

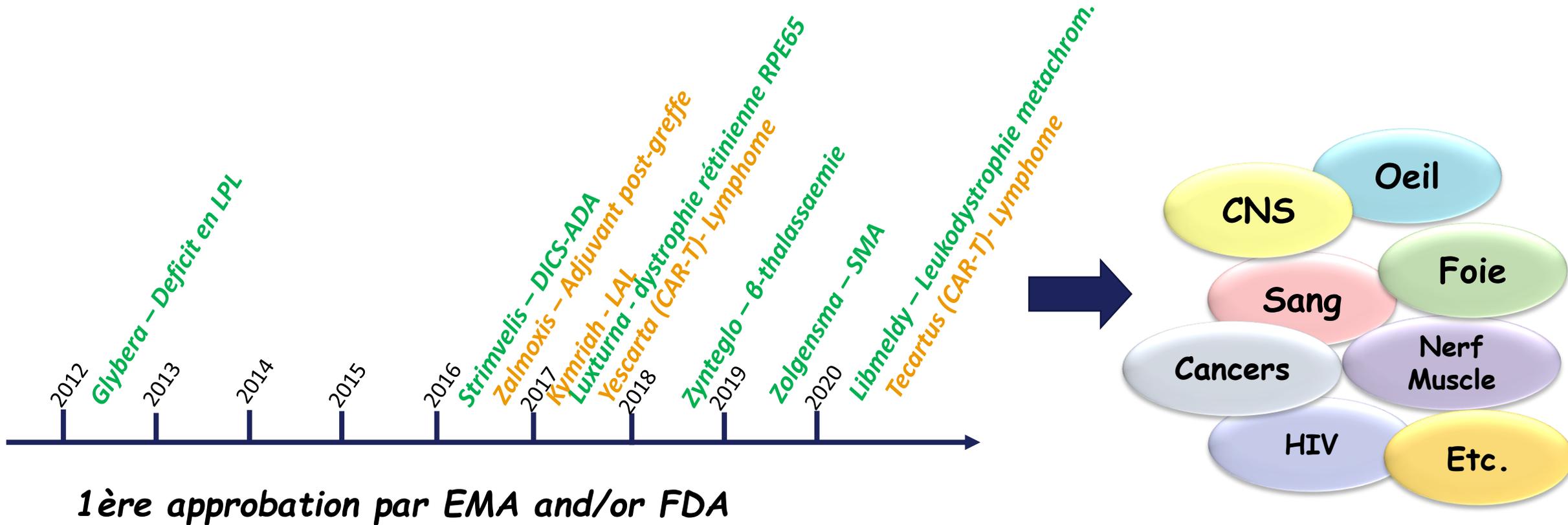


Vivet
THERAPEUTICS

Thérapie génique dans le foie: une approche thérapeutique émergente

Bernard Bénichou, MD, PhD
Chief Medical Officer, Vivet Therapeutics

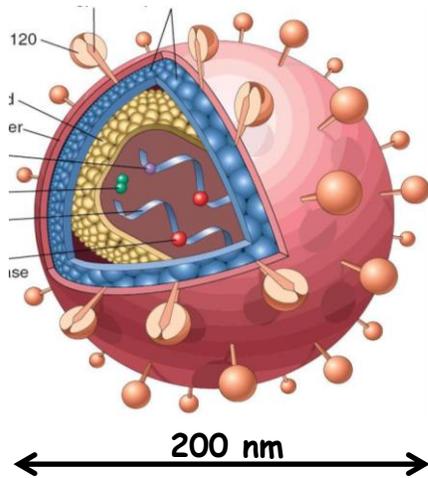
Thérapie génique: une réalité pour plusieurs maladies orphelines et cancers du sang



Quel vecteur pour transduire le foie?



Herpes virus

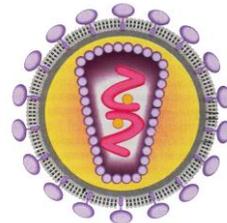


Can carry large genes, but difficult to produce and lead to acute inflammation

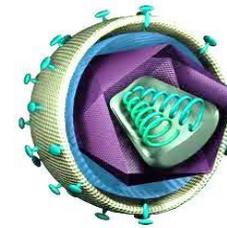
Adenovirus



Retrovirus



Lentivirus



Integrate into the host DNA

Adeno-Associated Virus (AAV)



Nonpathogenic
Defective
Natural liver tropism

Developments cliniques de thérapie génique AAV en cours ciblant le foie pour des maladies héréditaires



- Hémophilies A et B
- Maladies du foie: Wilson
- Maladies métaboliques: Crigler Najjar, PKU, OTC def., GSD1a, HF, MMA
- Maladies lysosomales de surcharge: MPSI, II, VI, Gaucher, Fabry, GM1 gangliosidosis

52 Week Efficacy and Safety of Etranacogene Dezaparvovec in Adults with Severe or Moderate-Severe Hemophilia B: Data from the Phase 3 HOPE-B Gene Therapy Trial

Steven W. Pipe¹, Frank W.G. Leebeek², Michael Recht³, Nigel S. Key⁴, Susan Lattimore³, Giancarlo Castaman⁵, Eileen K. Sawyer⁶, Stephanie Verweij⁶, Valerie Colletta⁶, David Cooper⁶, Ricardo Dolmetsch⁶, Wolfgang Miesbach⁷,

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Abstract No: PB065

Figure 3. Endogenous FIX activity over 52 weeks^a

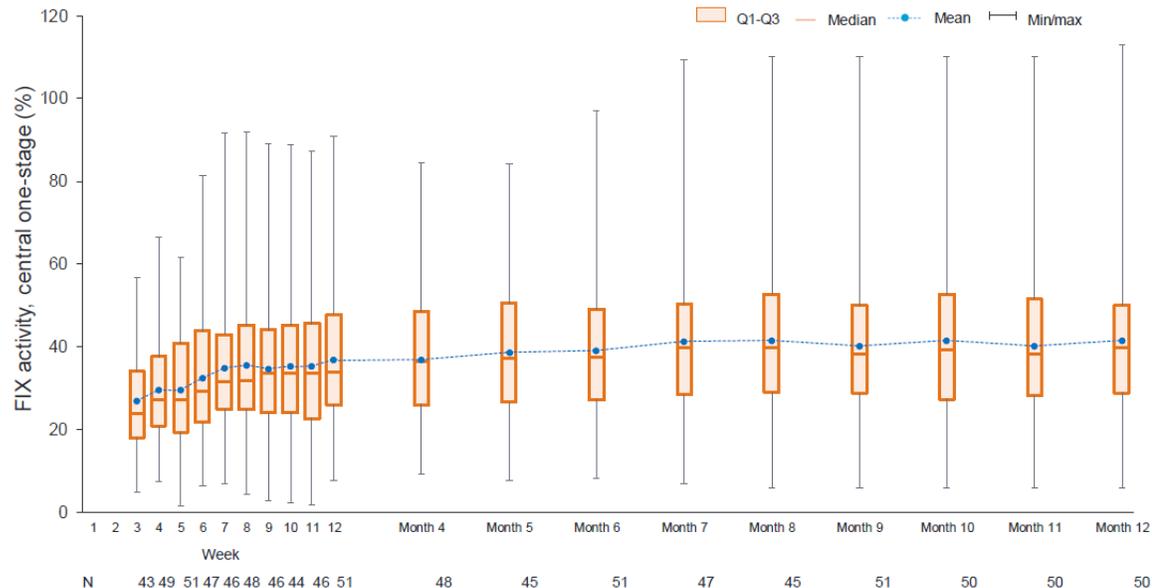


Table 3. Bleeding^a events in the first 12 months post-treatment

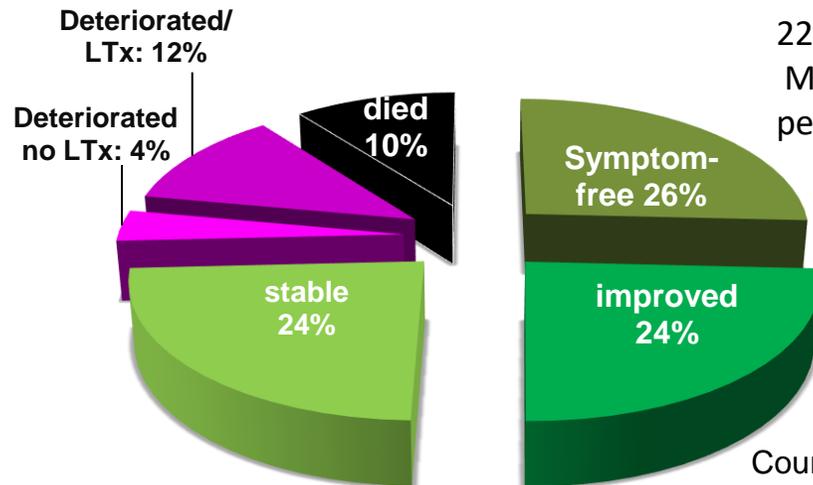
	All subjects (N=54)		Lead-in ^b		Months 0-6 ^c		Months 7-12	
	Subjects N (%)	Bleeds N	Subjects N (%)	Bleeds N	Subjects N (%)	Bleeds N	Subjects N (%)	Bleeds N
All bleeds	40 (74.1)	136	18 (33.3)	29	14 (25.9)	26		
All bleeds treated with FIX	37 (68.5)	118	10 (18.5)	15	9 (16.7)	14		
Spontaneous bleeds treated with FIX	22 (40.7)	44	4 (7.4)	6	2 (3.7)	2		
Traumatic bleeds treated with FIX	26 (48.1)	58	7 (13.0)	7	6 (11.1)	7		
Joint bleeds treated with FIX	31 (57.4)	70	5 (9.3)	8	5 (9.3)	6		

Table 4. FIX use in the first 12 months post-treatment

FIX replacement therapy usage	Lead-in N = 54	Month 0-6 N = 54	Month 7-12 N = 54
Patients on prophylaxis ^a , n (%)	54 (100%)	2 (4%)	2 (4%)
FIX usage (IU/year/patient), mean (SD)	257,070 (149,181.7)	12,913 (37,093.1)	8,401 (29,721.1)

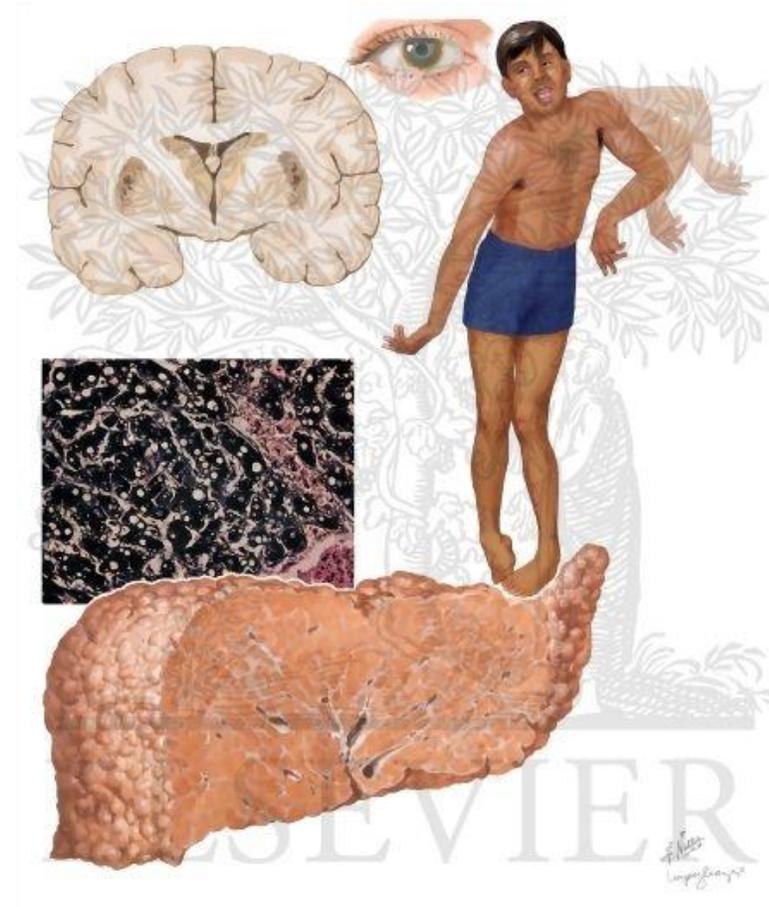
Maladie de Wilson

- Maladie du métabolisme du cuivre
- 1:30,000 naissances, mutations récessive sur gène *ATP7B* (transporteur hépatique du cuivre)
- L'accumulation de Cu dû à un défaut d'élimination biliaire conduit à un stress oxydatif

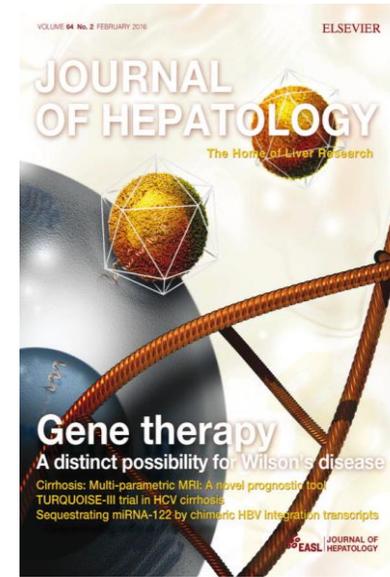


229 Austrian patients
Mean observation
period was 14.8 years

Courtesy of P Ferenci
Beinhardt et al, Clin. Gastr. Hepat. 2014



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Long-term metabolic correction of Wilson's disease in a murine model by gene therapy

Oihana Murillo^{1,2,†}, Daniel Moreno Luqui^{1,2,†}, Cristina Gazquez^{1,2}, Debora Martinez-Espartosa^{2,3}, Iñigo Navarro-Blasco^{2,7}, Jose Ignacio Monreal^{2,3}, Laura Guembe^{2,4}, Armando Moreno-Cermeño^{2,5}, Fernando J. Corrales^{2,5,6}, Jesus Prieto^{1,2,5,‡}, Ruben Hernandez-Alcoceba^{1,2,‡}, Gloria Gonzalez-Aseguinolaza^{1,2,*,‡}

¹Gene Therapy and Regulation of Gene Expression Program, CIMA, Foundation for Applied Medical Research, University of Navarra, Pamplona, Spain; ²IDISNA, Instituto de Investigacion Sanitaria de Navarra, Spain; ³Clinical Chemistry Department, University Clinic of Navarra, University of Navarra, Pamplona, Spain; ⁴Department of Morphology, CIMA, Foundation for Applied Medical Research, University of Navarra, Pamplona, Spain; ⁵Hepatology Program, CIMA, Foundation for Applied Medical Research, University of Navarra, Pamplona, Spain; ⁶CIBERehd, University of Navarra, Pamplona, Spain; ⁷Department of Chemistry and Soil Sciences, University of Navarra, Pamplona, Spain

Editorial

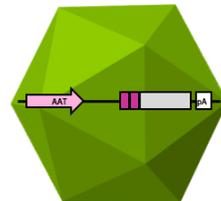
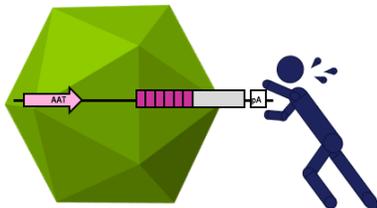


Gene therapy of Wilson disease: A “golden” opportunity using rAAV on the 50th anniversary of the discovery of the virus

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¹Department of Medicine (Gastroenterology and Liver Diseases), Department of Genetics and Marion Bessin Liver Research Center, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, USA; ²Division of Digestive Diseases and Transplantation and Immunology, Departments of Medicine and Surgery, Yale University, New Haven, CT 06520, USA

See Article, pages 419–426



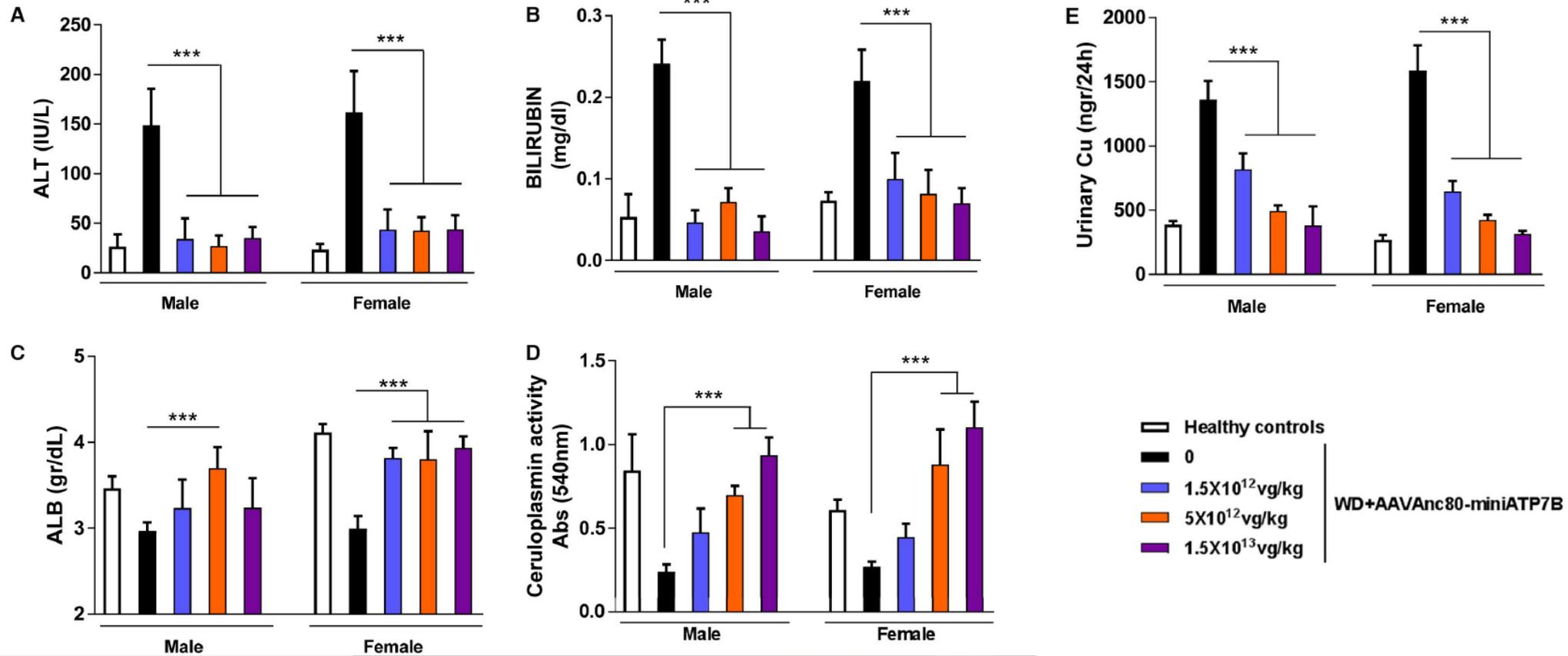
AAV-miniATP7B (VTX-801)

Original

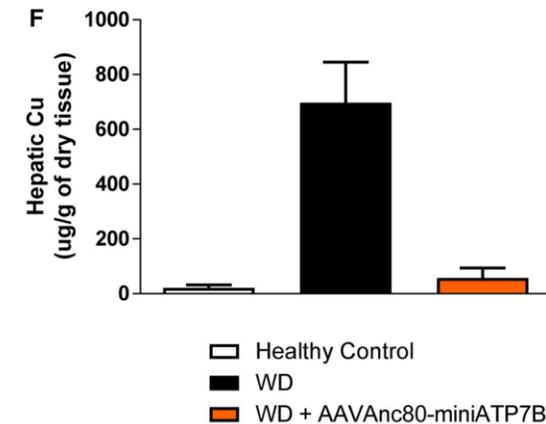
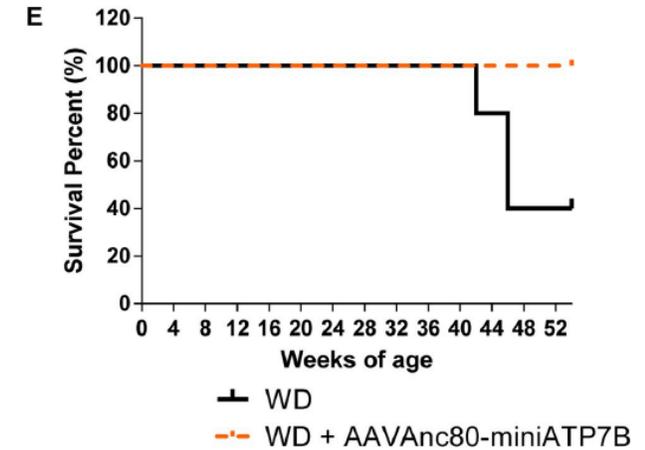
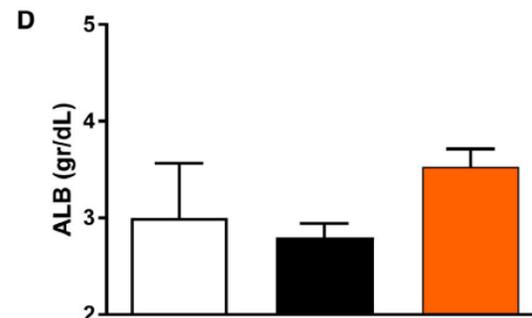
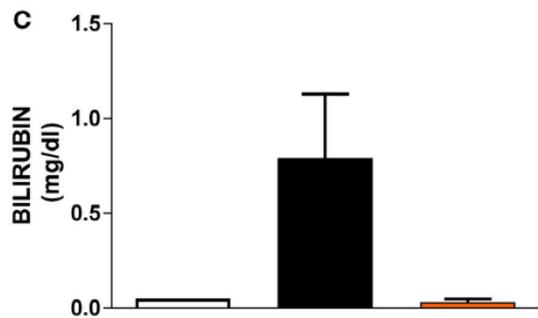
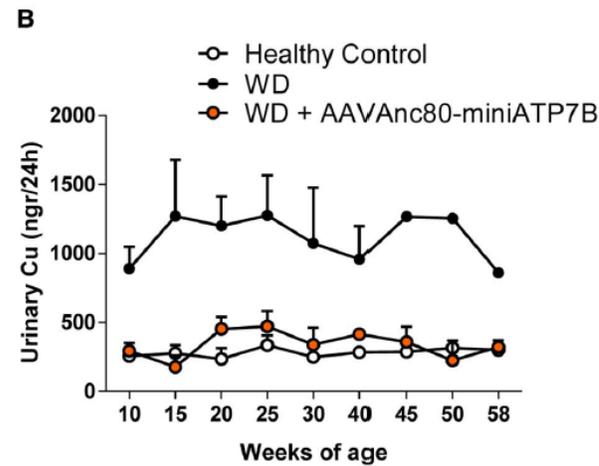
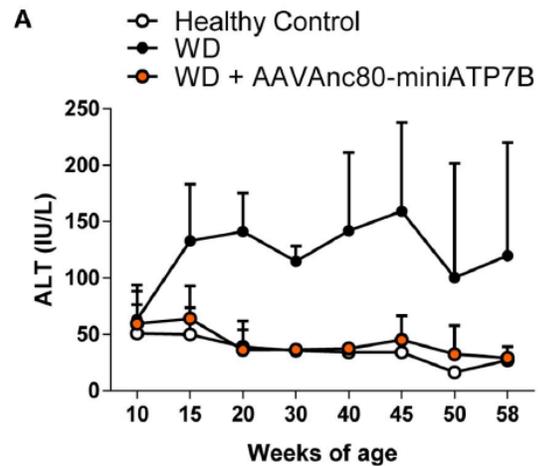
Liver expression of a miniATP7B gene results in long-term restoration of copper homeostasis in a Wilson's disease model

Oihana Murillo, Daniel Moreno, Cristina Gazquez, Miren Barberia, Itziar Cenzano, Iñigo Navarro, Iker Uriarte, Víctor Sebastian, Manuel Arruebo, Veronica Ferrer, Bernard Bénichou ... See all authors

Réponse à 3 mois après traitement avec le vecteur AAV-miniATP7B chez la souris Wilson (*atp7b* KO)



Réponse à 1 an après traitement avec le vecteur AAV-miniATP7B chez la souris Wilson (*atp7b* KO)



GaTeWay

Gene Therapy for Wilson disease



Essai de phase I/II, international, administration iv unique de VTX-801 chez des patients adultes atteints de maladie de Wilson

Objectifs:

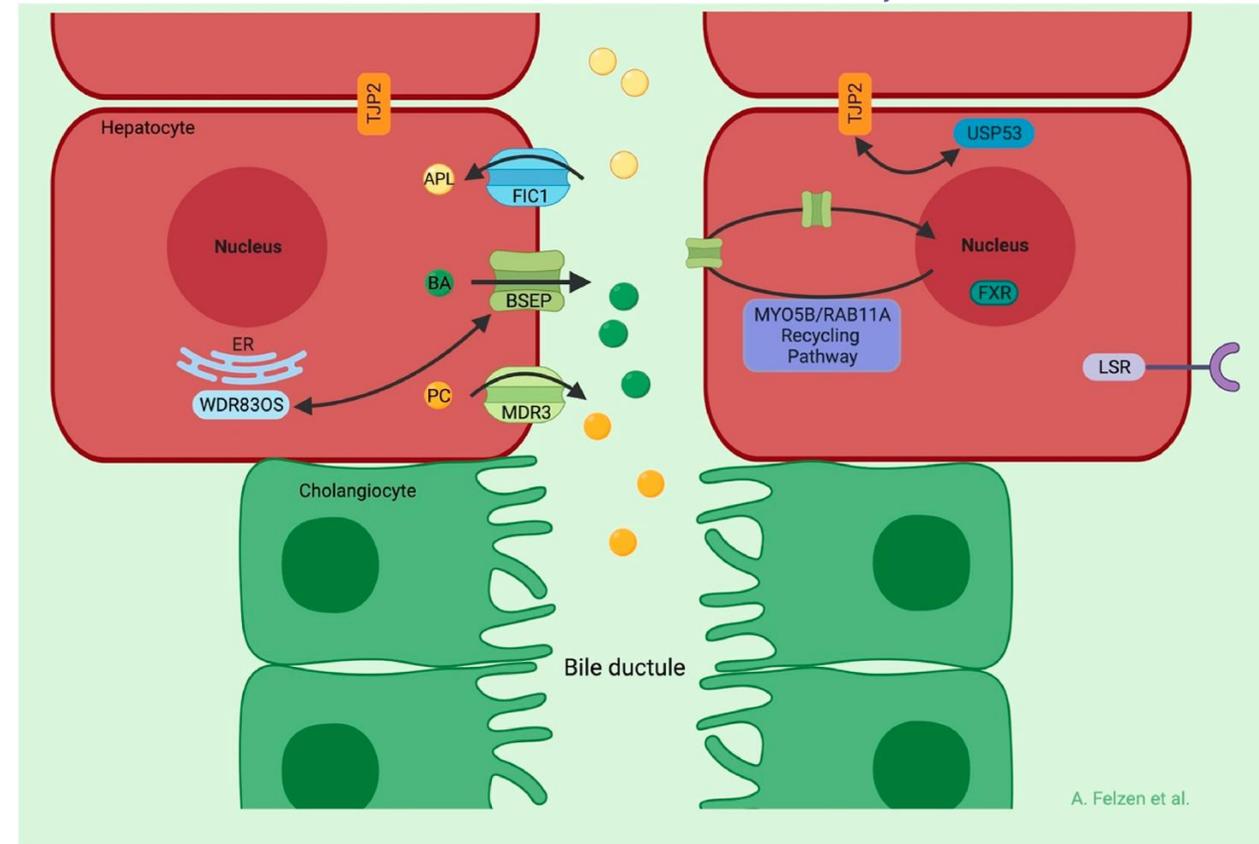
- Tolérance
- Pharmacodynamie/dose-réponse
- Réponse immunitaire



<https://www.gatewaytrialwilsondisease.com/>

Cholestases intrahépatiques familiales progressives (PFIC)

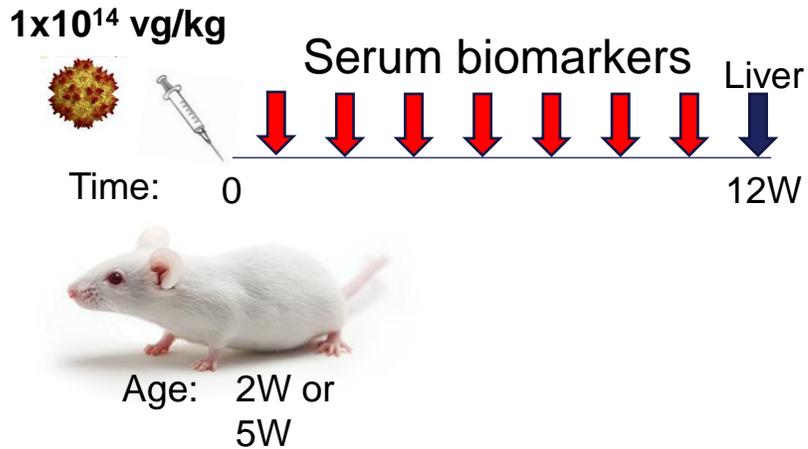
- Rares, héritées, autosomales, récessives
- Anomalies de la production de la bile et de la sécrétion des acides biliaires
- Génétiquement très hétérogène
- Présentation généralement dans la petite enfance
- Options thérapeutiques: UDCA, rifampicine, IBATi
- Évolution fréquemment sévère vers transplantation hépatique avant l'âge adulte



PFIC associated proteins. *FIC1*, familial intrahepatic cholestasis protein 1; *BSEP*, Bile Salt Export Pump; *MDR3*, multi-drug-resistance-protein 3; *TJP2*, Tight Junction Protein 2; *FXR*, Farnesoid X Receptor; *MYO5B*, Myosin 5 B; *RAB11A*, Ras-related protein Rab-11A; *USP53*, Ubiquitin Specific Peptidase 53; *LSR*, Lipolysis stimulated lipoprotein receptor; *WDR83OS*, WD Repeat Domain 83 Opposite Strand

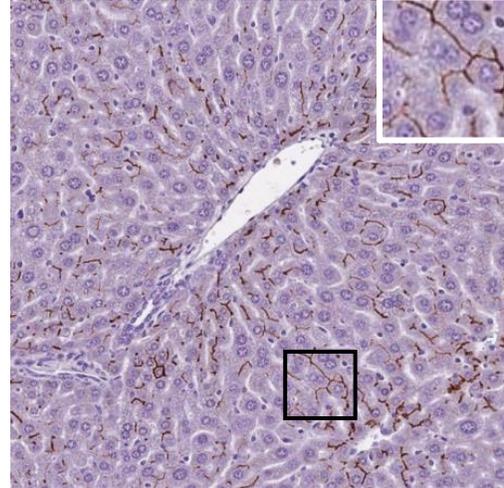
Felzen A, et al. Eur J Med Genet. 2021

Efficacité du vecteur AAV-MDR3 chez la souris PFIC3 (*abcb4* KO)

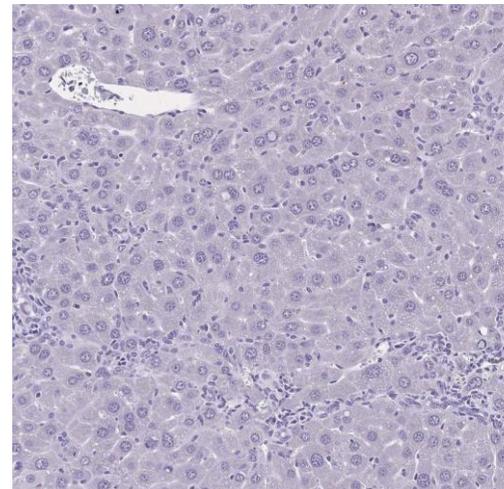


- MDR3 expression in biliary canaliculi
- Disease marker normalization

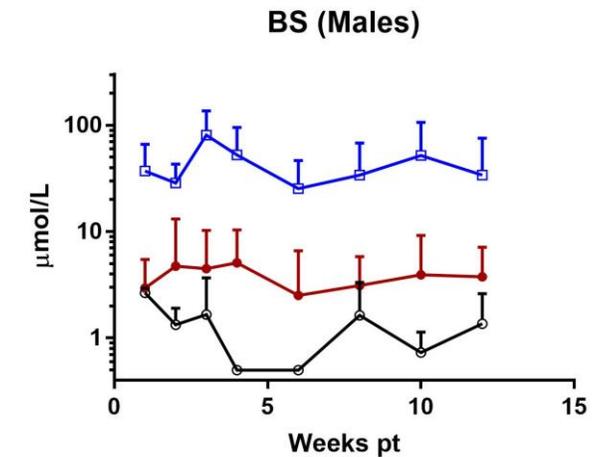
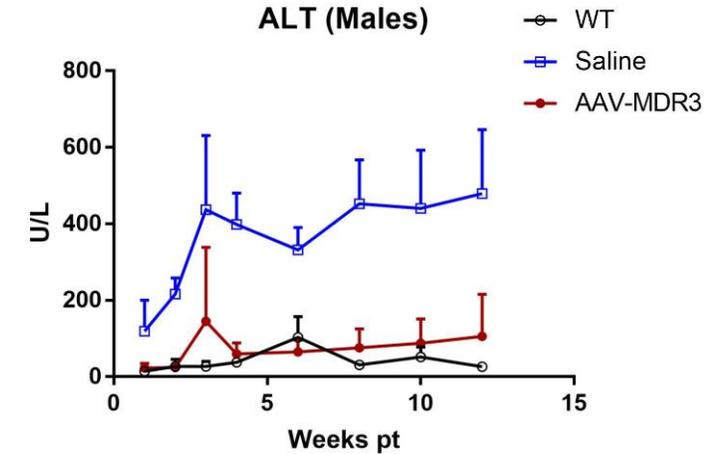
IHC (αMDR3)



KO male + AAV-MDR3

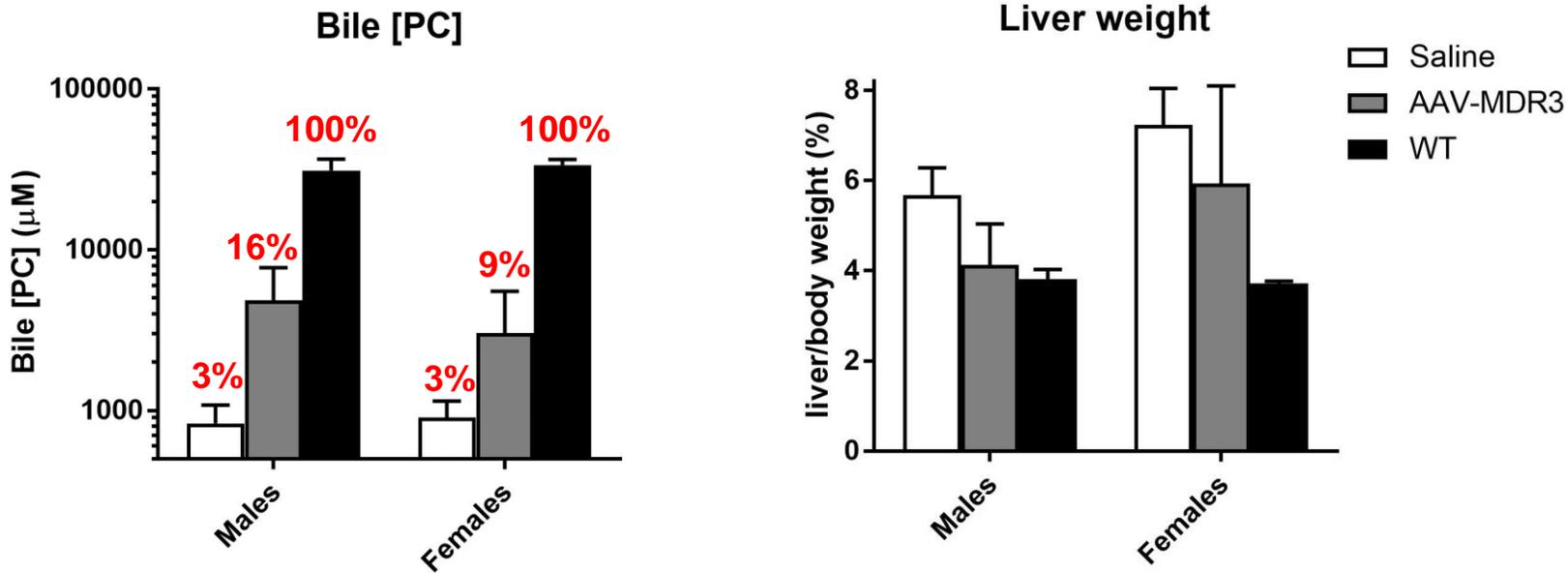


KO male + Saline

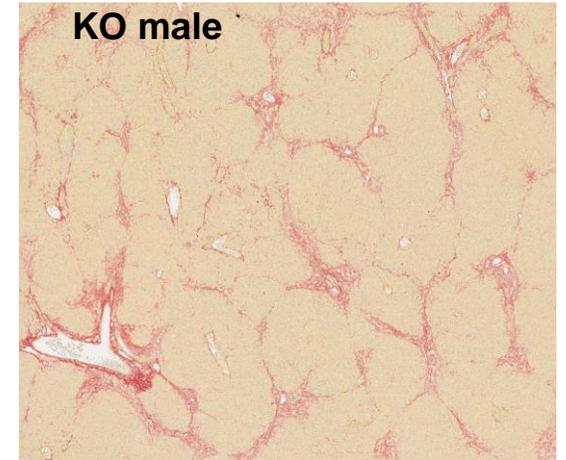


Weber et al. *Nat Comm* (2019)

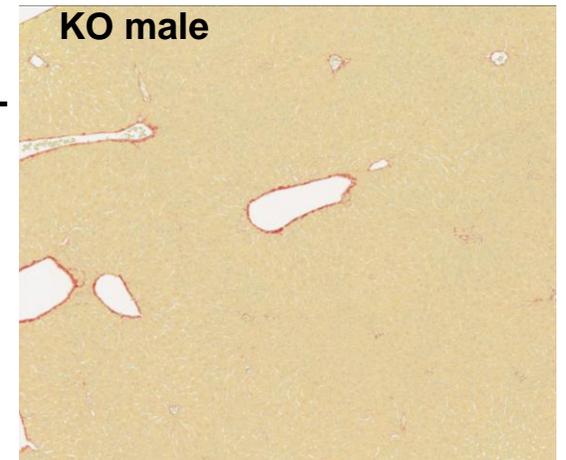
Efficacité du vecteur AAV-MDR3 chez la souris PFIC3 (*abcb4* KO) - 12 semaines post-injection



Saline-treated



VTX-803-treated



Weber et al. *Nat Comm* (2019)

- Phenotype improvement/correction
- Prevention of fibrosis

Thank you!

