

La génétique dans la maladie de Gaucher

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Place de la thérapie génique dans la maladie de Gaucher

Pr Yves-Marie PERS – PU-PH

Equipe d'immunologie clinique et Thérapeutique

Service de rhumatologie, CHU Montpellier

IRMB, INSERM U1183, Université de Montpellier

ym-pers@chu-montpellier.fr

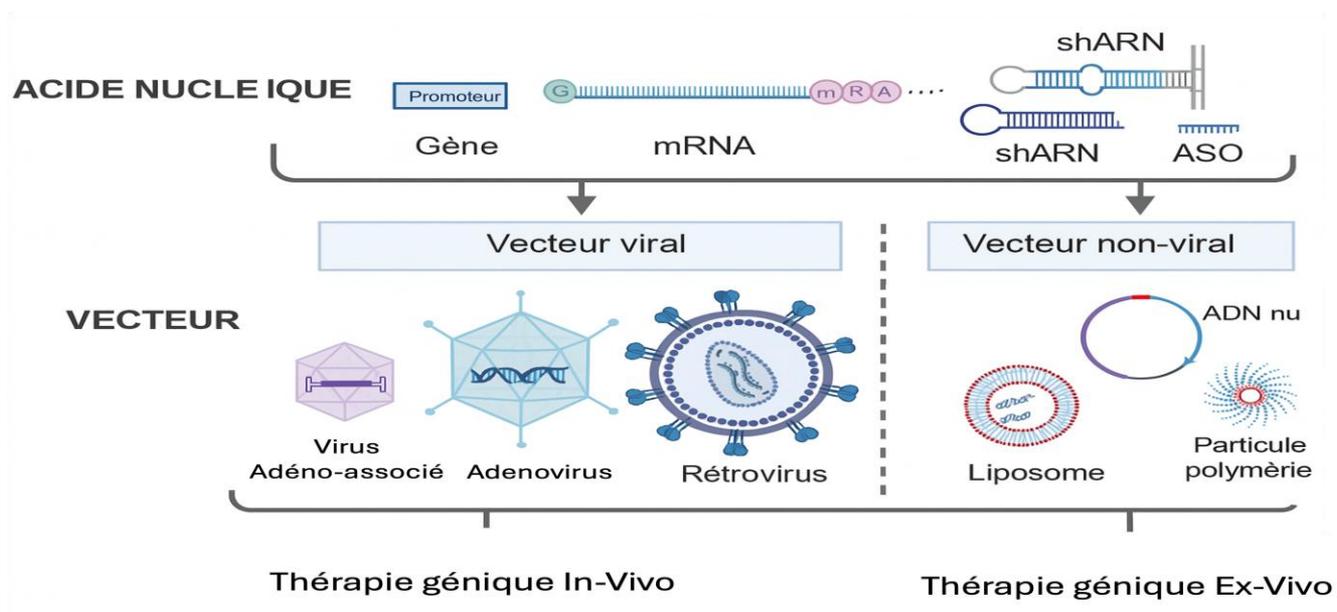


Liens d'intérêts

- Financement : Chugai, Amgen, Novartis
- Conseils : Pfizer, Abbvie, Novartis, IBSA
- Communications : Medac, BMS, Abbvie, UCB, IBSA, Jansen-Cilag

Introduction / Principes

- Définition Code de la santé publique (article L. 1131-1-1)
« une intervention consistant à transférer un acide nucléique ou un gène dans des cellules humaines à des fins thérapeutiques ou diagnostiques »

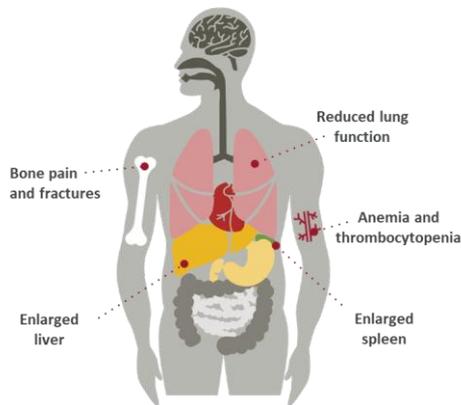
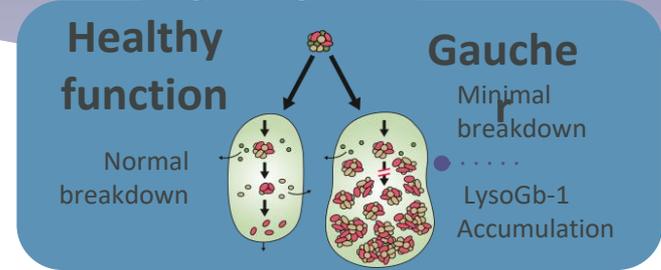


Types de vecteurs viraux

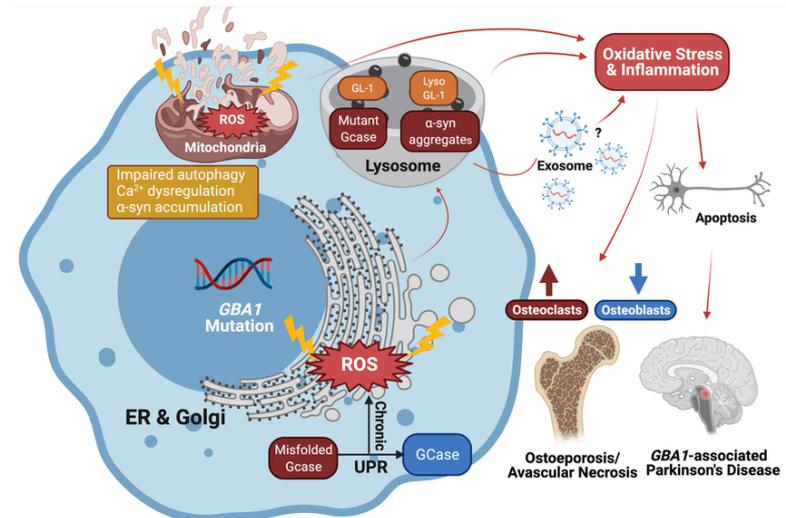
	Rétrovirus	Lentivirus	Herpès virus	Adénovirus	Virus adéno-associé	Plasmide
Type de provirus	ARN	ARN	ARN	ADN	ADN	ADN
Capacité	~9 kB	~10 kB	>30 kB	~30 kB	~4,6 kB	Illimitée
Intégration dans le génome du receveur	Oui	Oui	Oui	Non	Extrêmement rare	Non
Durée d'expression du transgène	Longue	Longue	Transitoire	Transitoire	Longue dans les cellules post-mitotiques	Transitoire
Immunité préexistante chez le receveur	Non	Non	Oui	Oui	Oui	Non
Effets indésirables	Mutagenèse insertionnelle	Mutagenèse insertionnelle	Réponse inflammatoire	Réponse inflammatoire	Réponse inflammatoire	Aucun
Transmission germinale	Possible	Oui	Non	Non	Possible	Non

Déficit en glucocérébrosidase due à une mutation du gène GBA1

- Accumulation de glucosylsphingosine (lysoGb-1)
 - Biomarqueurs diagnostiques et pronostiques



- Anemia, thrombocytopenia
- Liver, spleen enlargement
- Bone pathology, pain
- Fatigue



MG / Vecteurs viraux / Modèles animaux

Table 1. A summary of the pre-clinical gene therapy studies for Gaucher disease.

Promoter	Construct	Serotype/Viral Vector	Mouse Model	Delivery Method	Outcome and Additional Info	Source
human cytomegalovirus (CMV) immediate early promoter and enhancer	huGBA	Ad2	Chemically induced via CBE	IV to tail vein and intranasally through the nares by inspiration	High-level expression of glucocerebrosidase in the liver (100-fold endogenous levels), spleen (10-fold endogenous levels), lungs (10-fold endogenous levels), and serum (10 fold higher) compared to wild-type.	Marshall et al., 2002 [62]
DC172 promoter (hepatic restricted)	huGBA	AAV2/8	D409V/null	IV to tail vein @ 4 weeks	Expressions of (systemic) GC in animals administered AAV2/8-DC172-hGC were 50 to 100 fold higher than from the corresponding AAV2/2 vector and remained undiminished at 4 months.	Marshall et al., 2004 [63]
human elongation factor 1- α	huGBA	AAV2	C57BL/6J	IV to tail vein @ 7 weeks	GCCase activity was roughly 1.5–2 times higher than untreated mice and was maintained at least 20 weeks post-treatment.	Hong et al., 2004 [64]
human elongation factor 1- α	huGBA	Recombinant lentiviral vector	C57BL/6J	IV to tail vein @ 7 weeks	GCCase activity was 1.9 times higher (in spleen, lung, heart, and kidney) than untreated mice at 8 weeks after treatment. Increased GC activity persisted over 4 months.	Kim et al., 2004 [65]
DC172	huGBA	AAV8	D409V/null	IV to tail vein @ 4 weeks and 6 months	Supraphysiologic levels of glucocerebrosidase were achieved in the serum and liver and lasted roughly 6 months after treatment.	McEachern et al., 2006 [66]
spleen focus-forming virus promoter (SFFV)	huGBA	Retroviral GC vector	<i>Gba1</i> (flox/null); MX-Cre; plpC induced GD	Transplants of transfected bone marrow cells. Resuspended BM cells were transplanted into recipient 1.5–7.5-month-old mice	Robust increase in enzyme activity in BM, spleen, and liver from all mice treated with GC vector, 5 months post-transplantation.	Enquist et al., 2006 [67]
PGK, CD68, SFFV	huGBA	SIN Lentiviral vector	<i>Gba1</i> (flox/null); MX-Cre; plpC-induced GD	Transplants of transfected bone marrow cells. Resuspended BM cells were transplanted into recipient 5–8-month-old mice	SFFV.GBA increase GCCase levels ~10 fold, PGK.GBA, and CD68.GBA also significantly improved GCCase levels	Dahl et al., 2015 [68]
GUSB *	huGBA	AAV9	K14-Inl	First fetal transuterine injection targeting the anterior horn of the lateral ventricle of the left hemisphere of the brain. Second intracerebroventricular injection to P0 neonates. Third superficial temporal vein IV to P0–1 neonates	IV administration improved GCCase expression both neurologically and viscerally.	Massaro et al., 2018 [50]
CMV	Gba	AAV9	<i>Gba1</i> (flox/flox); UBC-creERT2 tamoxifen-induced GD	IV to tail vein injection @ 4 weeks	AAV9-CMV-Gba increased mean survival rate by 14x.	Du et al., 2019 [69]
Synapsin-1 (hSyn1 **)	Gba	AAV9	<i>Gba1</i> (flox/flox); Nestin-Cre	IP injection on day 5 postnatal	AAV9-SYN-Gba improved GCCase activity in the brain, reducing the neurological symptoms and extending the lifespan in nGD mice.	Du et al., 2019 [69]
hSynI **	huGBA	AAV9	K14-Inl	IV to superficial temporal vein to P1 neonates	Overexpression of GCCase did not promote neurotoxicity in the brain of injected animals and improved the lifespan for all treated animals.	Massaro et al., 2020 [70]

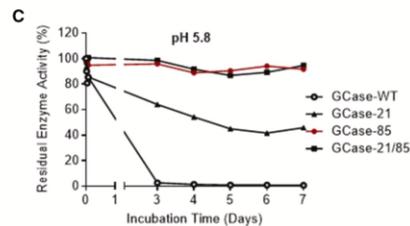
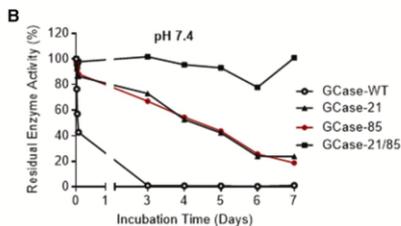
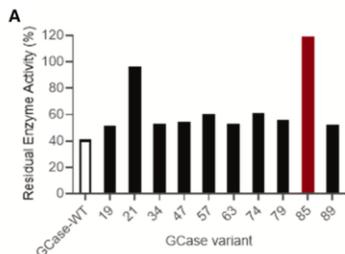
Essais cliniques en cours

- NCT04145037 (Avrobio) : Lentivirus / CSH autologues / GD1 --- > résultats modestes, safety OK
- NCT05815004 (Avrobio) : Lentivirus / CSH autologues / GD3
--- > retrait
- NCT04411654 (Prevail Therapeutics and Lilly) : AAV9 / GBA1 / GD2 intra-cérébral --- > PROVIDE study
- NCT05324943/44 (Spur therapeutics) : AAV8 >> SS3 / GBA1 / GD1 intraveineux --- > GALILEO study phase 1

Développement pré-clinique

Capside AAV (AAVS₃) contenant une cassette d'expression avec un transgène GBA1 modifié qui code pour une variante unique de la glucocérébrosidase (GCCase85)

- Différent de la glycosylation macrophage absorption / ERT
- Promoteur hépatique HCR/hAAT
- Pont disulfure GCCase85 / AAV8

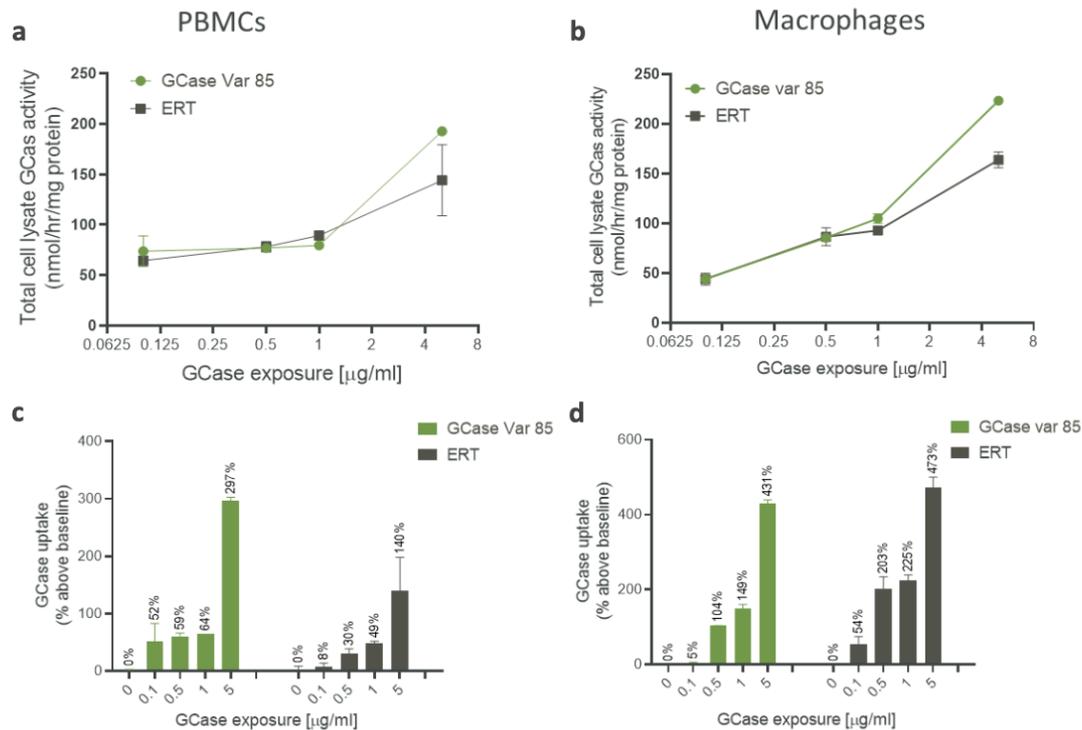


>> Demi-vie active 6 fois plus longue
>> Demi-vie active plus de 21 fois plus longue
dans des conditions de pH lysosomal

Développement pré-clinique

Résultats in vitro sur macrophages et PBMC (absorption)

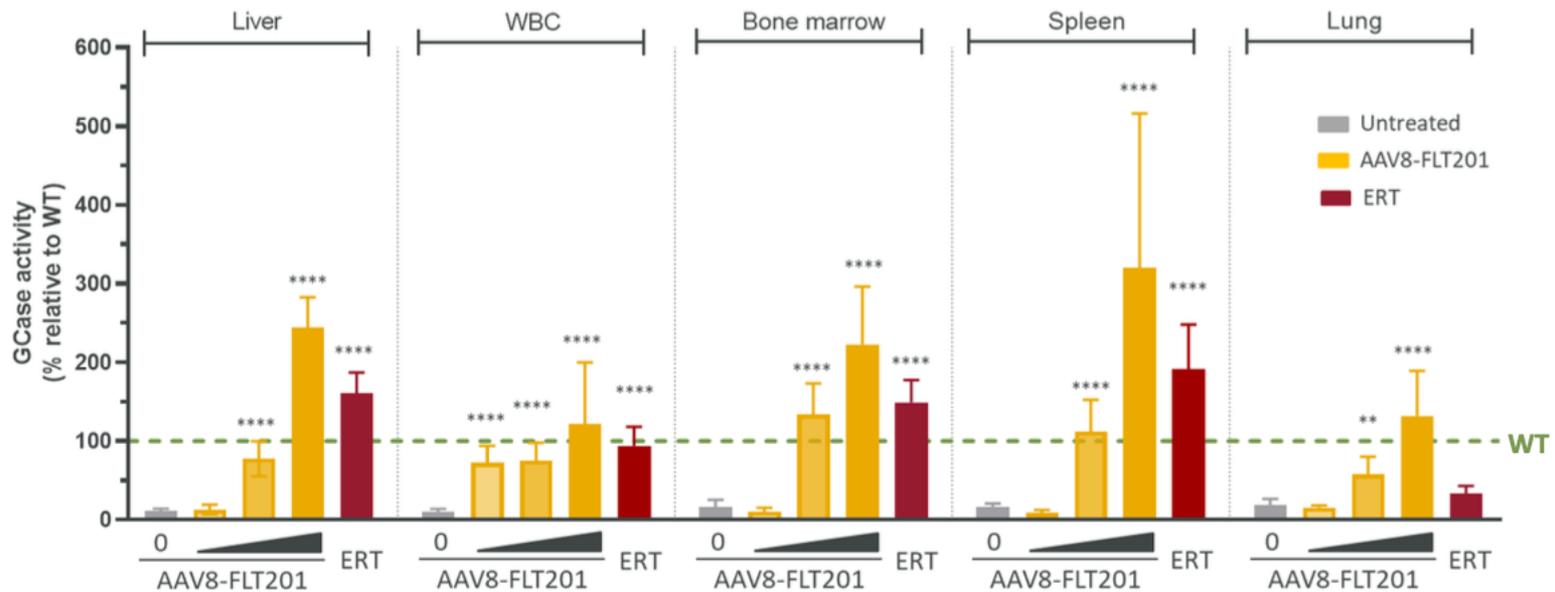
Figure 6: Uptake of GCCase_{var85} and ERT by human PBMCs (a,c) and macrophages (b, d)



ERT=velaglycerase alfa; PBMCs = peripheral blood mononuclear cells.

Développement pré-clinique

Restauration activité GCase dans les tissus chez souris GCase déficientes



AAV8-FLT201 = AAV8 pseudo-typed FLT201 genome; 2×10^{10} , 2×10^{11} and 2×10^{12} vg/kg; ERT = velaglucerase alfa 60 U/kg biweekly; WT = wild type mice; WBC = White blood cells; **p<0.01, ***p<0.001, ****p<0.0001 vs. vehicle control.

Développement pré-clinique

Maintenance activité GCase chez le primate (macaque)

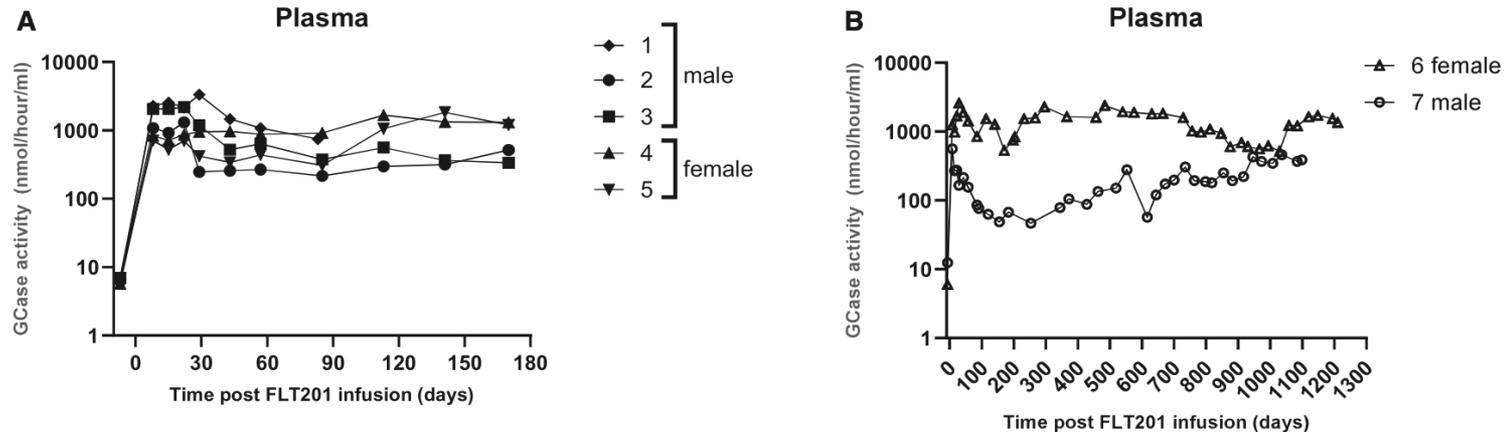


Figure 6. Plasma GCase activity in rhesus macaques following administration of FLT201

GALILEO-1 study

GALILEO-1: A first-in-human, open-label, multicenter study of FLT201

Adults with
Gaucher Type 1
on ERT or SRT

Cohort 1
4.5e11
vg/kg dose



	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age / Gender	35 / M	25 / M	24 / M	30 / F	24 / M	58 / F
Age at diagnosis	4	3	16	15	20	15
GBA1 Variant	p.Val433Leu; p.Asn409Ser (c.1297G>T; c.1226A>G)	p.Asn409Ser; p.Leu483Pro (c.1226A>G; c.1448T>C)	c.334_338del (p.(Gln12Valfs*32)) / c.1265_1319del55; 1448T>C; 1483G>C; 1497G>X	p.Asn409Ser; p.Leu483Pro (c.1226A>G; c.1448T>C)	p.Asn409Ser; p.Leu29Alafs*18 (c.1226A>G; c.84dup)	p.Asn409Ser; p.Trp223Arg c.1226A>G; c.667T>C
Duration of SoC	4 years	22 years	9 years	14 years	4 years	24 years
Therapy at entry	ERT	SRT	SRT	ERT	SRT	SRT
Plasma GCase activity (µmol/L/h)	0.1	0.09	0.04	<0.1*	0.5	<0.1*
DBS Lyso-Gb1 (ng/mL)	102.85	10.29	486.41 [#]	72.6	257	52.6
Hemoglobin (g/dL)	15.1	15.2	14.5	13.3	17.0	12.6
Platelet count (x10 ³ /mL)	200	213	124	176	167	113
Spleen volume (MN)	1.88	1.39	2.20	1.73	8.39	5.65
Liver volume (MN)	1.14	1.06	0.81	0.75	1.11	0.88

* Below lower limit of quantification; # average of two baseline values

DBS: dried blood spot; ERT: enzyme replacement therapy; GBA1: glucosylceramidase beta 1; GCase: Glucocerebrosidase; lyso-Gb1: Glucosylsphingosine; MN: Multiples of normal; SoC: standard of care; SRT: substrate reduction therapy

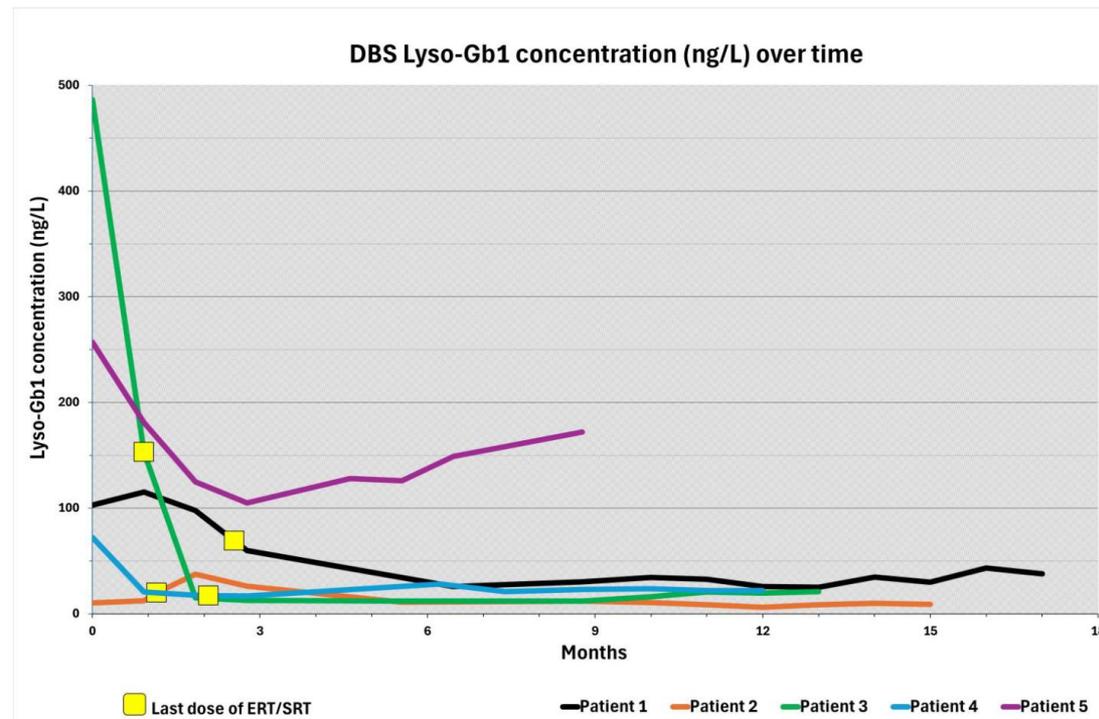
- All participants treated with a single dose of FLT201 (4.5e11 vg/kg)
- Immune management regimen begins 3 weeks post-infusion
- Post FLT201 follow up between 9 and 17 months
- Withdrawal of Standard of Care treatment (ERT or SRT) 4-11 weeks post FLT201

GALILEO-1 study

Substantial and durable reductions of Lyso-Gb1 in patients with persistently high levels despite years of prior treatment

Lyso-Gb1 is a reliable and validated biomarker for GD¹ and highly correlated to disease severity² and treatment response³

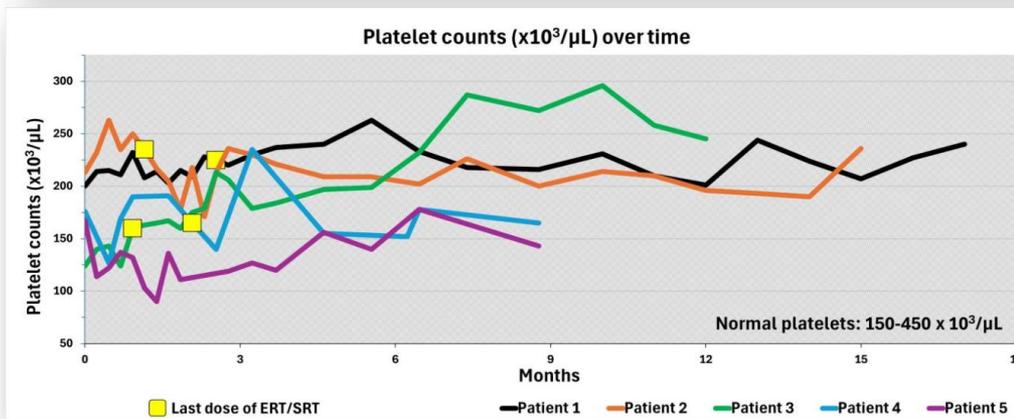
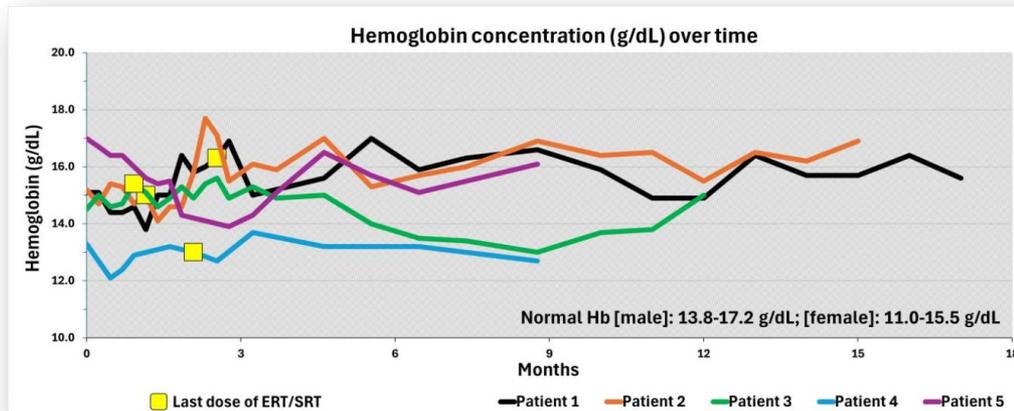
- Reductions in Lyso-GB1 seen as early as 1 month and sustained after SoC discontinuation (out to 14 months)
- 4/5 patients had elevated levels at baseline despite 4-24 years of SoC
- Low levels maintained in patient who entered trial with well-controlled lyso-Gb1



Data cut off as of 06 December 2024

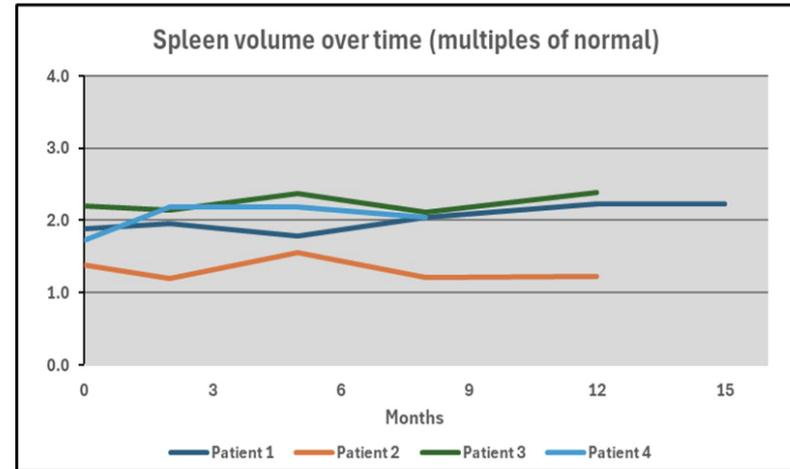
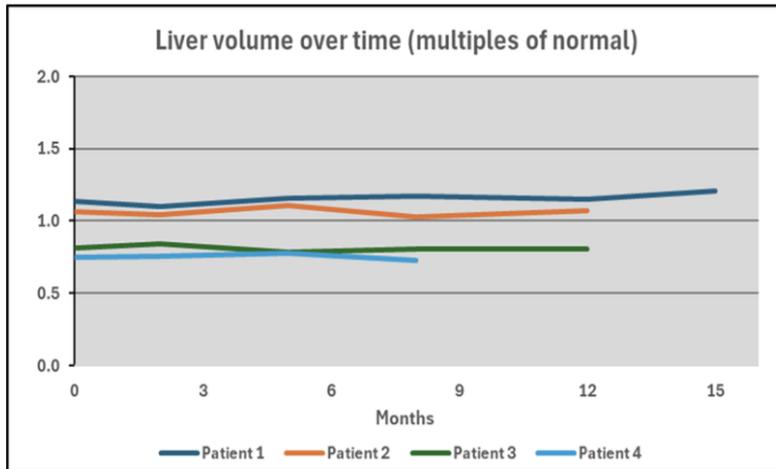
GALILEO-1 study

FLT201: Sustained improvement or maintenance of hemoglobin and platelets



GALILEO-1 study

FLT-201 – sustained effect on liver and spleen



GALILEO-1 study

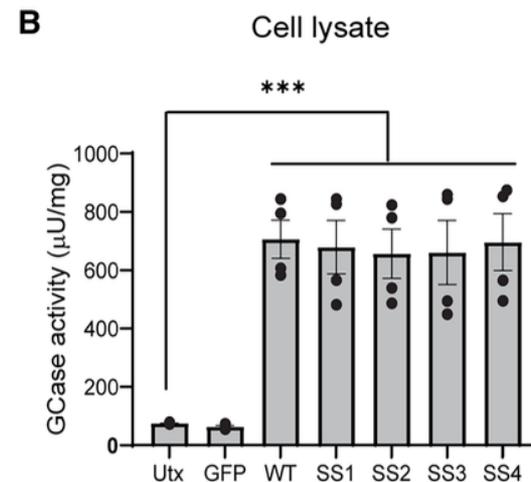
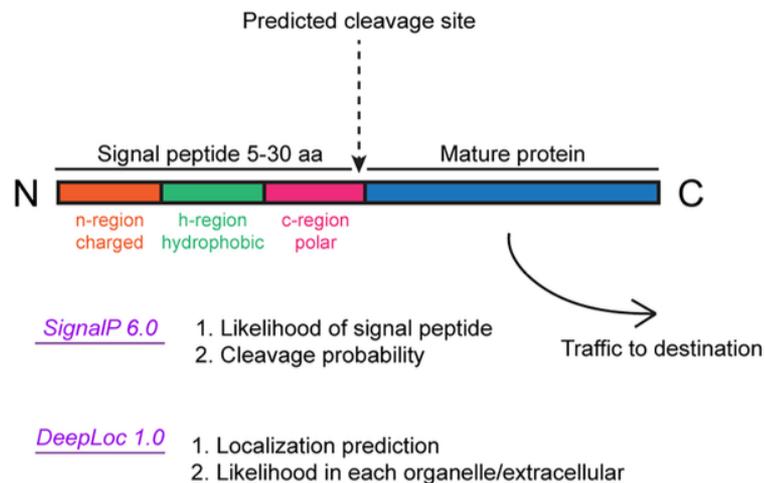
FLT201: well tolerated, with a favorable safety profile

- Infusions well tolerated; no infusion-related reactions
- ADRs were mild to moderate
- No dose-limiting toxicities
- 2 cases of ALT elevations above normal range ($\leq 2 \times \text{ULN}^*$) deemed related to therapy
 - Spontaneously resolved or managed with immune therapy
- Transient Anti-GCase antibodies in 2 patients
- ADRs related to immune management consistent with known profile

Summary of Adverse Drug Reactions for FLT201 and Immune Management (n\geq2)	
Adverse Drug Reactions (ADR)	# events (# patients)
FLT201	
Elevated Alanine aminotransferase (ALT)	7 (6)
Fatigue	4 (3)
Activated partial thromboplastin time prolonged	2 (2)
Anti-GCase neutralizing antibodies	2 (2)
Prednisone	
Hyperglycemia	3 (3)
Weight increase	2 (2)
Panic attack	2 (1)
Tacrolimus	
Diarrhea	4 (4)

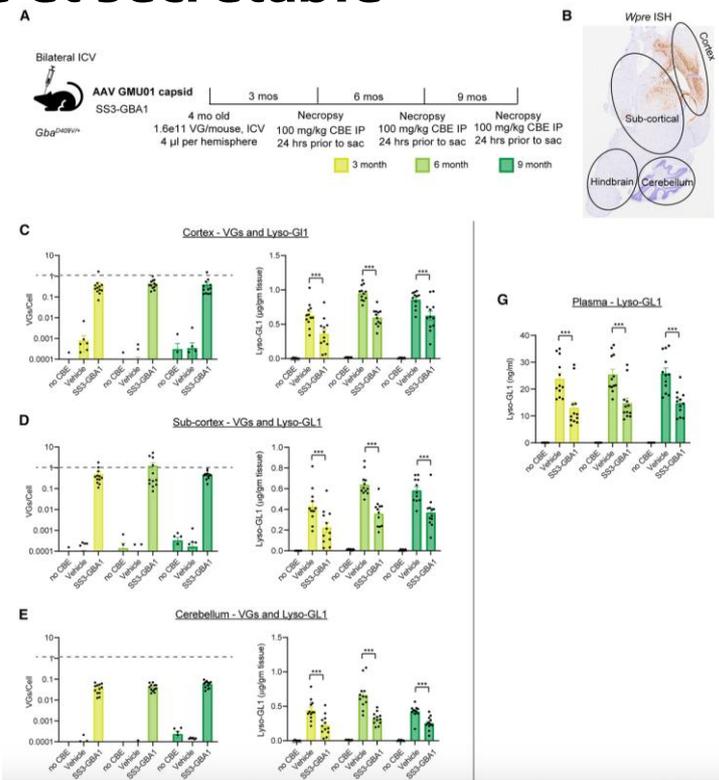
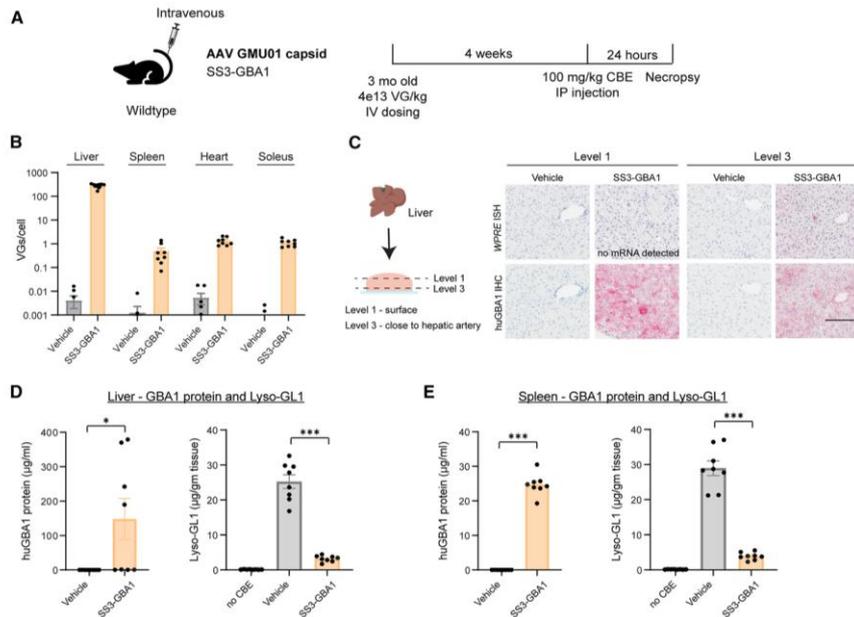
Perspectives

Combinaison d'une nouvelle capside, AAV.GMU0125, exprimant une protéine humaine GCCase modifiée et sécrétable



Perspectives

Combinaison d'une nouvelle capside, AAV.GMU0125, exprimant une protéine humaine GCase modifiée et sécrétable



Sécurité, et efficacité >>> Perspectives dans GD2 ?

Limites

- Risque d'une injection intra-cérébrale vs expression + faible du vecteur post-injection IV
- Pas de suivi long-terme de l'expression GBA1 : multiple injection
- Réponse immune :
 - Allo-immunisation --- > baisse efficacité
 - Adenovirus --- > inflammation +++ (meningite, encephalite....)
 - Mutagenese ---- > CHC
 - Microangiopathie thrombotique (AAV)
- Coût important

*Sun, J.Y. Gene Ther. 2003,
Chandler, R. Hum. Gene Ther. 2017
Venditti, C.P. Nat. Biotechnol. 2021
Ling, Q. Nat. Rev. Drug Discov. 2023*

Conclusions

- Stratégie prometteuse
- Résultats très préliminaires
- Prudence sur la tolérance: allo-immunisation
- Etudes longitudinales nécessaire pour durée expression génique
- Phase 3 en cours

