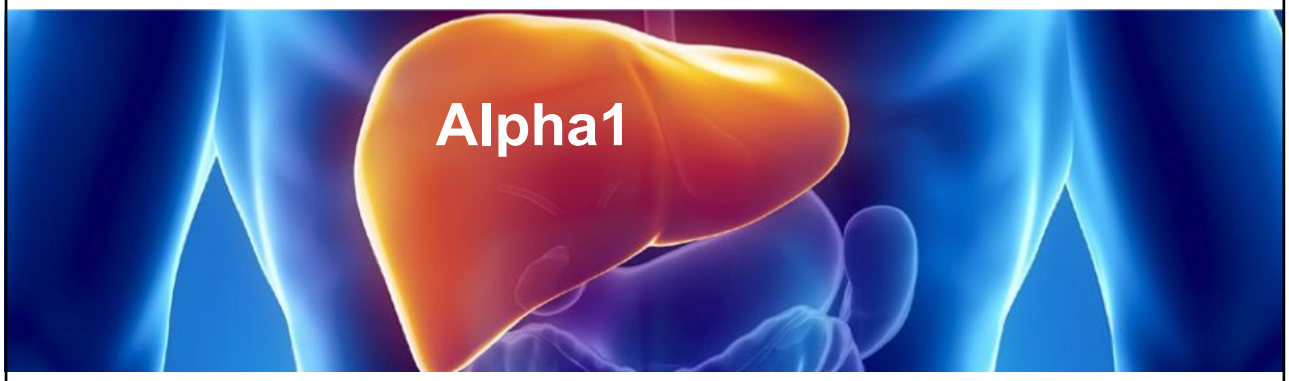


(si)RNA-based therapies of genetic liver diseases

Pavel Strnad, RWTH University Aachen, Germany

January 30th 2025

1

Presenter Disclosure

- Presenter's Name: Pavel Strnad
- I have the Relationships with commercial interests:
  - Advisory Board/Speakers Bureau: AiRNA, Albireo, Arrowhead, Biomarin, Dicerna, GSK, IPSEN, Intellia, Korro Bio, Novo Nordisk, Takeda, Wave
  - Funding (Grants/Honoraria) : Advanz, Alnylam, CSL Behring, Gilead, Grifols, Sanofi, Sobi
  - Research/Clinical Trials: Arrowhead, CSL Behring, Dicerna/Novo Nordisk, Grifols, Vertex, Takeda
  - Speaker/Consulting Fees: Biomarin, Dicerna, Gondola, GSK, Intellia, Novo Nordisk, Ono, Takeda
  - Other: none

2

(si)RNA therapy in Hepatology

- General introduction
- A1-AT deficiency
- Beyond AATD and siRNA

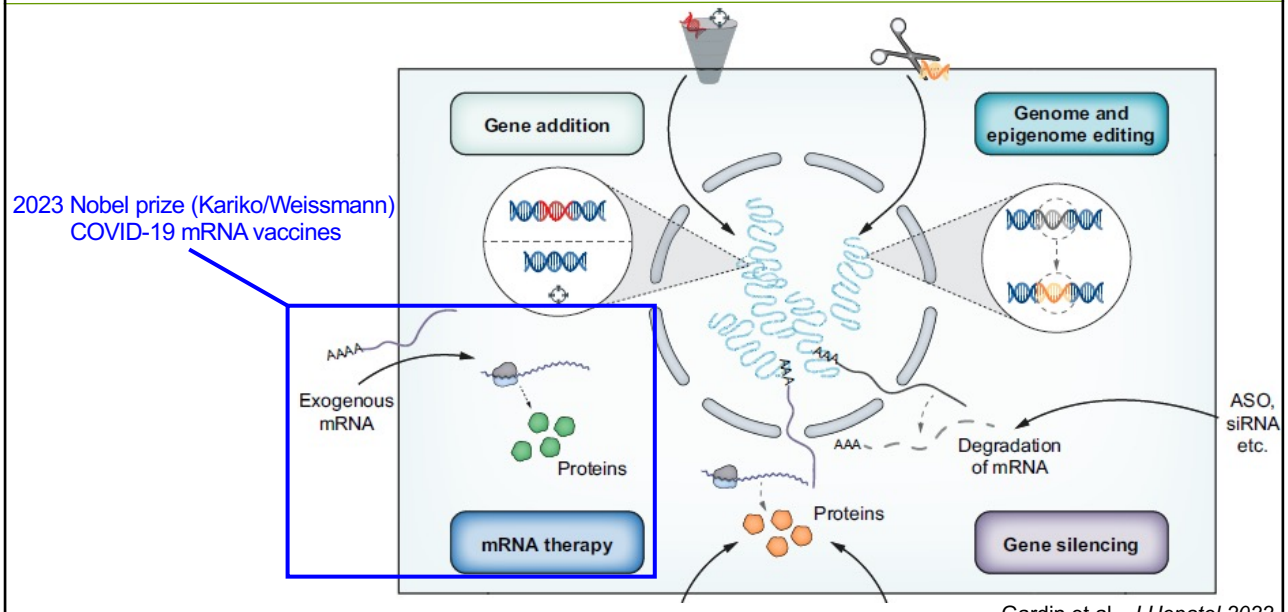
3

(si)RNA therapy in Hepatology (and beyond)

- General introduction
- A1-AT deficiency
- Beyond AATD and siRNA

4

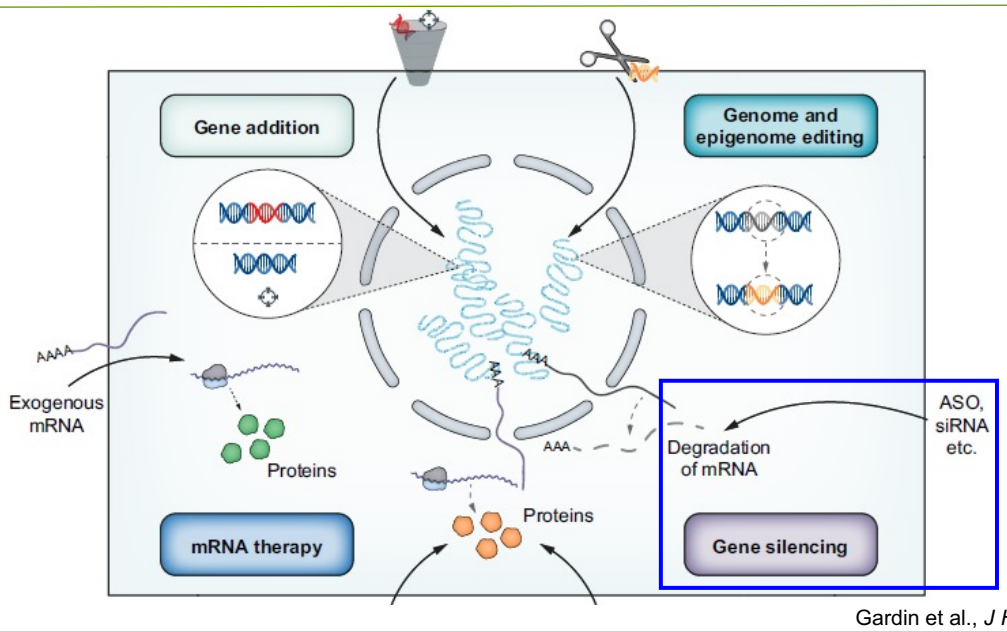
Nucleic acid-based therapies



Gardin et al., *J Hepatol 2022*

5

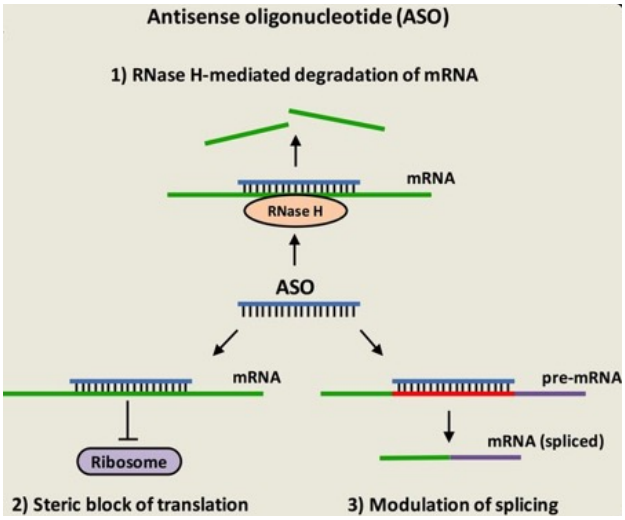
Nucleic acid-based therapies



Gardin et al., *J Hepatol 2022*

6

Anti-sense oligonucleotides (ASOs)



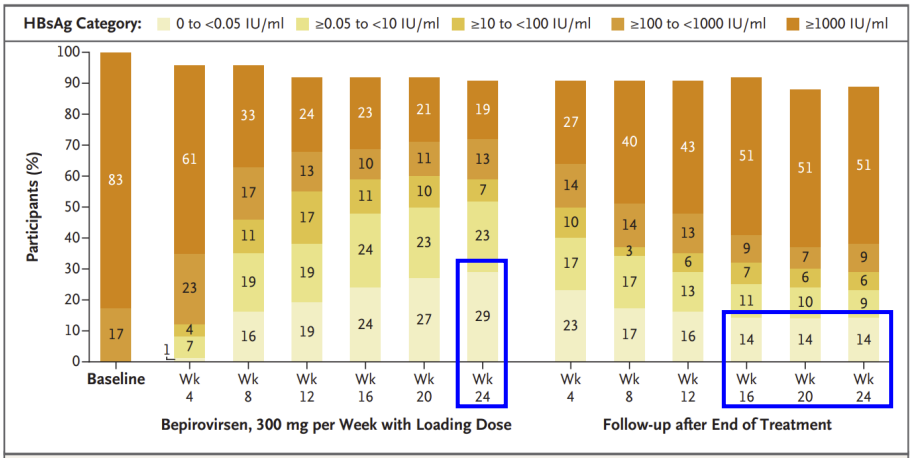
- Single-stranded RNA, 12-30 nucleotides
- Broad, unspecific distribution, easy delivery
- First systemically used ASO approved in 2013 (Mipomersen-ApoB100)
- 9 drugs approved up to date
- Mainly for neuromuscular disorders
- Side effects: hepatotoxicity, thrombocytopenia, glomerulonephritis

Rossor et al., *Pract Neurol 2018*

7

Bepirovirsen for hepatitis B cure

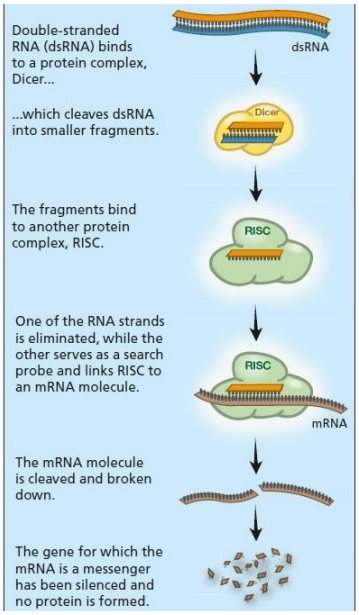
- Bepirovirsen: ASO against hepatitis B RNA
- Co-stimulation of TLR8
- Primary end-point: Loss of HBsAg and HBV-DNA 24 weeks after end of treatment



Yuan et al., Nat Med 2021; *NEJM 2022*

8

Small interfering RNAs (siRNAs)



RNAi: selective inhibition of target genes via degradation of its mRNA

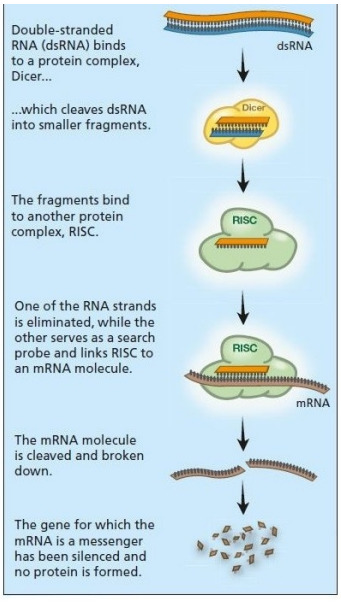
- Defense against RNA viruses

Fire und Mello: 2006 Nobel prize for medicine

RISC acts as an enzyme
→ Long-term effect

9

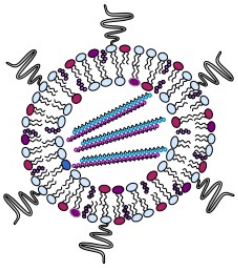
Small interfering RNAs (siRNAs)



- Double-stranded RNA, 19-22 base pairs
- Require an active delivery, immunostimulatory
- First siRNA approved in 2018 (Patisiran-transthyretin amyloidosis)
- 5 drugs approved up to date
- Targetting was a major issue!

10

siRNAs: made for hepatocytes



LNP (lipid nanoparticle) encapsulation

- LNP: Interaction with ApoE → Uptake into the hepatocyte
- Intravenous (i. v.) administration
- Induces immunological reaction: Pre-treatment with corticosteroids and antihistamines

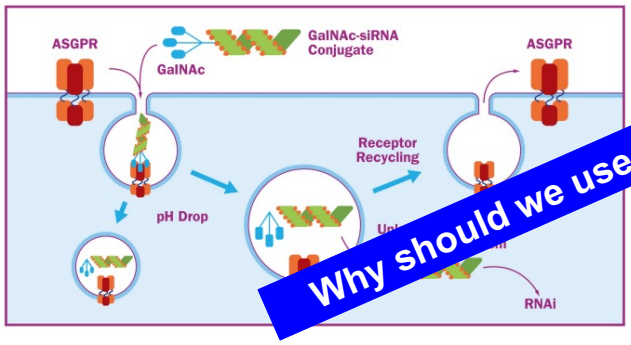
GalNAc (N-acetyl-galactosamine)-conjugation

- Special glycosylation
- Uptake via asialoglycoprotein-receptor
- Subcutaneous (s. c.) administration
- Well tolerated

Gardin et al., *J Hepatol 2022*

11

siRNAs: made for hepatocytes



Why should we use siRNA for AATD?

Drug	Disease	Approval	Delivery
[illegible]	Transthyretin amyloidosis	2018	LPN
[illegible]siran	Acute hepatic pophyria	2019	GalNac
Lumasiran	Primary hyperoxaluria	2020	GalNac
Inclisiran	Hypercholesterolaemia	2020	GalNac
Vutrisiran	Transthyretin amyloidosis	2022	GalNac

Adapted from Springer and Dowdy, Nucleic Acid Therapeutics 2018

12

siRNA therapy in Hepatology (and beyond)

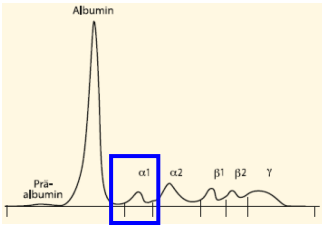
- General introduction
- **A1-AT deficiency**
- Beyond AATD and siRNA

13

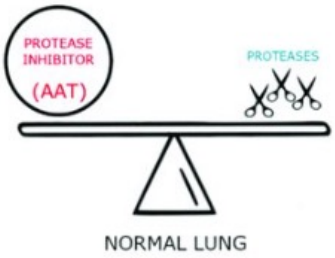
Alpha1-antitrypsin

European AATD liver study group

Normal electrophoresis

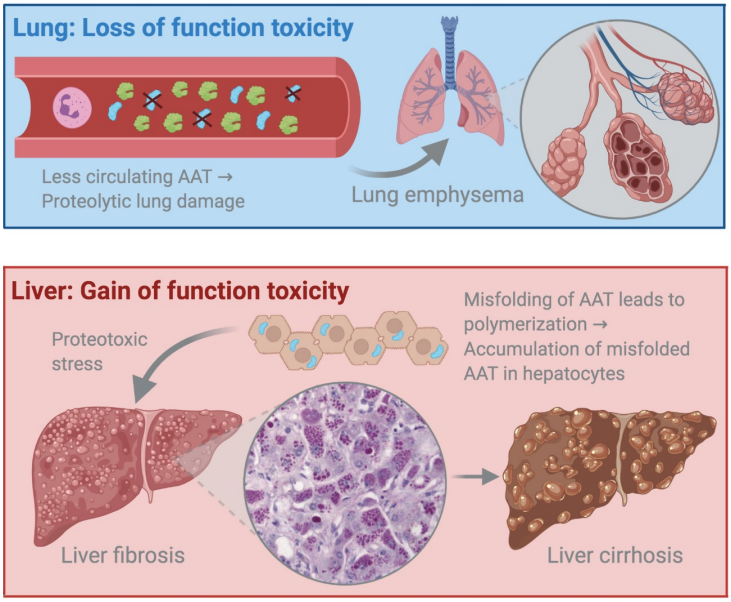


- AAT produced in the liver, secreted into bloodstream
- Major component of alpha1-globulin band
- ´Protease inhibitor
- Acute phase protein (similar to CRP) →prevents an inadequate stress response, acts as a „pacifier“



14

AATD pathomechanism

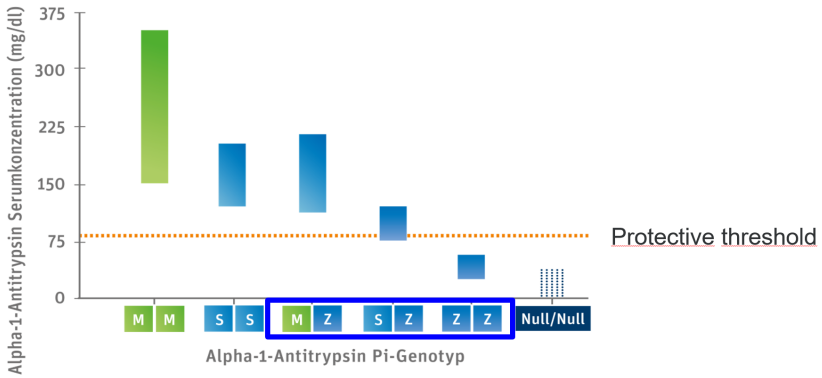


Strnad et al., *NEJM 2020*

15

AATD genotypes

Genotype	Pi*ZZ	Pi*SZ	Pi*MZ
Frequency	~1:2000	~1:500	~1:30
Lung phenotype	Strong predisposition	Mild predisposition	Predisposition (only) with concomitant risk factors



16

THE BEST OF TWO WORLDS

biobank uk

- Publicly available, community-based cohorts
- Large, long-term follow-ups
- Insurance-based data, link to death registries etc.

Gainesville, FL, USA
Sydney, Australia

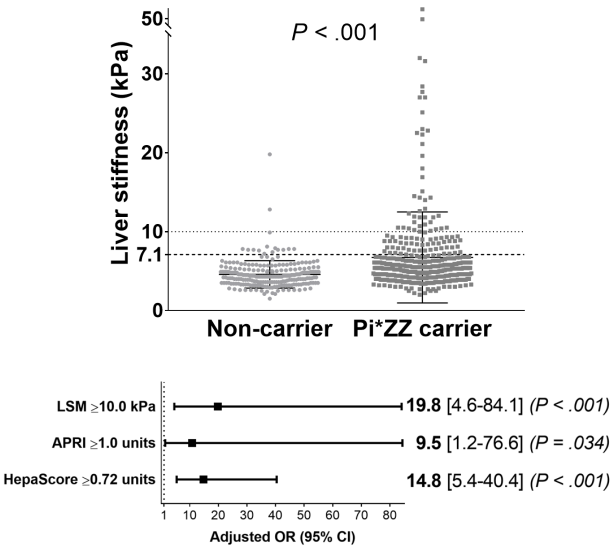
- European AATD Register >2500 patients
- 30 centers, healthcare-associated

Schneider.. Strnad, Gastroenterology 2020; Am J Gastroenterol 2021; Aliment Pharmacol Ther 2021; JAMA Int Med 2022, J Hepatol 2023; Fromme,... Strnad, Br J Dermatol 2022, Gut 2022

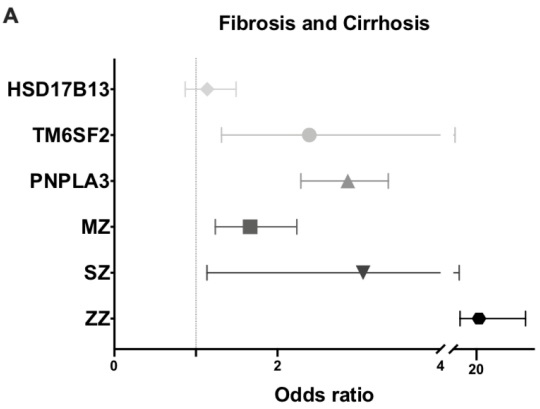
17

Fibrosis in Pi*ZZ individuals

European AATD liver study group



Hamesch et al., *Gastroenterology 2019*



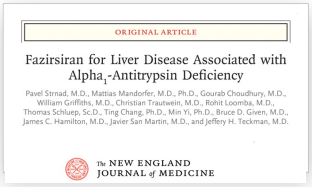
Liver fibrosis/cirrhosis
Pi*ZZ: 21.7 [8.8–53.7], p<0.0001
Pi*SZ: 3.1 [1.2–8.2], p=0.027
Pi*MZ: 1.7 [1.2–2.2], p=0.001

Fromme et al., *Gut 2022*

18

European AATD liver study group

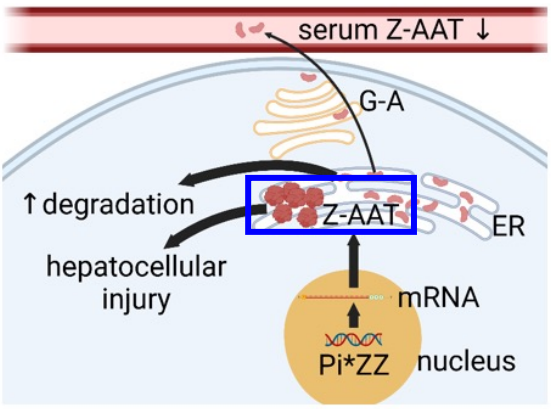
Why siRNA in AATD?

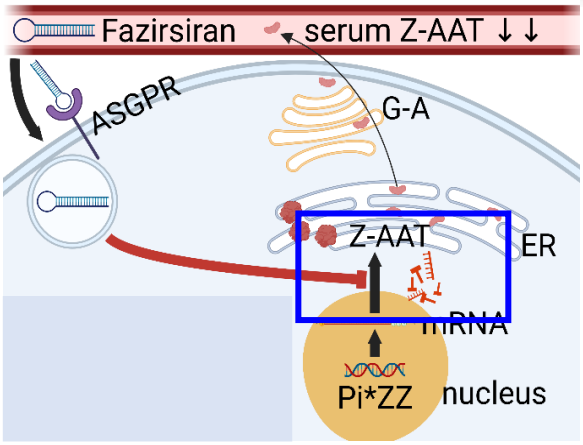

ORIGINAL ARTICLE

Fazirsiran for Liver Disease Associated with Alpha$_1$-Antitrypsin Deficiency

Pavel Strnad, M.D., Mattias Mandorfer, M.D., Ph.D., Gourab Choudhury, M.D., William Griffiths, M.D., Christian Trautwein, M.D., Rohit Loomba, M.D., Thomas Schluep, Sc.D., Ting Chang, Ph.D., Min Yi, Ph.D., Bruce D. Given, M.D., James C. Hamilton, M.D., Javier San Martin, M.D., and Jeffery H. Teckman, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

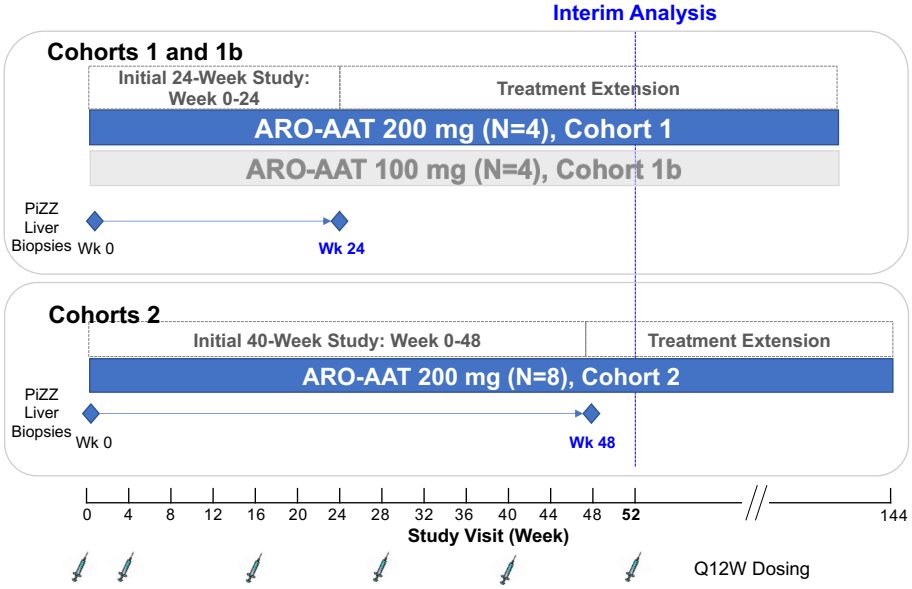




19

AROAAT-2002 study design (fazirsiran)

European AATD liver study group

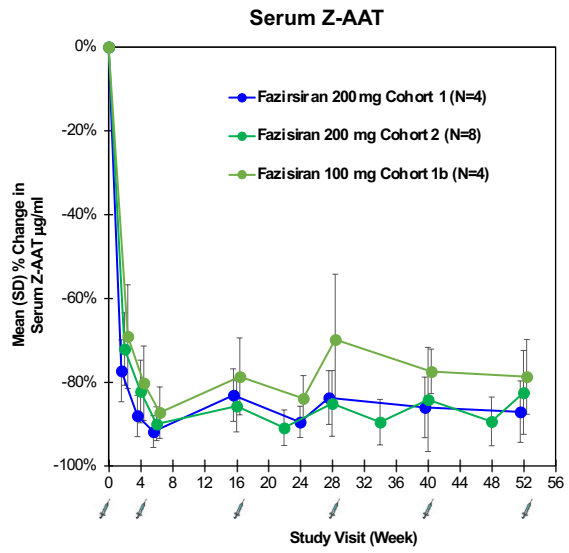


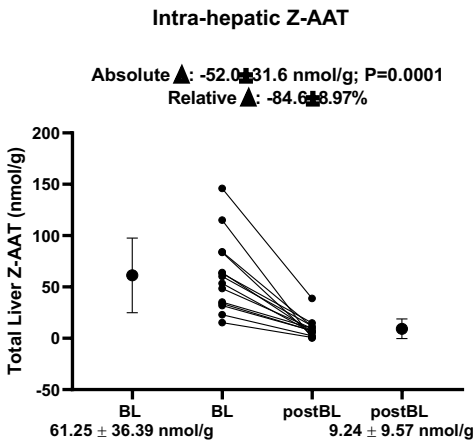
Interim Analysis
- Laboratory: up to 52 wks
- Biopsy: 24 or 48 wks
- Safety: up to 1.5 years

Strnad et al., *NEJM 2022*

20

Primary end-point: AAT accumulation





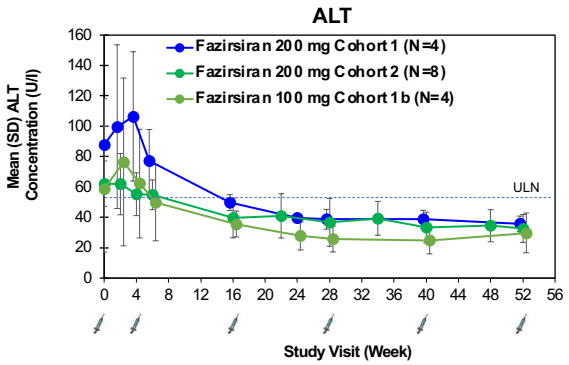
Two patients in Cohort 2 had insufficient liver biopsy samples for LC-MS/MS analysis.

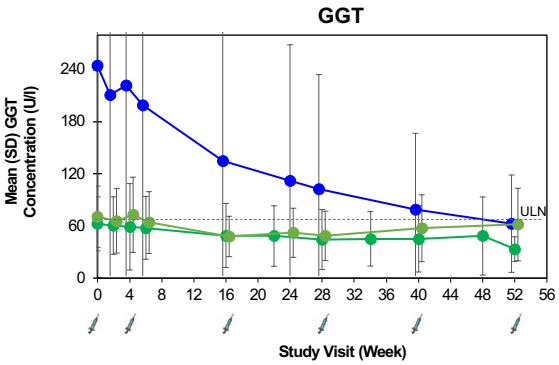
BL denotes baseline, postBL postbaseline at Week 24 or 48
Z-AAT = alpha-1 antitrypsin Z-mutant protein

Strnad et al., *NEJM 2022*

21

Fazirsiran Improved Biomarkers of Liver Health





- Mean reduction in liver stiffness (VCTE)
  - Cohort 1: -18% at Week 24
  - Cohort 2: -15% at Week 48
  - Cohort 1b: -2% at Week 24
- Mean reduction in serum Pro-C3
  - Cohort 1: -36% at Week 28; -39% at Week 52
  - Cohort 2: -21% at Week 28; -17% at Week 52
  - Cohort 1b: +5% at last observation at Week 28

Strnad et al., *NEJM 2022*

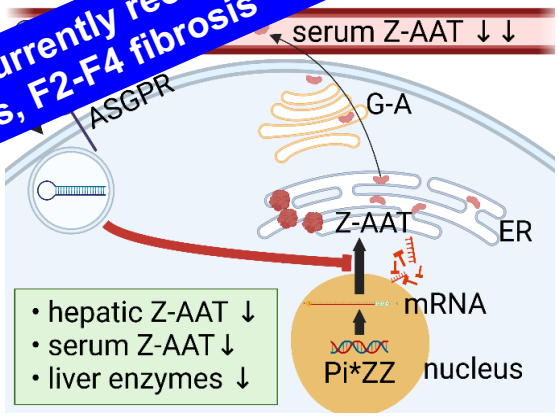
22

Summary and conclusions

- Fazirsiran reduced serum and liver Z-AAT and histological globule burden in all patients leading to:
  - Reduction in histological signs of portal inflammation in t… …ls of patients
  - Substantial and sustained reductions in clinically … …ers of liver health
  - Improvement in liver fibrosis
- Fazirsiran was generally well …
- No TEAEs leading t…

ation/interruptio…

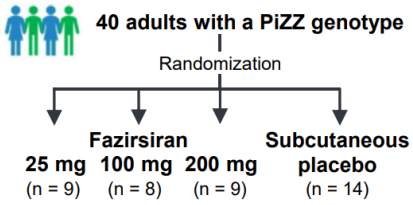
Phase 3 study currently recruiting: Pi*ZZ, adults, F2-F4 fibrosis



Strnad et al., *NEJM 2022*

23

ARO-AAT-2001 (SEQUOIA-RCT)

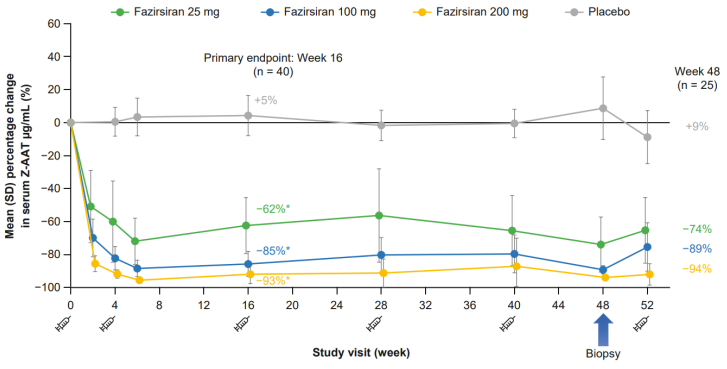


Primary endpoint

Serum Z-AAT at 16 weeks

LS mean % decline vs placebo

Fazirsiran		
25 mg	−61%	*P* < .0001
100 mg	−83%	*P* < .0001
200 mg	−94%	*P* < .0001



Clark et al., *Gastroenterology 2024*

24

ARO-AAT-2001: safety

Subject Incidence, n (%)	Fazirsiran 25 mg (N=9)	Fazirsiran 100 mg (N=8)	Fazirsiran 200 mg (N=9)	PBO (N=14)
Treatment-emergent AEs (TEAEs)	9 (100%)	8 (100%)	9 (100%)	13 (92.9%)
TEAEs in 4 or more subjects				
COVID19	0 (0%)	2 (25%)	6 (67%)	2 (14%)
Headache	4 (44%)	1 (13%)	2 (22%)	3 (21%)
Procedural pain	1 (11%)	0 (0%)	4 (44%)	
Arthralgia	2 (22%)	2 (25%)		
Diarrhoea	1 (11%)	1 (13%)		2 (14%)
Nausea	1 (11%)		(11%)	3 (21%)
Back pain	1 (11%)		2 (22%)	0 (0%)
Fatigue	1 (11%)	1 (13%)	0 (0%)	2 (14%)
Treatment-related TEAEs	2 (22%)	4 (50%)	3 (33%)	8 (57%)
Serious TEAEs	0 (0%)	0 (0%)	2 (22%)	3 (21%)
TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal	0 (0%)	0 (0%)	0 (0%)	0 (0%)
TEAEs causing deaths	0 (0%)	0 (0%)	0 (0%)	0 (0%)

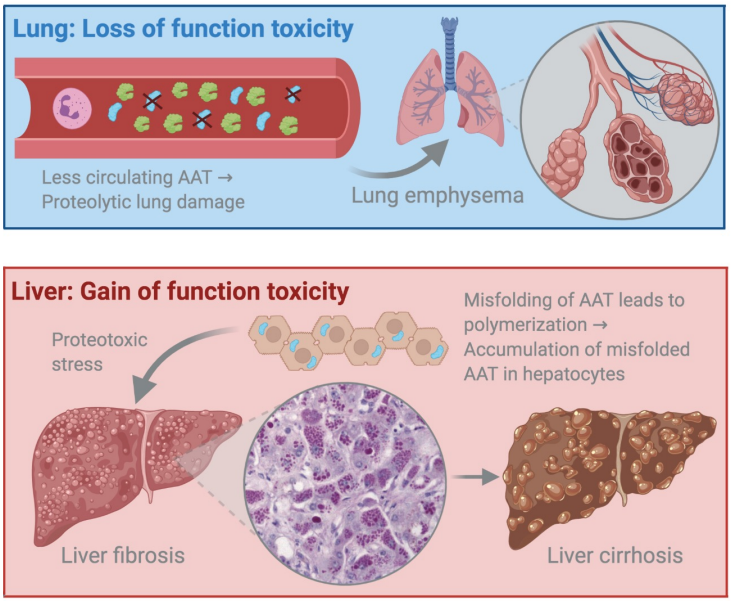
Phase 3 study recruiting

- No TEAE-related study drug discontinuation, dose interruptions, or premature study withdrawals
- 2 subjects with 2 TESAEs reported in the 200 mg cohort
  - Both were infective exacerbations of bronchiectasis (both with history of multiple pulmonary infections)
- 3 subjects with 6 TESAEs in PBO
  - One subject reported Influenza, Staph wound infection, and Acute pancreatitis
  - One subject reported PFT decreased and Hypertensive crisis
  - One subject reported Presyncope

Clark et al., *Gastroenterology 2024*

25

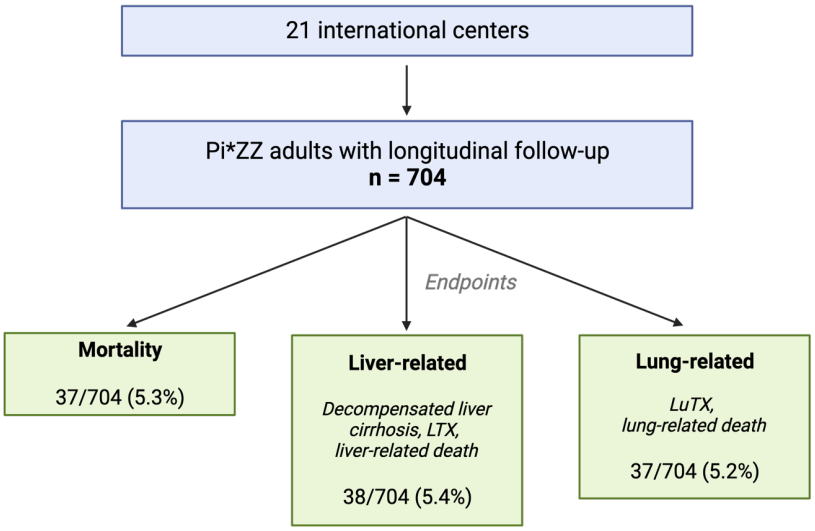
Whom to include in the trials?



Strnad et al., *NEJM 2020*

26

Longitudinal study



27

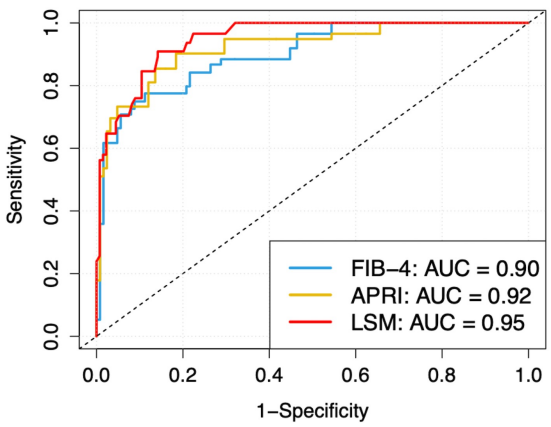
LSM<7.1kPa as a rule-out criterium

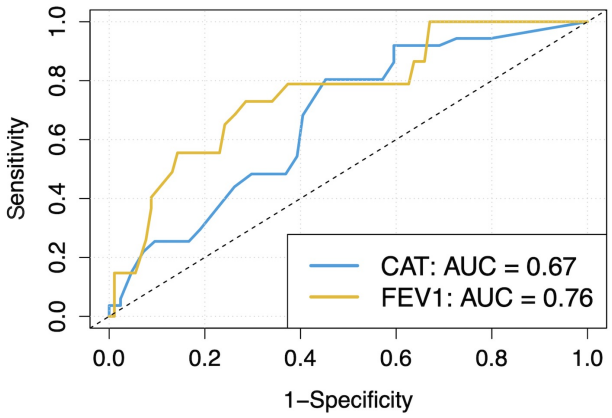
LSM (kPa)	n	Follow-up years (cumulative)	Liver-related endpoints	Endpoints/100 FU years
<7.1	514	**1782.6**	**0**	0
7.1 – 10	103	395.0	6	1.5
10.1 – 14.9	45	168.2	6	3.6
≥15	42	**111.6**	**26**	23.3

APRI (units)	n	Follow-up years (cumulative)	Liver-related endpoints	Endpoints/100 FU years
<0.5	530	**1862.2**	**3**	0.2
0.5 – 0.99	118	423.5	14	3.3
1.0 – 1.49	18	42.1	9	21.4
≥ 1.5	15	**35.8**	**12**	33.5

28

Fibrosis surrogates predict liver-related endpoints





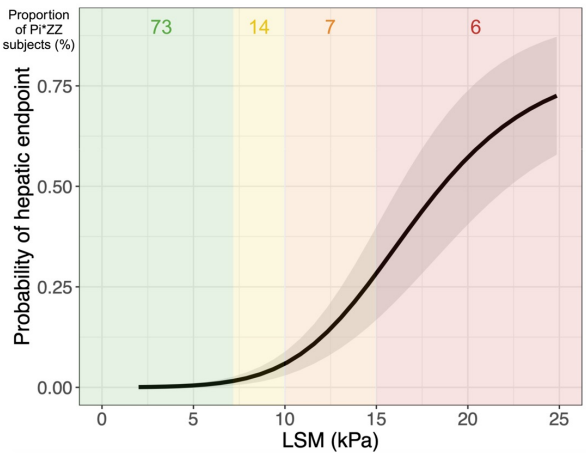
→ LSM by FibroScan was the most accurate predictor of hepatic endpoints, while lung parameters displayed only a moderate predictive utility for lung-related endpoints

Fromme et al., Gastroenterology 2025

29

Balancing the lung and the liver

A



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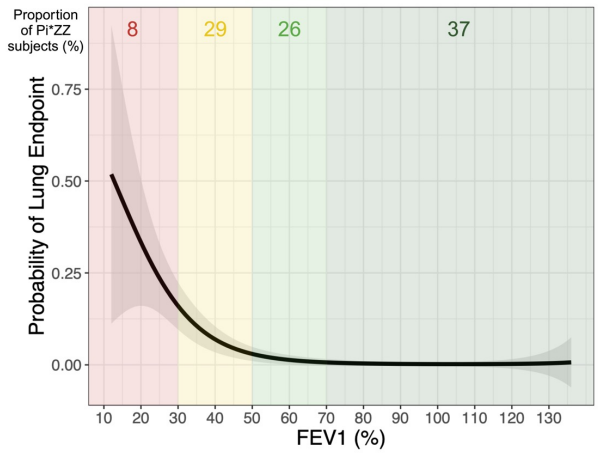


Fromme et al., Gastroenterology 2025

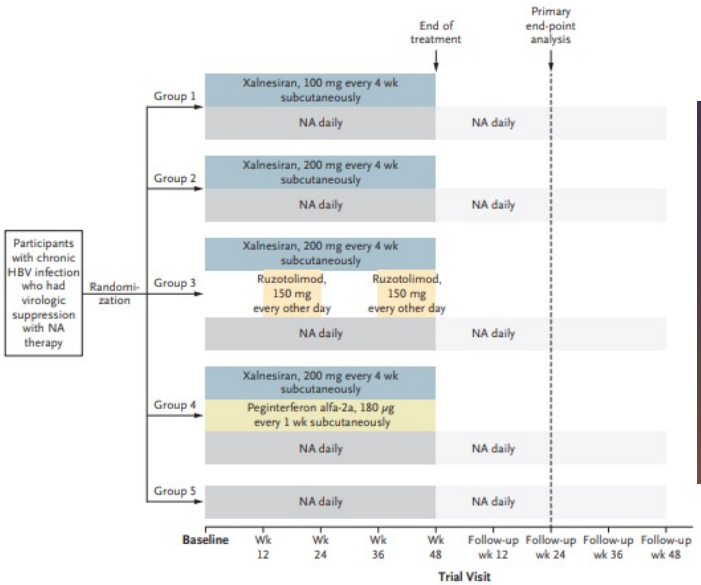
30

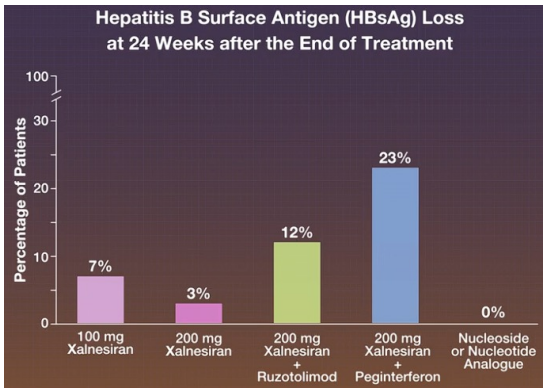
(si)RNA therapy in Hepatology

- General introduction
- A1-AT deficiency
- **Beyond AATD and siRNA**

31

siRNA for hepatitis B

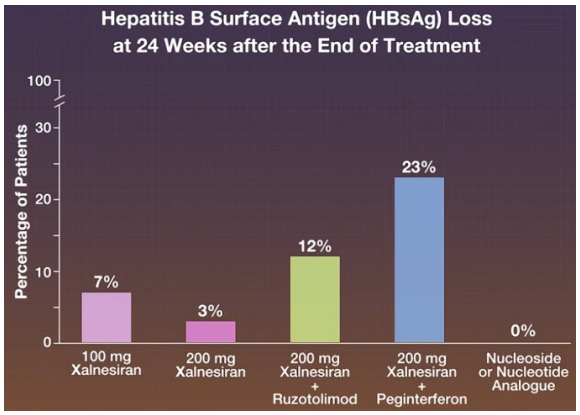


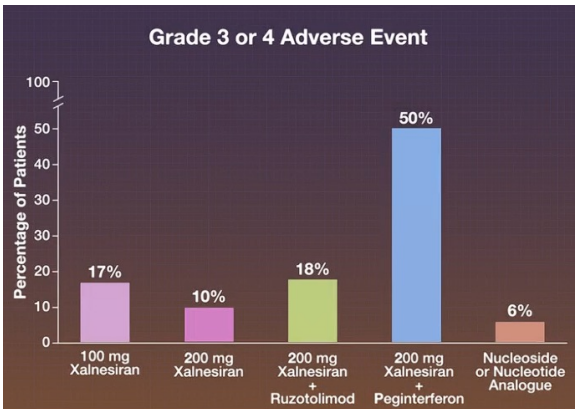


Hou et al., NEJM 2024

32

siRNA for hepatitis B

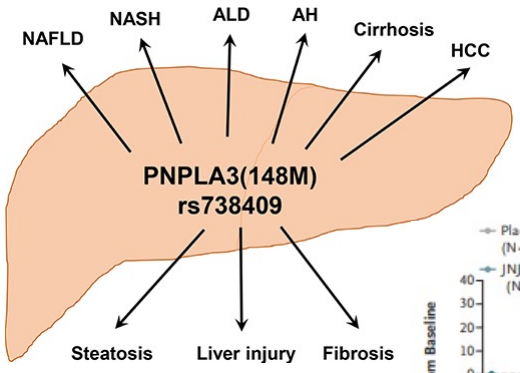


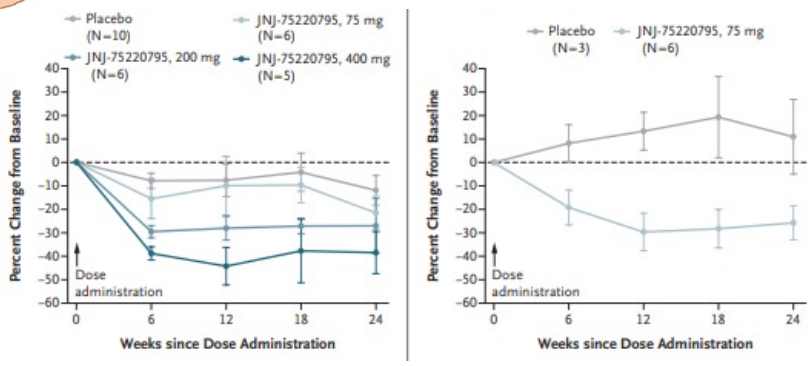


Hou et al., NEJM 2024

33

siRNA for personalized hepatogy

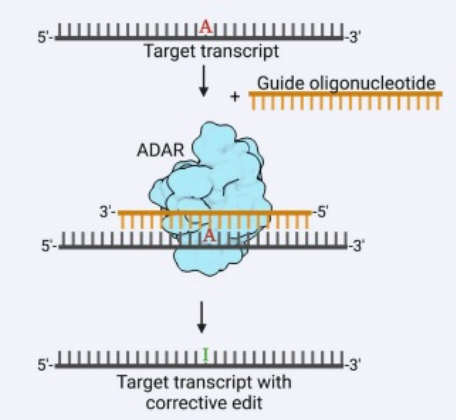




Fabbrini et al., NEJM 2024

34

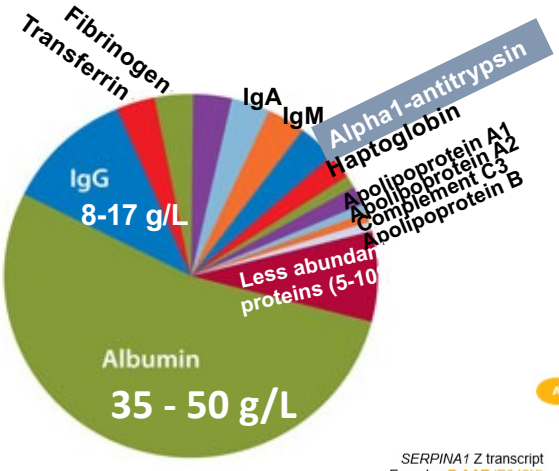
RNA editing-new kid on the block

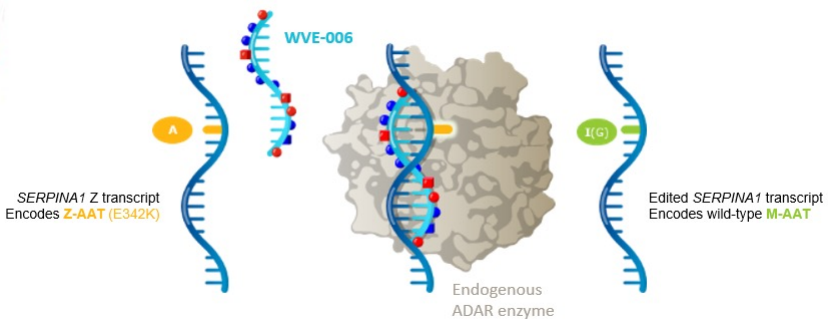


- AIMer (A-to-I RNA editing oligonucleotide)
- Recruiting ADAR (Desamidase)
- Inosin is read as guanin

35

Why AATD?

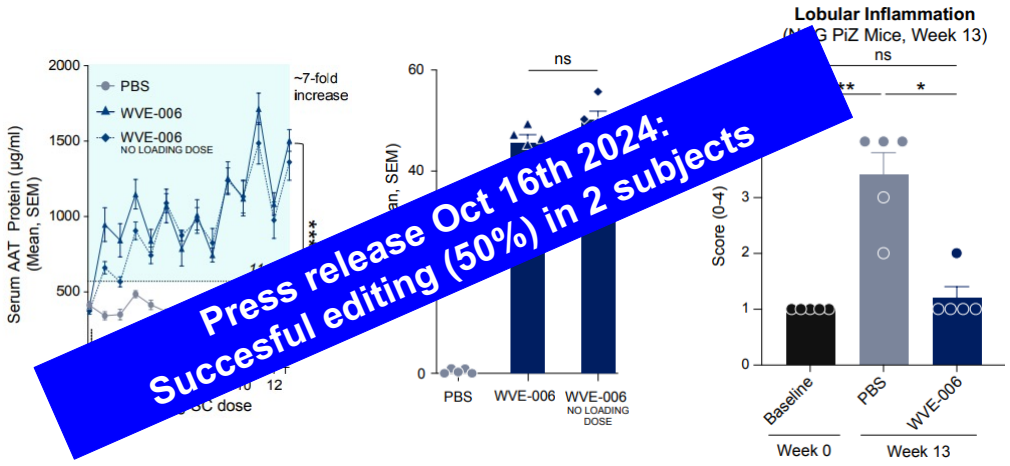




36

WVE-006 (experimental data)

European AATD liver study group



Press release Oct 16th 2024: Succesful editing (50%) in 2 subjects

37

Nucleic acid-based therapies

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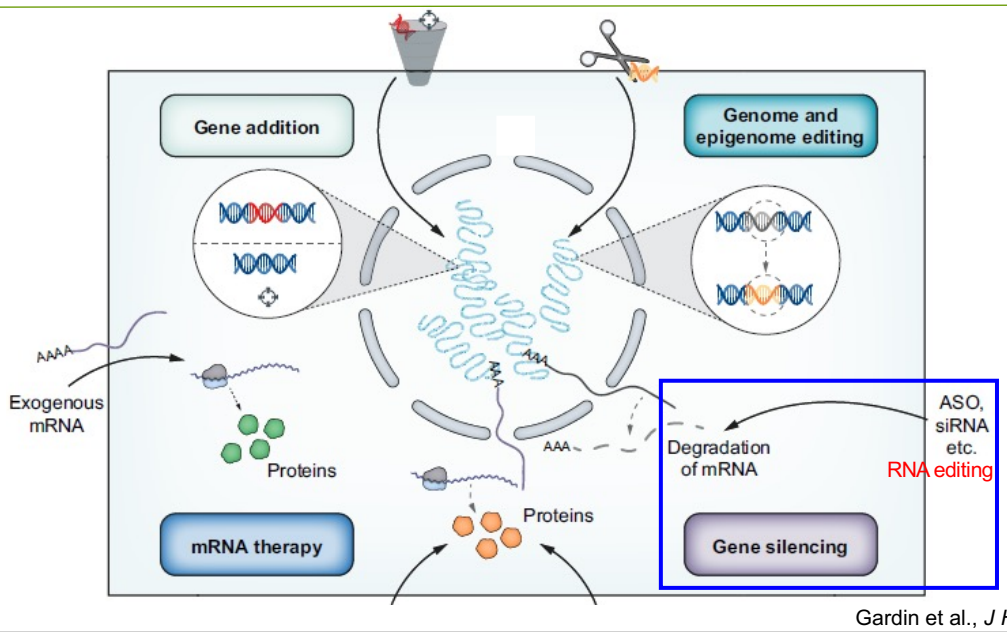

Gardin et al., *J Hepatol 2022*

38