Avancées dans la thérapie génique des leucodystrophies de l'enfant

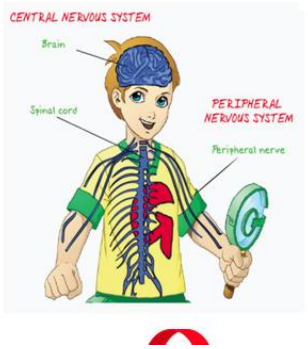
6ème Journée nationale de la filière Brainteam , Mardi 23 Mars 2021

C Sevin, CRMR leucodystrophies, hôpital Bicêtre et Inserm U1169

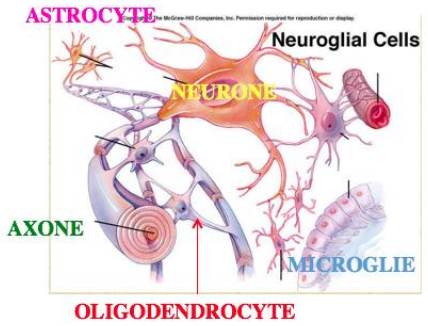
Thérapie génique (des leucodystrophies héréditaires)

- Pénétrer dans le SNC: franchir/éviter la BHE
- Soigner les bonnes cellules…
  au bon endroit …et au bon moment
- Faible réaction immune (vecteur, transgène)
- Absence de toxicité (surexpression…)
- Etre administré le plus tôt possible

Cerveau…
Mais aussi moelle,
nerf périphérique



Oligodendrocyte…
Mais aussi neurone,
astrocyte, microglie



Particularités de l'enfant

- Maladies rares (petites cohortes)
- Début antenatal ou précoce
- Variabilité clinique
- Diagnostic souvent tardif
- Evolution rapide

- Histoire naturelle??
- Physiopathologie ??
- Aspects réglementaire
- Procédures +/- difficiles à adapter

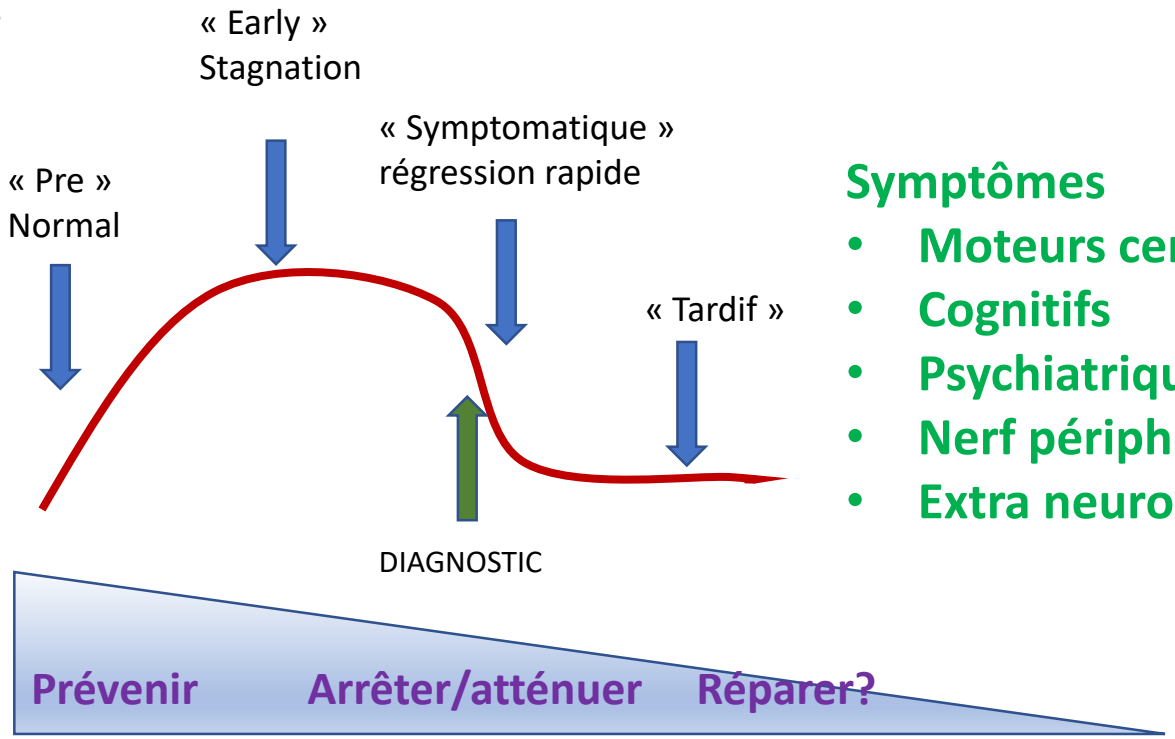
Quelles leucodystrophies? Quand traiter?

- Intervalle libre -> fenêtre thérapeutique
- Gène connu…
- Evolution pas trop rapide...

Adrénoleucodystrophie liée à l'X

Leucodystrophie métachromatique

(Maladie de Krabbe infantile)



Symptômes

- **Moteurs centraux**
- **Cognitifs**
- **Psychiatriques**
- **Nerf périphérique**
- **Extra neurologiques?**

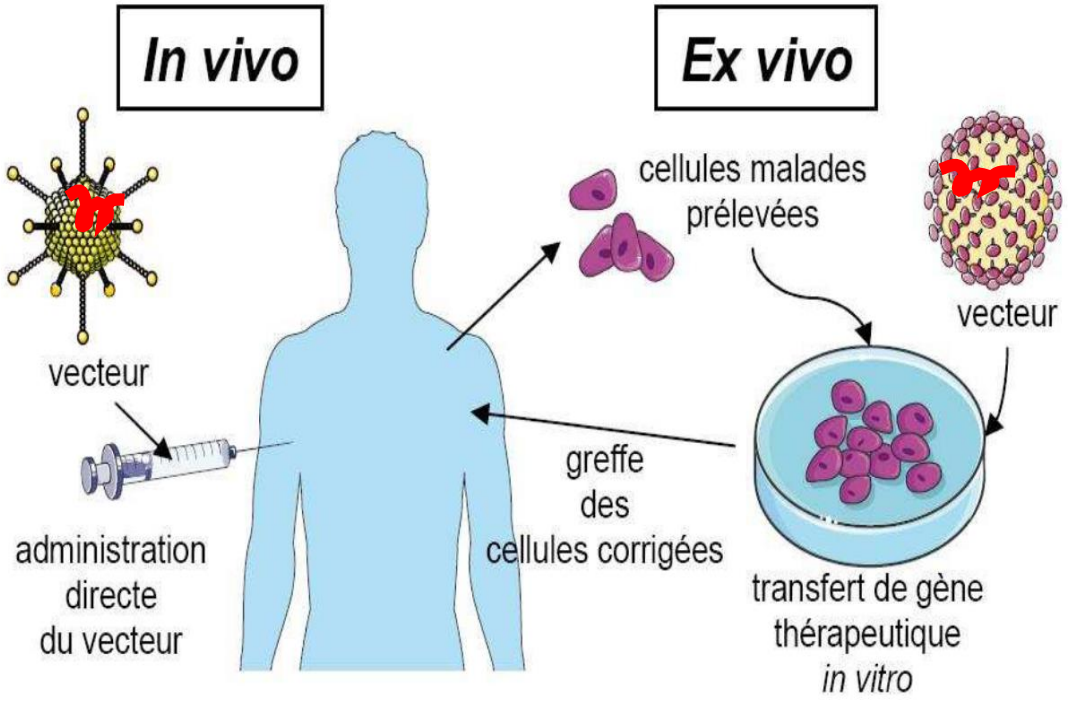
Thérapie génique: *in vivo* vs. *ex vivo*

AAV

Intracérébral
Intrathécal/ICV
Intraveineux

Simple, peu invasif
Action rapide
Variété de sérotypes
Diverses voies (IC, IT, IV)

Ciblage non spécifique
Réponse immune-> iS?
Pas d'intégration
Perte lors des divisions
Ré-administration?
BHE à franchir (IV)



Gène « sauvage »
Silencing
Autre gène thérapeutique
CRISPR cas9

Lentivirus

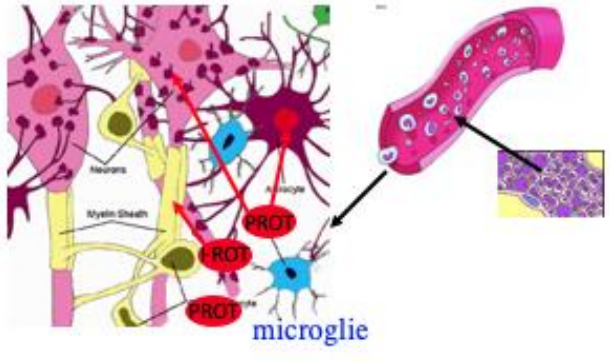
Autotransplantation de CSH génétiquement modifiées

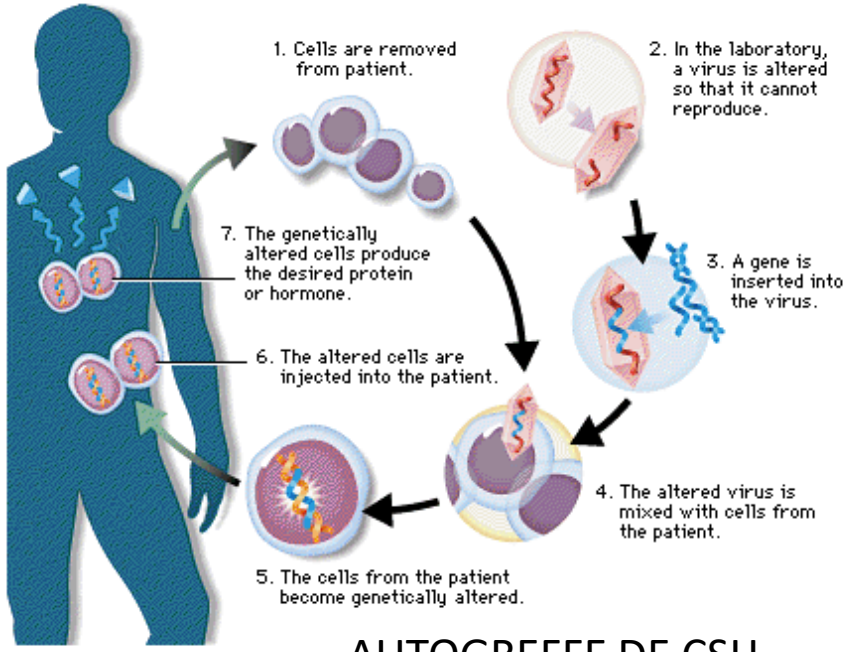
Ciblage spécifique
Immuno-compatibilité
Intégration
Effet thérapeutique additionnel (immuno-modulation, « reset »)

Invasif (greffe)
Mutagénèse insertionnelle
Délai d'action (12 mois)

Rationnel de la thérapie génique ex vivo dans les leucodystrophies

L'allogreffe « conventionnelle »:
effet thérapeutique dans certaines leucodystrophies





AUTOGREFFE DE CSH
GÉNÉTIQUEMENT CORRIGÉES

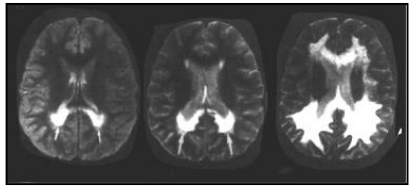
- Délai d'action retardé (9-12 mois)
- Protéine sécrétée vs non sécrétée
- Histoire naturelle (évolution rapide ->lente)
- Stade de la maladie (présymptomatique -> stade avancé)
- Physiopathologie (« inflammation », rupture de la BHE)

Adrénoleucodystrophie
Leucodystrophie métachromatique
Krabbe

Thérapie génique dans l’adrénoleucodystrophie lié à l’X

Adrénoleucodystrophie liée à l'X (ABCD1)

1/15.000 garçons, 35 nouveaux cas / an en France



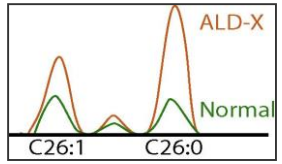
- **ALD cérébrale** (5-12 ans): 35%

- **Adrénomyéloneuropatie** (AMN55%):
  - paraparésie spastique
    - hommes (pénétrance 100% >55ans)
    - et femmes conductrices (>80%)
  - non léthale , mais atteinte motrice sévère
  - troubles sphinctériens, ataxie sensitive, NP
  - Et 35% des patients AMN développent une ALD cérébrale

- **Forme limitée à une Insuffisance surrénale** (10%) -> CCALD ou AMN

- **Pré-symptomatique**

Tous les patients accumulent des AGTLC (marqueur diagnostic)



- **100% garçons**
- **80% femmes Hz**

60% des patients mâles vont développer une atteinte cérébrale

ALD cérébrale de l'enfant

Initial Symptoms

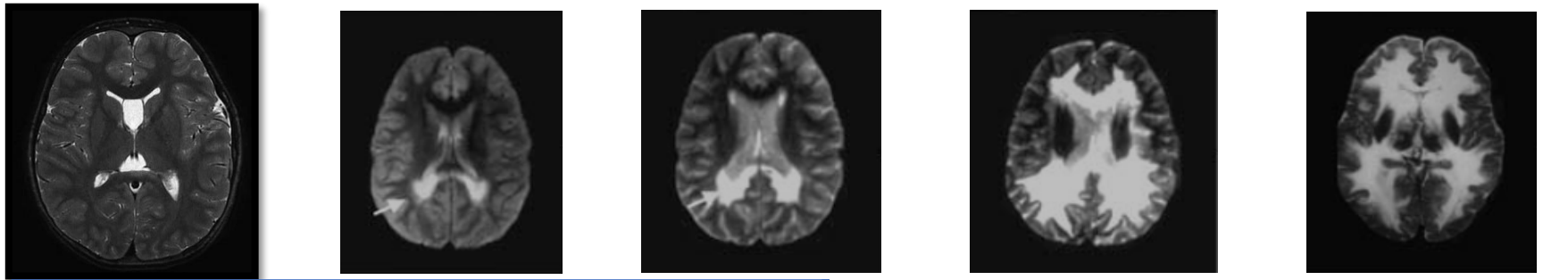
- Poor school performance
- Behavioral problems
- May be misdiagnosed as ADHD

Moderate Disability

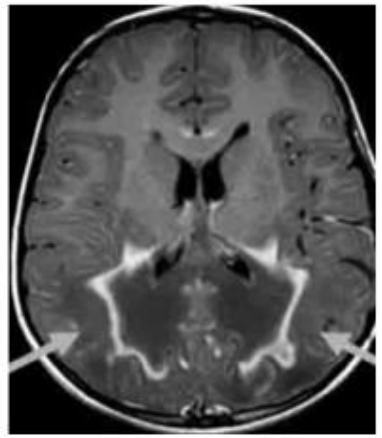
- Hearing impairment
- Aphasia/apraxia
- Vision impairment
- Swallowing dysfunction
- Walking/running difficulties
- Episodes of incontinence
- Seizures

Major Functional Disability

- Cortical blindness
- Loss of communication
- Tube feeding
- Wheelchair dependence
- No voluntary movement
- Total incontinence



12-18 mois

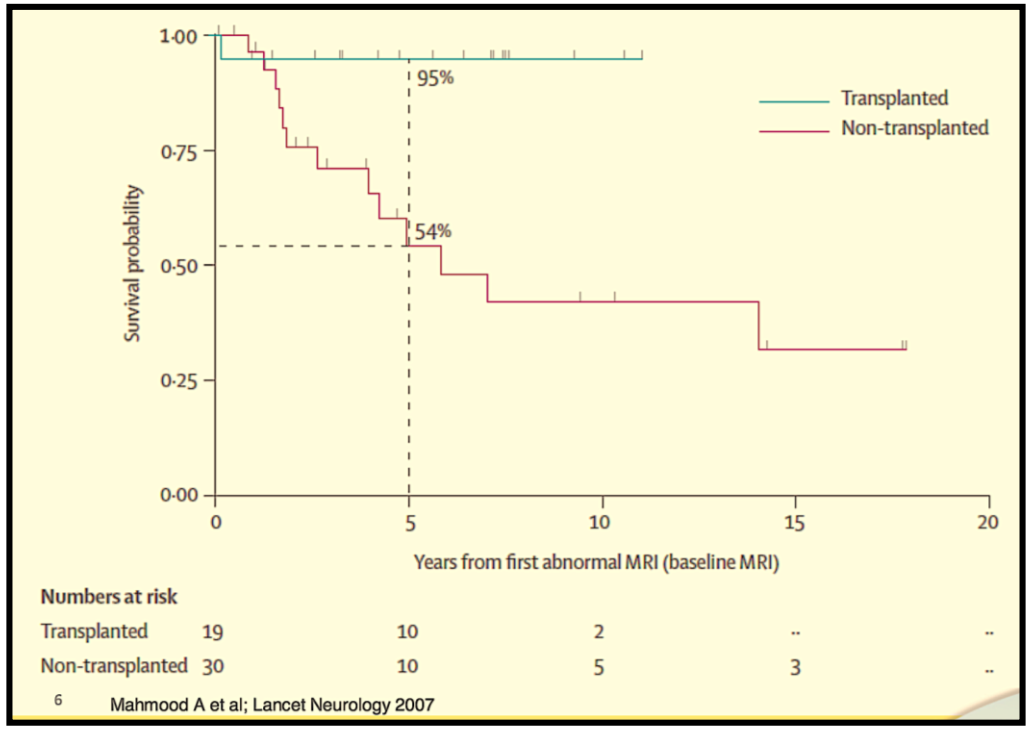


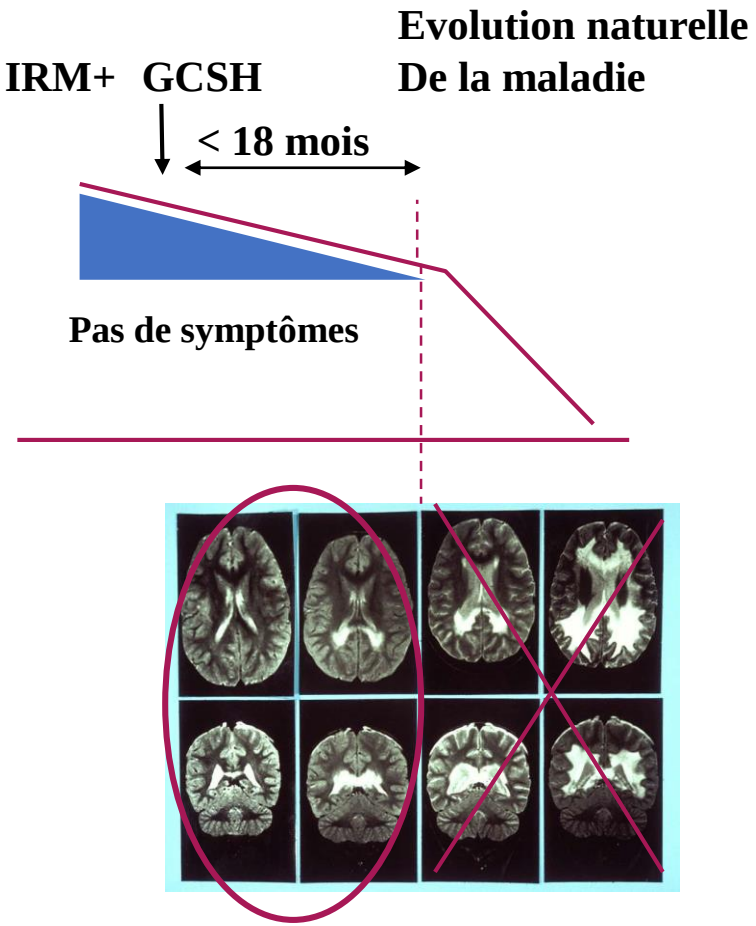
Leucodystrophie Inflammatoire+++

La GCSH peut stopper la démyélinisation cérébrale dans l'ALD

Si elle est réalisée suffisamment tôt:

- Lésions minimes à l'IRM (score de Loes ≤ 9)
- Inflammation (prise de gadolinium à l'IRM)
- Pas/(peu) de symptômes
- Intérêt du dépistage/suivi IRM
- Délai d'action 12-18 mois





Thérapie génique *ex vivo* dans l'ALD
(Bluebird bio)

- **Key enrollment criteria**
  - Age ≤17 years, evidence of active CALD (GdE+) with early disease (Loes score 0.5-9.0; NFS ≤1), and no matched sibling donor
- **Primary efficacy outcome**
  - Proportion of patients who are alive and free of major functional disabilities (MFD) at Month 24

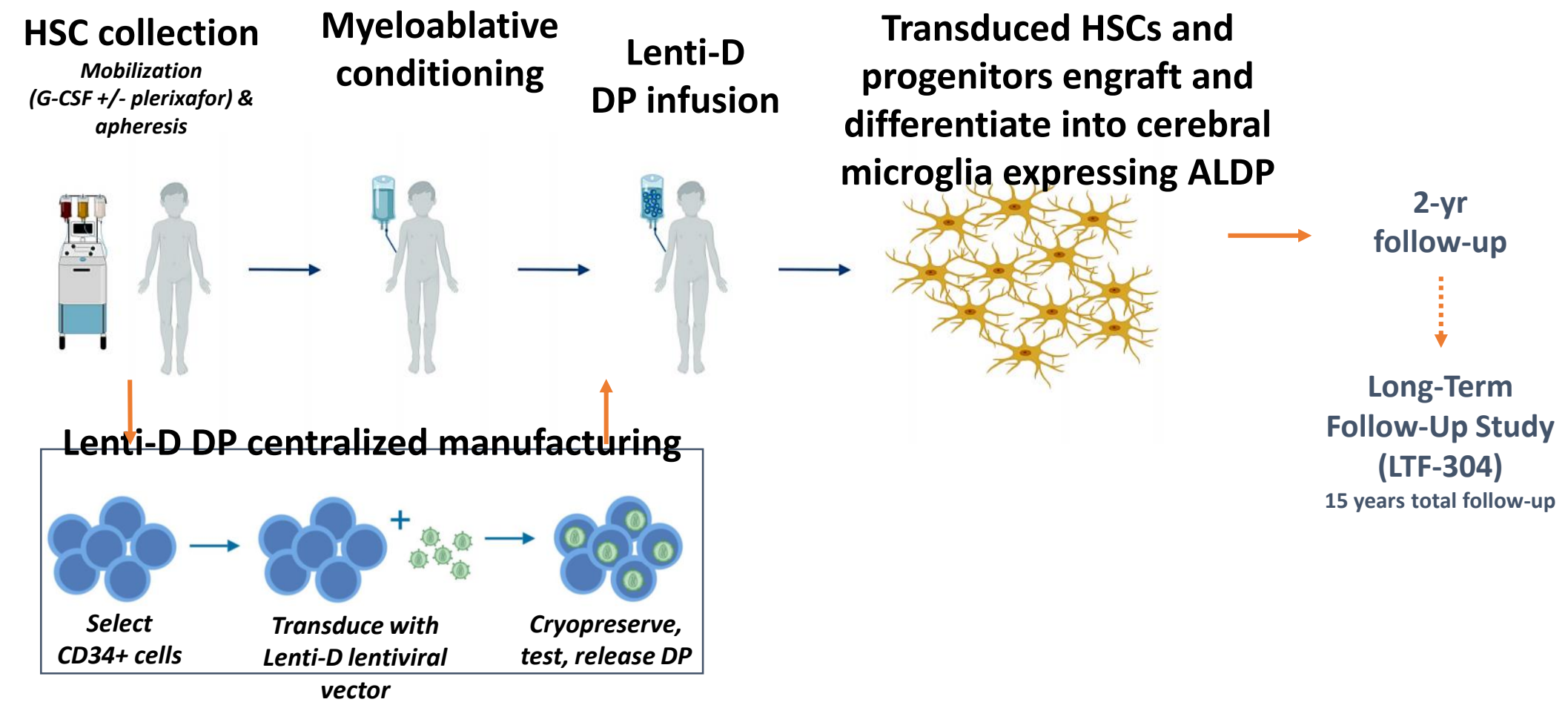
- **Primary safety outcome**
  - Proportion of patients who experience Grade ≥2 acute graft-versus-host disease (GVHD) or chronic GVHD by Month 24 post-treatment
- **Secondary and exploratory efficacy outcomes**
  - Changes in neurologic function score (NFS), gadolinium (GdE+) resolution, overall survival, and change in Loes score
- **Additional key safety parameters**
  - Engraftment failure, adverse events, detection of replication-competent lentivirus, and insertional oncogenesis

Eichler F. et al. *NEJM* 2017;377:1630.

CALD, cerebral adrenoleukodystrophy; GdE+, positive for gadolinium enhancement; GVHD, graft-versus-host disease; NFS, neurologic function score

Thérapie génique *ex vivo* dans l'ALD

Protocole



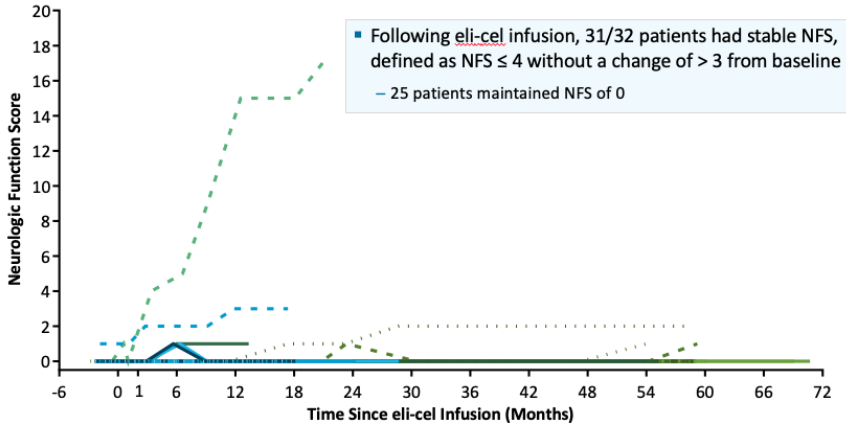
ALDP, adrenoleukodystrophy protein; DP, drug product; HSC, hematopoietic stem cell; LTF, long-term follow-up

Kuhl et al. EBMT 2020

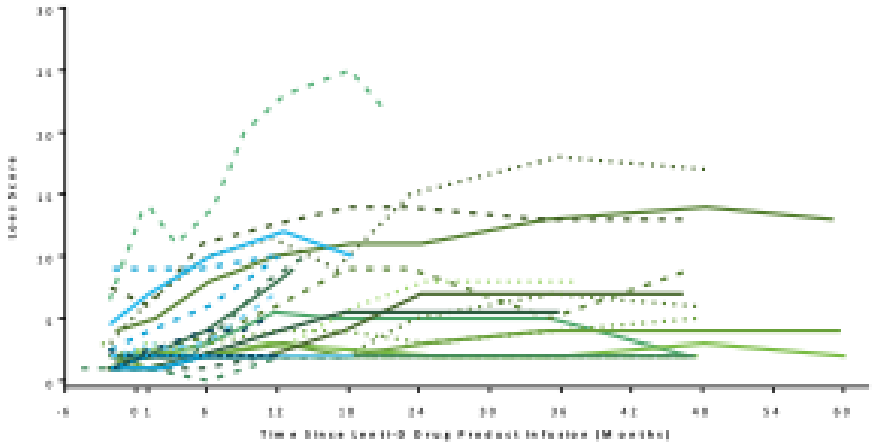
Score neurologique fonctionnel

Follow-up		
Parameter	**ALD-102 (N=32)**	**ALD-104 (N=13)**
	Median (min – max)	
Age at ICF (years)	**6** (3 – 13)	**8** (5 – 12)
Follow-up (months)	**30.0** (9.1 – 70.7)[a]	**6.1** (2.2 – 10.3)
	20.2 (9.1 – 22.1)[b]	
Loes score at baseline[c]	**2** (1 – 9)	**3** (1 – 7)
NFS at baseline[d]	**0** (0 – 1)	**0** (0 – 1)

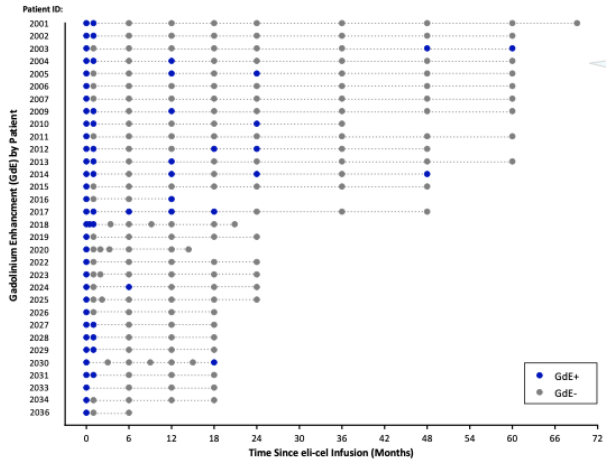
- Neurologic function score (NFS) is a 25-point score used to evaluate the severity of gross neurologic dysfunction in CALD b scoring 15 symptoms across 6 categories (hearing, communication, vision, feeding, locomotion, and incontinence)[8]



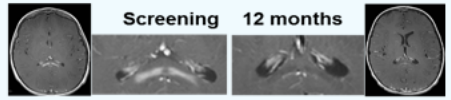
Score de démyélinisation



Prise de gadolinium



GdE is an indicator of active inflammation but was less extensive after treatment



- GdE resolves in most patients following eli-cel infusion
- Re-emergence of GdE does not correlate with neurologic function score or MFDs

Conclusions

- **Autogreffe de CSH génétiquement corrigées** -> mêmes indications que l'allogreffe
- **Profil de sécurité favorable** (N=45 patients)
  - celui du conditionnement myéloablatif (idem pour l'allogreffe)
  - Pas de GVH, reconstitution précoce
- **Stabilisation de la progression de la maladie neurologique (identique à l'allogreffe)**

-> **Alternative à l'allogreffe?** En particulier pour les patients sans donneur apparenté?

- Pas de recherche de donneur -> plus rapide
- Autogreffe -> 100% compatible
- Pas de nécessité d'immunosuppression (GVH)

-> **Résultats à long terme à évaluer**

- Perte d'efficacité?
- Mutagénèse insertionnelle?

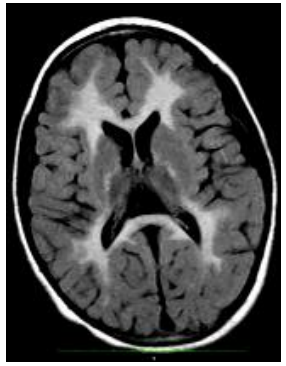
-> **Démarches en cours pour accès au marché (EMEA, CHMP,EC -> été 2021?**

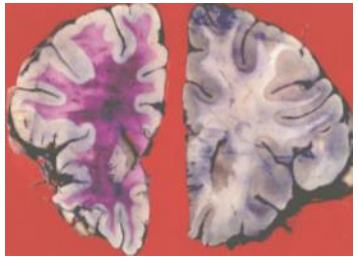
-> ATU de cohorte Q2-Q3 2021?

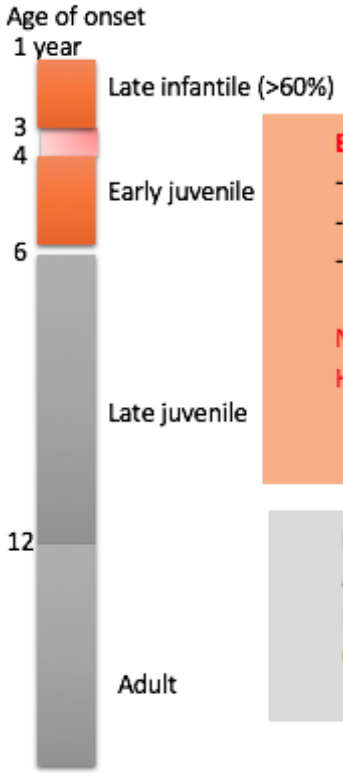
Thérapie génique dans la leucodystrophie métachromatique (LDM)

Metachromatic Leukodystrophy (MLD)

- Lysosomal disease (1/40 000) autosomal recessive
- Deficiency of ArylSulfatase A (ARSA) -> Sulfatide storage
- Demyelination and neuronal degeneration in CNS and PNS







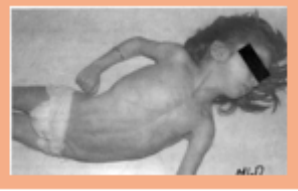
Clinical phenotypes and therapeutic options

EARLY ONSET FORMS (1 to 4 years) : homogeneous

- Motor impairment: hypotonia, ataxia, loss of walk and sit -> complete loss of motor functions
- Cognitive impairment -> complete loss of cognitive functions
- Rapid progression (12-18 months) leading to vegetative state and premature death

No treatment

HSCT/HSCT-GT for presymtomatic patients



LATE ONSET FORMS (>6 years): more heterogeneous

Age at onset, evolution, severity

More progressive

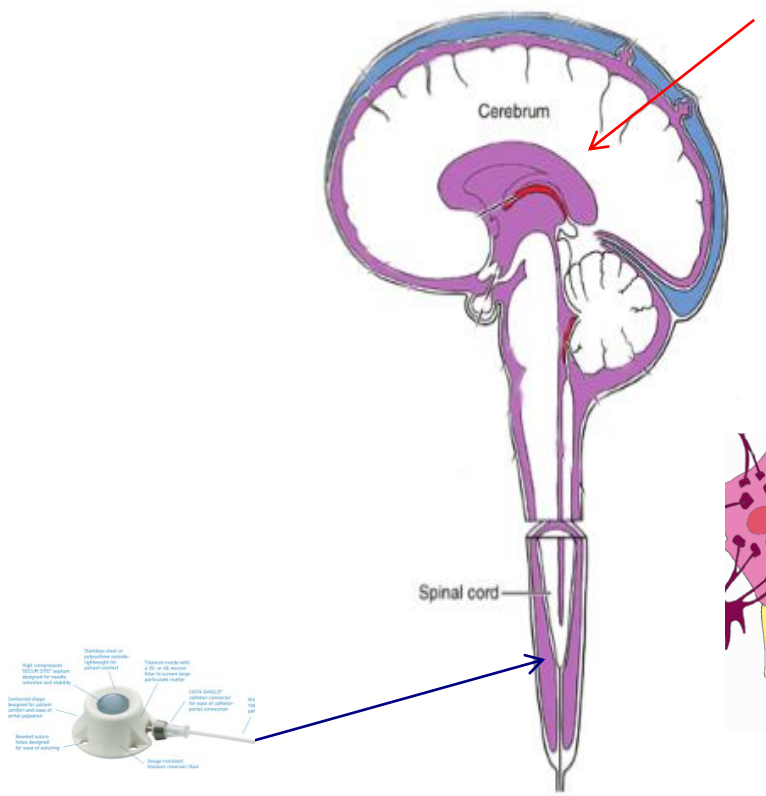
Can be improved but not cured by HSCT

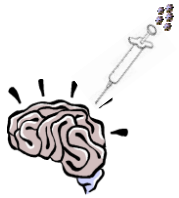
THERPAUTIC OPTIONS

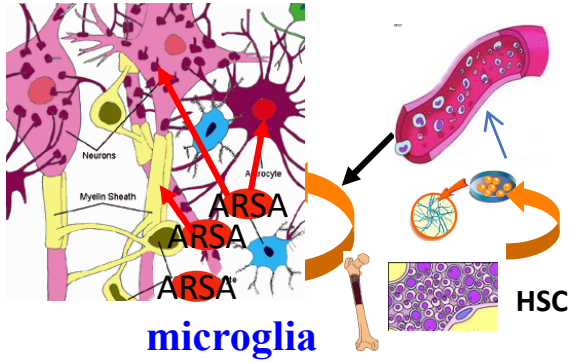
- HSCT
- HSCT-GT
- IT-ERT
- IC-GT (C-1109)

LDM: une maladie => 3 approches en essai clinique

Thérapie génique *in vivo*







Enzymothrapie intrathécale

Thérapie génique *ex vivo*

Thérapie génique *ex vivo* dans la LDM
(Orchard therapeutics)

- **Presymptomatic/ early-symptomatic patients with early-onset MLD (LI/EJ; N=20)**

- 20 early-onset MLD subjects treated with experimental autologous, ex-vivo, lentiviral-mediated hematopoietic stem cell gene therapy (HSC-GT) followed for ≥3 years post-treatment (range 3-8 years).

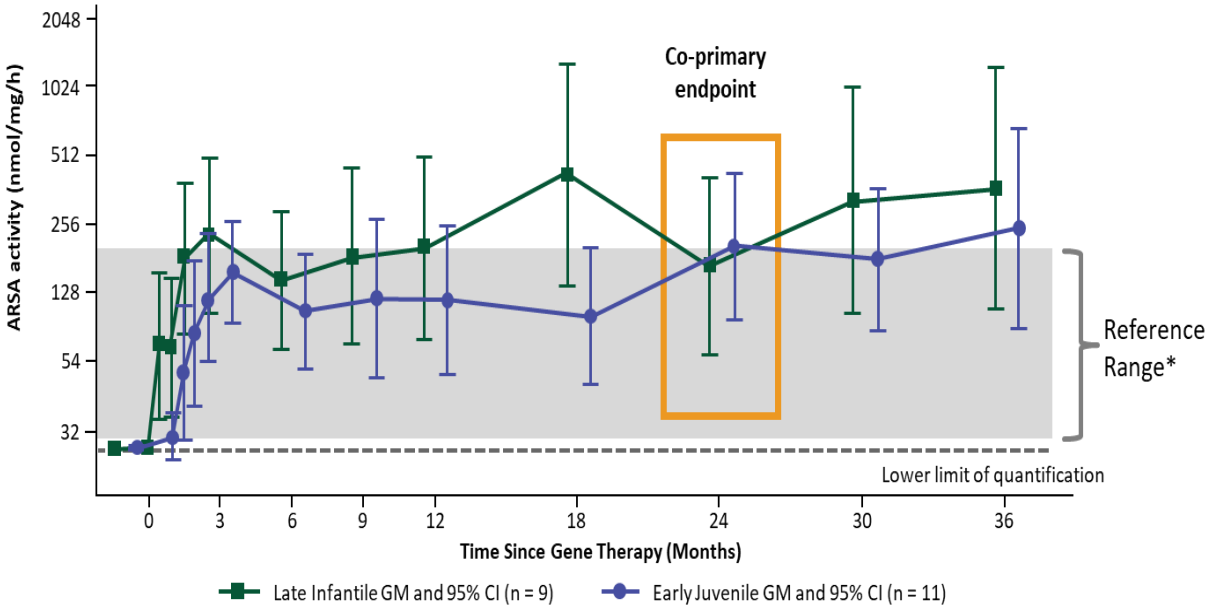
Safety and Survival:

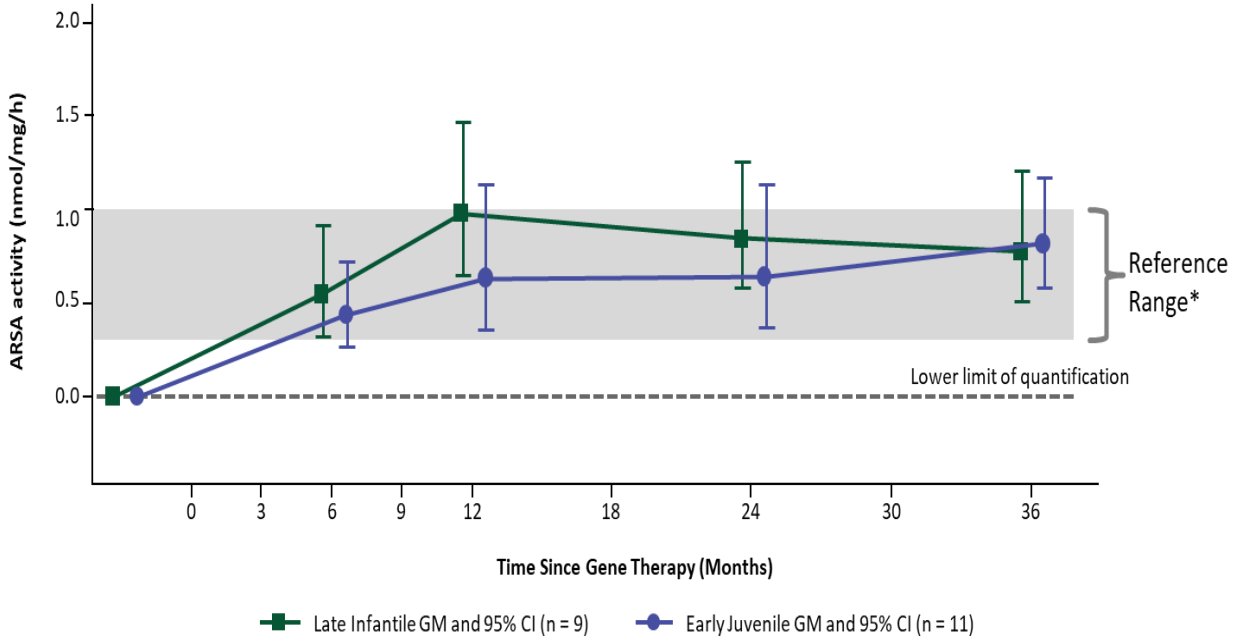
- 18/20 patients are alive
- 2 patients treated after the onset of symptoms, died 8- and 15- months post-treatment due to disease progression
- No evidence of malignant abnormal clonal proliferation, replication competent lentivirus or infusion related reactions
- Adverse events typically associated with busulfan conditioning and reported within the first 3 months of treatment included febrile neutropenia, infections, liver disorders, stomatitis and mucosal inflammation.

Slides provided by F Fumagalli with permission of Orchard Therapeutics

Results: Engraftment of Gene-corrected Stem cells Results in Reconstitution of ARSA Activity

ARSA Activity in Peripheral Blood Mononuclear Cell	ARSA Activity in Cerebrospinal Fluid





All patients achieved high levels of multi-lineage engraftment, polyclonal hematological reconstitution, and ARSA activity reconstitution in CSF and peripheral blood within or above normal levels

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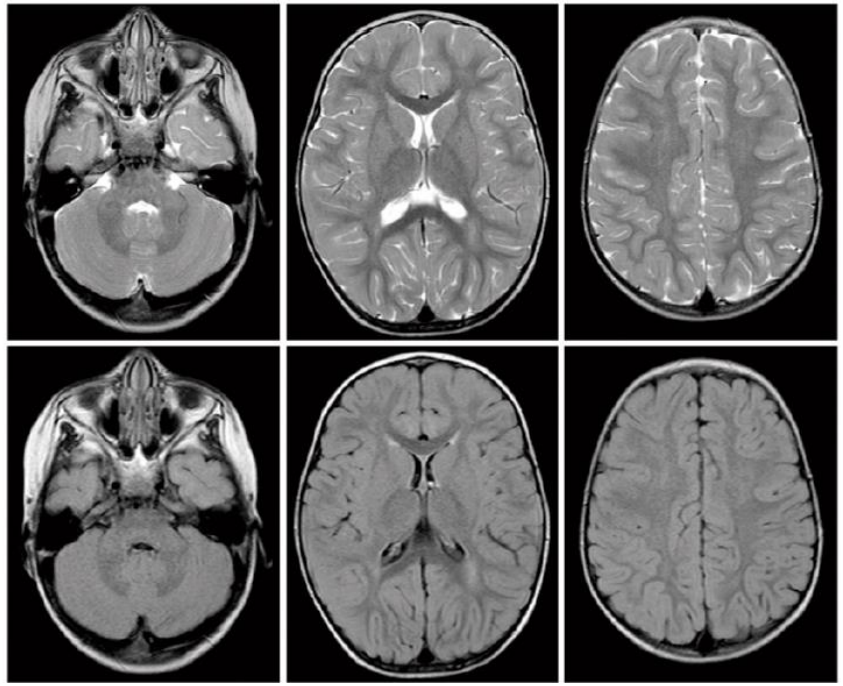
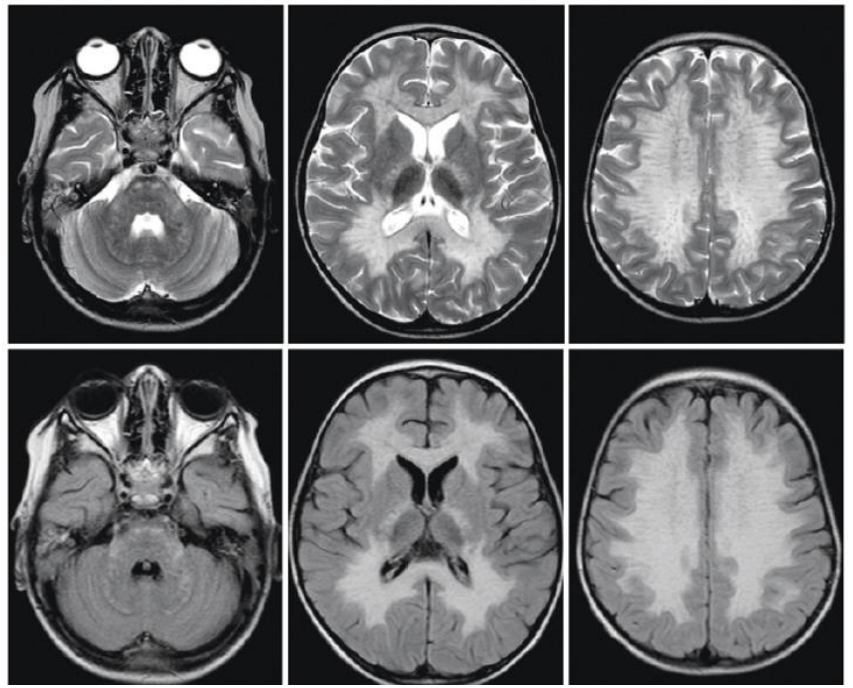
Brain MRI

MLD06 aged 40 months



MLD06 sib aged 40 months



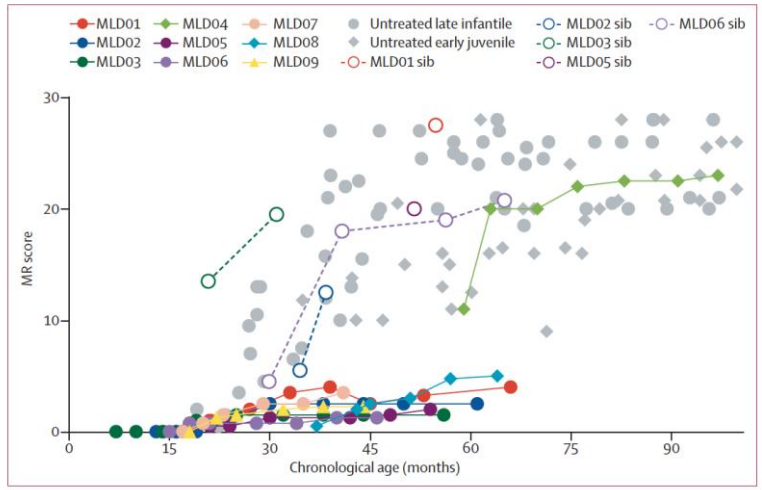
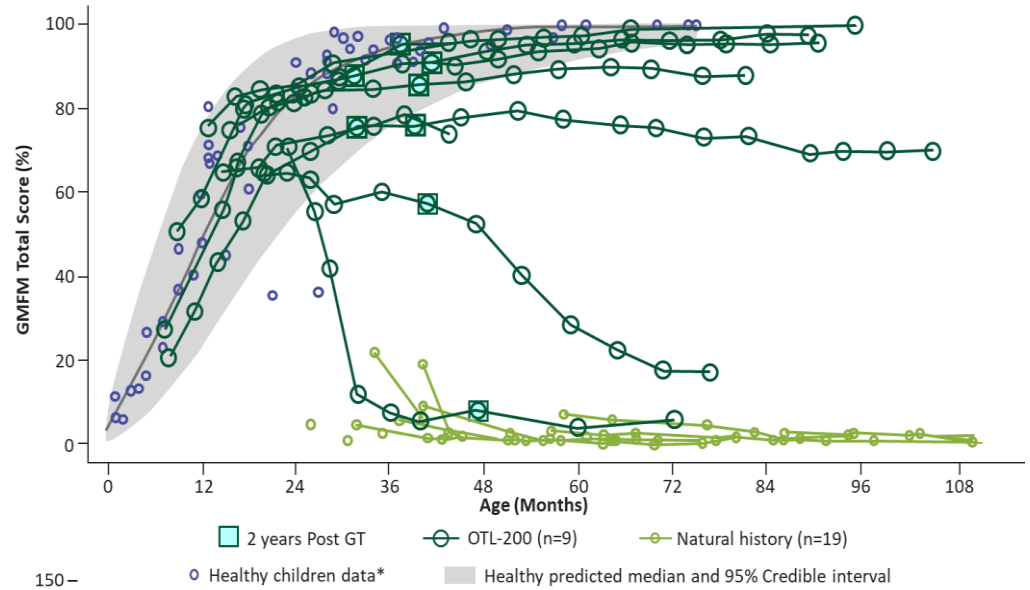


Figure 4: Effect of the treatment on brain MR scores

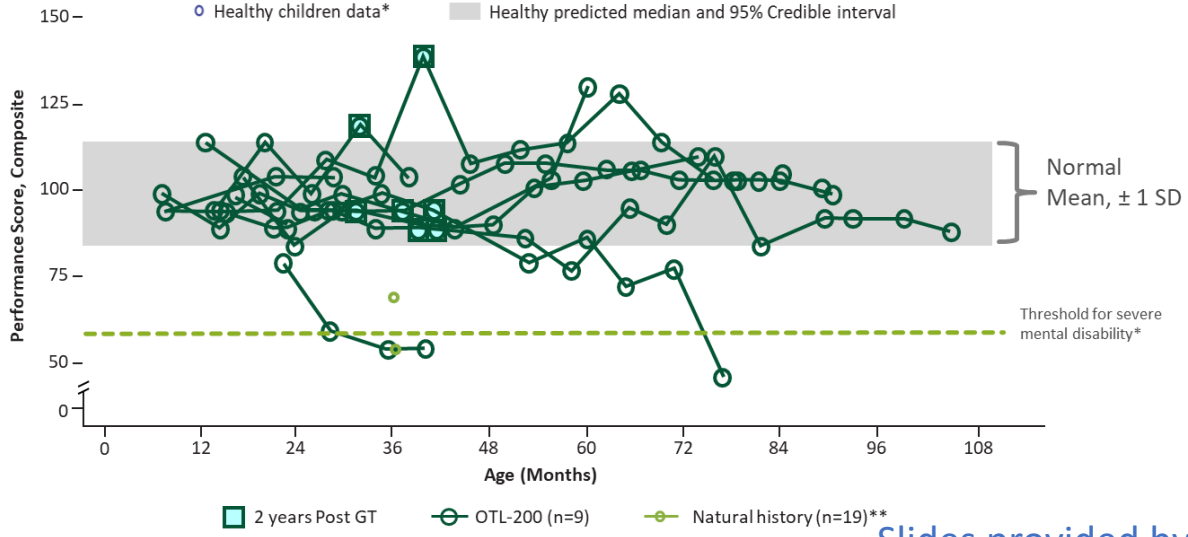
Sessa et al. Lancet 2016

Results: Gross Motor Function Measure and Cognitive performance Score Post-Gene Therapy vs. Natural History (Late Infantile)

Individual Gross Motor Function Scores



Individual Cognitive Performance Scores



Sustained positive effects of treatment on gross motor function, cognition, brain imaging and other instrumental biomarkers **have been shown up to 7.5 years post-treatment.**

Overall, these results suggest that OTL-200 is effective in modifying the disease course of early-onset MLD, particularly when subjects were treated prior to the onset of overt clinical manifestations of the disease

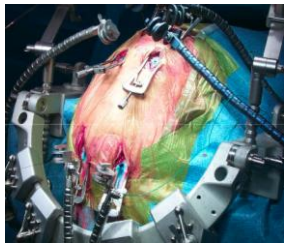
Slides provided by F Fumagalli with permission of Orchard Therapeutics

Summary

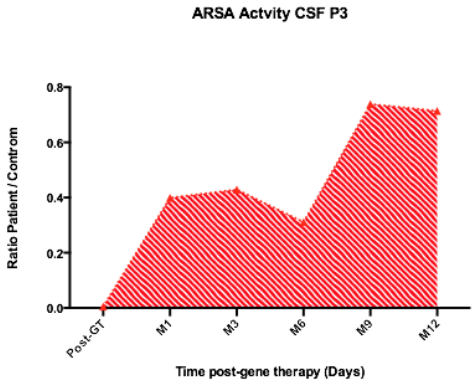
- Safety of the procedure
- Benefit for presymptomatic LI-MLD and pre/early-symptomatic EJ-MLD
- Long-term follow-up needed
- Under commercialization process
- Future?
  - Treatment for late-juvenile and adult MLD?
  - Combined therapy for symptomatic LI-MLD?

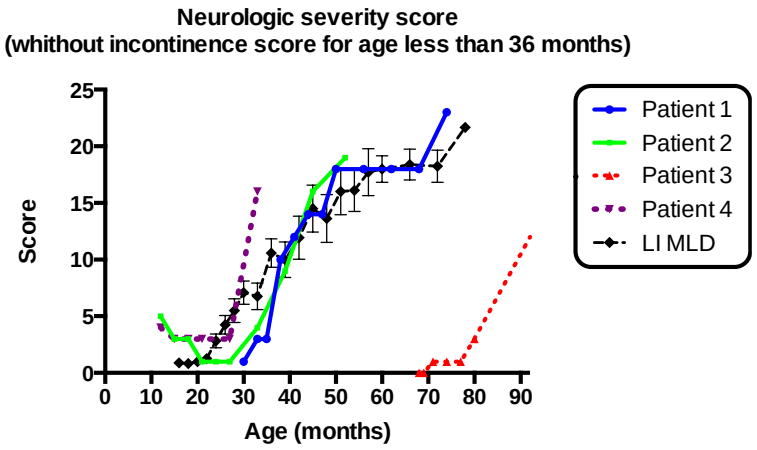
Thérapie génique intracérébrale de la LDM

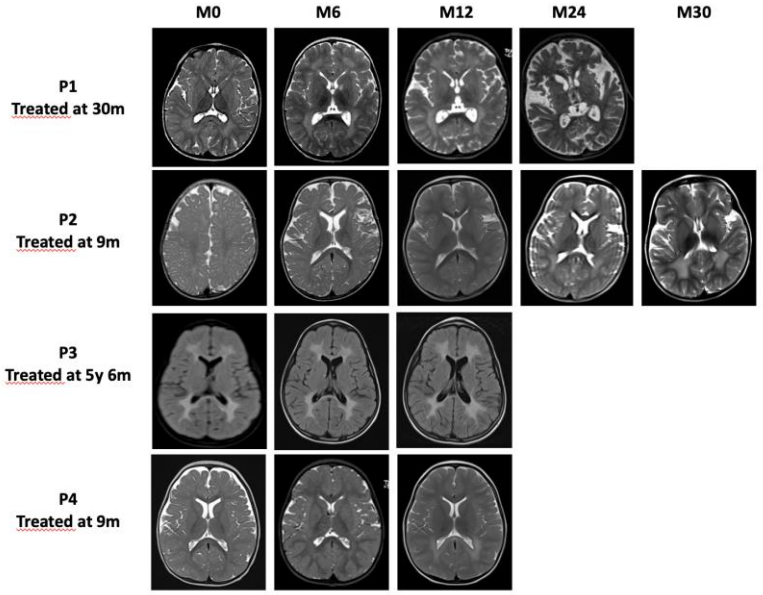
Inserm, P Aubourg, C Sevin, N Cartier, M Zerah



- Vecteur AAV10-ARSA (6 trajets, 12 sites)
- Formes précoces (LI, EJ) (age 6 mois-5 ans)
- 4 Patients (3/4 LI-MLD); 2 pré-symptomatiques + 2 symptomatiques
- Profil de sécurité démontré
- Restauration d'une activité de l'ARSA (20-70% des contrôles)
- Effet insuffisant pour prévenir/stabiliser la maladie





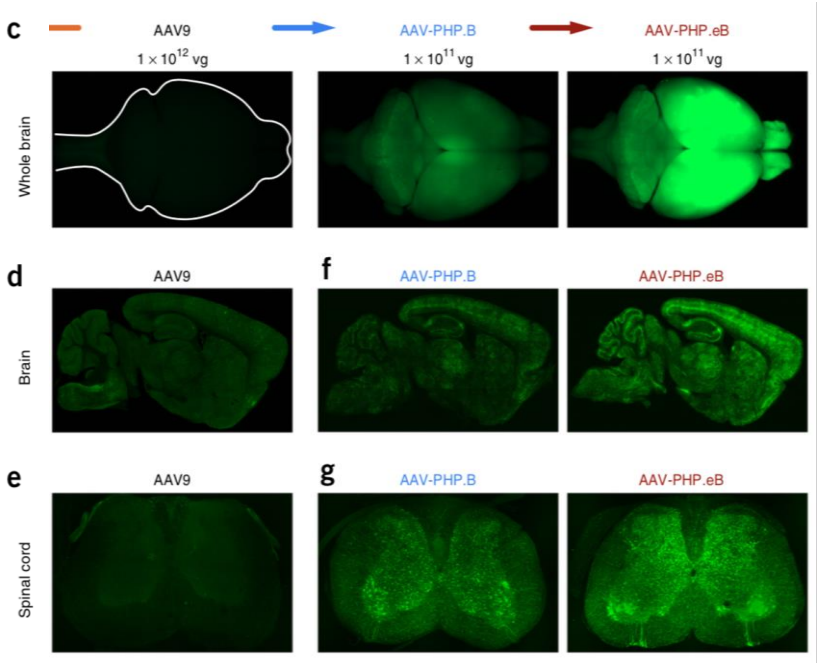


Thérapie génique in vivo du SNC: perspectives

- Plusieurs essais utilisant d’autres voies d ’administration (IV, intra-thécale, ICV), vecteur AAV9 ou AAV10
- Nouveaux sérotypes plus performants en particulier après administration IV
  - ex: PHP.eB
- Combinaison de traitements
  - ex: Krabbe infantile essai clinique -> AAV10 IV + HSCT

De nouveaux vecteurs AAV pour franchir la BHE après administration intraveineuse

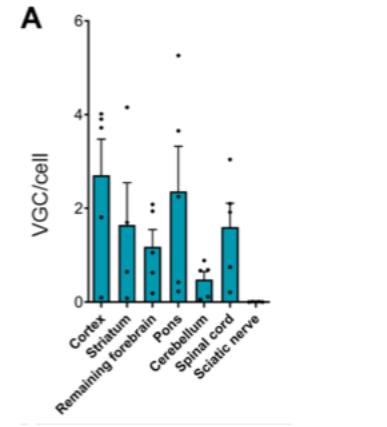
AAV-PHPeB

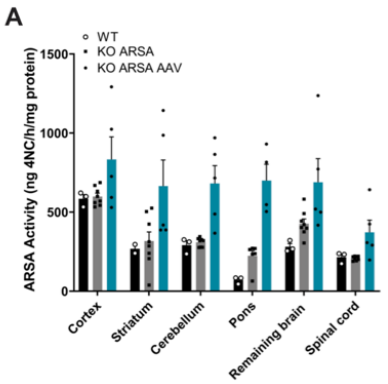


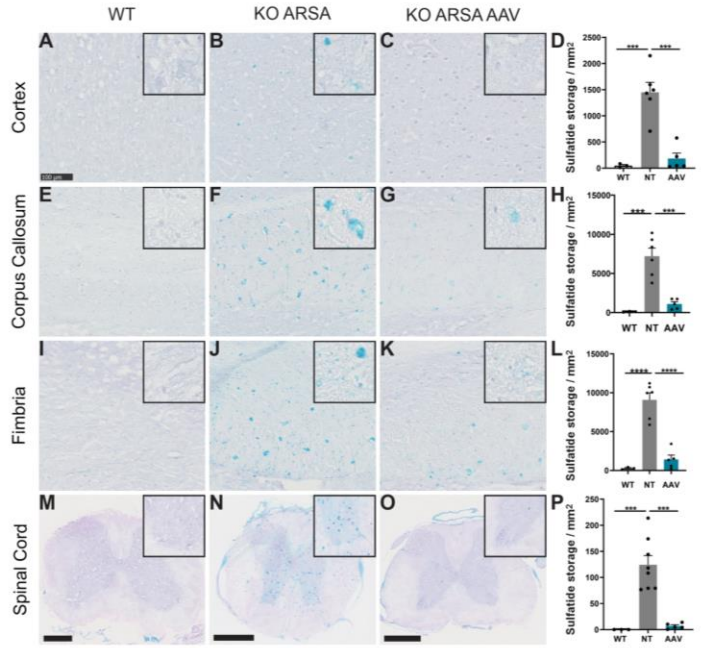
Engineered AAVs for efficient noninvasive gene delivery to the central and peripheral nervous systems

Ken Y Chan, Min J Jang, Bryan B Yoo, Alon Greenbaum, Namita Ravi, Wei-Li Wu, Luis Sánchez-Guardado, Carlos Lois, Sarkis K Mazmanian, Benjamin E Deverman & Viviana Gradinaru

Résultats positifs dans le modèle murin de LDM







Correction de la surcharge en sulfatides
Correction de l'astrogliose
Correction de l'activation microgliale

Audouard et al., soumis