



FILFOIE

Filière de Santé Maladies Rares du Foie de l'Adulte et de l'Enfant

Journée Recherche Filfoie

14 octobre 2021





Perspectives de thérapie génique dans le déficit en alpha1-antitrypsine

Mathias RUIZ
CRMV AVB-CG
Hépatologie pédiatrique - Lyon

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Hospices Civils de Lyon

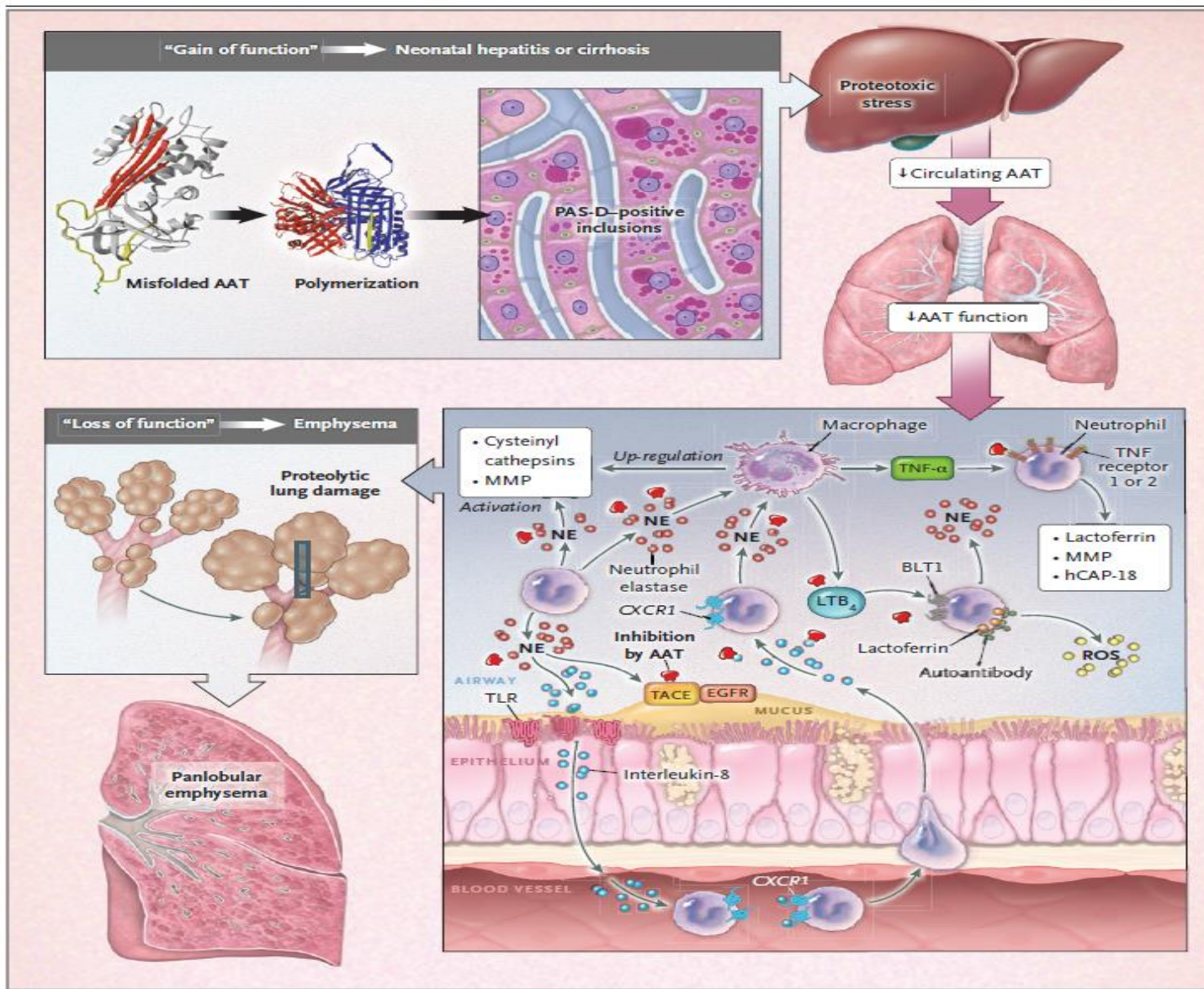


Conflits d'intérêt :

Grifols

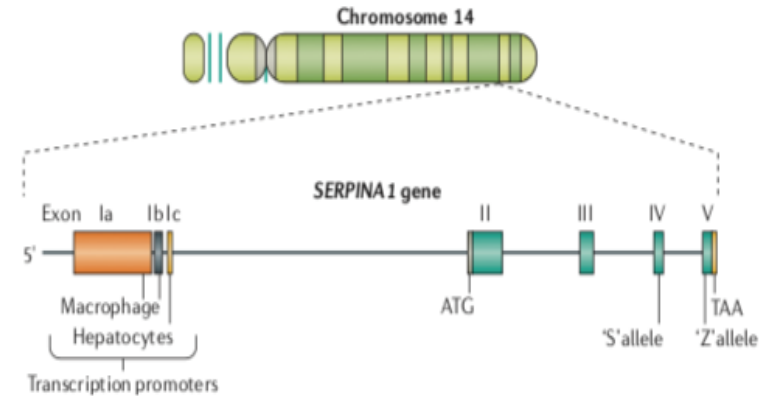
- Physiopathologie et clinique du déficit en $\alpha 1$ AT
- Thérapie génique
- siRNA
- ASO
- CRISPR/Cas9
- Conclusion

Physiopathologie

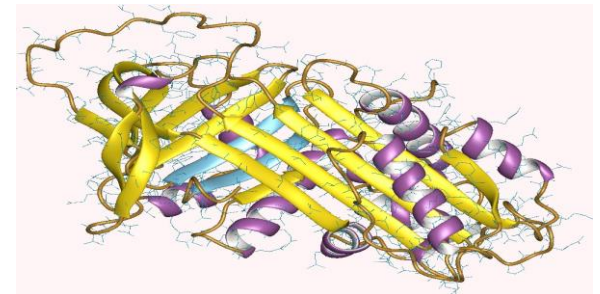


- Génétique :

- *SERPINA1* => AAT
- Allèle sauvage = PiM
- Principale mutation => **PiZ**
 - homozygote : génotype/phénotype PiZZ => synthèse de **Z-AAT**



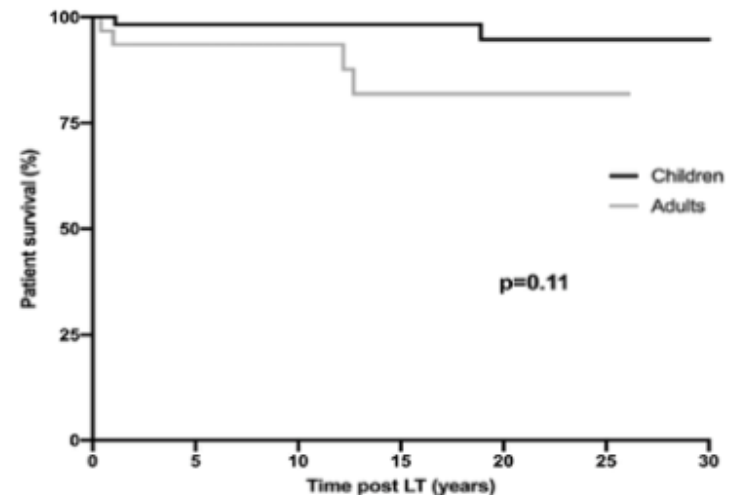
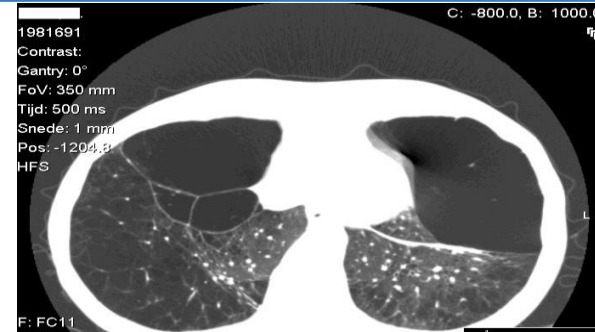
- Autres mutations: S, M_{Malton}, null... > 100 variants
 - +/- pathologique (déficient, précipitant, dysfonctionnel...)
 - Phénotypes intermédiaires



Stoller *et al.* Lancet. 2005

Renoux *et al.* Orphanet J Rare Dis. 2018

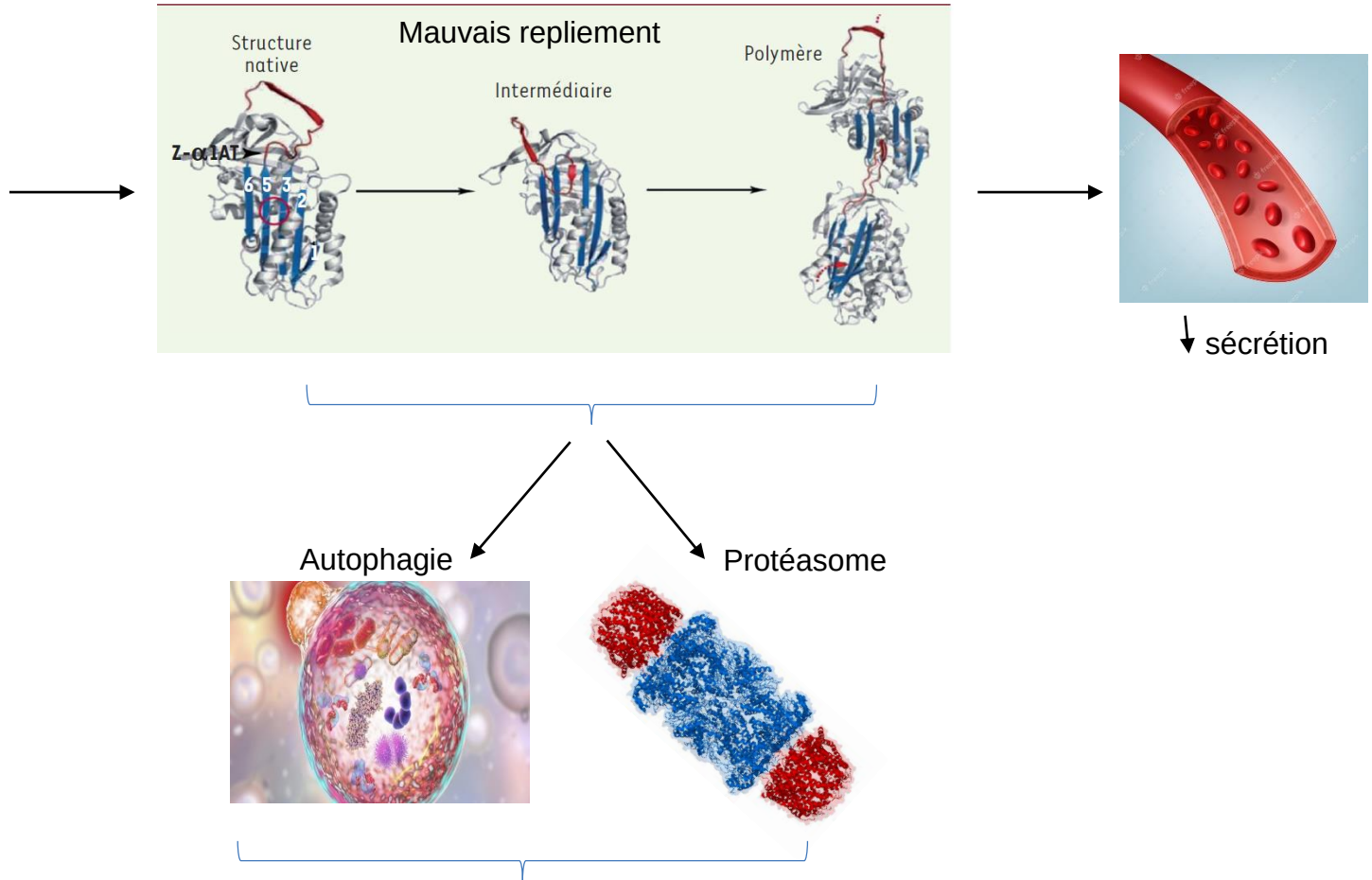
- Atteinte pulmonaire :
 - Asymptomatique => emphysème pulmonaire
 - Traitement : supplémentation a1AT
- Atteinte hépatique :
 - Asymptomatique => cirrhose (3-20%)
 - Traitement :
 - Préventif : alcool, obésité, vaccination VHB, VHA
 - Complications : HTP, cholestase
 - +/- acide ursodésoxycholique
 - Transplantation hépatique



Physiopathologie



Mutation *SERPINA1*
(Glu342Lys) => Allèle Z



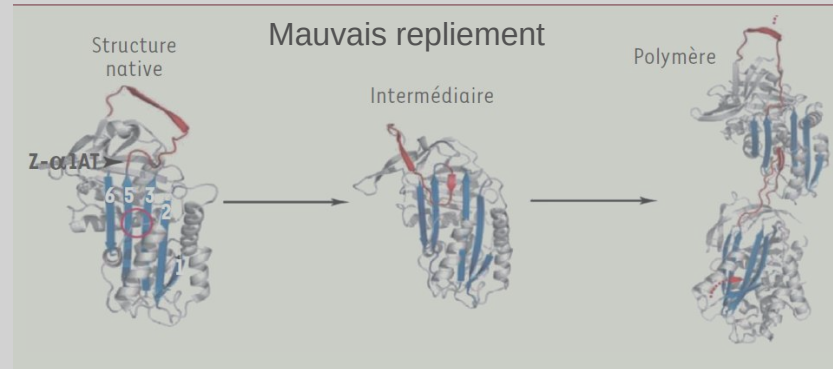
Stress protéique =
« gain de toxicité hépatique »

Strnad, NEJM 2020
Remih, Curr Op Pharmacol 2021



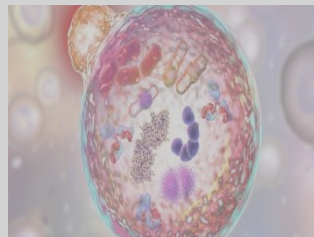
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Thérapie génique

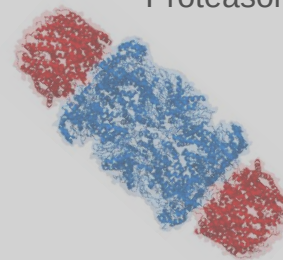


↓ sécrétion

Autophagie

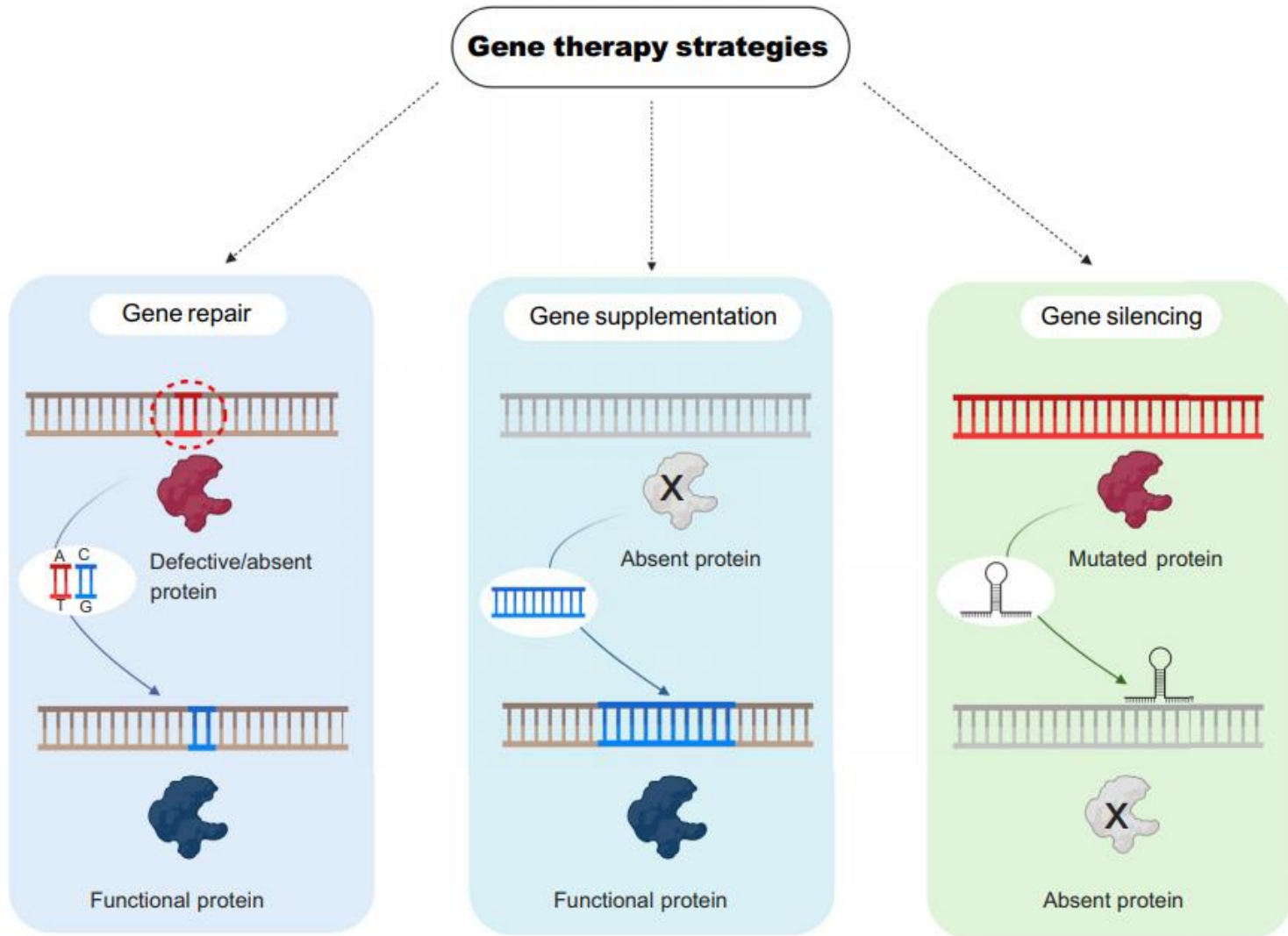


Protéasome

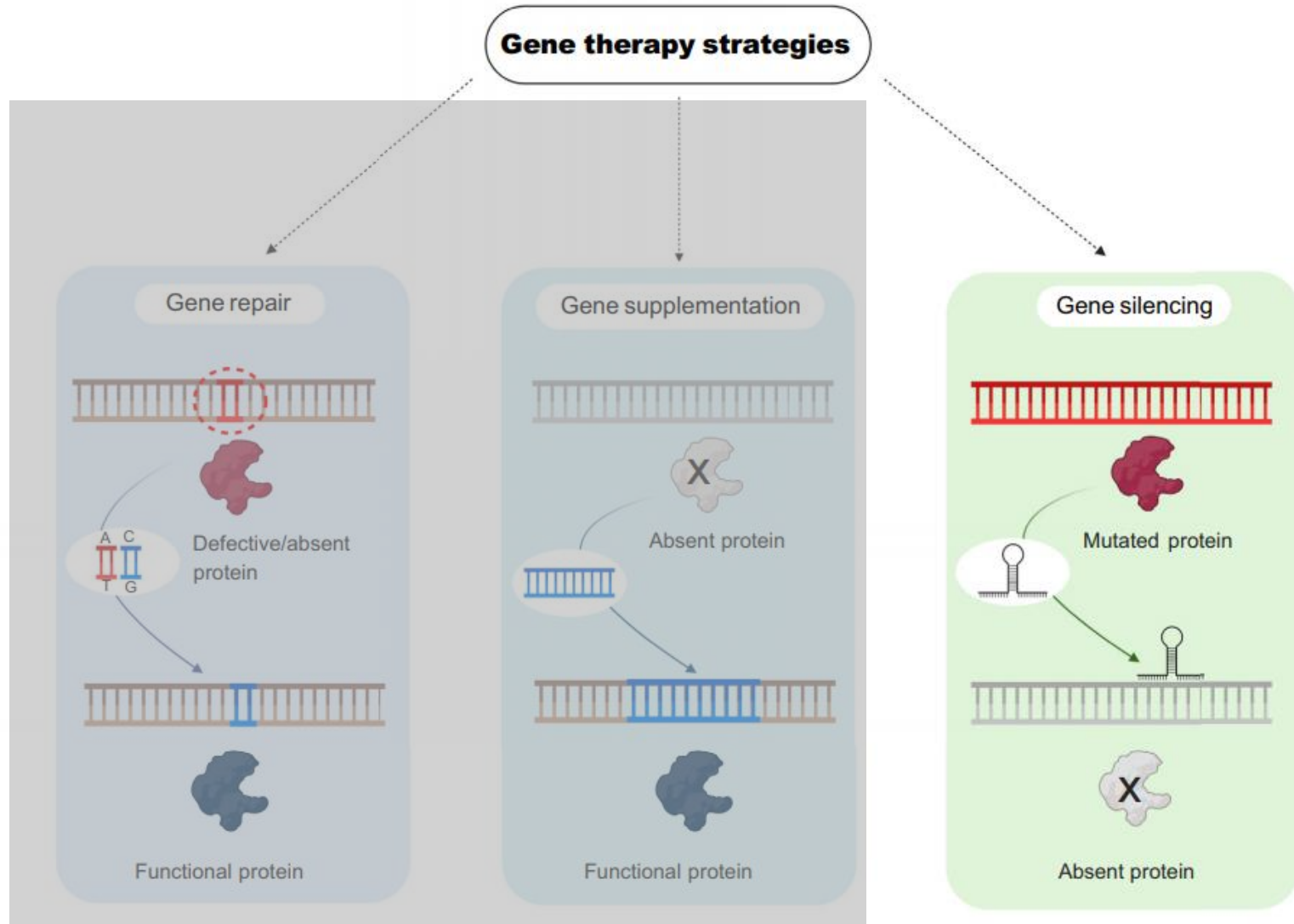


Stress protéique =
« gain de toxicité hépatique »

Thérapie génique

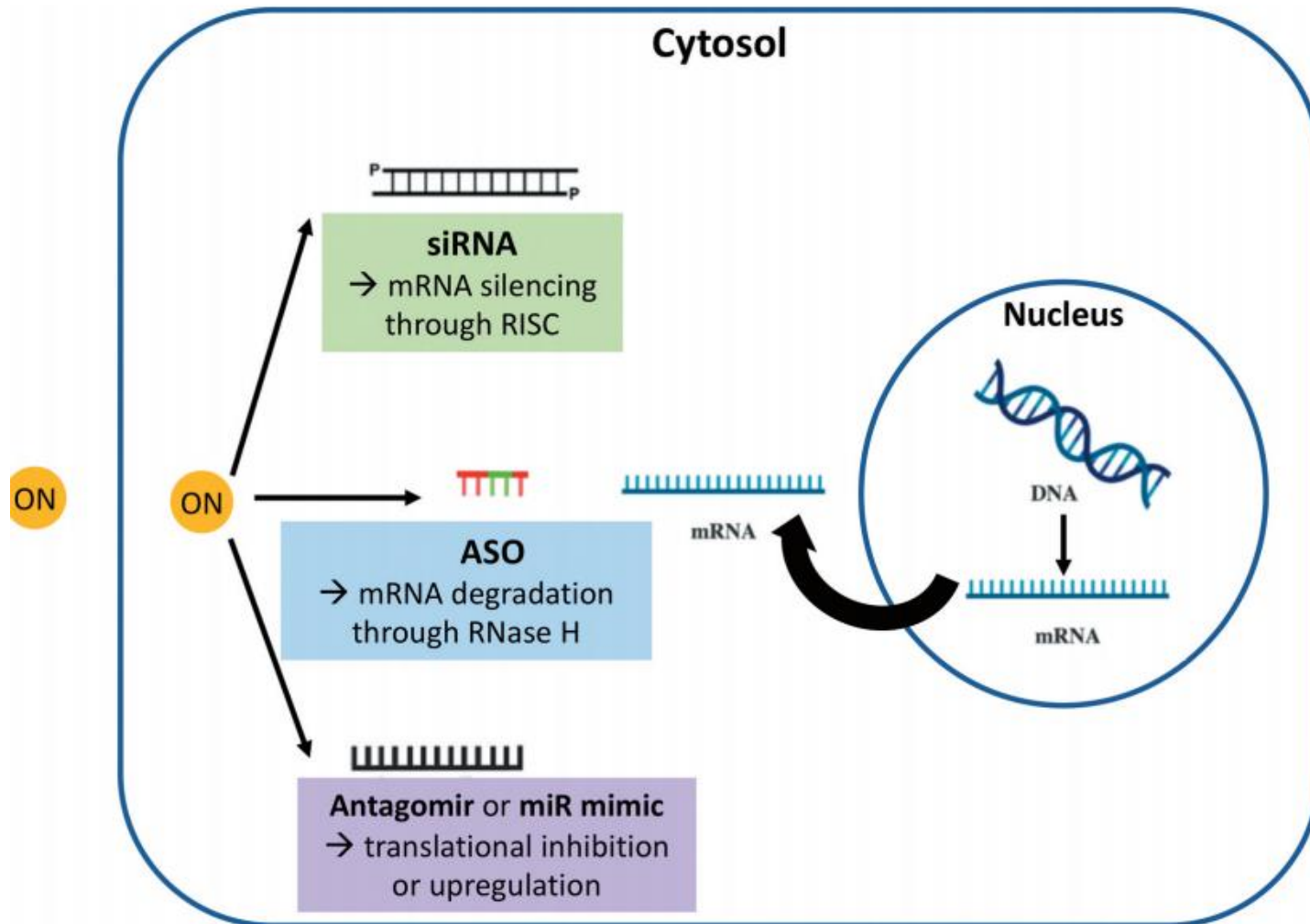


Thérapie génique



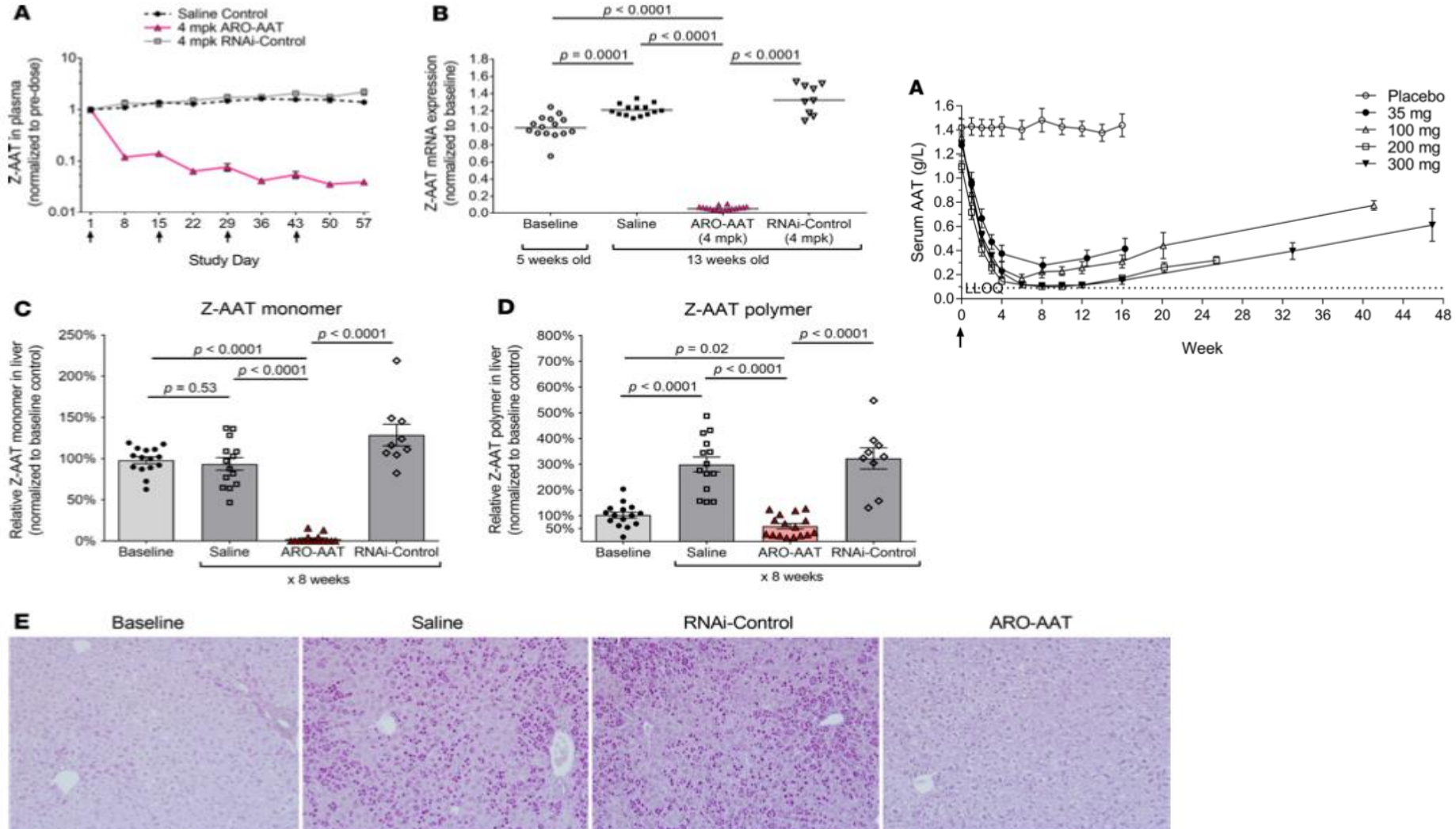
Interférence ARN

=> Inhiber le fonctionnement d'un gène muté ou inactiver son produit protéique



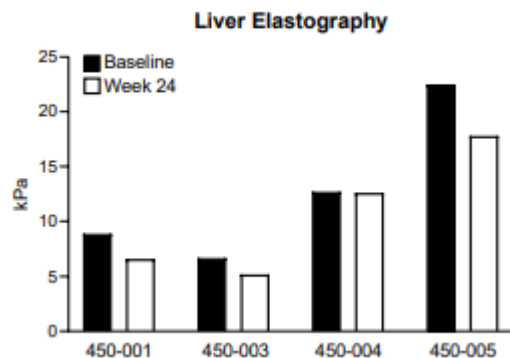
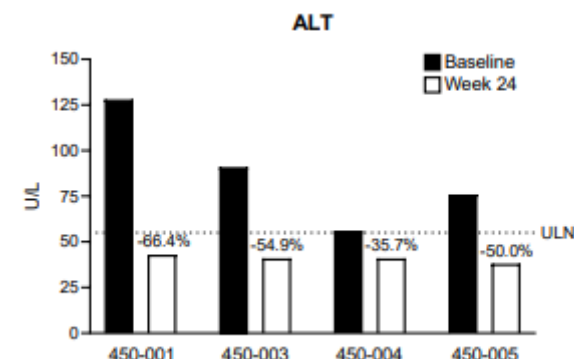
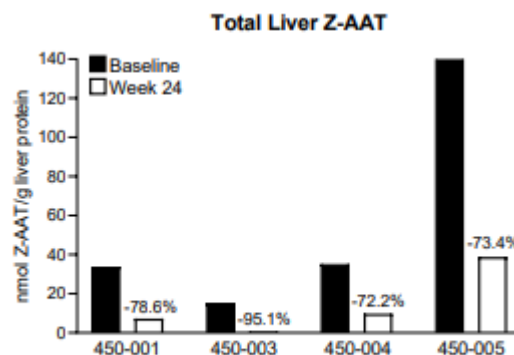
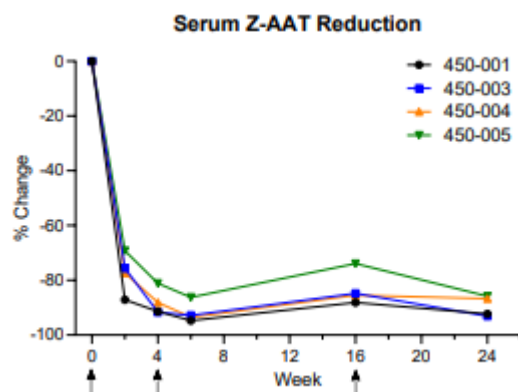
Gene silencing « siRNA »

ARO-AAT



Gene silencing « siRNA »

ARO-AAT reduces serum and intra-hepatic Z-AAT protein in PiZZ alpha-1 antitrypsin deficient patients with liver disease leading to improvements in clinically relevant liver biomarkers

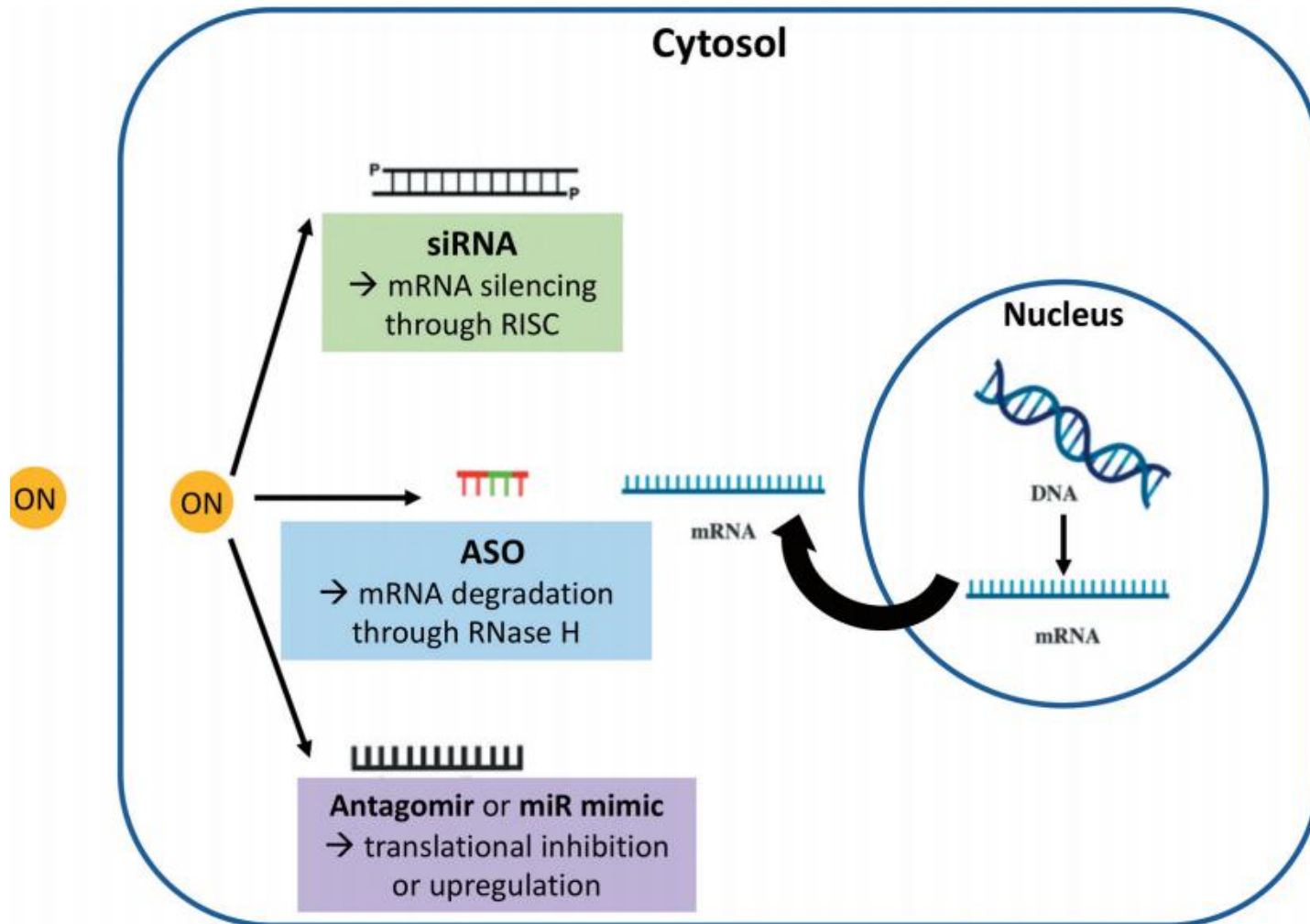


Pulmonary Function Overtime (FEV1pp)

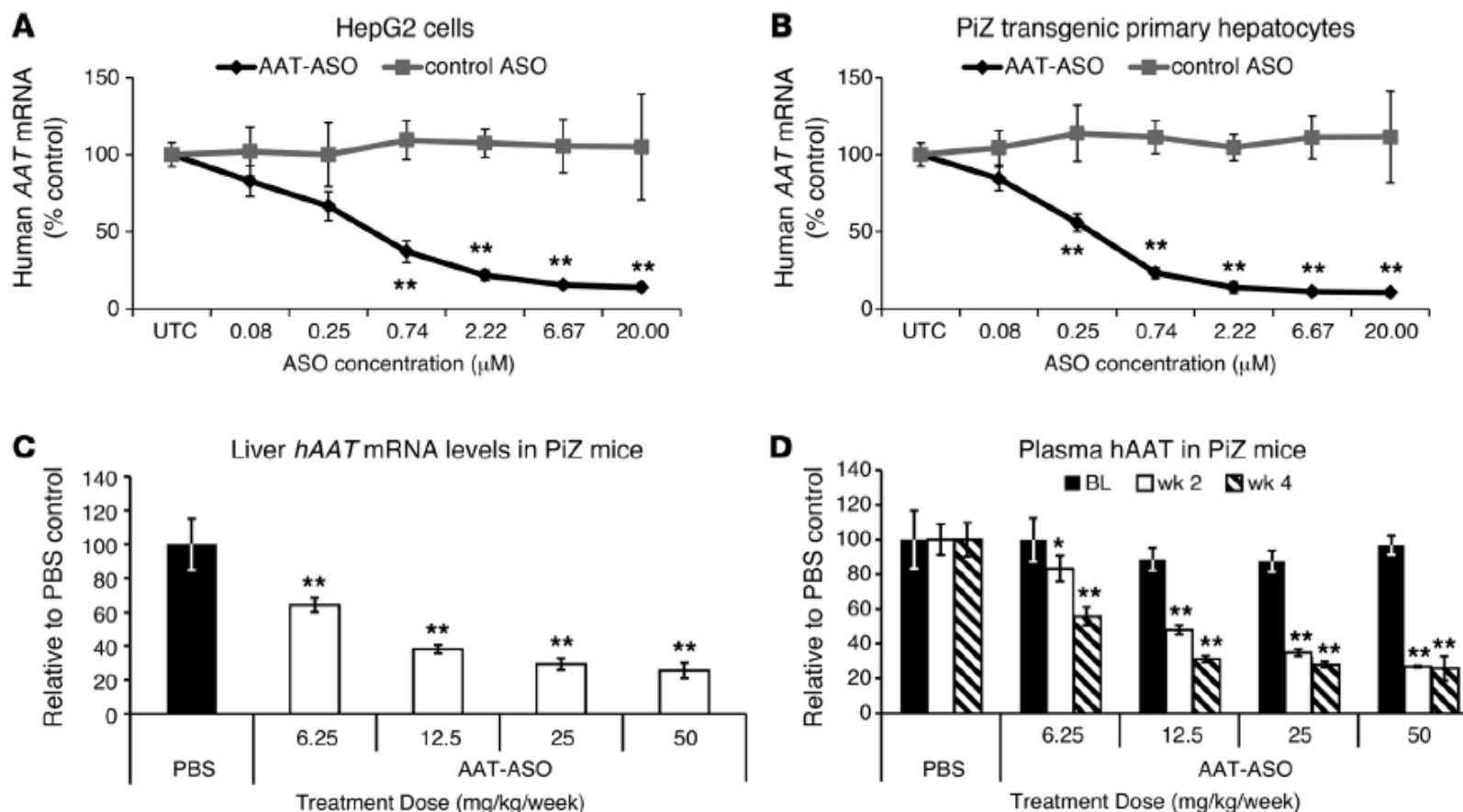
Subject	Baseline	Wk4	Wk16	Wk24
450-001	56.0	51.0	55.0	52.0
450-003	87.0	83.0	84.0	78.0
450-004	106.0	106.0	107.0	108.0
450-005	106.0	98.0	101.0	104.0

Interférence ARN

=> Inhiber le fonctionnement d'un gène muté ou inactiver son produit protéique

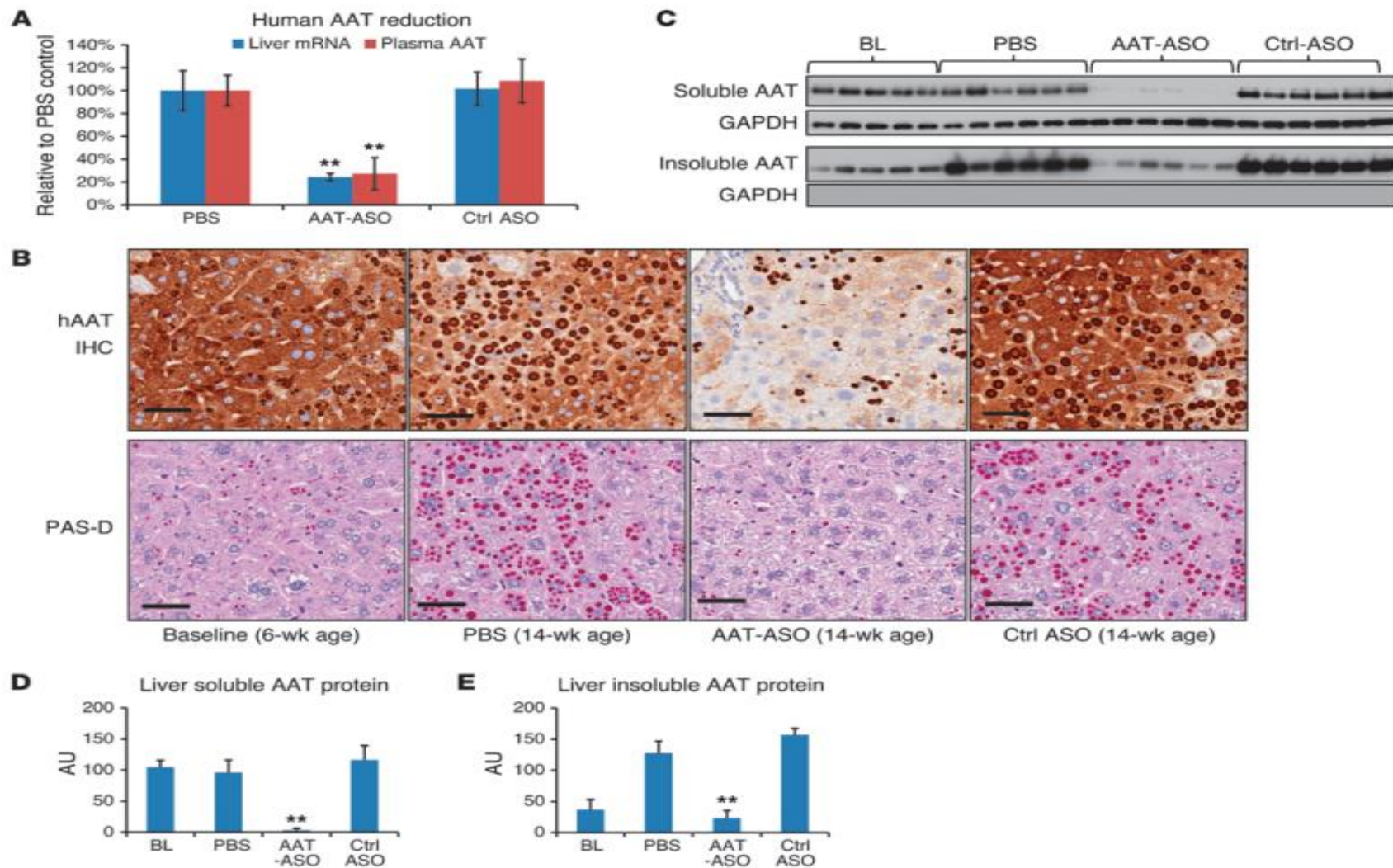


Oligonucléotides antisens (ASO)



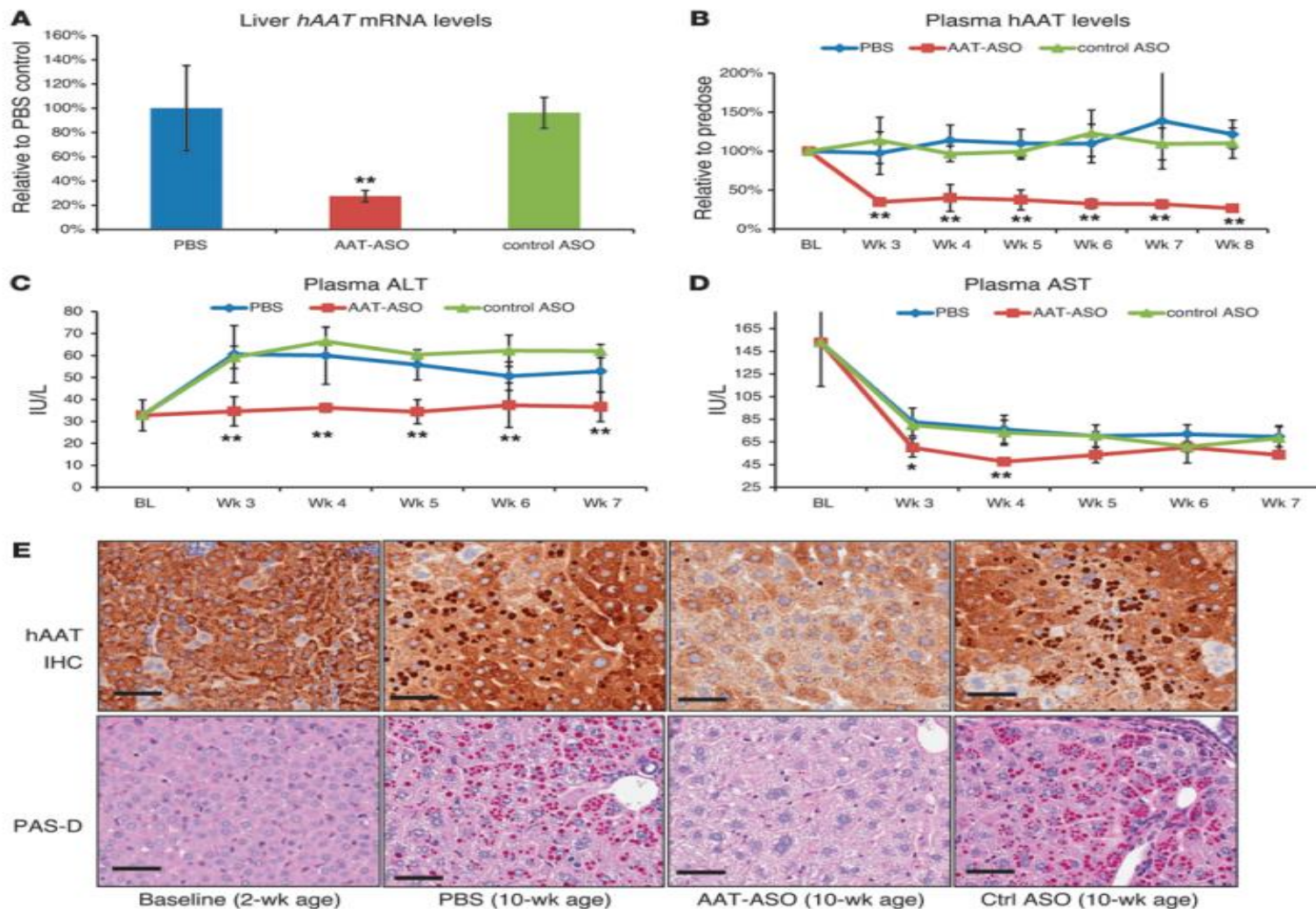
Characterization of an ASO that effectively reduces AAT levels in cells.

Oligonucleotides antisens (ASO)



Soluble and aggregated AAT protein levels were reduced in PiZ mouse livers after AAT-ASO treatment.

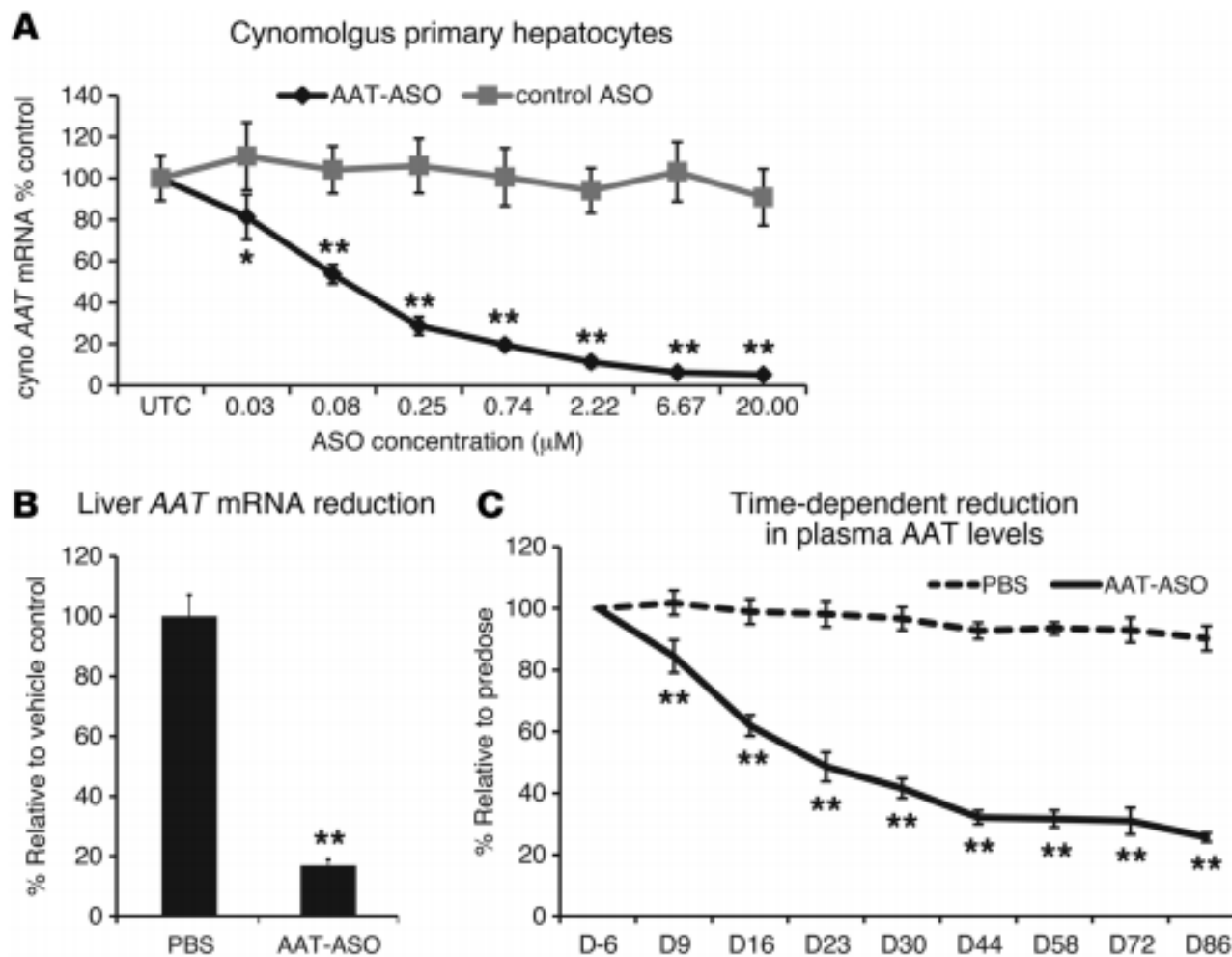
Oligonucléotides antisens (ASO)



AAT-ASO treatment prevented Z protein aggregate formation and liver injury in young PiZ mice

Guo et al. JCI, 2014

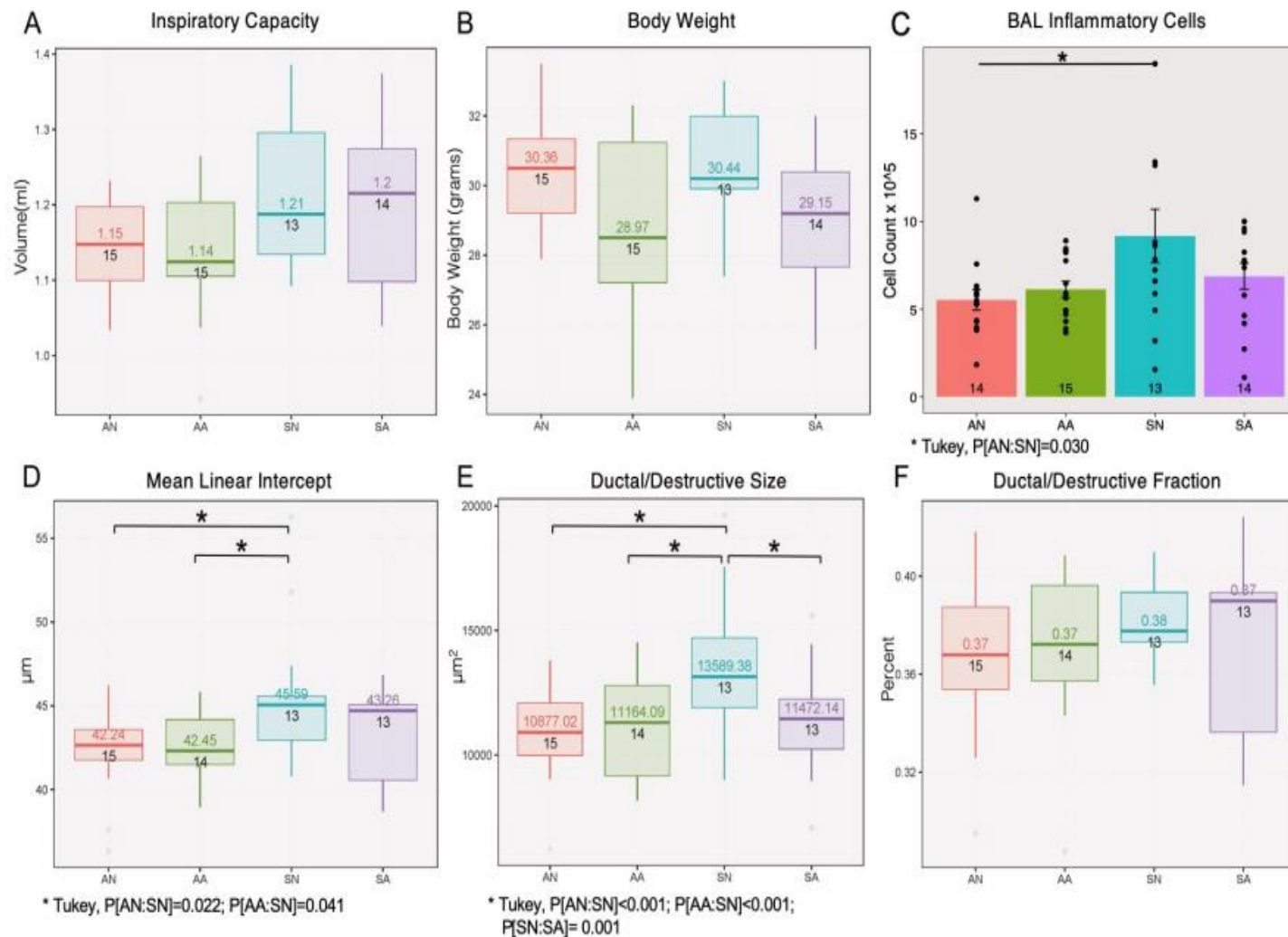
Oligonucleotides antisens (ASO)



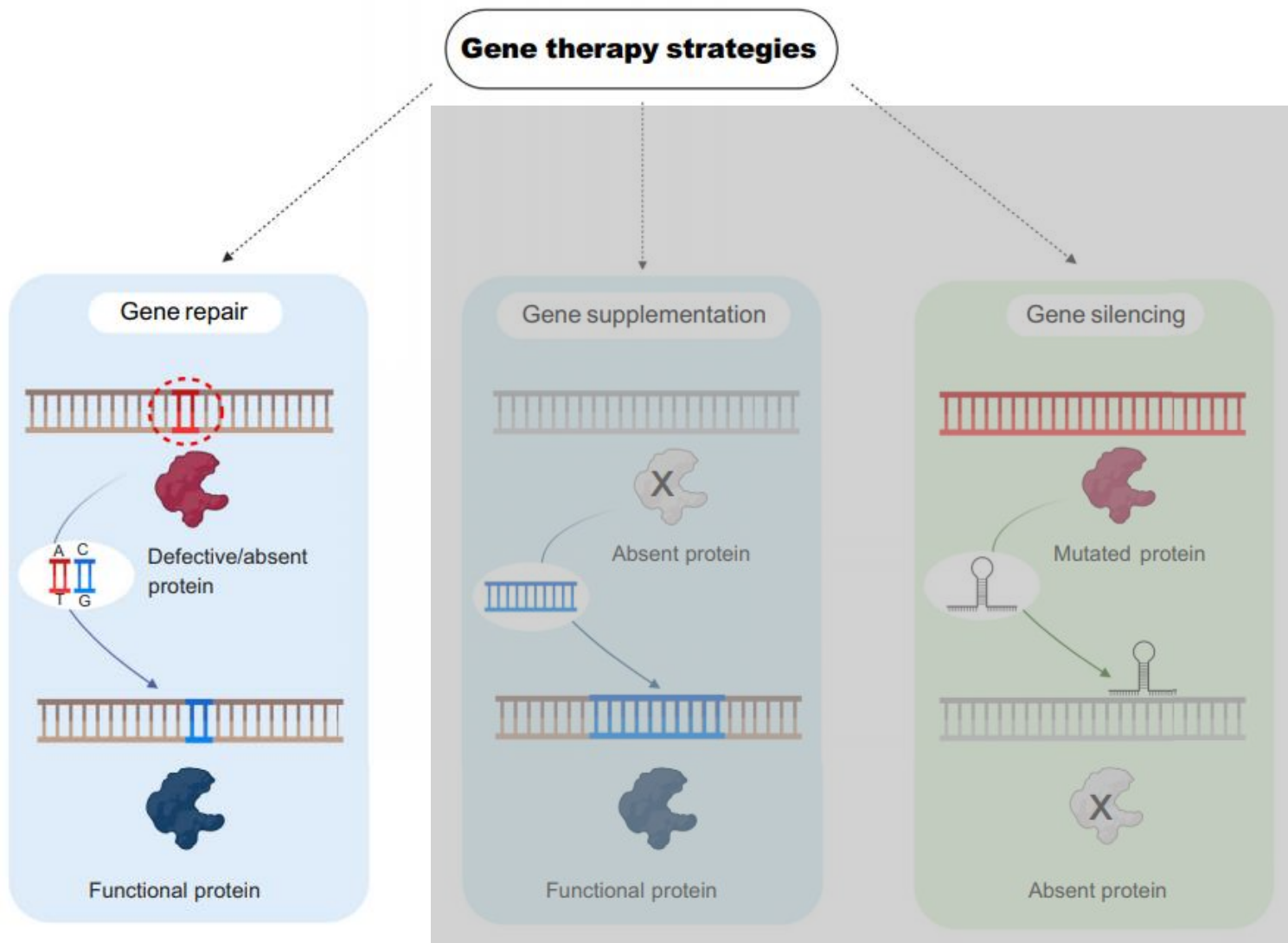
Robust AAT reduction in cynomolgus hepatocytes and in vivo after AAT-ASO treatment

Guo et al. JCI, 2014

Oligonucléotides antisens (ASO)



Thérapie génique

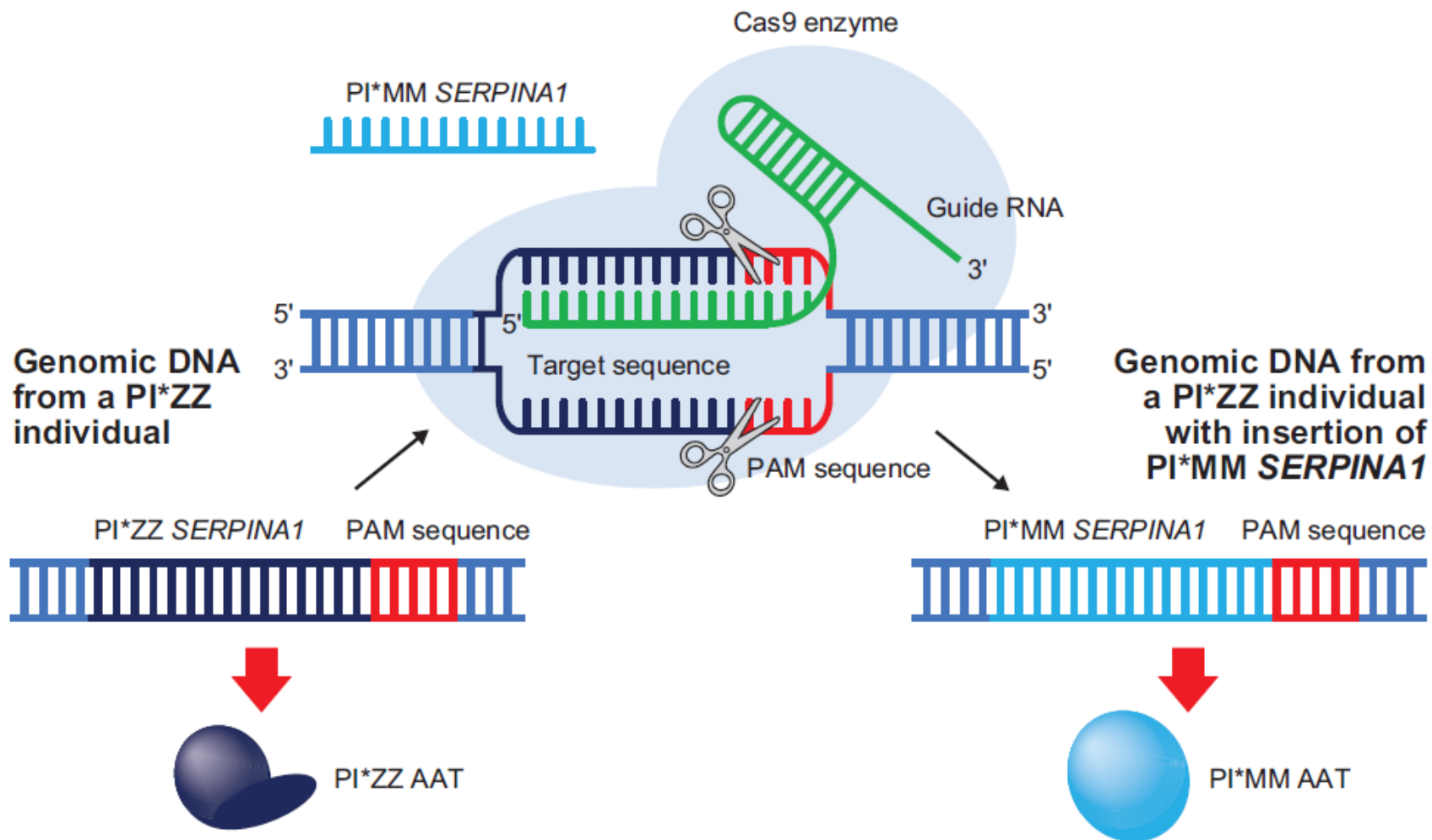


CRISPR/Cas9

- CRISPR = Clustered Regularly Interspaced Short Palindromic Repeats
- « Ciseaux moléculaire »

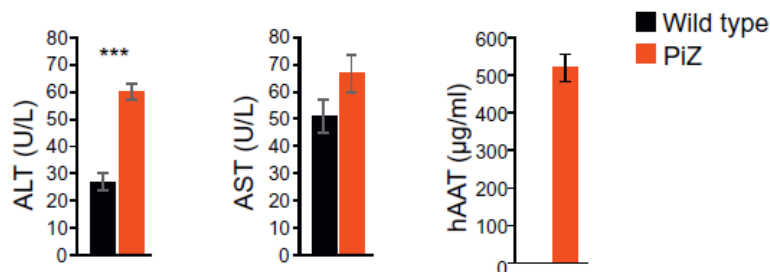


CRISPR/Cas9

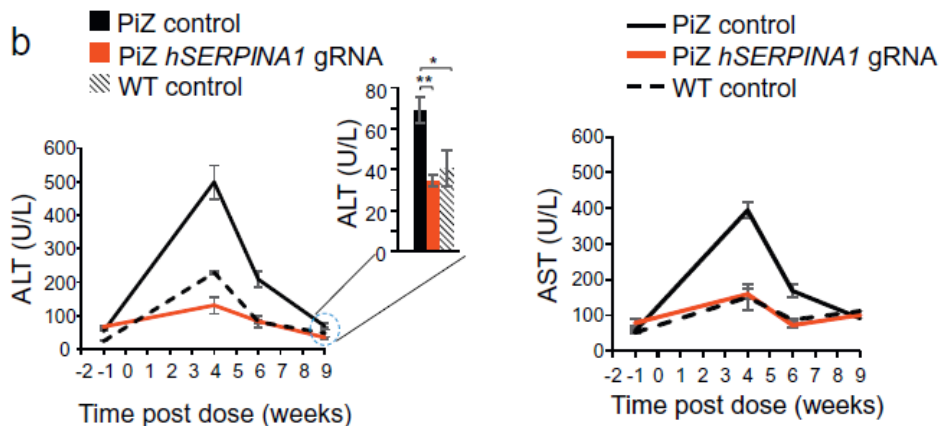


CRISPR/Cas9

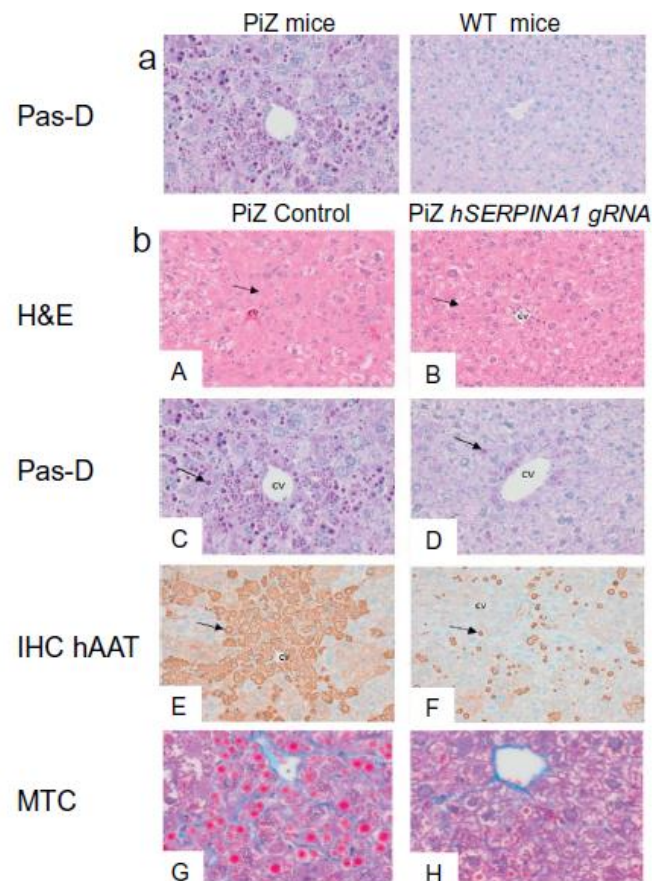
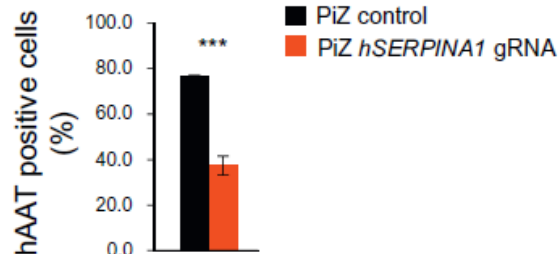
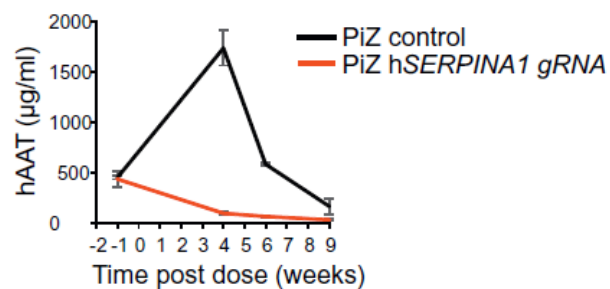
a



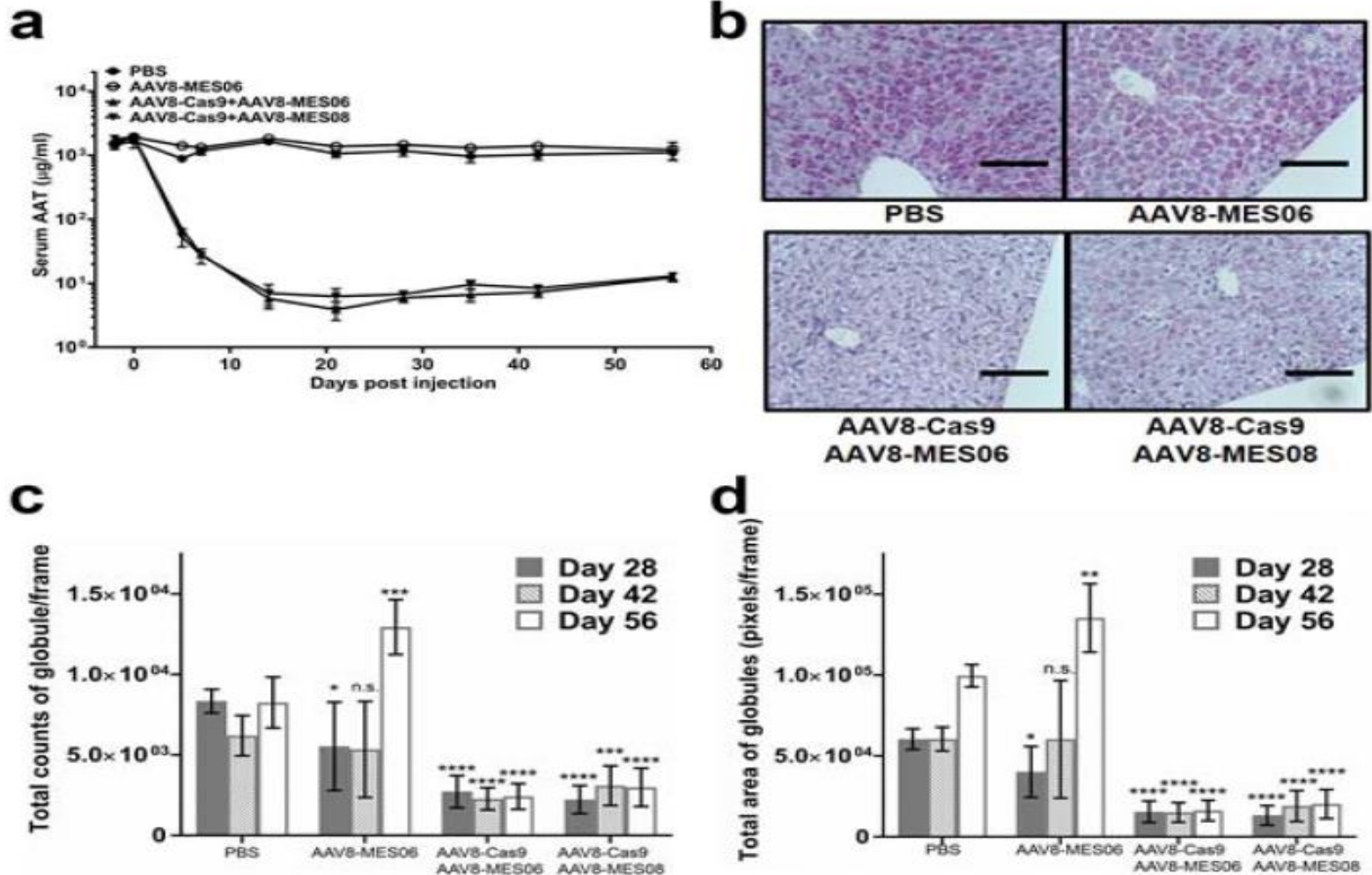
b



c



CRISPR/Cas9

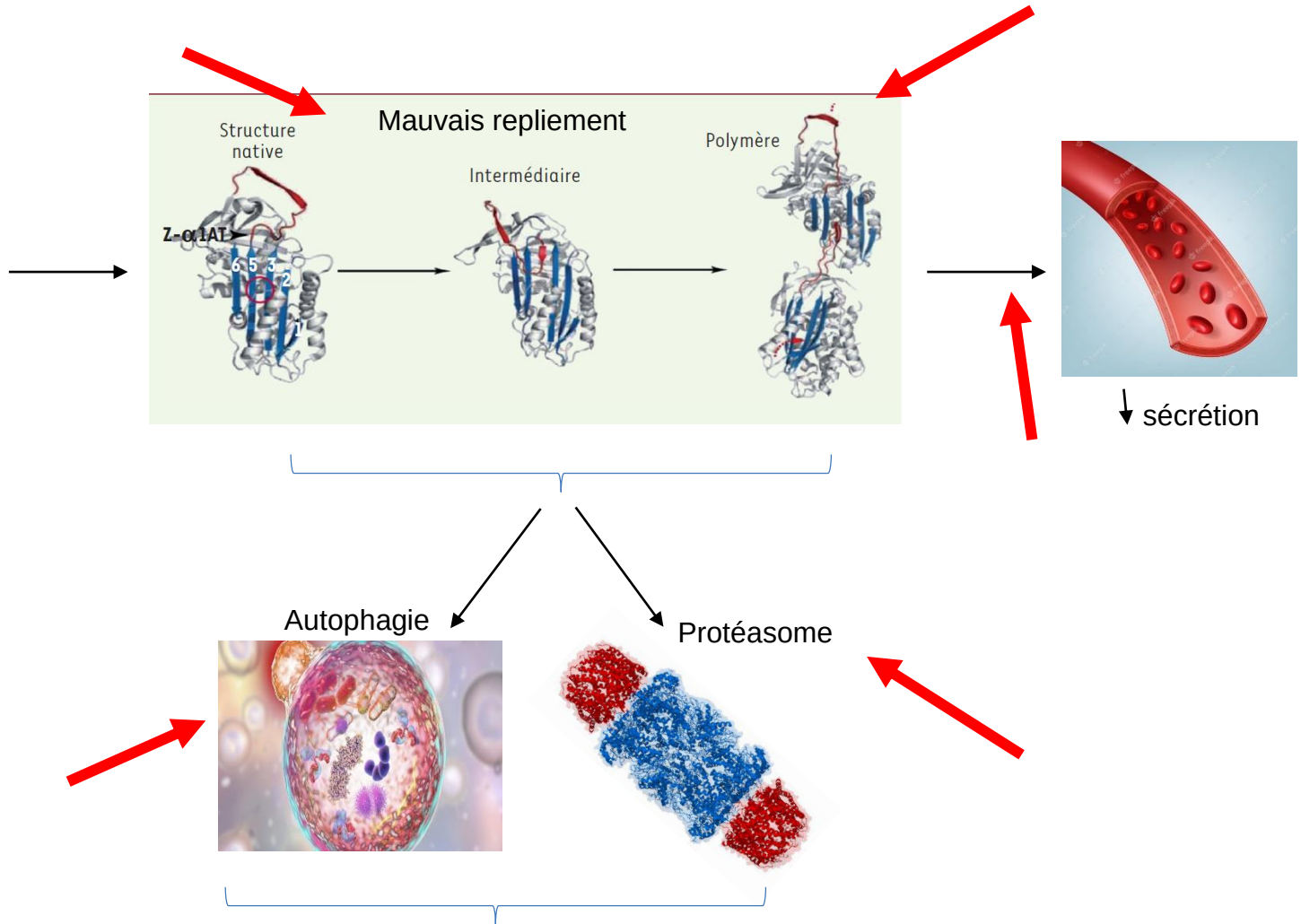


- Thérapie génique = axe prometteur du ttt du DAAT
- Interférence ARN = blocage de la synthèse de Z-AAT
 - siRNA et ASO
 - Réduction de Z-AAT circulante et dans le foie
 - Amélioration du BH, diminution de la fibrose
 - Risque d'aggravation de l'atteinte pulmonaire ?
- CRISPR/Cas9 = « réparation de l'ADN »

Perspectives



Mutation *SERPINA1*
(Glu342Lys) => Allèle Z



Stress protéique =
« gain de toxicité hépatique »

- Essais thérapeutiques à venir / en cours
- Identifier les patients à risque d'atteinte sévère
 - Identification de polymorphismes génétiques
 - Registre EASL/ERN
- Cohorte française (DEFI-ALPHA 2 ?)

Merci de votre attention

mathias.ruiz@chu-lyon.fr