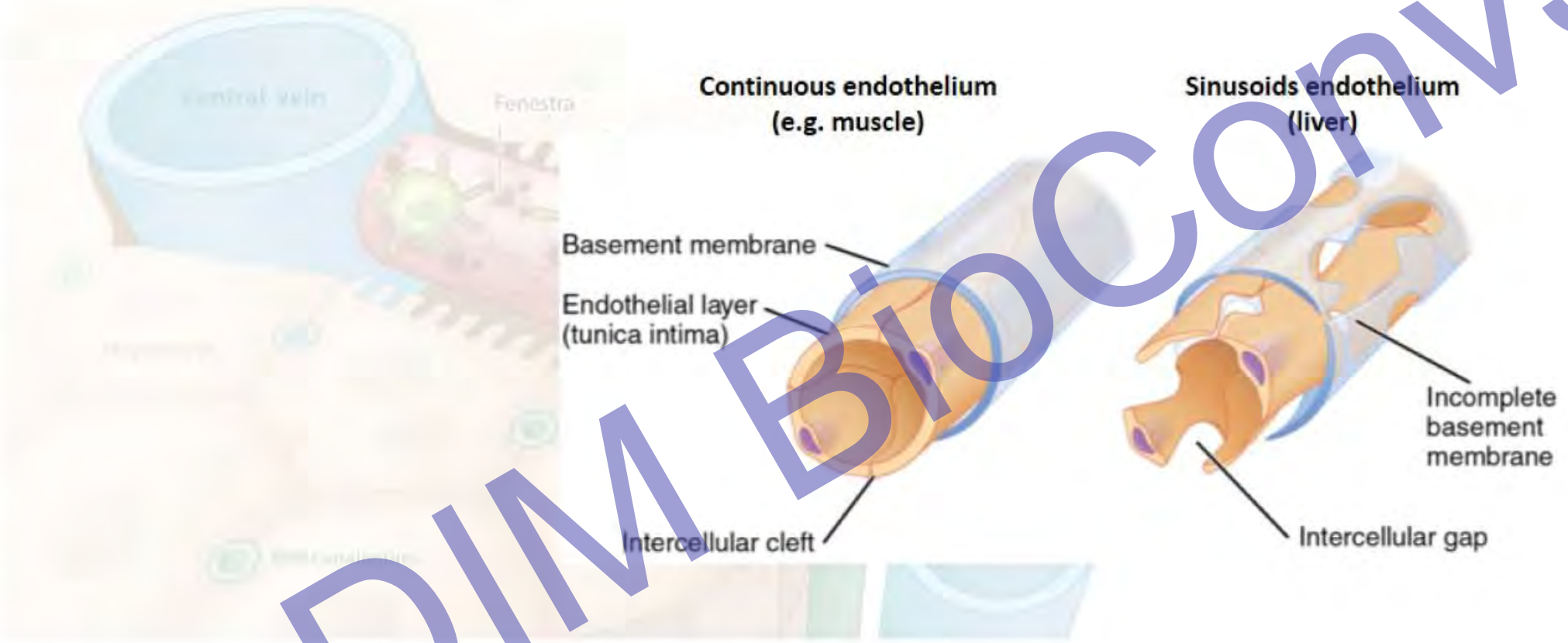
Spark + NCT04093349

# Why the liver?

# The liver advantage in gene therapy explained: delivery



# The liver advantage in gene therapy explained: delivery, delivery, delivery






Discontinuous capillaries in liver represent an advantage in gene transfer as they provide a clear way in for gene therapy vectors and an easy way out for secreted proteins

# Why the liver?

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# Crigler-Najjar Syndrome

- Ultra-rare liver disorder, 1 person in 1 million at birth, persists during the entire life time
- Deficiency of a liver enzyme that is normally responsible for the elimination of a toxic compound, the bilirubin, which is formed when red blood cells are recycled
- Abnormal accumulation of bilirubin in the body causes jaundice. If left untreated, it can cause irreversible and fatal neurological damages

# No cure except phototherapy

- Allows patients survival
- 10-14h / day
- Only symptomatic treatment
- Very restrictive and strongly impacts the quality of life of patients and their families
- Efficacy decreases over time
- Transplantation remains the only curative treatment

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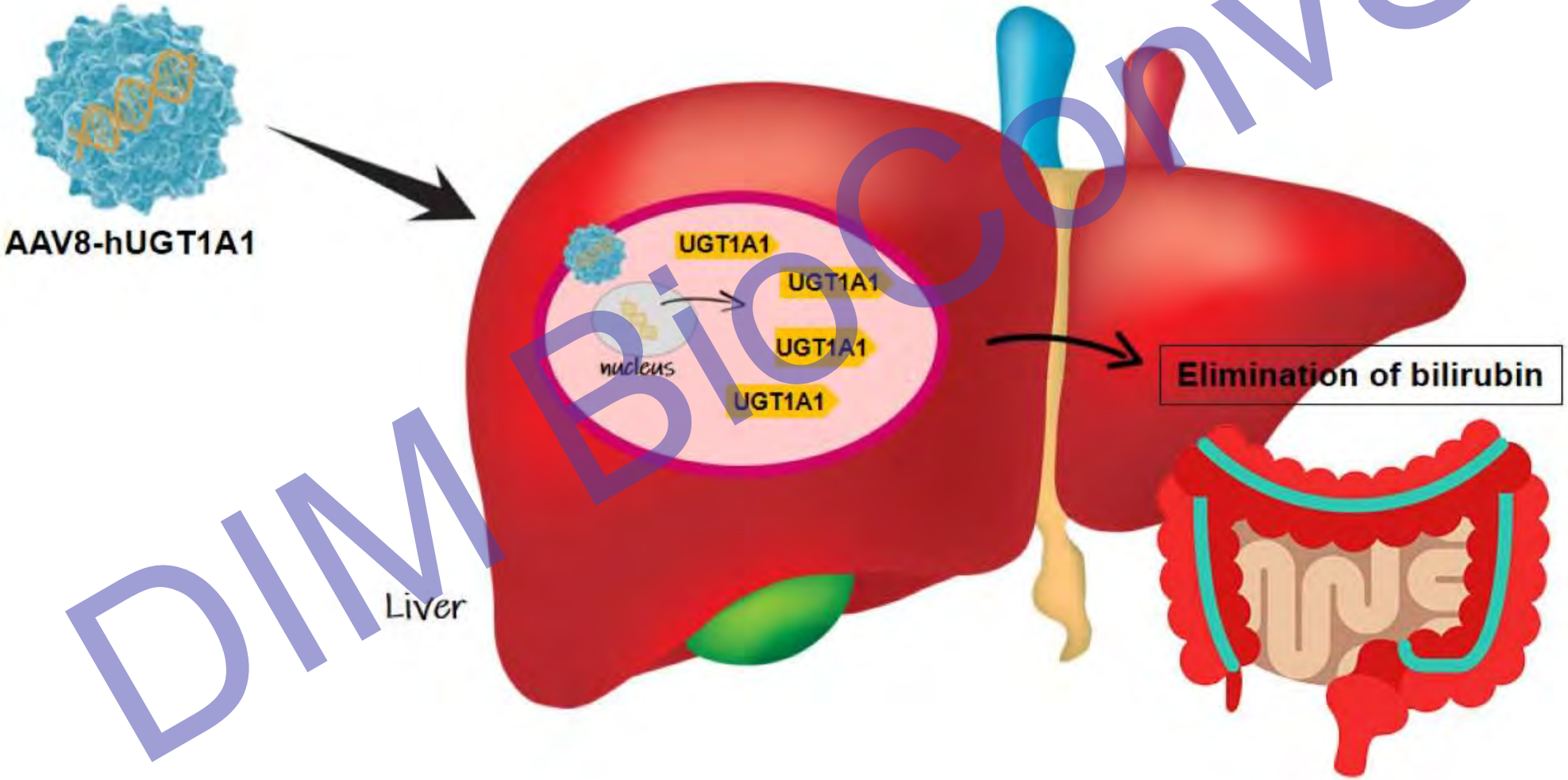
# AAV gene therapy for CN



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# From bench to bedside…

*Early Research* | *Preclinical Development* | *Clinical Development*

Proof concept studies → Optimization of the product → Pharmacology & Toxicology studies → Clinical trial CareCN NCT03466463

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INNOVER POUR GUÉRIR

**2006**
First gene therapy studies
in the labs of P. Bosma (Amsterdam, NL) and
N. Ferry (Nantes, FR), on a rat model of CN


**2012**
The group of Andres Muro (Trieste, IT)
demonstrated liver gene transfer
faisability in a mouse, model of severe CN

**2014**
Development of
a lead candidate

**2016**
Definition of the large-scale
production process


**2018**
CTA

CureCN

*European Union's Horizon 2020 grant agreement No 755225*

*Seppen et al., 2006*
*Bortolussi et al., 2012*
*Bortolussi et al., 2014*
*Ronzitti et al., 2016*
*Aronson et al., 2019*
*Collaud et al., 2019*
*Aronson & Bakker et al., 2020*
*Shi et al., 2021*

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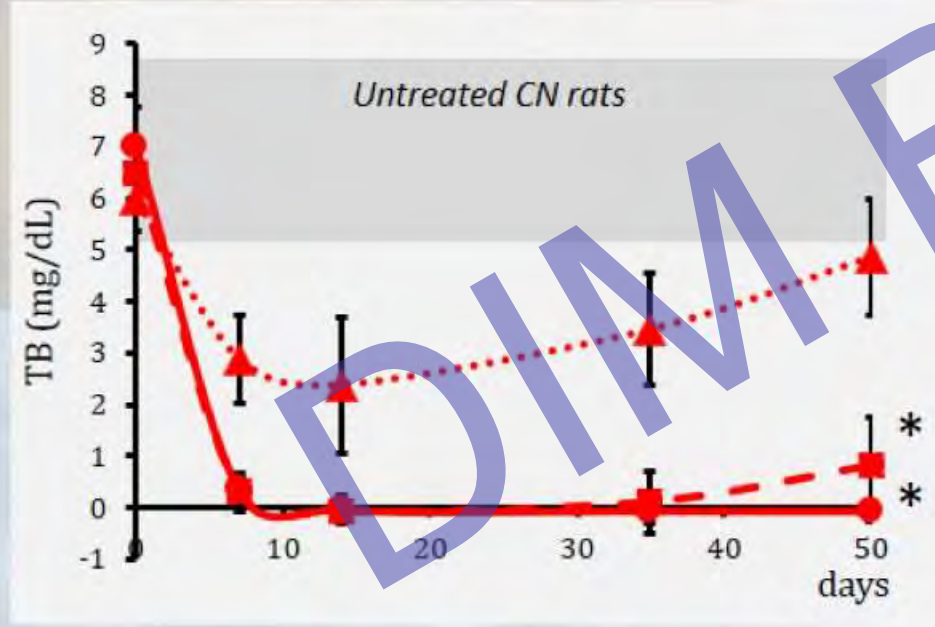
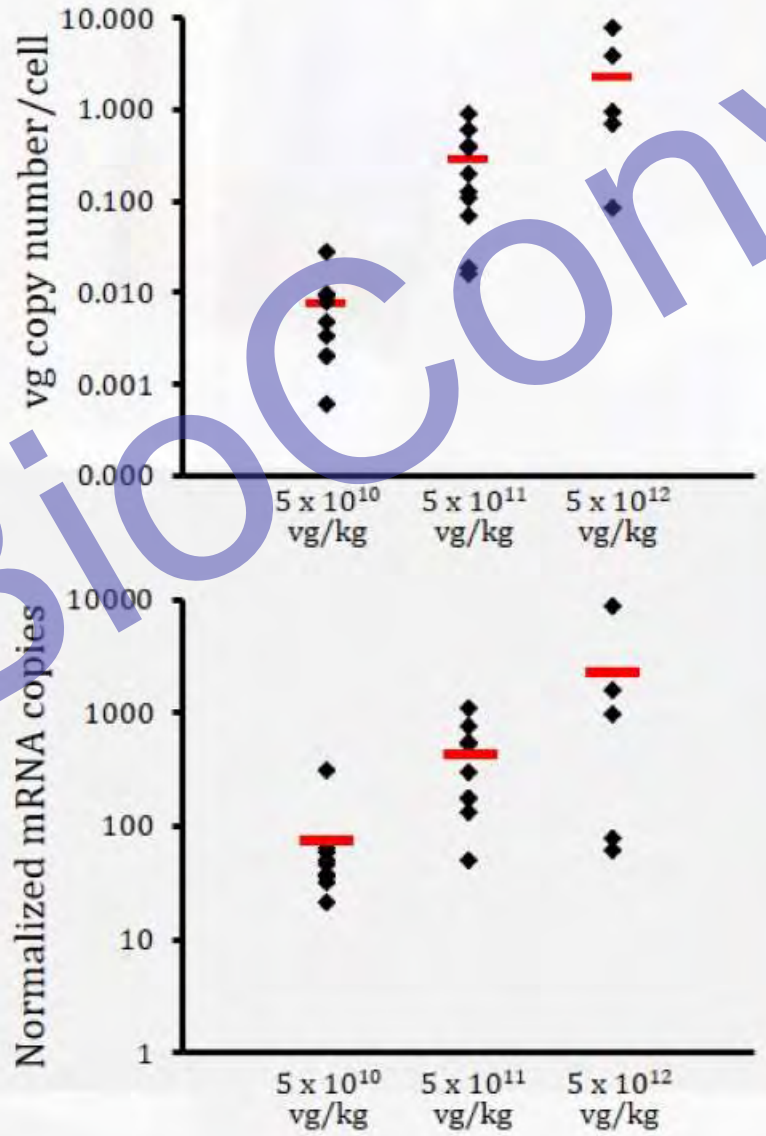
# From bench to bedside… but first rats!

Dr. Fanny Collaud




**In the Gunn's rat AAV-UGT1A1 vector corrects bilirubin accumulation starting from $5 \times 10^{11}$ vg/kg**

*Ronzitti et al., Mol Ther Methods Clin Dev 2016*

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# CareCN clinical trial

## Multicentre, Phase I/II, open-label, dose-escalation study followed by a pivotal efficacy part

### INCLUSION CRITERIA

- Adults > 18 ans
- Phototherapy (PT) ≥ 6h/day
- No NAbs against AAV8
- Fibrosis score ≤ 3 (METAVIR) or elastography ≤ 10 kPa

### GNT0003 DOSES

**Single infusion**

- Cohort 1: $2x10^{12}$ vg/kg
- Cohort 2: $5x10^{12}$ vg/kg

### ENDPOINTS

**Primary**

- Safety of GNT0003
- Efficacy: Safe interruption of PT at week 16

**Exploratory**

- Immune response to GNT0003

- Overall 7 patients enrolled and dosed in Cohort 1 (n=2), Cohort 2 (n=3)
- **No SAEs related to IMP have been reported**

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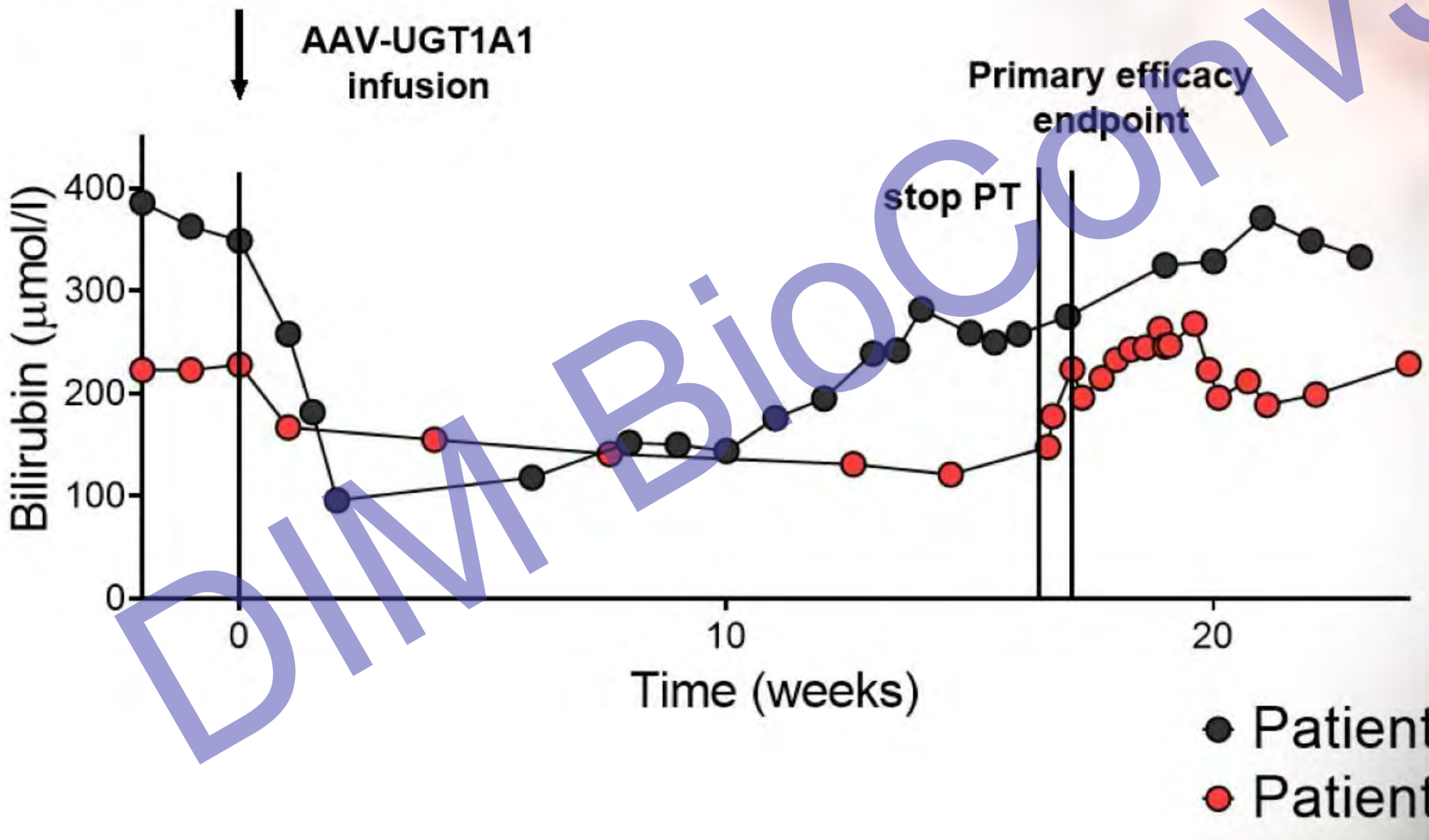
# Essai Clinique CareCN

## Bilirubinémie Totale

Cohorte 1






With patients permission

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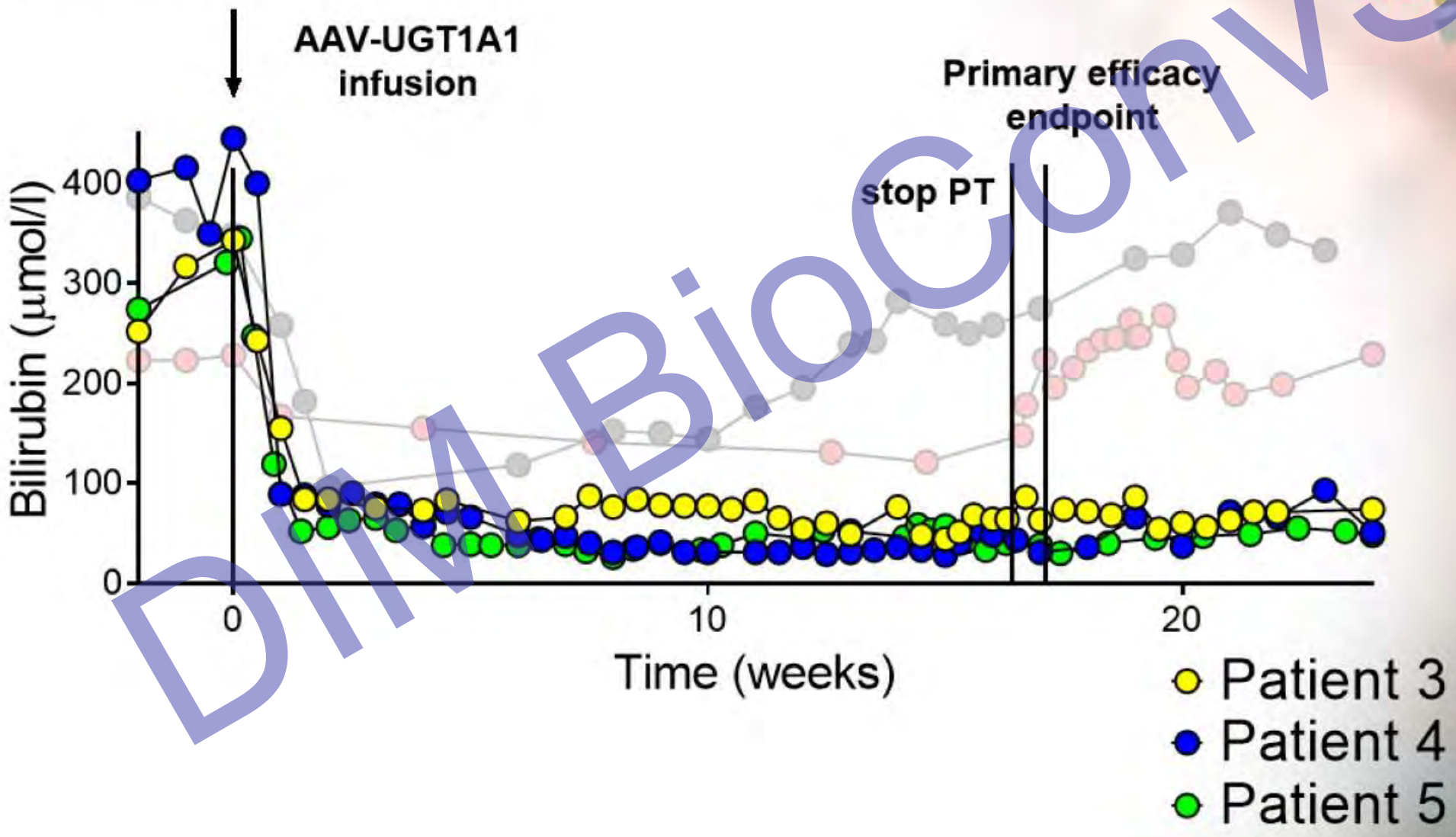
# Essai Clinique CareCN

## Bilirubinémie Totale

Cohorte 2



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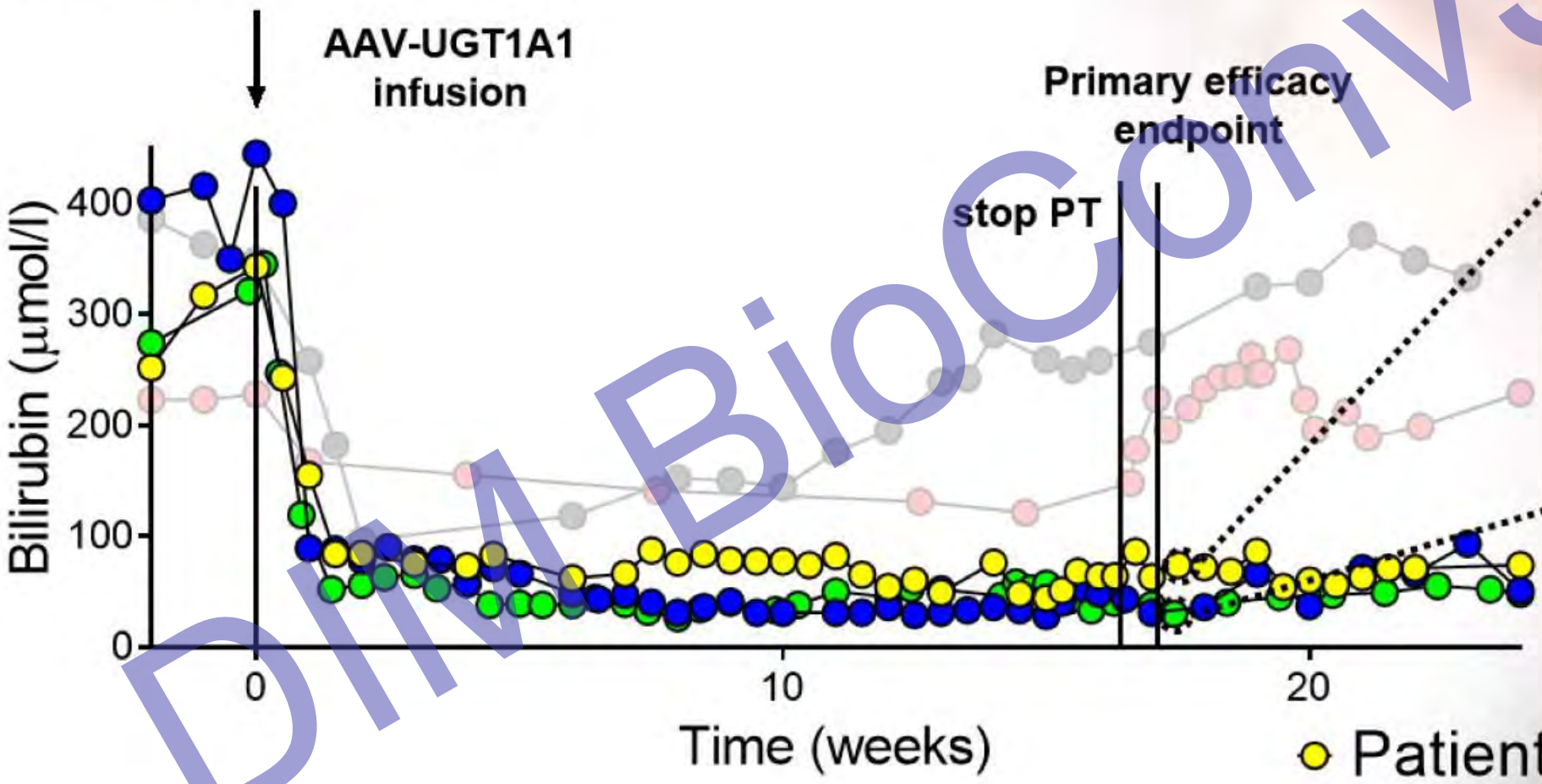
# Essai Clinique CareCN

## Bilirubinémie Totale




Cohorte 2

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# Essai Clinique CareCN

## Bilirubinémie Totale

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Gene Therapy in Patients with the Crigler–Najjar Syndrome

Lorenzo D'Antiga, M.D., Ulrich Beuers, M.D., Giuseppe Ronzitti, Ph.D., Nicola Brunetti-Pierri, M.D., Ulrich Baumann, M.D., Angelo Di Giorgio, M.D., Sem Aronson, Ph.D., Aurelie Hubert, Ph.D., Roberta Romano, M.D., Norman Junge, M.D., Piter Bosma, Ph.D., Giulia Bortolussi, Ph.D., Andrés F. Muro, Ph.D., Ravaka F. Soumoudronga, M.D., Philippe Veron, Ph.D., Fanny Collaud, Ph.D., Nathalie Knuchel-Legendre, M.A.Sc., Philippe Labrune, M.D., and Federico Mingozzi, Ph.D.

Time (weeks)

20

August 17, 2023
N Engl J Med 2023; 389:620-631
DOI: 10.1056/NEJMoa2214084

Patient 5

Cohorte 2

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# Conclusions

- Chez tous les patients traités avec une maladie de CN, **le vecteur GNT0003 a été très bien toléré**

- A la dose de 5 x $10^{12}$ vg/kg, le vecteur GNT0003 **restore une expression d'UGT1A1 permettant un arrêt de la photothérapie (> 80 semaines)**

**La thérapie génique est un traitement prometteur pour la maladie de Crigler-Najjar, et pourrait potentiellement remplacer la transplantation**


## Cliniciens :

Hôpitaux universitaires Paris-Sud — Assistance Publique Hôpitaux de Paris

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Università degli Studi di Napoli Federico II

N. Brunetti-Pierri

MHH Hannover Medical School

U. Baumann
N. Junge
M. Ott

## Associations de patients :

najjar

Association Française de Crigler-Najjar Maladie rare

CRIGLER-NAJJAR ITALIA ONLUS associazione malati iperbilirubinemici

## R&D:

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Design du vecteur
Etude pré-clinique
Développement & production
Conception de l'essai clinique

International Centre for Genetic Engineering and Biotechnology

A. Muro
G. Bortolussi

Amsterdam UMC Universitair Medische Centra

P. Bosma

AFMTÉLÉTHON INNOVER POUR GUERIR

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AFMTÉLÉTHON INNOVER POUR GUERIR

HORIZON 2020

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Rouillon Jeremy
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Tedesco Novella
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Wissa Danella

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All our collaborators

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MVolution
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imi innovative medicines initiative
eurostars™
dim Thérapie Génique
WORLD ANTI-DOPING AGENCY play true
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association GEN & ZIC
pxe FRANCE
AFG