Investor and Analyst R&D Day

September 14, 2017

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Welcome
Vince Anzalone, CFA

Safe Harbor Statement

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including, without limitation, our developmental stage and limited operating history, our ability to successfully and timely develop products, enter into collaborations and achieve other projected milestones, rapid technological change in our markets, demand for our future products, legislative, regulatory and competitive developments and general economic conditions. Our Annual Report on Form 10-K, recent and forthcoming Quarterly Reports on Form 10-Q, recent Current Reports on Forms 8-K, and other SEC filings discuss some of the important risk factors that may affect our ability to achieve the anticipated results, as well as our business, results of operations and financial condition. Readers are cautioned not to place undue reliance on these forward-looking statements. Additionally, Arrowhead disclaims any intent to update these forward-looking statements to reflect subsequent developments.

Panelists

Hepatitis B Virus

Stephen Locarnini, M.D., Ph.D.
Head of Research and Molecular Development, Victorian Infectious Diseases Reference Laboratory
Director of WHO Collaborating Centre for Virus Reference and Research

Alpha-1 Antitrypsin Deficiency

Jeffrey Teckman, M.D.
Professor, Division Director, Division of Pediatric Gastroenterology & Hepatology, Saint Louis University School of Medicine

Hypertriglyceridemia

Ira Goldberg, M.D.
Director, Division of Endocrinology, Diabetes, and Metabolism, NYU Langone Medical Center

Arrowhead Pharmaceuticals

Chris Anzalone, Ph.D. - President and CEO
Bruce Given, M.D. – COO and Head of R&D
Vince Anzalone, CFA – Vice President, Investor Relations

Agenda

- TRiM™ Platform and Pipeline Review - Chris Anzalone, Ph.D.
- Chronic Hepatitis B Virus Infection
  - Disease Background – Stephen Locarnini, M.D., Ph.D.
  - ARO-HBV – Bruce Given, M.D.
- Alpha-1 Antitrypsin Deficiency Liver Disease
  - Disease Background – Jeffrey Teckman, M.D.
  - ARO-AAT – Bruce Given, M.D.
- Hypertriglyceridemia: Acute and Chronic Disease
  - Disease Background – Ira Goldberg, M.D.
  - ARO-APOC3 and ARO-ANG3 – Bruce Given, M.D.
- Concluding Remarks – Chris Anzalone, Ph.D.
- Q&A - Panel

TRiM™ Platform and Pipeline Review
Chris Anzalone, Ph.D.

Arrowhead Goal

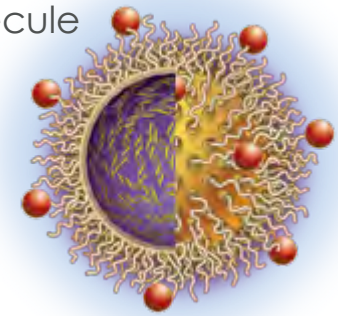
Treat intractable medical conditions by silencing the genes that cause them

- Select the right genes
- Ensure sufficient activity (knockdown)
- Well tolerated
- Manufacturability

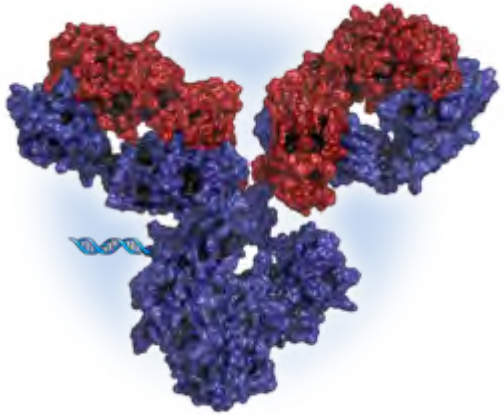
This has been our destination and our path has been a story of evolution

Evolution in RNAi: Drive toward Max Activity

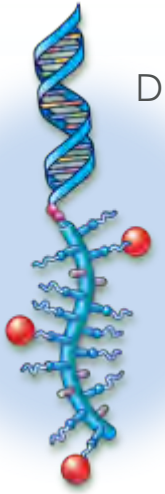
Rondel Molecule



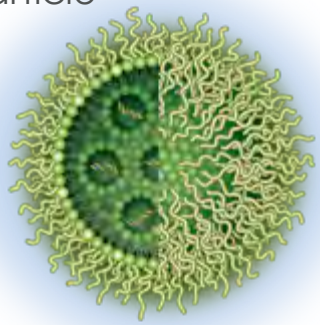
Antibody Conjugate



DPC-1



Lipid Nanoparticle



DPCs provided deepest KD; Required active endosomal escape

DPC-2

DPCs in the Clinic

- >350 people received doses of ARC-AAT, -520, and -521
- Unprecedented activity: up to 99.9% knockdown
- Appeared well tolerated in humans
  - Only 3 SAEs during studies
    - 2 Fevers, controlled by acetaminophen
    - A hepatic tumor deemed unrelated to treatment

But…in a long-term GLP tox study with ARC-521, monkey mortalities at supra-clinical doses of ARC-521 and DPC alone (none with RNA alone)

- Informed regulatory agencies in 17 countries where ARC-520, -521, and -AAT studied
- Began evaluations of possible causes of monkey deaths
- Discussions with regulators of differences between clinical record and monkey deaths
  - Monkey deaths occurred at non-clinical doses
  - Possibly species specific
  - Monkeys were not pretreated with antihistamine
  - Monkeys had faster infusion rates

FDA Clinical Hold

- FDA informed us of clinical hold
- We reported this publically the same day
- Continued discussions with other regulatory agencies
- Completed analysis of data from necropsies and blood samples, and consulted with regulatory and toxicology experts for possible paths forward

Conclusions

- Consensus that high dose DPCs (not RNA) led to the toxicity
- Mechanism of fatal DPC toxicity in monkeys was likely multifactorial
- In consultation with experts, determined that satisfying the FDA would require new studies to:
    - Confirm cause(s) of monkey mortalities
    - Provide clear evidence that mortality could be prevented in humans

Discontinuation of DPC platform

DPC path forward presented unacceptable risk

- **Time risk**: 18 months in the best case
- **Outcome risk**: no guarantee of clear answers after long study
- **Regulatory risk**: no guarantee of clear path forward even with clear answers
- **Mode of administration risk**: iv vs. subQ

Made difficult decision to discontinue platform

- Had >$100m + new Amgen partnership: sufficient resources to drive new platform
- New platform development was well underway
  - Had already decided that all future candidates would be built on new platform: advantages of subQ vs. iv
  - Good preliminary non-clinical data
    - New platform does not include DPCs: confident in wider safety margin

Targeted RNAi Molecules

TRiM™ platform

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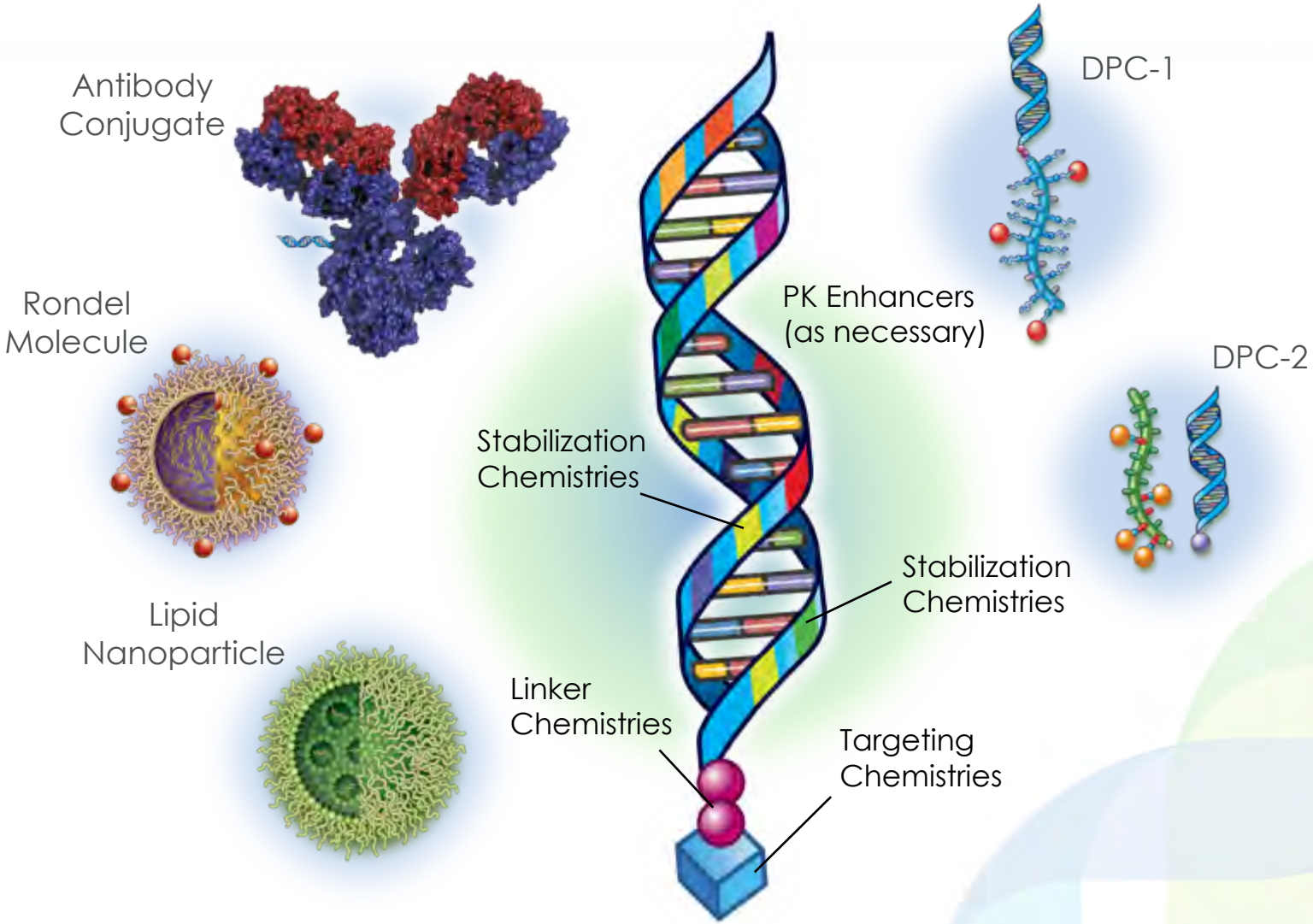
TRiM™: Evolution of Simplicity, Specificity, and Activity



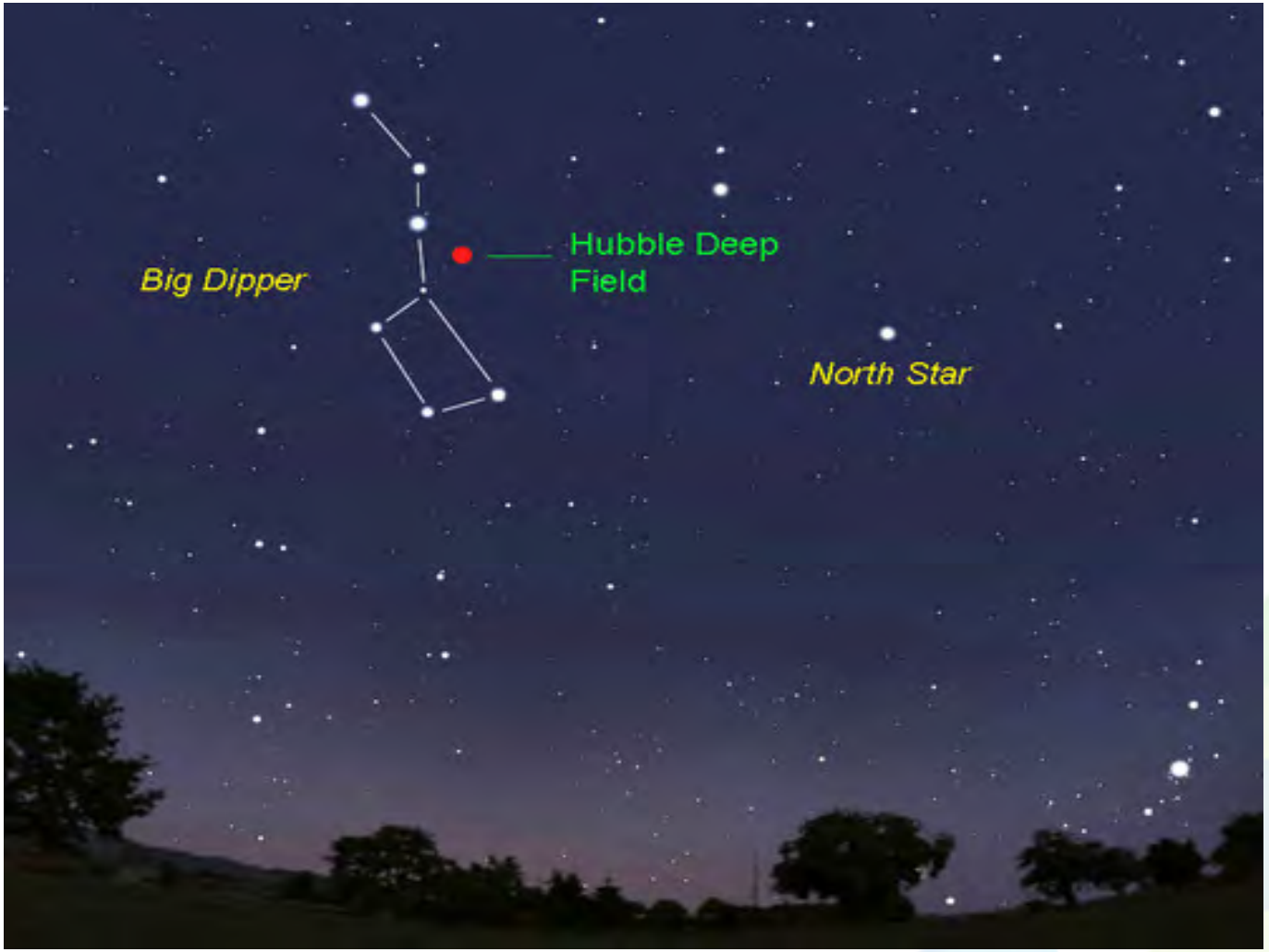
Trigger Selection: Seeing What Others Have Not

TRiM™ has rules and algorithms to optimize trigger sequence

- Limit cross reactivity with off target genes
- Maximize activity
- Maximize innate stability
- Optimize use and placement of modifying chemistries
  - Chemical stabilization strategies with target duration of 30-90 days
  - Limit the use of longer duration strategies because we anticipate they will increase long-term safety risks

Not a commodity: IP tools, including trade secrets, enable optimal performance and rapid development

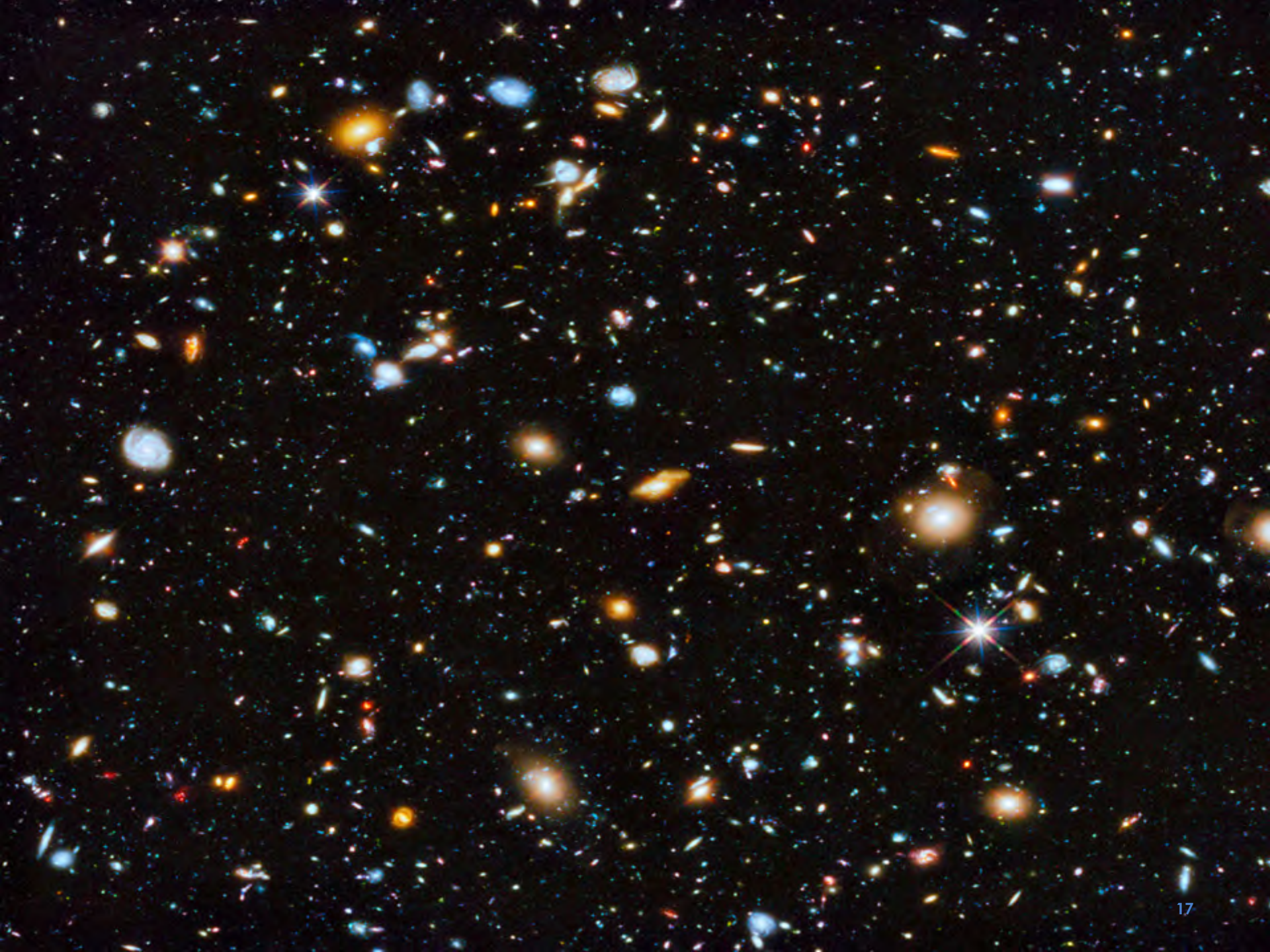
Hubble: Took a New Tool to See What Nobody Else Could



The Big Dipper

Noel Carboni, NCarboni@att.net

Canon EOS-20D and 17-40 zoom lens at f/4 piggybacked on 10" LX200 GPS UHTC
15 x 30 second ISO 1600 exposures



TRiM™ Chemical Modifications

Linker Chemistries

Targeting Ligands

Stabilization Chemistries

Structures to Enhance Pharmacokinetics

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TRiM™: A Dynamic Platform

The result of a drive toward simplicity

Superior activity and targeting capabilities without engineered endosomal escape

Growing libraries of targeting agents, linkers, stabilization chemistries, and PK enhancers enable modular approach…but in a simple structure of decorated RNA, that we believe will provide:

- Simplified manufacturing at reduced cost
- Multiple routes of administration
- Faster time to clinical candidates
- Wide safety margins
- Promise of taking RNAi to tissues beyond the liver

Evolution from biologic complexity to small molecule precision and execution

First Liver-targeted Programs Using TRiM™ Platform

ARO-AAT

- Up to 90% KD in monkeys, thought to be near complete suppression of hepatic source
- SubQ administration
- In non-GLP rat and monkey tox studies, no changes in clinical chemistries and no histopathology suggestive of organ tox at doses up to 300mg/kg (100x expected human dose)

CTA planned in Q1 2018 pending completion of GLP tox

ARO-HBV

- >99.9% KD of HBsAg, HBeAg, and HBV DNA in rodent models
- SubQ administration
- In non-GLP rat tox study, no changes in clinical chemistries and no histopathology suggestive of organ tox at doses up to 300mg/kg (75-100x expected human dose)

CTA planned in Q2 2018 pending completion of cross-reactivity studies and GLP tox

Given our knowledge of these diseases and clinical experience with 64 sites in 15 countries, we expect to *fly* once in the clinic

Building Out CV Portfolio Using TRiM™ platform

Already building candidates ARO-LPA and ARO-AMG1 with Amgen,
Now adding as wholly-owned assets:

ARO-APOC3

- Up to 90% KD in rodent models (intestines also a source of production)
- SubQ administration
- NHP work and non-GLP tox studies to follow

CTA planned in 2018

ARO-ANG3 (against ANGPTL3)

- >90% KD in rodents with several good triggers
- SubQ administration
- Still optimizing chemistries
- NHP work and non-GLP tox studies to follow

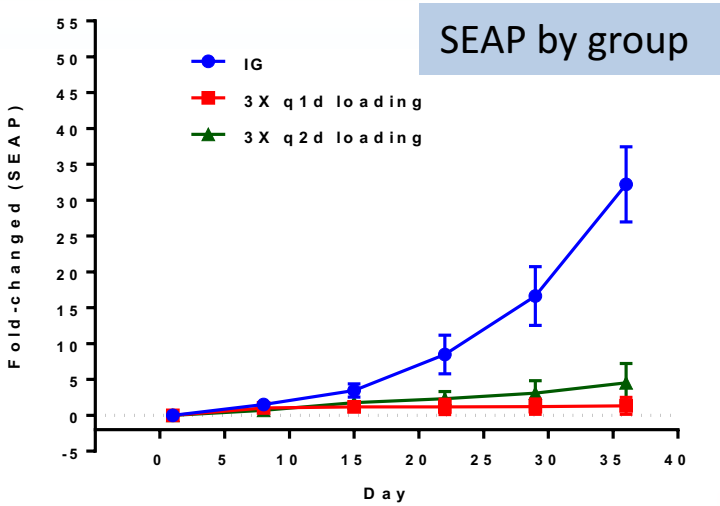
CTA planned in 2018

Targeting New Tissues Using TRiM™ Platform

ARO-Hif2

- Up to 85% KD in rodent tumor model
- iv administration
- Solid tumor targeting
- Non-GLP tox studies planned
- Broaden tumor model testing

CTA planned in 2019

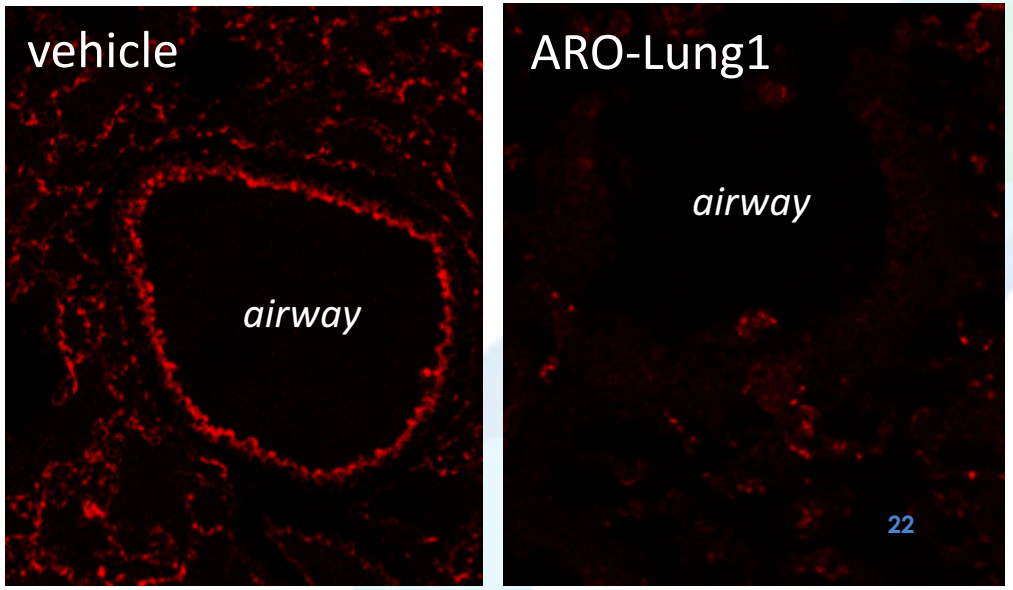


ARO-Lung1

- Almost 90% KD in rodent models
- Inhaled administration
- Large animal studies and disease models underway
- Non-GLP tox studies underway

CTA planned in Q4 2018

Red: lung target protein expression by IHC



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Extra-hepatic Delivery is upon Us

Treat intractable medical conditions, wherever they are, by silencing the genes that cause them

Targeting lung and tumors with the TRiM™ platform

- Demonstrates flexibility of the TRiM™ platform
- Fundamentally changes RNAi competitive landscape
- Expands opportunities into new markets/indications
  - Once RNAi activity is validated in a new organ, allows expansion into other disease areas within that organ
  - Becomes entire franchise
  - Powerful engine of growth
- Expands partnership opportunities

Big Expectations for 2018

Q1 2018
- ARO-AAT CTA planned

Q2 2018
- ARO-HBV CTA planned

Q4 2018
- ARO-Lung1 CTA planned
- ARO-APOC3 CTA planned
- ARO-ANG3 CTA planned

Amgen-partnered programs
- ARO-LPA progressing well: Amgen provides/controls guidance
- ARO-AMG1 progressing well: Amgen provides/controls guidance

Chronic Hepatitis B Virus

Stephen Locarnini, M.D., Ph.D.

Head of Research and Molecular Development, Victorian Infectious Diseases Reference Laboratory

Director of WHO Collaborating Centre for Virus Reference and Research

New Insights into HBV Biology

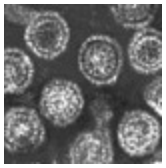
Professor Stephen Locarnini
WHO Regional Reference Centre for Hepatitis B
Victorian Infectious Diseases Reference Laboratory,
Doherty Institute, Melbourne, Victoria 3000, AUSTRALIA

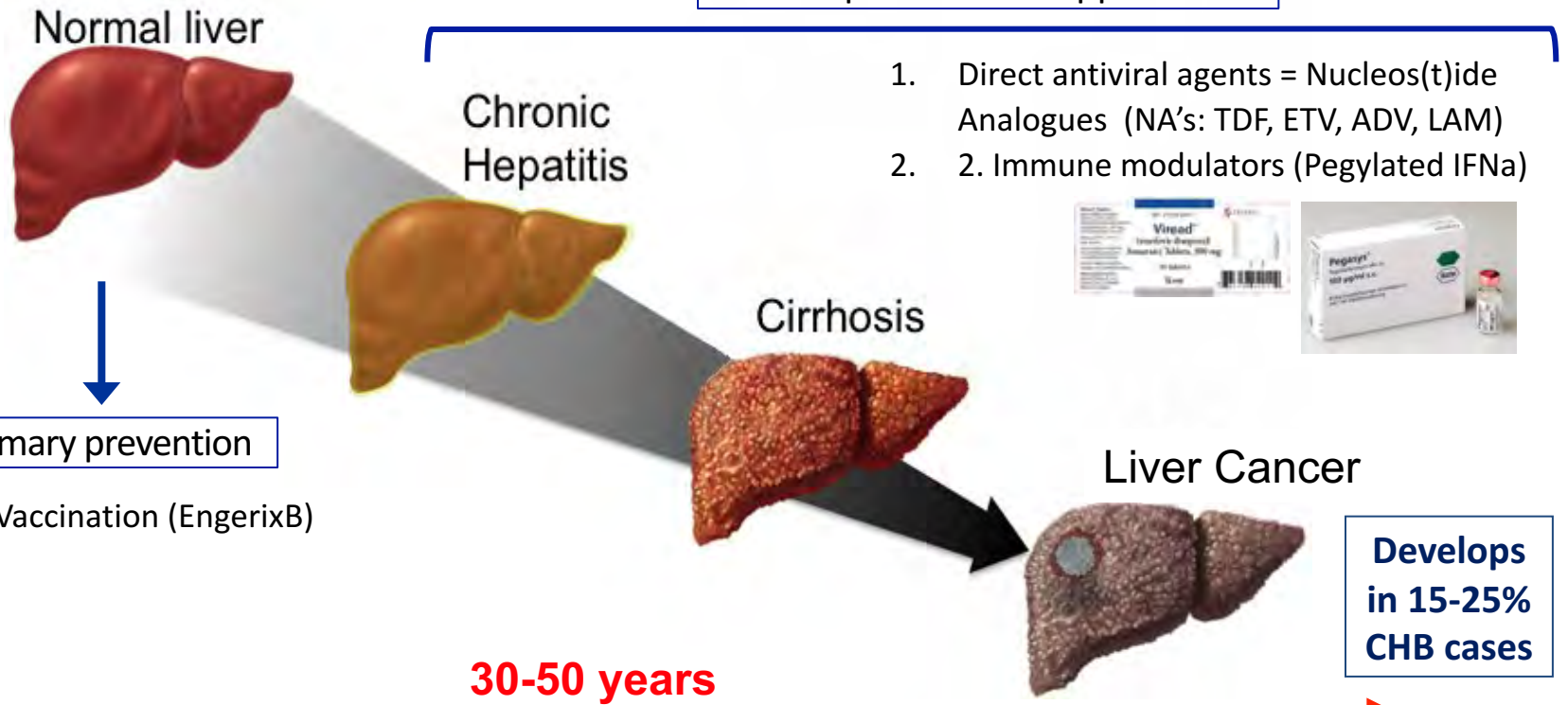
Disclosure

	Gilead Sciences Inc	Arrowhead Pharmaceuticals	Spring Bank Pharmaceuticals, Inc.
Consulting Fees (eg. Advisory Boards)	yes	yes	no
Contract Research (grant)	yes	no	yes

Chronic hepatitis B (CHB): Disease pathogenesis

2 billion infected with HBV → **250 million living with chronic HBV infection**





Therapeutic Virus suppression

1. Direct antiviral agents = Nucleos(t)ide Analogues (NA's: TDF, ETV, ADV, LAM)
2. 2. Immune modulators (Pegylated IFNa)

Primary prevention

1. Vaccination (EngerixB)

Develops in 15-25% CHB cases

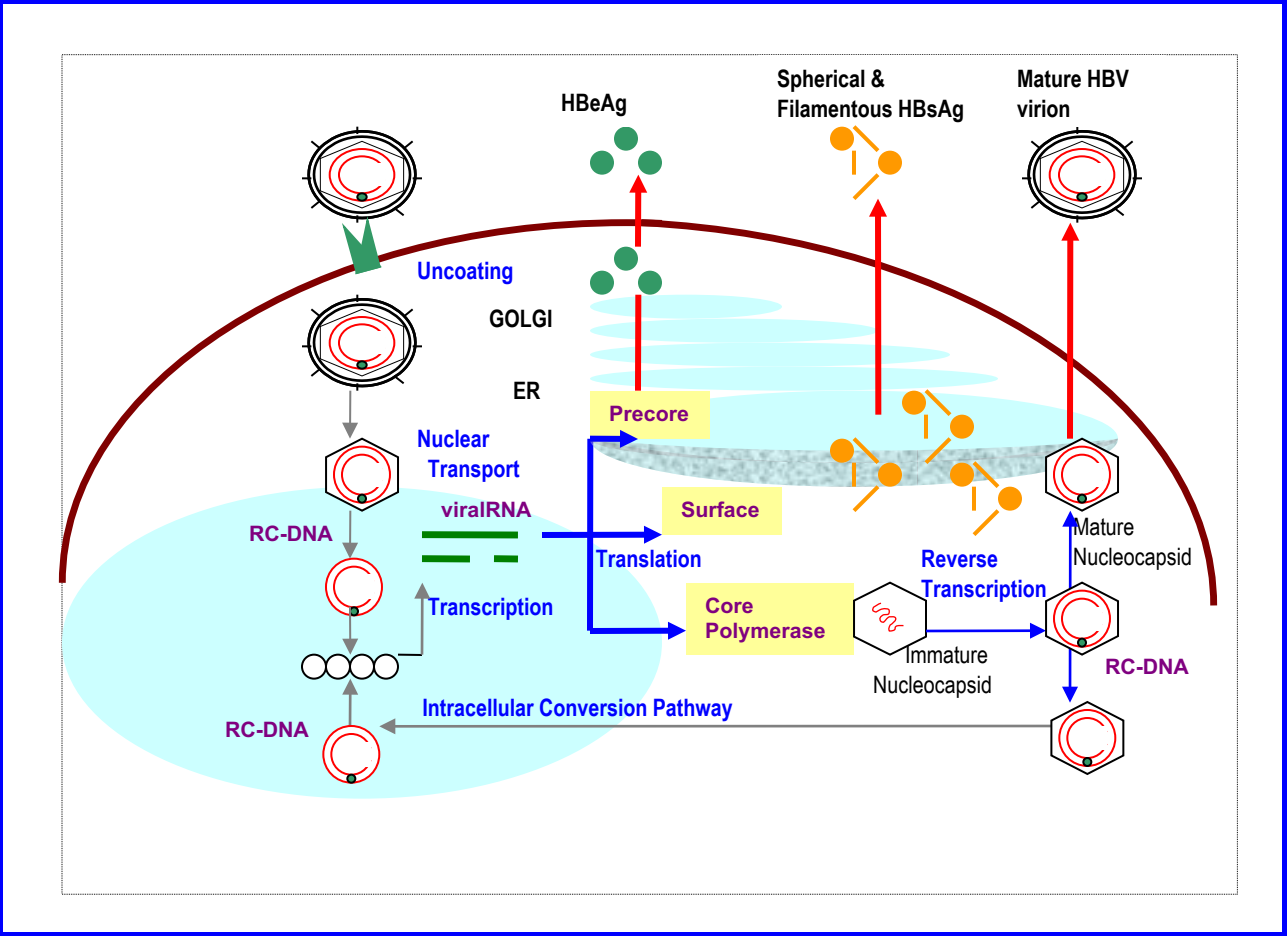
Chronic HBV infection occurs following:

- 95% neonate infections
- 10% adult infections

Neither preventative vaccination nor viral suppression influence CHB cure

Liaw YF et al, N Engl J Med. 2004; Chang et al, Hepatology 2010; Marcellin et al, Lancet 2013; Hosaka et al, Hepatology 2013; Kim et al, Cancer 2015; Papatheodoridis et al, J Hepatol 2015; Seeger, Zoulim, Mason; Fields Virology; 2007-2013

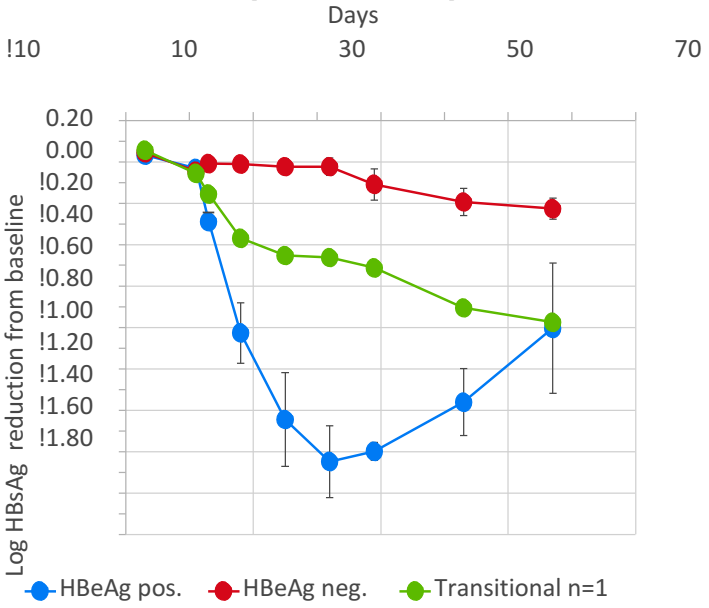
HBV Replication: Pre ARC-520 [cccDNA Driven Replication]



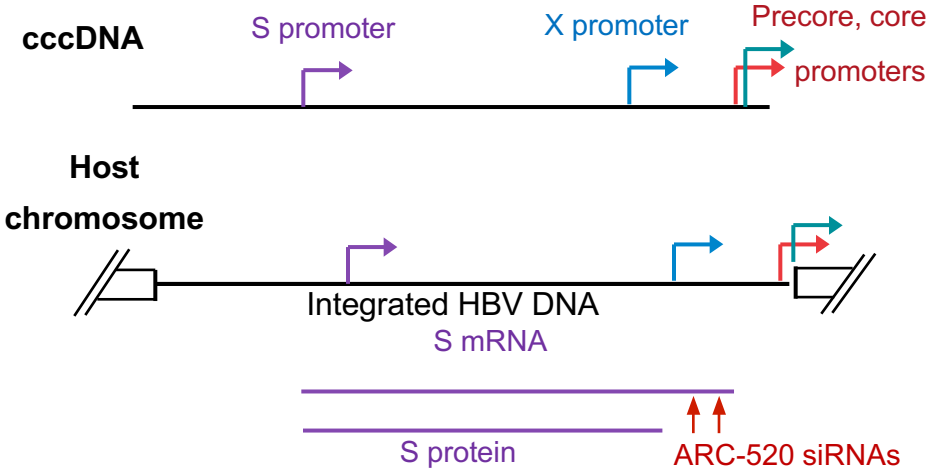
- Incorporates both HBeAg-Pos and HBeAg-Neg HBV Replication

Phase II siRNA ARC-520 Produces Knockdown of Viral Antigens and DNA

HBsAg reduction in ETV naive patients with a single 4 mg dose (cohort 7)



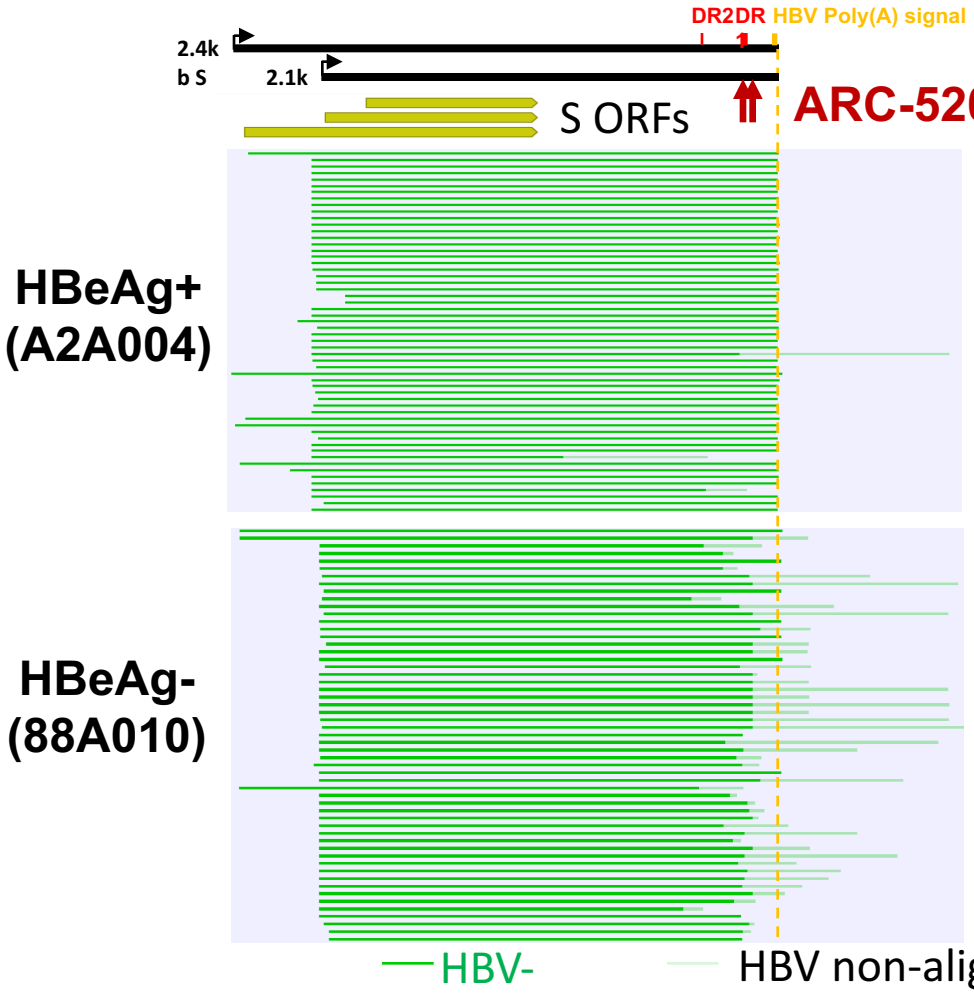
Impact of integrated sequences on siRNA efficacy



Yuen M-F, et al. AASLD 2015, San Francisco. #LB-9

HBV Transcripts Differ Between HBeAg+ and HBeAg- Chimps

PacBio Single Molecule Real-Time (SMRT) Sequencing



HBeAg+

- Most S transcripts terminate near HBV poly(A) signal as expected

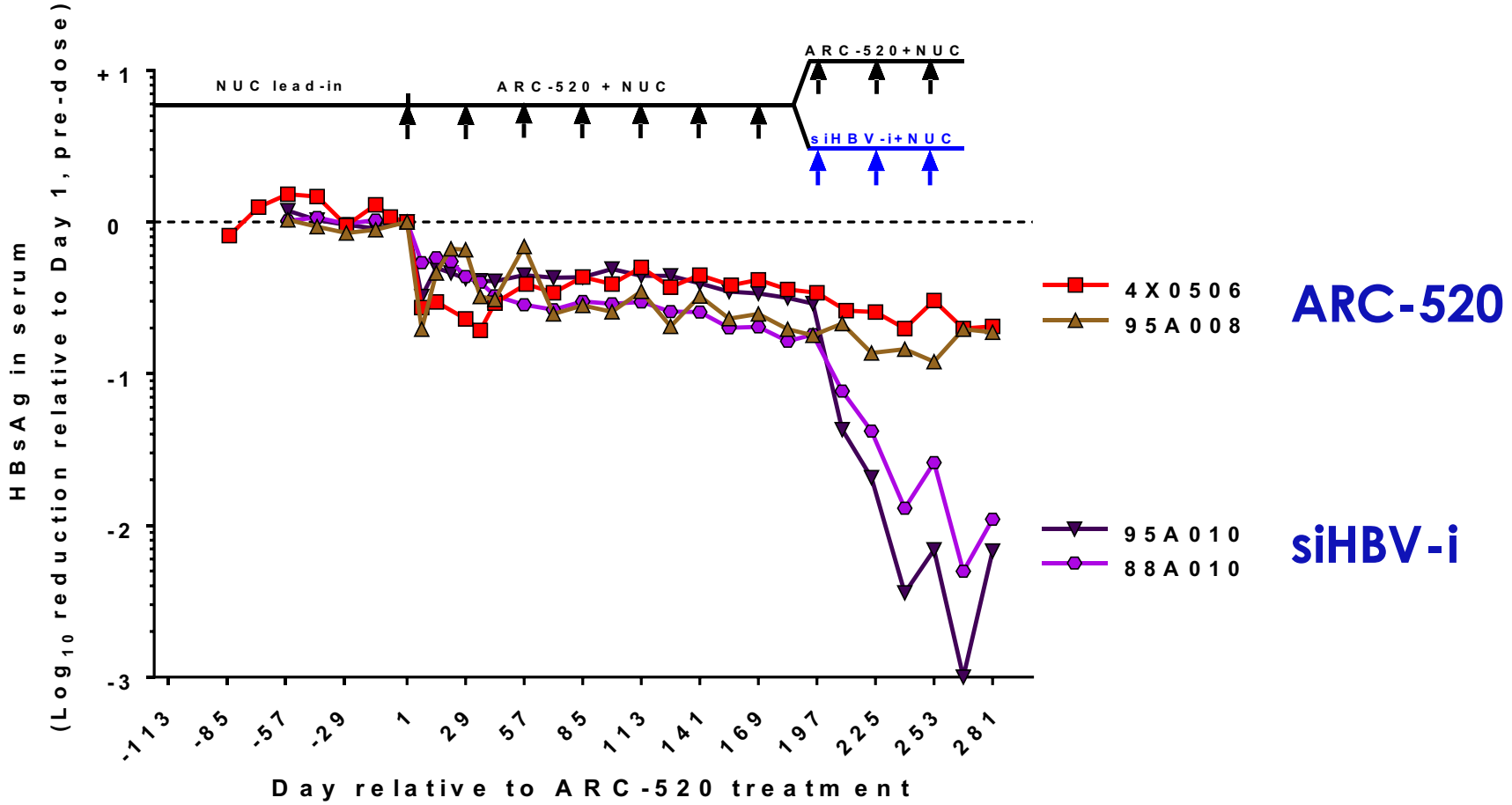
HBeAg-

- Majority of S transcripts are fused at the 3' end to chimp sequence
- Fusion points typically between DR2 and DR1as expected if transcripts arose from integrated HBV dslDNA

S transcripts in HBeAg- chimps often lack target sites for ARC-520

Wooddell, C et al. 2017. Sci Transl Med (in press)

Treatment of HBeAg Negative Chimpanzees with siRNA Targeted Outside the DR1-DR2 Region



Wooddell, C et al. 2017 Sci Trans Med. in press

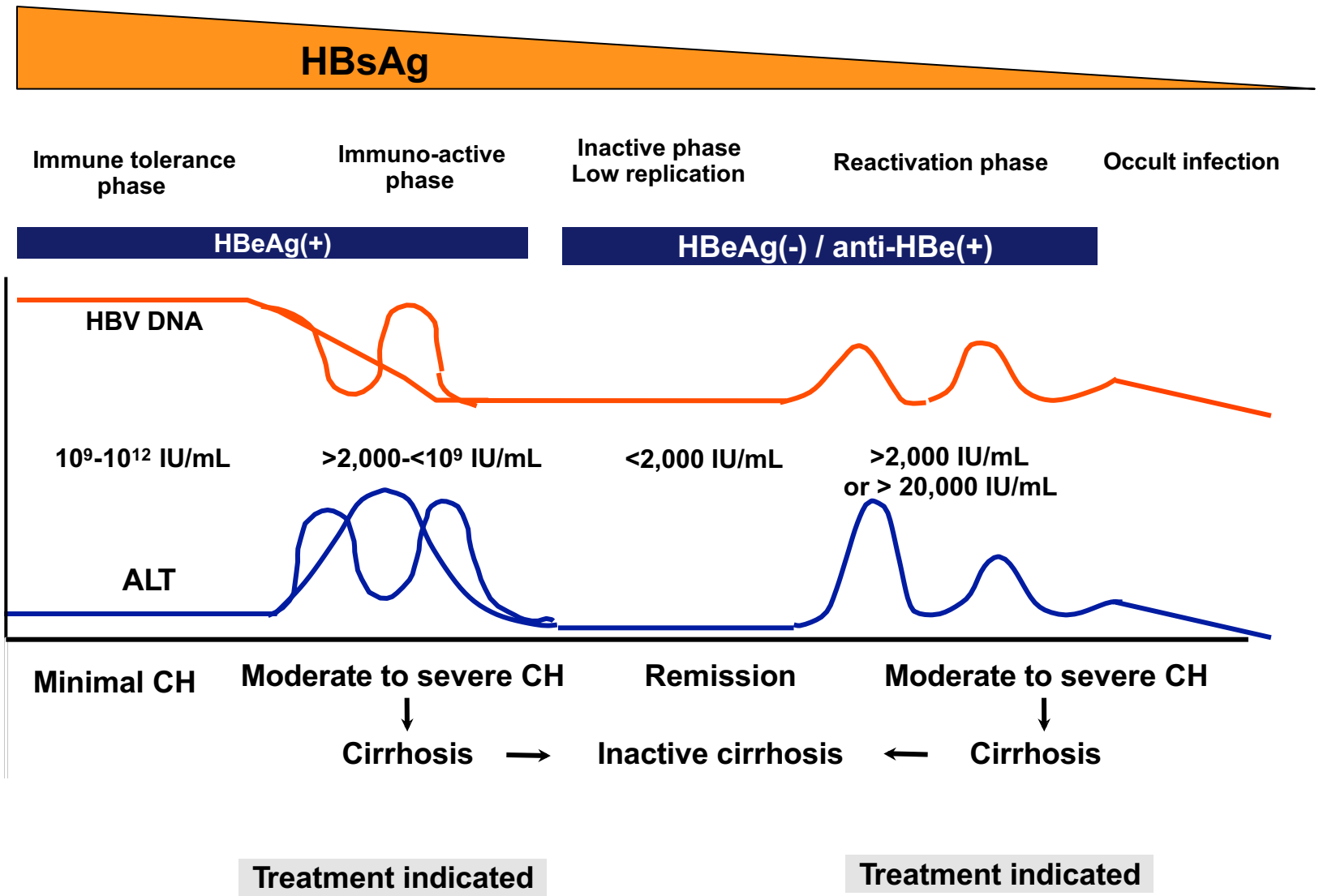
Novel Findings: Predominant Liver HBV DNA Differs in HBeAg Neg and HBeAg Pos Chimps

Liver biopsy at initiation of ARC-520 treatment revealed:

- Most HBV DNA in liver of HBeAg pos is cccDNA
- 500-fold less cccDNA in HBeAg neg
  - Only 5% of total HBV DNA in liver in HBeAg neg was cccDNA and total HBV DNA levels were not affected by NUCs
- HBV DNA profile in HBeAg neg chimps is consistent with a high proportion of integrated HBV DNA

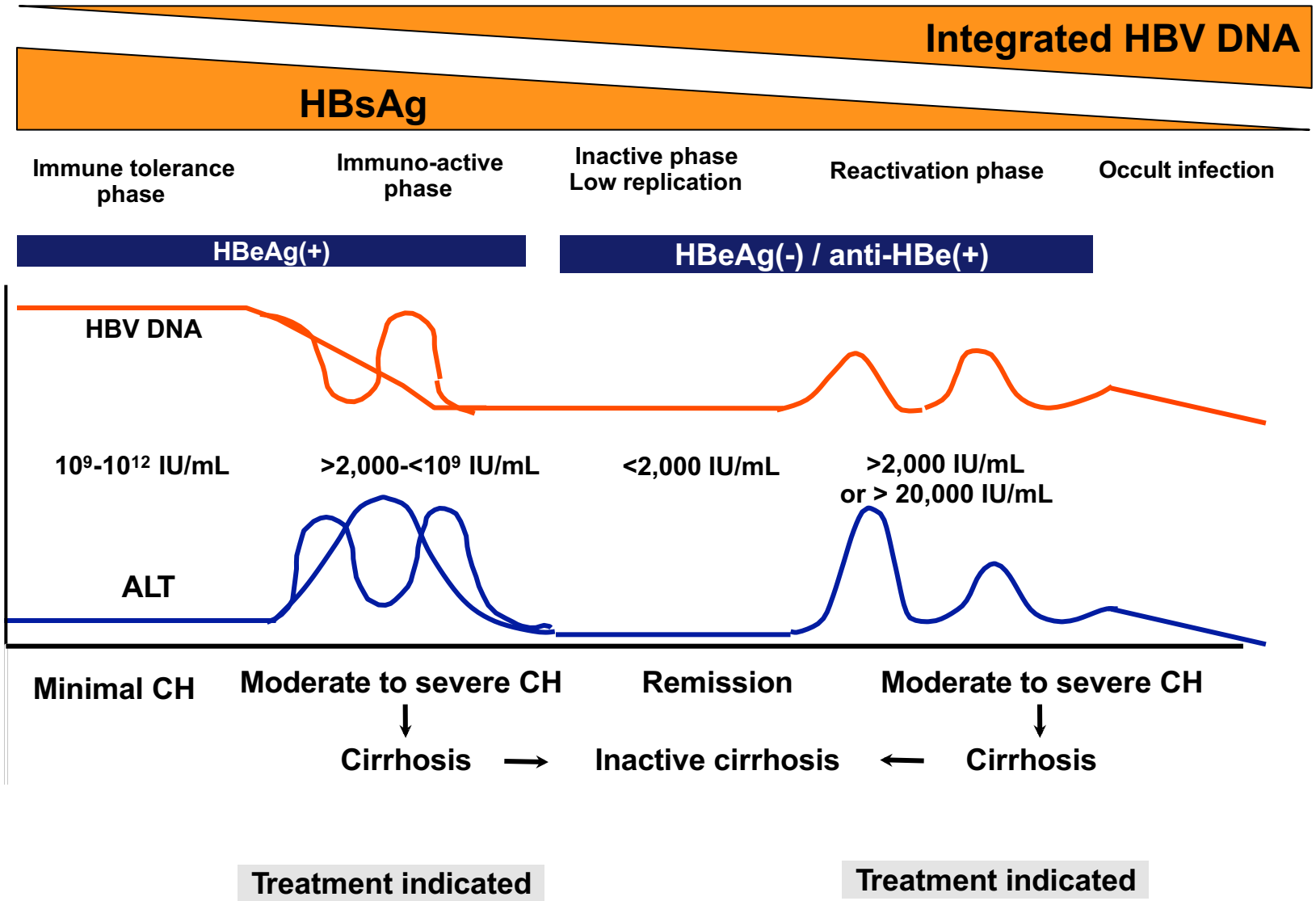
Wooddell, C et al. 2017 Sci Trans Med. in press

Natural History and Treatment



EASL Clinical Practice Guidelines, J Hepatol 2012; AASLD guidelines 2015

Natural History and Treatment

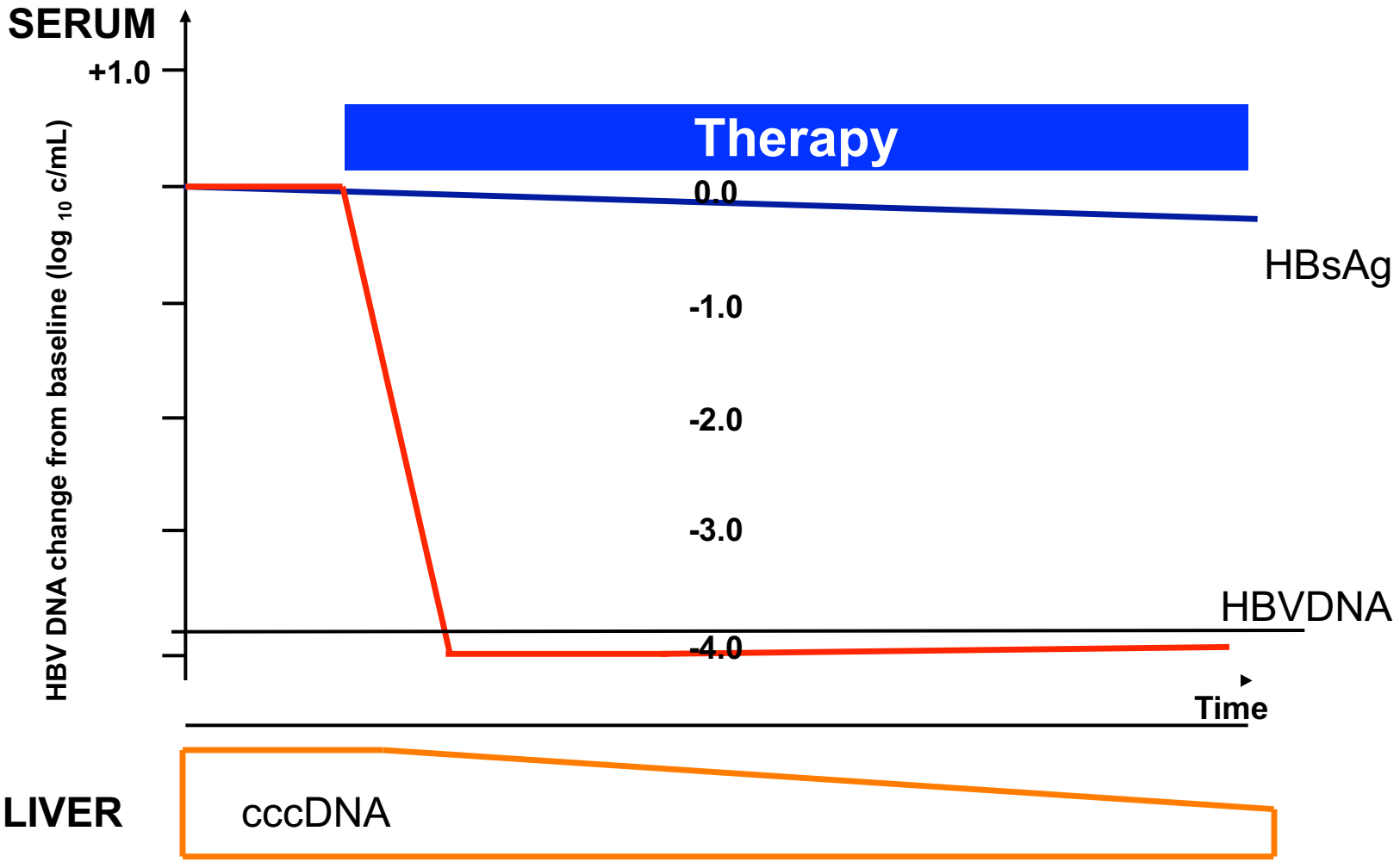


EASL Clinical Practice Guidelines, J Hepatol 2012; AASLD guidelines 2015

A Complex Virus Becomes More Complex

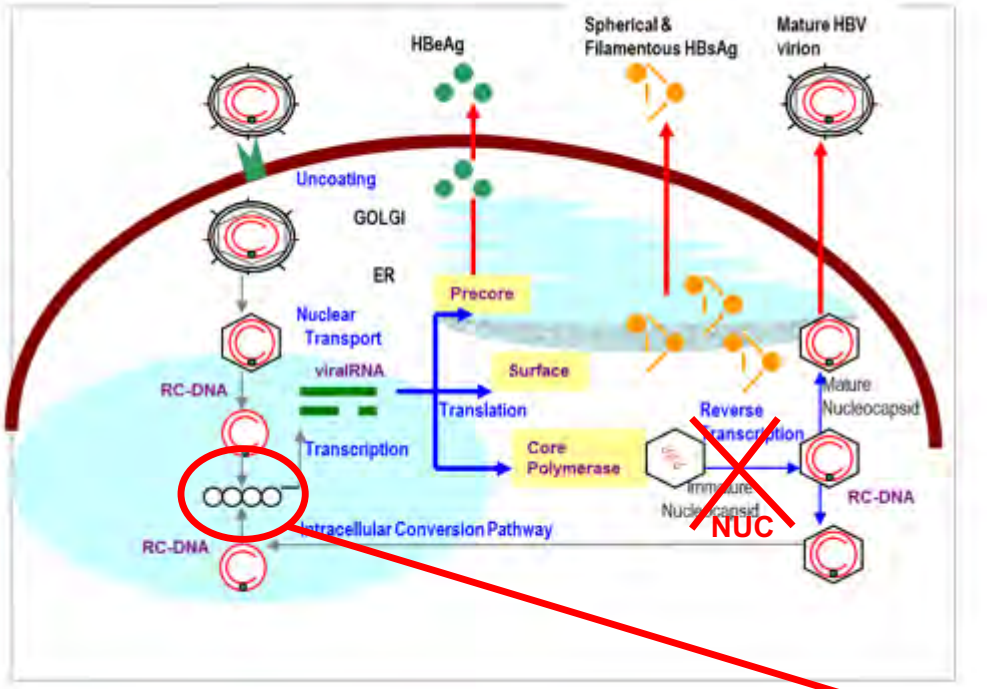
- HBV DNA integration is not uncommon
  - perceived to be caused by inefficient/inaccurate reverse transcription in viral replication (DSL DNA)
  - thought to perhaps play an important role in HCC tumorigenesis
  - has not received much attention as a source of mRNA transcription or as a critical component to the chronic HBV lifecycle
- Previous understanding was that NUCs did not effect cccDNA levels
  - data has emerged showing large reductions in cccDNA levels with NUC therapy in humans
  - the same was observed to occur in the Arrowhead chimps
  - even at baseline, HBeAg negative chimps were near/below LLOQ for intrahepatic cccDNA levels
- This data will force a rethink on the role of integrated DNA in the overall lifecycle of chronic HBV (irrespective of its proposed role in tumorigenesis) and impact of long term NUC therapy

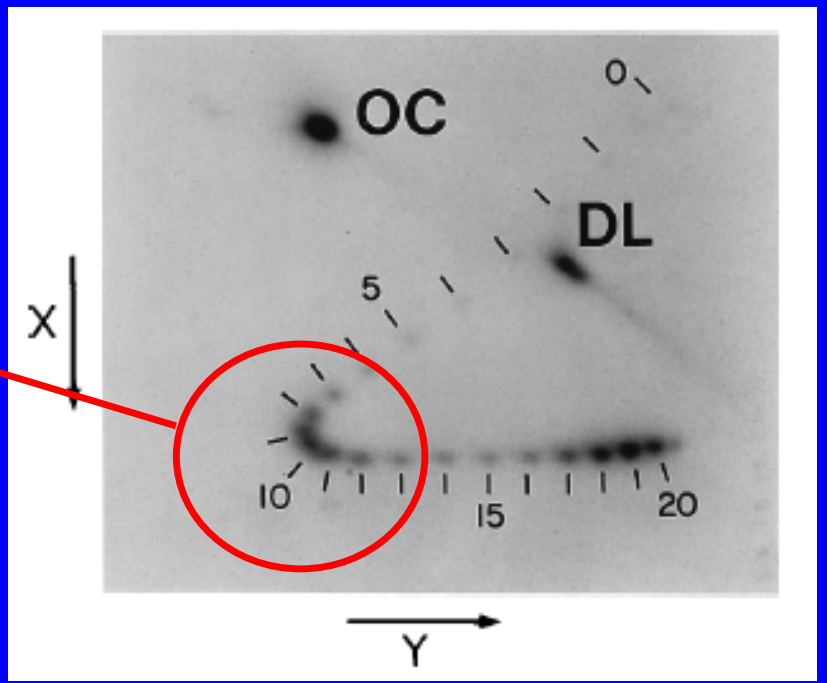
Long-Term Therapy is Required to Maintain Viral Suppression



Werle et al, Gastroenterology 2004; Wong et al, Clin Gastroenterol Hepatol 2013; Boyd et al, EASL 2016

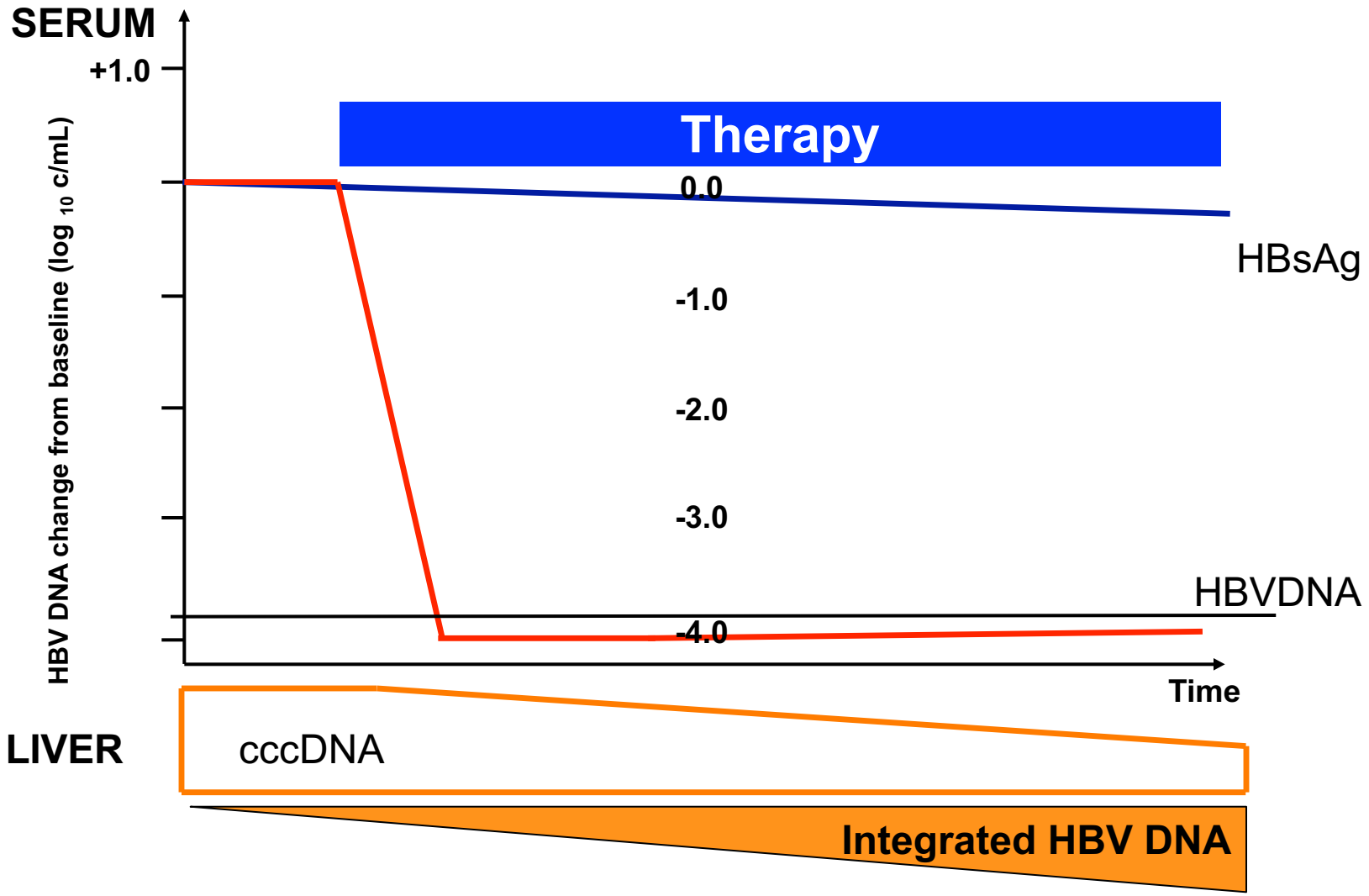
Partial Reduction of cccDNA by NUCs





Newbold, J. et al 1995. J.Virol;69:3350

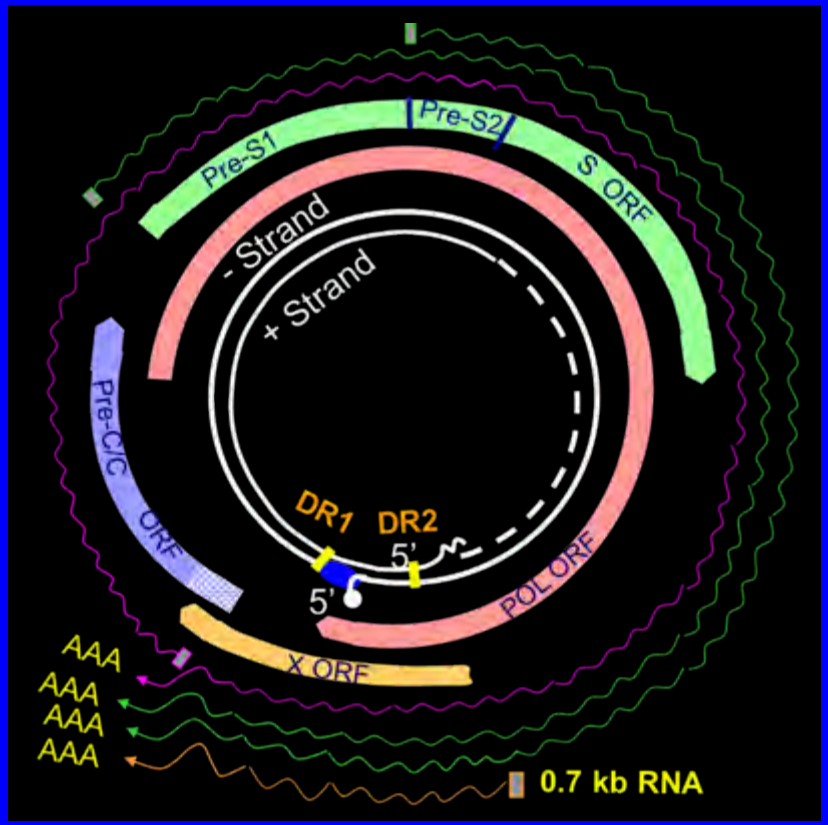
Long-Term Therapy is Required to Maintain Viral Suppression



Werle et al, Gastroenterology 2004; Wong et al, Clin Gastroenterol Hepatol 2013; Boyd et al, EASL 2016

What About RNAi and HBV (#1)

- The main focus has been on the HBsAg effects but have other important effects been overlooked?
  - HBeAg
  - HB core antigen [minichromosome stability]
  - HBx [minichromosome activity (Smc5/6)]



What About RNAi and HBV (#2)

- The “late responders” for HBsAg are intriguing
  - Could this be an epigenetic effect on integrated DNA ?
  - Intracellular HB core and HBx antigens have epigenetic effects and their knockdown could be important, in cccDNA repression (Smc5/6) and stability
  - This could explain 1) the drift downward in HBsAg in the chimpanzee model, 2) the late responders in the clinical trials, and 3) the prolonged effects in the clinical “normal responders”

Key Virological Findings for ARC-520

Monarch 2008

- An effect that induced a decline (>0.5log) of HBeAg and HBsAg were observed for 50% and 71% of the study cohort respectively
- direct antiviral effect on serum HBsAg, HBeAg, and HBcrAg levels which are substantial
- no rebound to baseline from nadir
- new set point established
- HBeAg-Pos CHB and HBeAg-Neg CHB have very different viral patho-physiologies
- this has important therapeutic and prognostic significance

Wooddell, C et al. 2017. Sci Transl Med (in press); Walsh, R et al. EASL (2016)

Therapeutic Rationale for HBeAg-Pos AND HBeAg-Neg HBV

Types of Chronic HBV Control and Cure

Inactive State

Sustained, off drug:

- No inflammation; normal ALT and liver biopsy
- HBV DNA low or undetectable
- HBsAg-positive, still at risk of HCC

Functional Cure (Clinical Resolution)

Seroclearance of HBsAg and seroconversion to anti-HBs antibody

Sustained, off drug:

- No inflammation; normal ALT and liver biopsy
- cccDNA inactivated or controlled by host mechanisms
- **Linked to improved clinical outcome (reduced HCC risk) if achieved before the age of 50**
- **Achieved rarely (1-2% per annum) in the natural history of CHB**

Complete Cure (Complete Viral Clearance)

HBsAg seroconversion and cccDNA eradication

Functional cure plus:

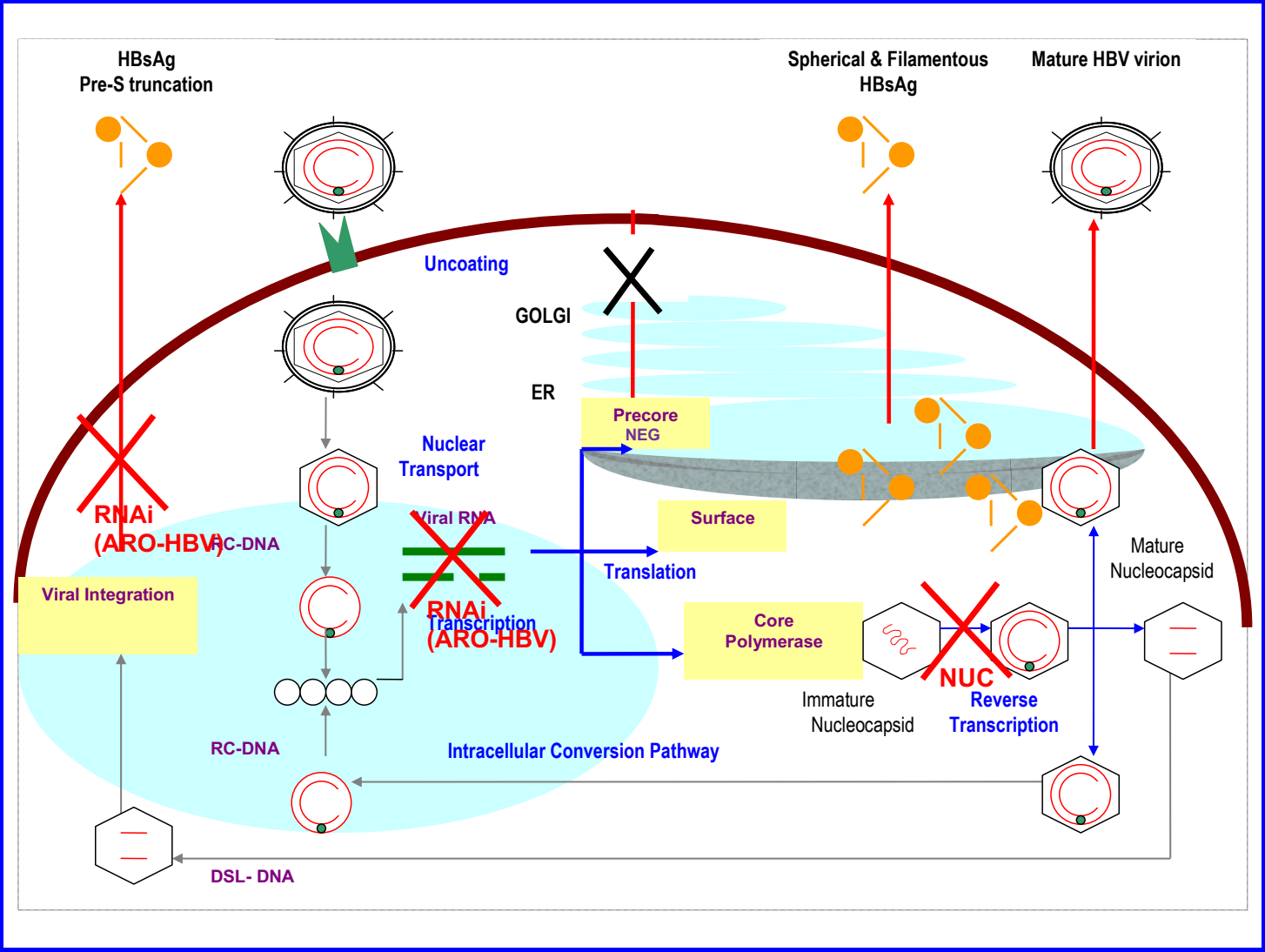
- Loss of cccDNA in the liver
- Integrated viral sequences? *(Impact needs to be addressed)*

Peters, MG & Locarnini, S. 2016. Gasroenterol and Hepatol;13(6):348-356.;
Lok, A et al 2017. Hepatol; in press

Combination With NUC

- potentially complementary mechanism at the Intracellular Level

New Targets in HBeAg-Pos and -Neg HBV: ARO-HBV + NUC

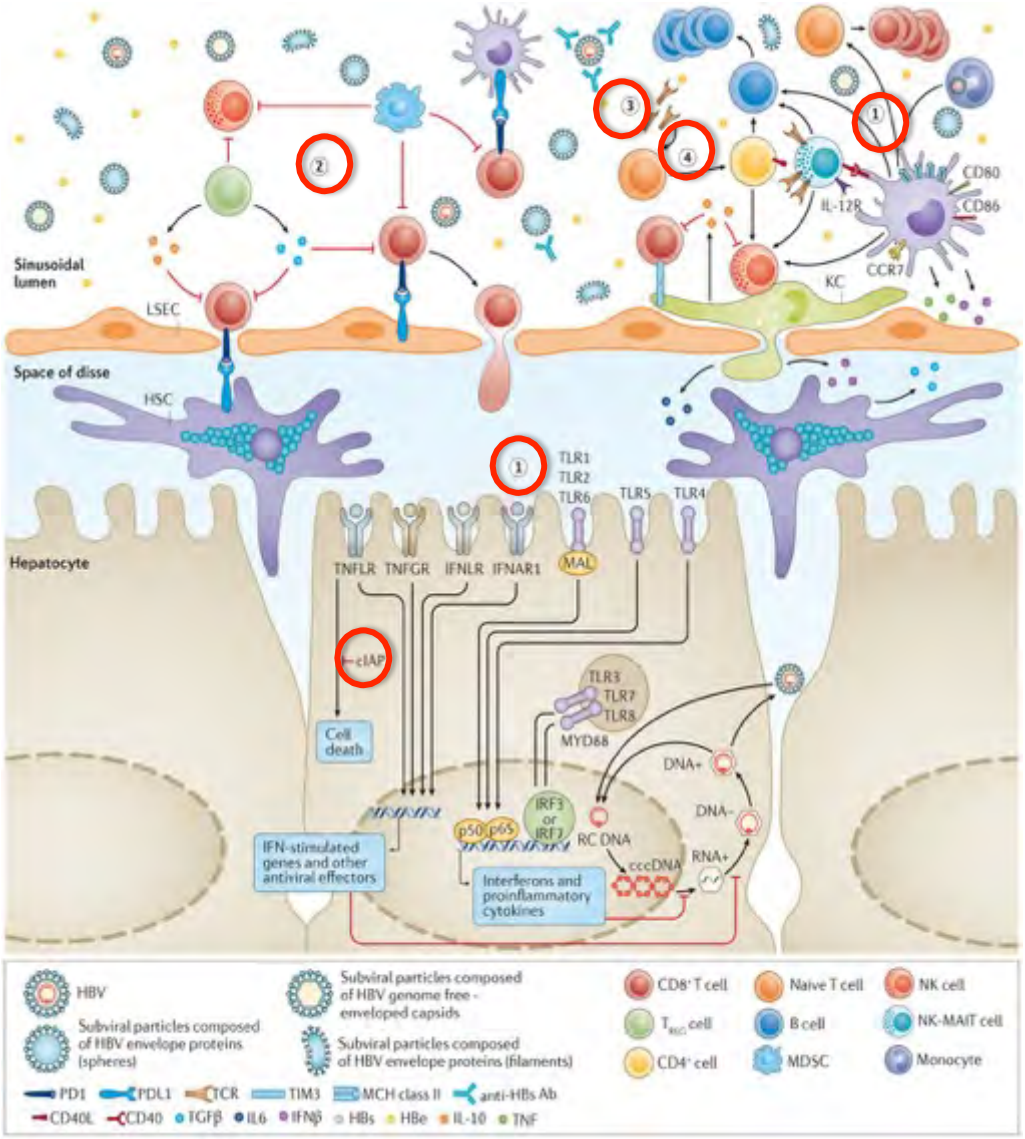


- Potentially Complementary Mechanism: Intracellular Level

Combination With An Immune Activator

- potentially complementary mechanism at the Extracellular Level

Immune Modulation in the Liver Microenvironment



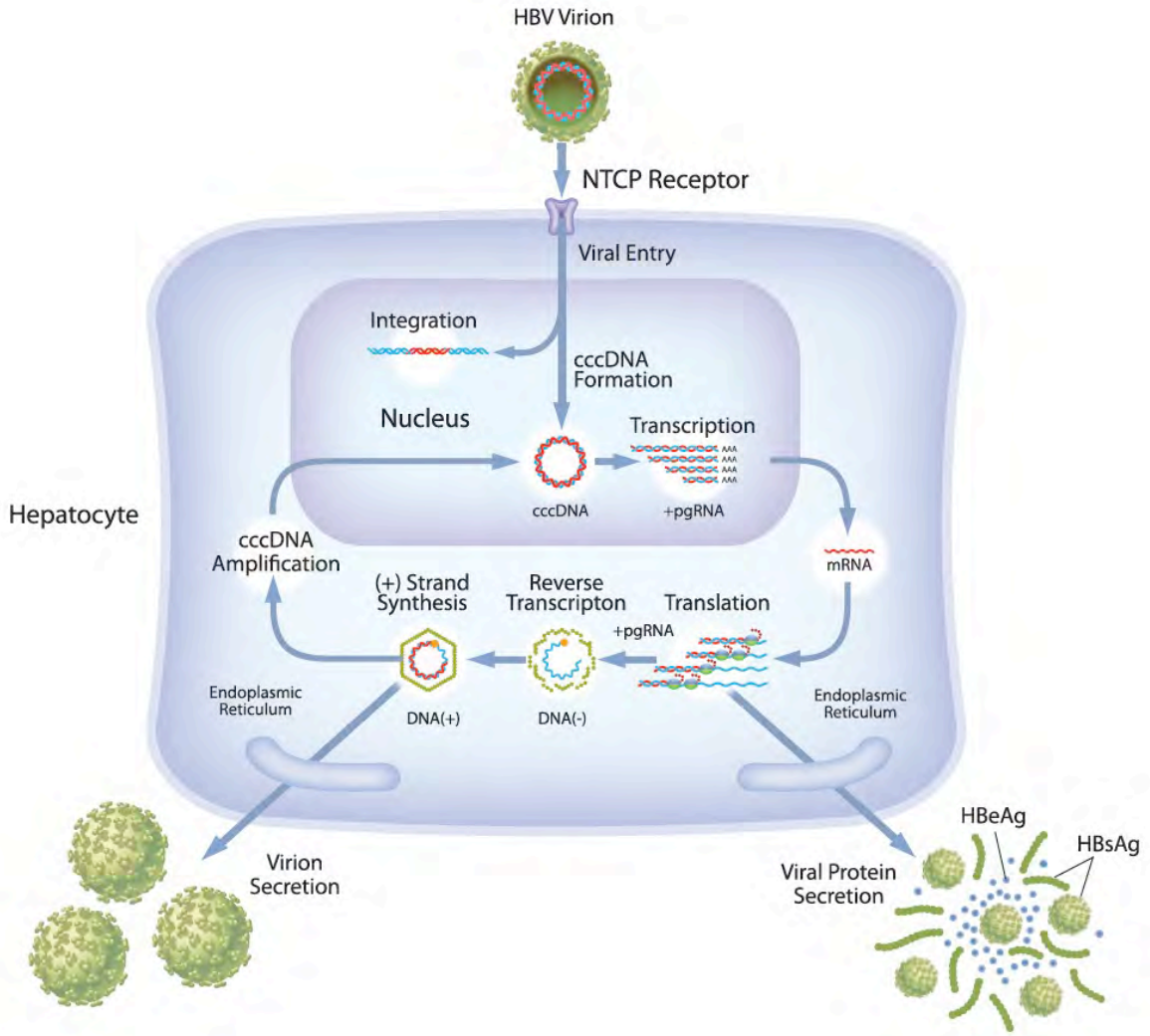
Locarnini, S. & Zoulim, F. et al. Nat. Rev. Gastroenterol. Hepatol 2016

These Considerations Raise Some Interesting Questions for Future HBV Antiviral Drug Development

- Will capsid inhibitors impact on HBV replication in the context of NUCs and effects on downstream effects on cccDNA?
- For functional cure, do we also need to control/eliminate integrated DNA?
  - How will this be proven?
- Will epigenetic approaches to control cccDNA also have to account for integrated DNA?
- What has been learned from pre-clinical models that don't include integrated DNA? Will they be predictive of human clinical trials?
- Will enhancing part or all of the various arms of the immune response be enough to achieve functional cure?
- Can this 'enhancement' be quantitated/controlled?

Arrowhead HBV Program
Bruce Given, M.D.

Hepatitis B Virus Life Cycle

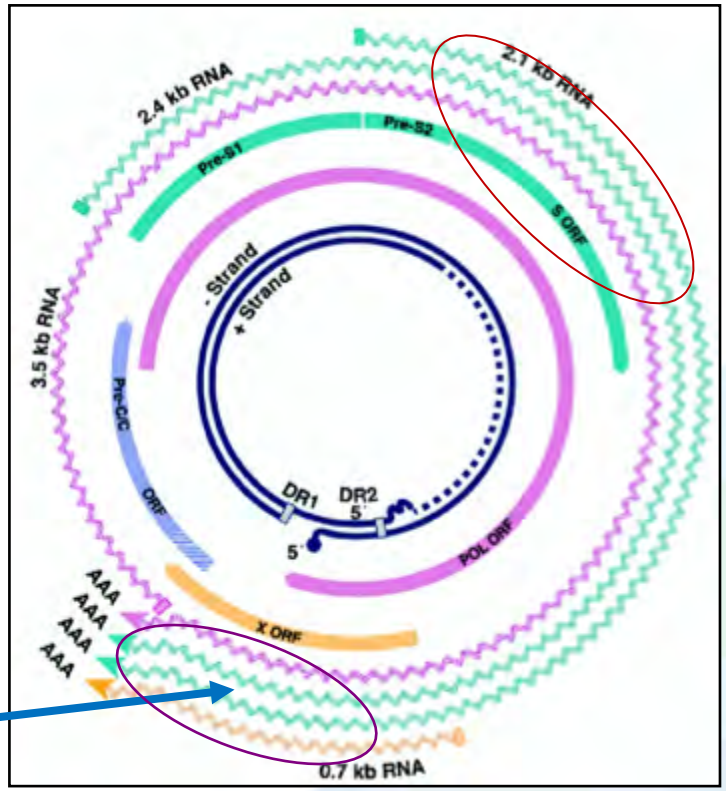


Importance of Integrated DNA as mRNA Source has Changed RNAi Strategy

- All HBV transcripts, including pregenomic RNA, overlap and terminate with the same polyadenylation signal
- A single siRNA targeting this common region can reduce all HBV transcripts derived from cccDNA

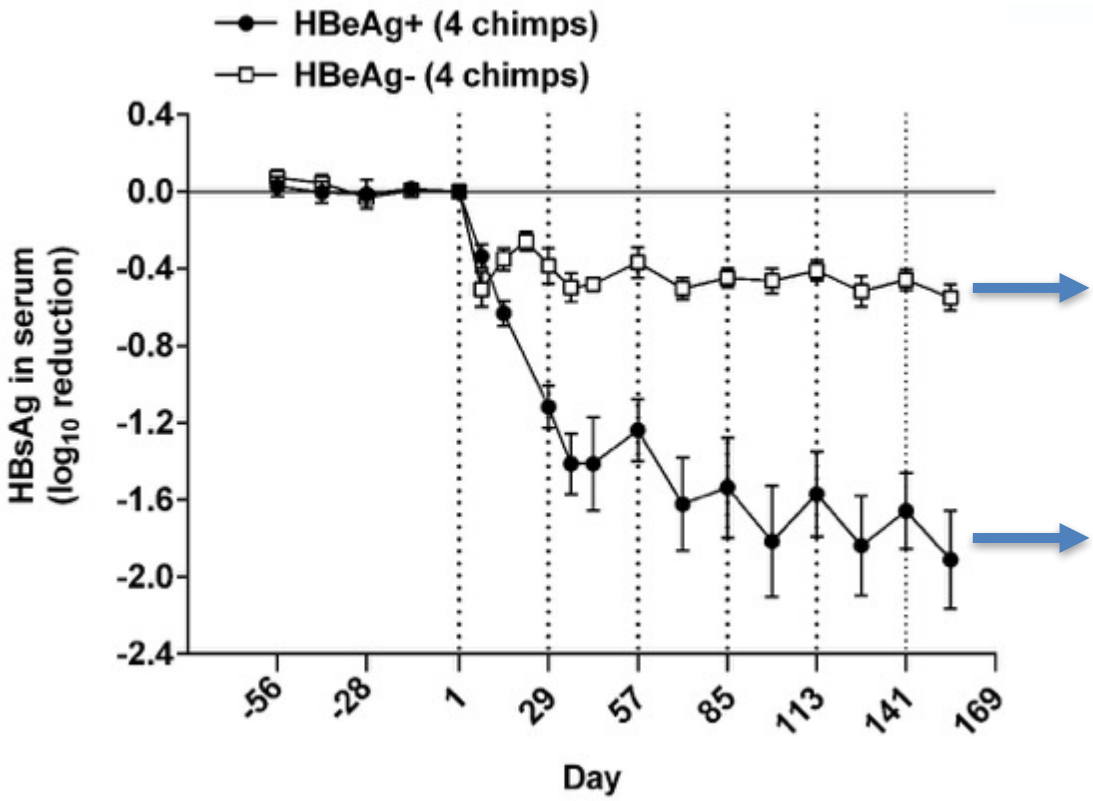
Single siRNA can reduce all mRNA from cccDNA but can miss integrated-derived mRNA

HBV Transcript Map



Ghany & Liang (2007), *Gastroenterology* **132**: 1574-1585

Differential HBsAg Reduction Observed in Chimpanzees (and Humans) with ARC-520



HBeAg-
0.5 - 0.9 log_{10} reduction at nadir

HBeAg+
1.5 - 2.7 log_{10} reduction at nadir

HBeAg positive responded better than HBeAg negative chimps

The same observation was made for treatment-naïve humans

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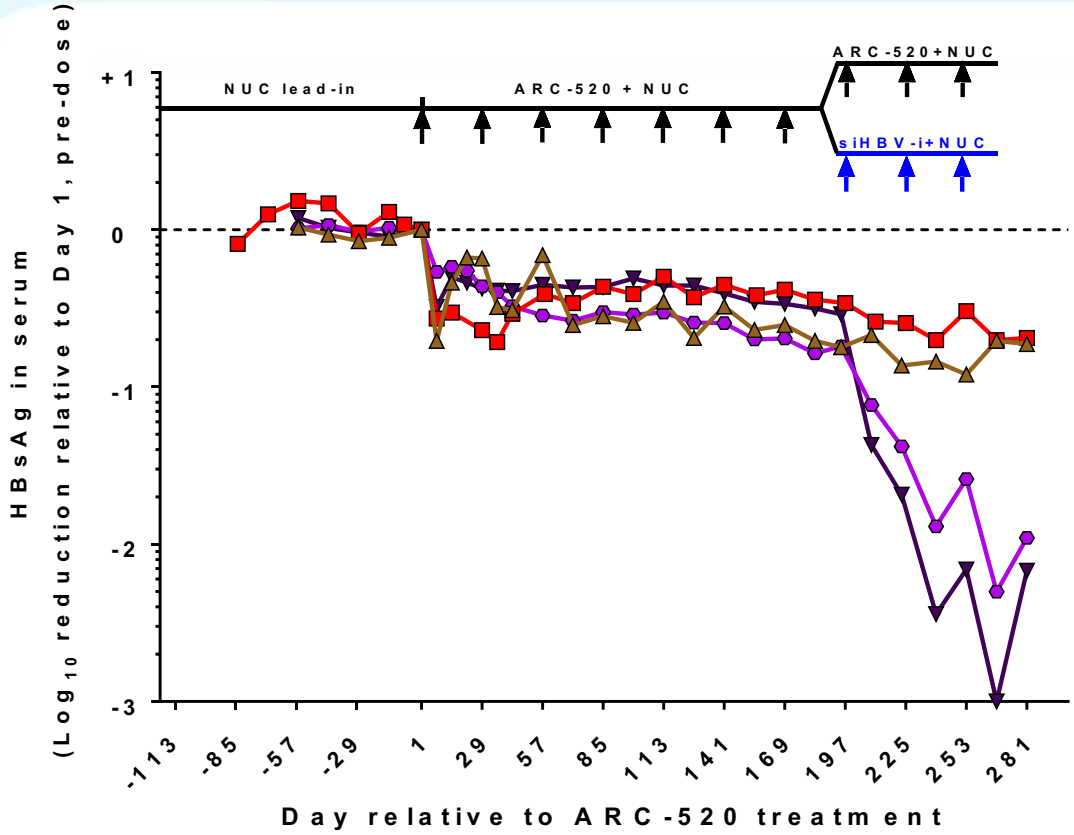
siRNA Targeting Integrant-derived RNA Produced Sharp HBsAg Reductions in HBeAg- Chimps



ARC-520

siHBV-i + EX1

siHBV-i gave deep reductions in HBsAg in HBeAg- chimps, similar to those observed using ARC-520 in HBeAg+ chimps

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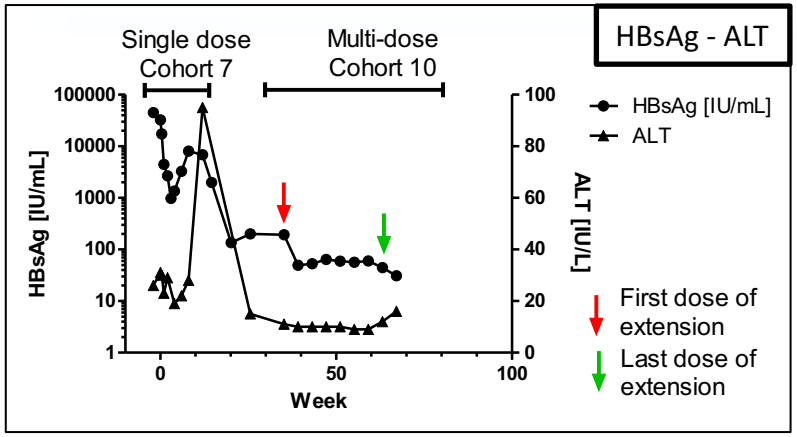
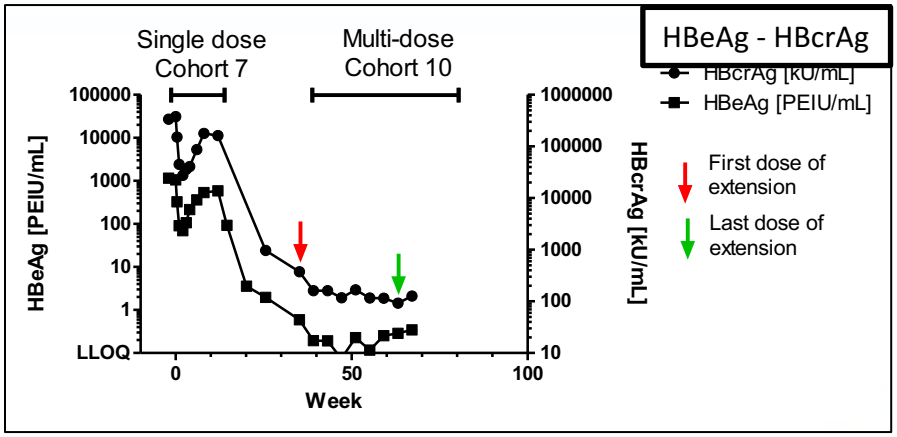
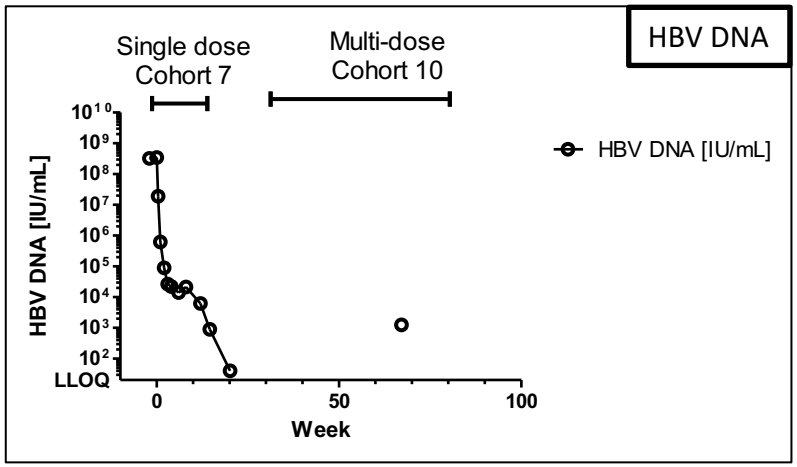
The Potential of RNAi – One Patient's Story

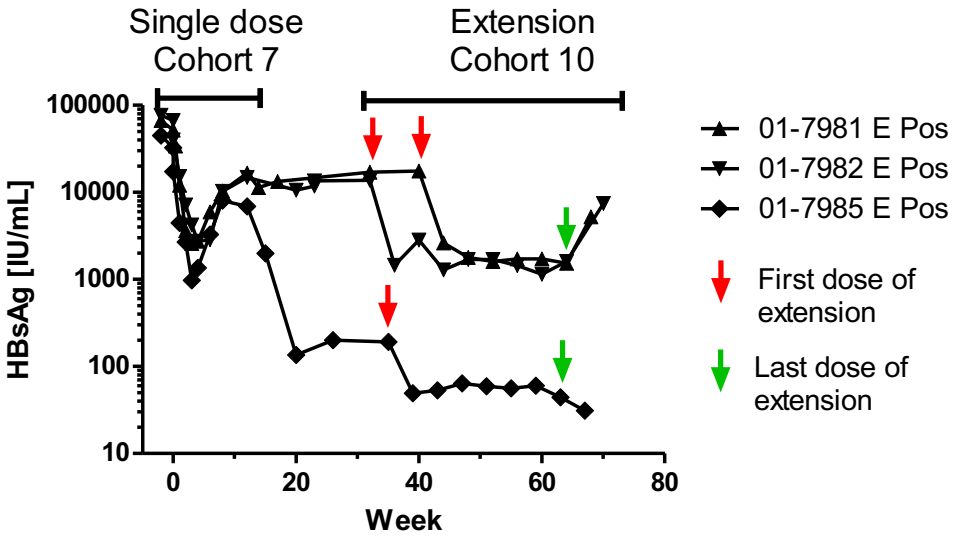






- 3.1 Log10 HBsAg reduction from baseline
- 3.6 Log10 HBcrAg and 4.2 Log10 HBeAg reduction
- Rapid reduction of HBV DNA to BLOQ
- ALT elevation after initial antigen reductions
- Antigen decrease during ARC-520 treatment holiday consistent with increased immune control of HBV virus

HBsAg Reduction in HBeAg Positive Patients



- In 3/3 patients HBsAg did not return to baseline after single dose of ARC-520
  - Effect persisted for >30 weeks
- Multi-dose re-challenge further reduced HBsAg in all patients
- HBeAg pos patients showed immediate reductions in HBsAg with 1st and 2nd doses
  - Mean max -2.2 Log10
  - Max observed -3.1 Log10

2.2 - 3.1 log HBsAg knockdown with ARC-520

Similar to observations in HBeAg positive chimps

Why We see a Central Role for RNAi in HBV

- Attacks the entire transcriptome
  - Should synergize with **most/all** hepatocyte-active compounds (e.g. NUCs, capsid inhibitors, x protein drugs, RigI inhibitors, etc) by reducing their viral inputs
  - Can reduce HBsAg from integrated DNA, which other mechanisms likely can't
- Monthly (or less frequent) SQ dosing with unusually good tolerability should fit well with oral regimens
- ARC-520 data suggests that immune recovery and control in humans and chimps is possible
  - Creates real excitement that future combination work can build on this

Learnings from 9 clinical studies of ARC-520/521 inform development path of ARO-HBV

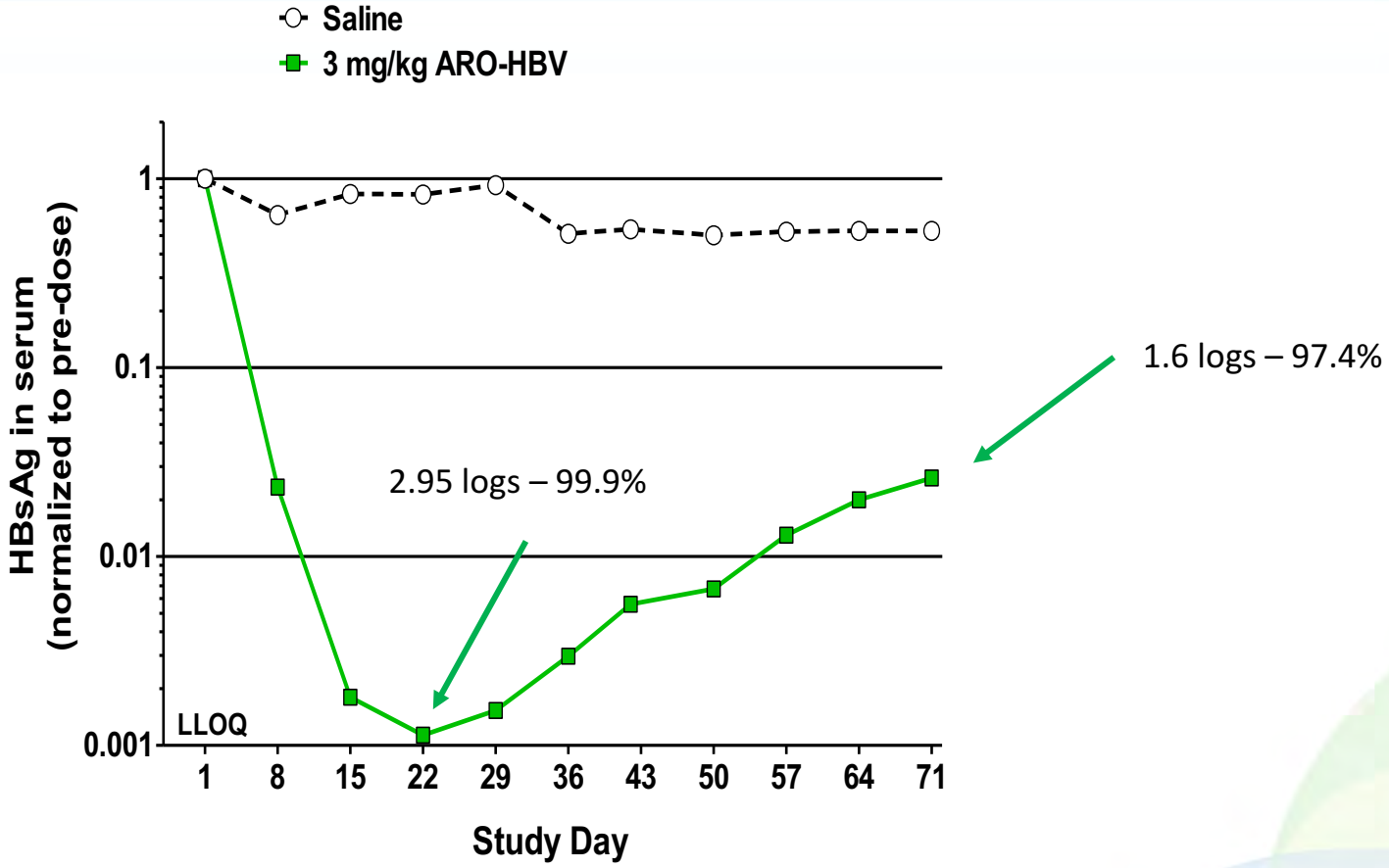
ARO-HBV

ARO-HBV: Key Design Elements Expected for the Next Generation

The Wish List:

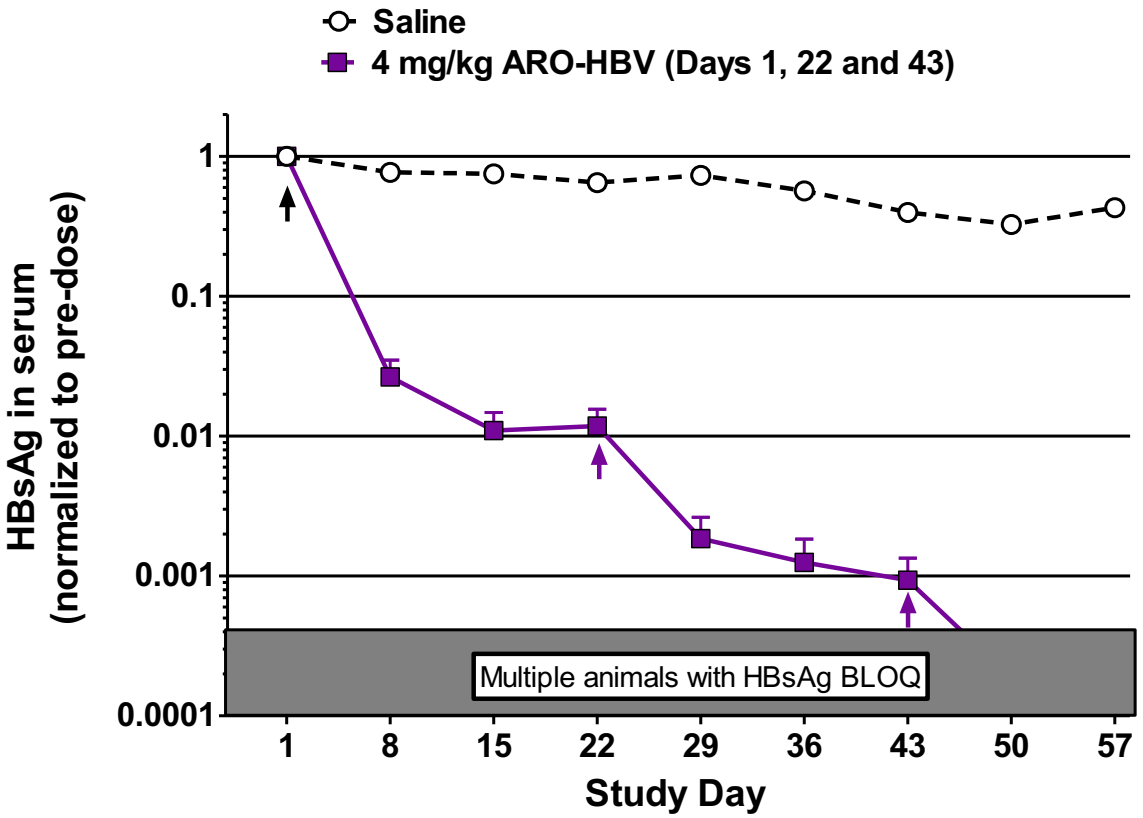
- Subcutaneous dosing, monthly or less frequent
- No need for active endosomal escape agent
- Addresses full HBV transcriptome
  - Works for cccDNA *and* integrated-derived transcripts
- Multiple triggers to avoid resistance development
- Powerful HBsAg reduction
- Expectation of wide therapeutic index
- Efficacy and safety in HBV patients

For ARO-HBV We Modeled Integration in a New, Mutated pHBV Transfected Mouse



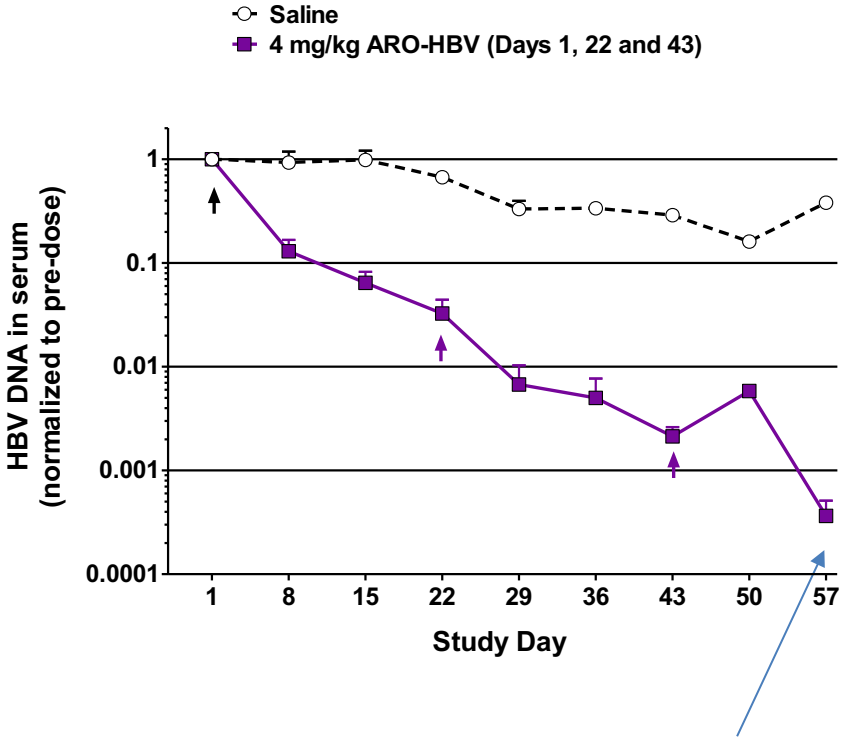
HBsAg knockdown is deep and prolonged despite loss of x trigger site

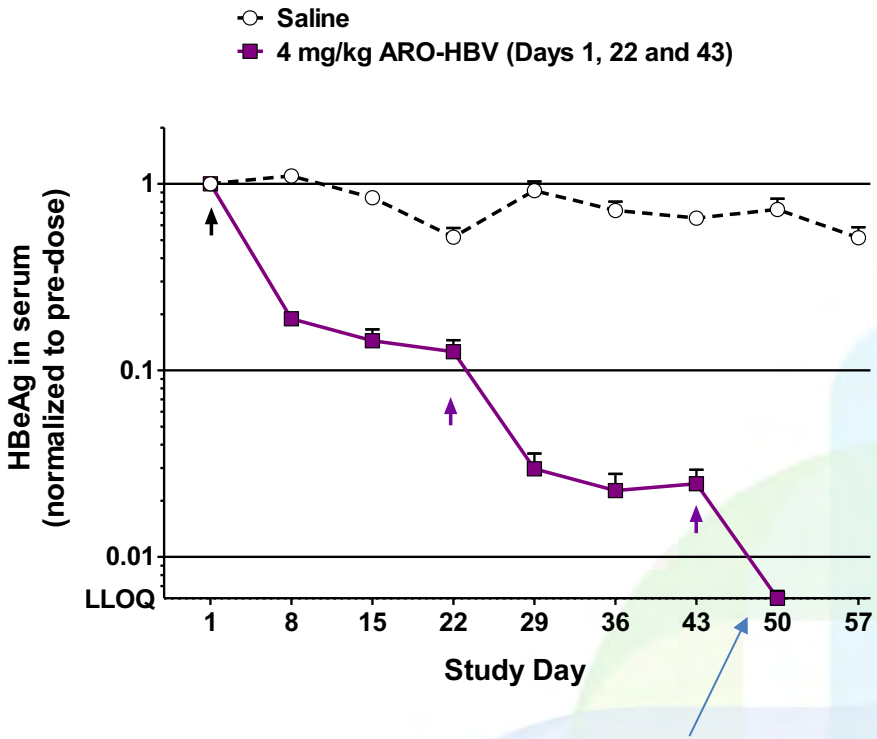
Multiple Dosing in Intact pHBV Mice Reduces HBsAg Below Level of Quantitation



>3 $\log_{10}$ reduction after 3 doses

.....With Deep Knockdown also Observed for HBeAg and HBV DNA





3.44 $\log_{10}$ =
>99.9% reduction

2.2 $\log_{10}$ =
99.4% reduction
to LLOQ

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ARO-HBV Preliminary Safety Evaluation

- Based on clinical observations, clinical pathology and limited histopathology evaluations, ARO-HBV was well tolerated in a repeated dose study in rats administered 3 weekly subcutaneous doses at dose levels of 30, 60, 120, and 300 mg/kg
  - Expected human dose 3-4 mg/kg

ARO-HBV: Key Design Elements Expected for the Next Generation

The Wish List:

- ✓ Subcutaneous dosing, monthly or less frequent
- ✓ No need for active endosomal escape agent
- ✓ Addresses full HBV transcriptome*
  - ✓ Works for cccDNA *and* integrated-derived transcripts
- ✓ Multiple triggers to avoid resistance development
- ✓ Powerful HBsAg reduction
- ✓ Expectation of wide therapeutic index

Efficacy and safety in HBV patients (pending)

CTA planned for Q2 2018 pending completion of cross-reactivity studies and GLP tox

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* No direct assay available for x-protein

Alpha-1 Antitrypsin Deficiency Liver Disease

Jeffrey Teckman, M.D.
Professor, Division Director, Division of Pediatric Gastroenterology & Hepatology, Saint Louis University School of Medicine

Alpha-1-Antitrypsin Deficiency Liver Disease

Jeffrey Teckman, M.D.

Professor of Pediatrics and Biochemistry and Molecular Biology

Director, Pediatric Gastroenterology and Hepatology

St. Louis University School of Medicine

Cardinal Glennon Children's Hospital

Disclosures

Dr. Teckman has recently worked with a wide range of academic and industry partners:

Arrowhead Pharmaceuticals, Alnylam Inc, Alpha-1 Foundation, AstraZenica, Dicerna, Editas Inc, Gilead, GLG, Grifols, Intellia, NIH, Proteostasis, The Alpha-1 Project.

Alpha-1-antitrypsin (A1AT)

- An abundant serum protein primary synthesized in the liver.
- Physiologic function is inhibition of neutrophil proteases to protect host tissues during inflammation. This is especially important in the lung.
- Z mutant is the common disease variant

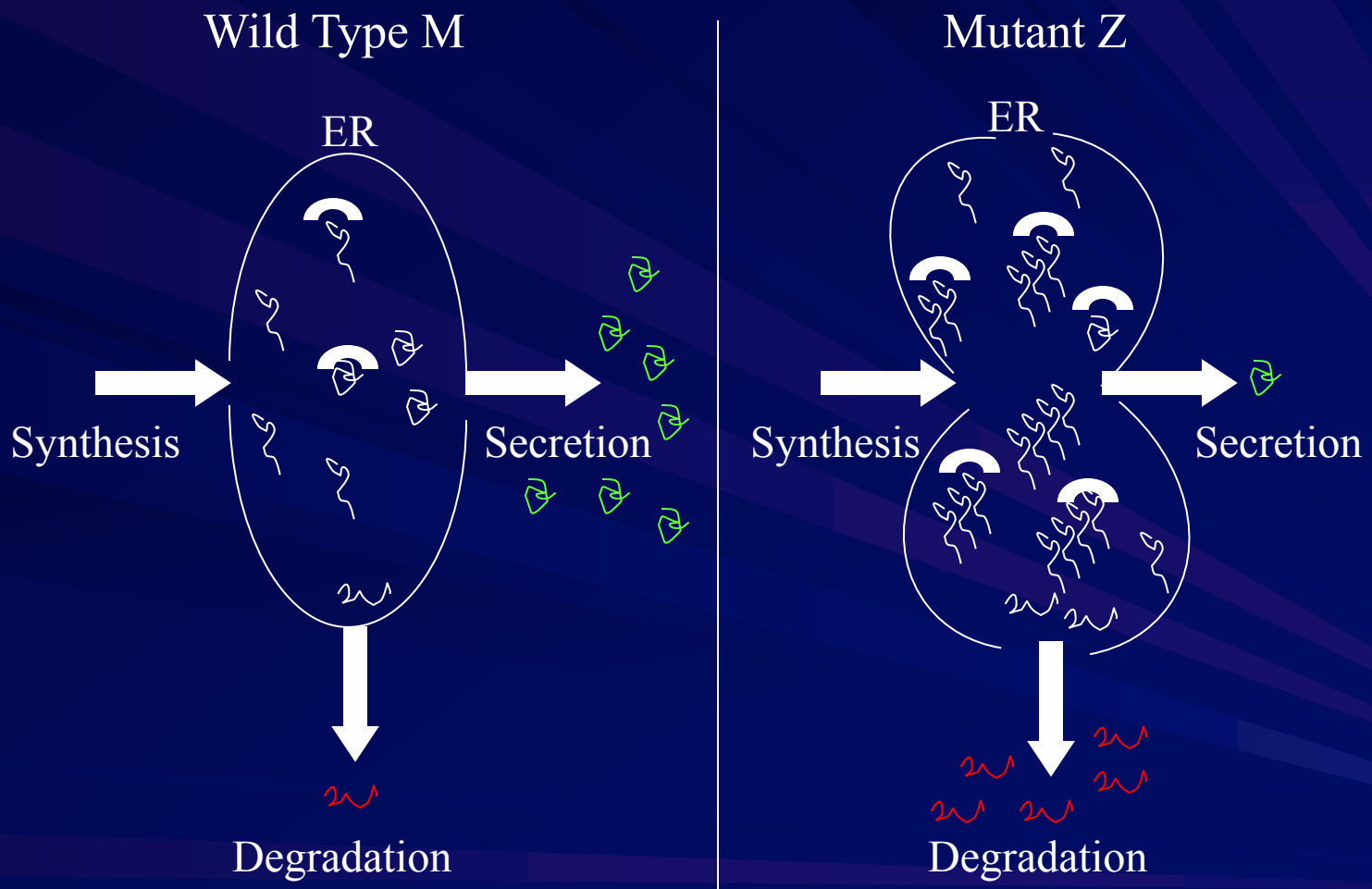
Alpha-1-antitrypsin Mutant Z

- Mutant Z: A point mutation that encodes a single aa substitution.
- Z mutant accumulates and polymerizes in the liver – not secreted into blood.
- Low secretion results in overload in the liver but “deficient” blood level.

ZZ Alpha-1-antitrypsin Deficiency

- Autosomal recessive (co-dominant).
- Homozygous ZZ form, 1 in 2,000-3,500 births in US and Europe.
- Associated with liver disease in children and adults, and lung disease in adults.
- Highly variable disease progression.

A1AT Processing in Liver

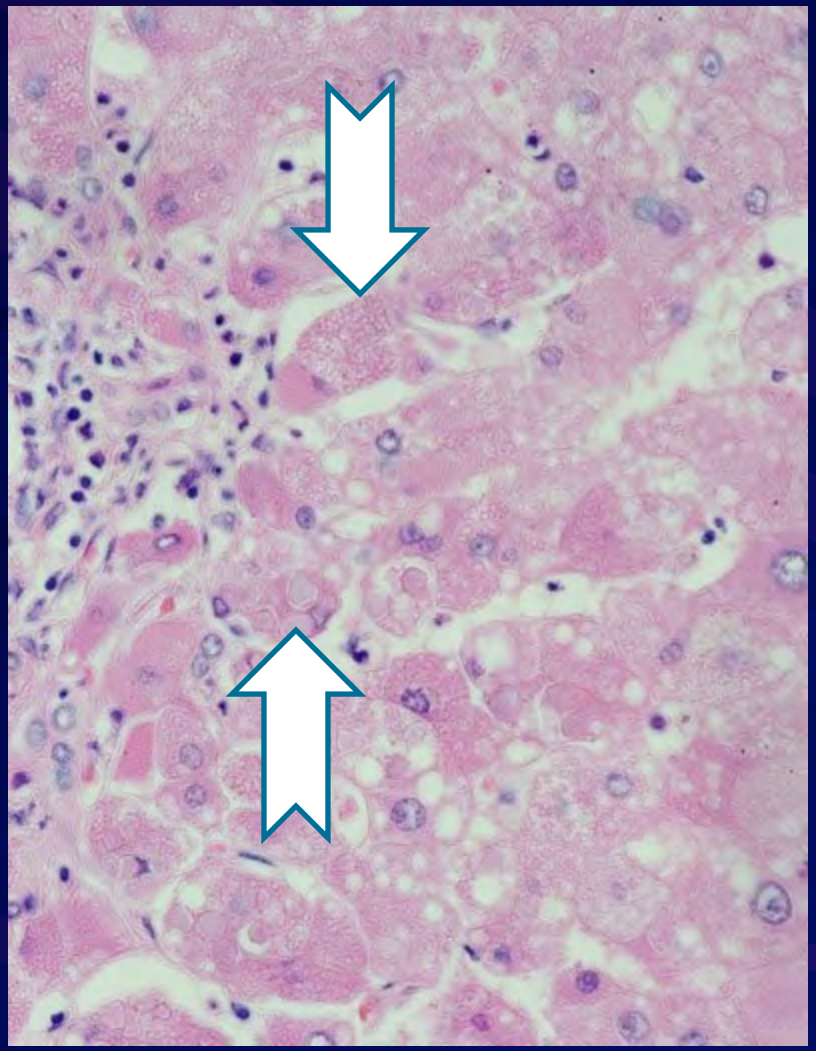


Disease Pathophysiology

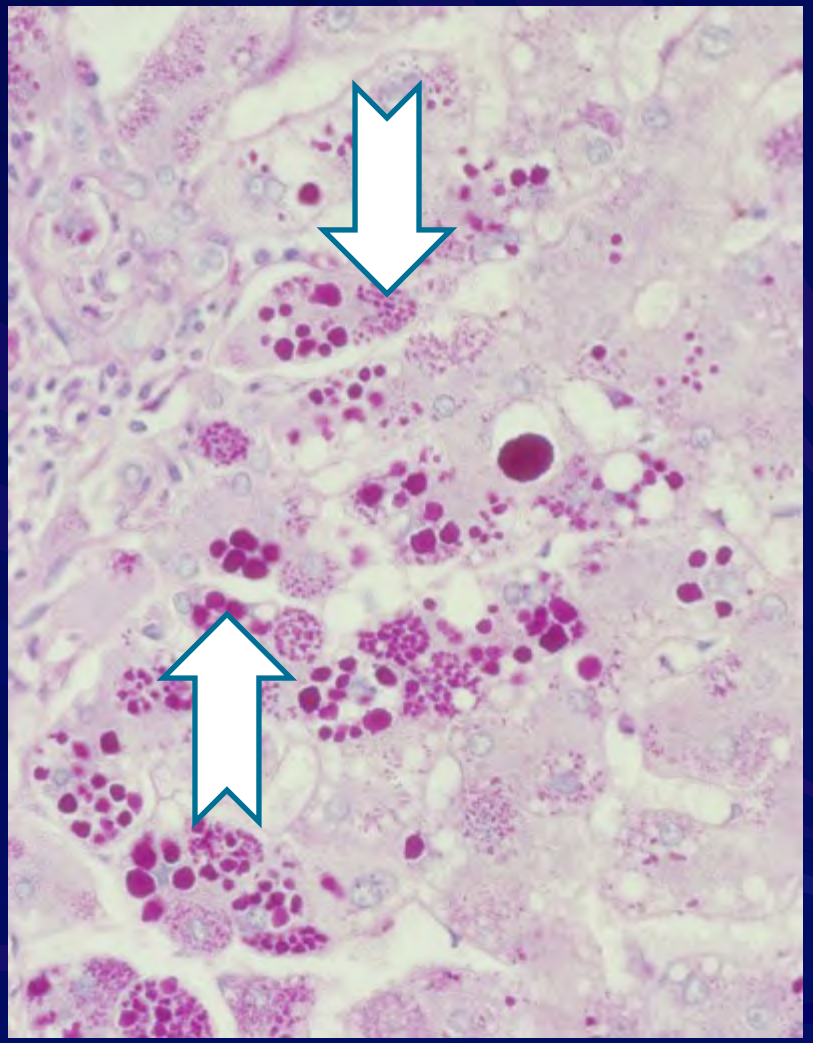
- Liver: Accumulation of mutant Z protein in hepatocytes causes liver injury.

- Lung: “Deficient” serum level leaves host tissues susceptible to damage by neutrophil proteases. Exquisitely susceptible to smoking injury.

Human ZZ Liver

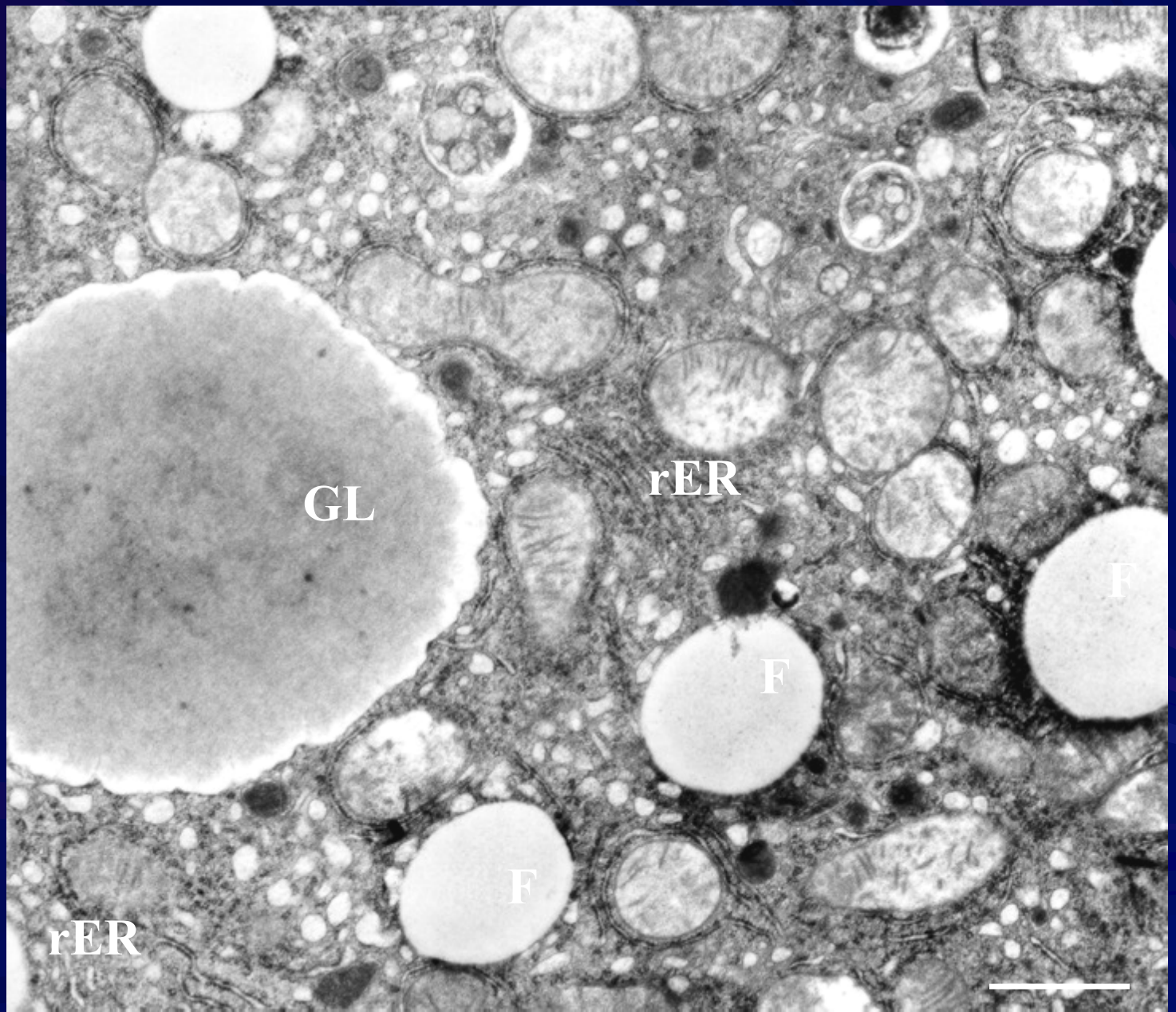


H&E



PAS with Digestion

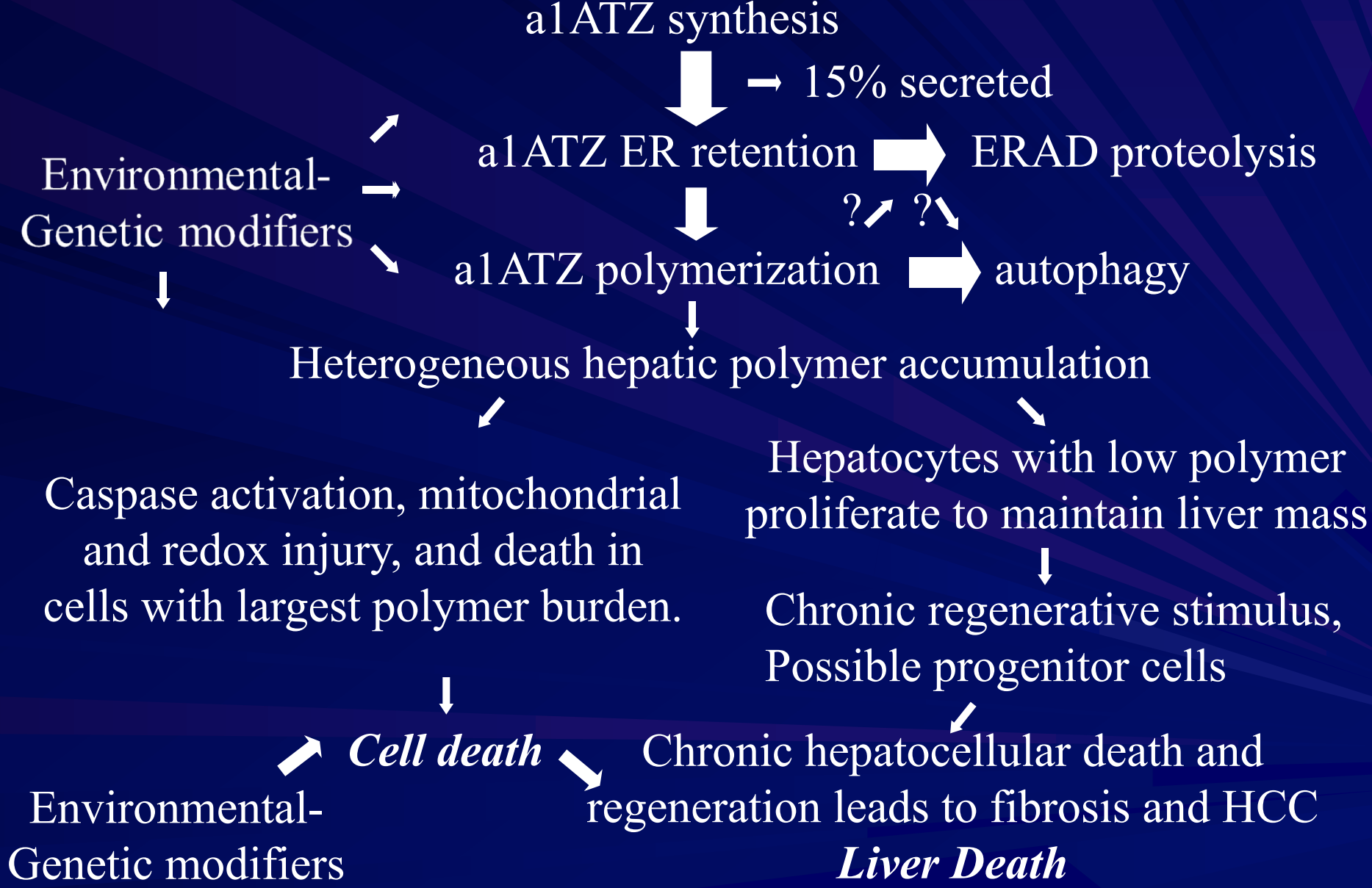
Electron microscopy ZZ liver



Pathophysiology-Liver

- Mutant Z protein accumulates in hepatocytes.
- Compensatory proteolytic pathways degrade most of the mutant Z protein.
- Some mutant Z molecules escape degradation
- Hepatocytes with the largest burdens of mutant Z protein suffer a cascade of intracellular damage ending in apoptosis.
- The chronic cycle of hepatocellular apoptosis and regeneration leads to fibrosis and organ injury.

Liver Injury Cascade



Newborn Screening Study, Sweden

127 ZZ newborns identified out of 200,000 screened

Neonatal period

22 (16%) cholestasis

53 (42%) high ALT

52 (42%) normal

15/18 normalized

Likely not diagnosed
Outside screening

4 died in infancy;
2 of liver failure
All 4 had severe fibrosis

Adulthood
(f/u may not be complete)

No further deaths or evidence of portal hypertension
116/127 (91%) normal ALT age 18 years, but not clear later life
In the last 20 years systemic examination minimal, no ultrasounds

Autopsy Study, Sweden

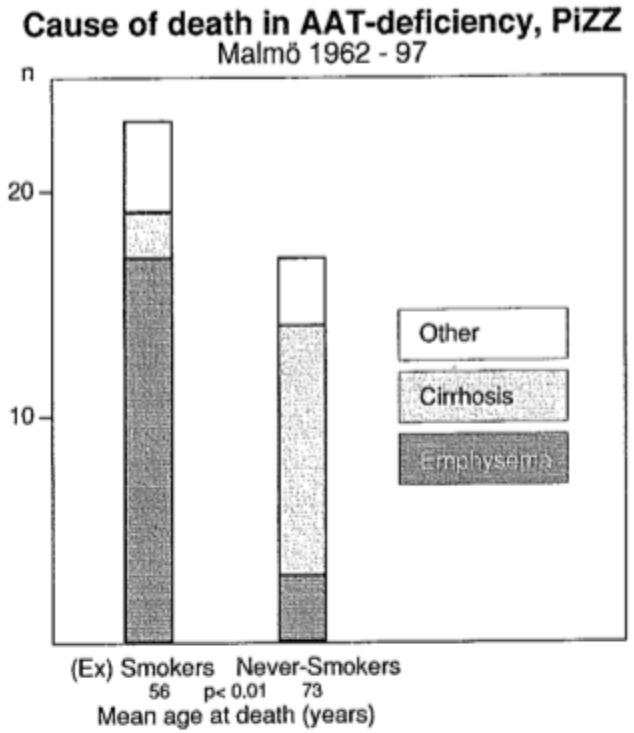


Figure 1 Cause of death in AAT deficiency.

Table 1 Liver histopathology at autopsy in 37 PiZZ cases

	Smokers (22)	*Never-smokers (15)*	*All (37)*
Cirrhosis	2* $p < 0.001$	11**	13
Hepatocellular carcinoma	0	5	5
Fibrosis	4	0	4
Steatosis	3	3	6
Normal	14	3	17

* In one case alcohol + hemochromatosis
Hepatitis B and C markers absent
** Severe, refractory encephalopathy in two.

ZZ Disease Risk – Variable

- 100% have protein accumulation in the liver.
- 3-5% risk of life-threatening liver disease in childhood?
- 15-50% risk of various liver dysfunction in childhood.
- 40% life-long risk of cirrhosis??
- Risk of liver cancer increased, but magnitude is unclear (usually found in older adults).

Genotypes

- ZZ homozygous, classical disease.
- SZ similar disease to ZZ, ? Less risk.
- MZ heterozygous carrier state (2% of population), regarded as healthy and asymptomatic, possible effect as modifier condition in adults. *Many other rare genotypes.*

Diagnosis

- Gold standard is “phenotype” analysis of protein in serum or “genotype” of DNA. *Not performed in US newborn screen.*
- Some clinicians use serum level as a screening test. Gold standard test must be applied if ANY deviation from normal.
- Liver biopsy not required for diagnosis

Co-morbid Associations

- Increased risk of low birth weight.
- Risk of feeding difficulties, FTT.
- Coagulopathy (subclinical cholestasis?)
- Risk of asthma and recurrent, non-destructive respiratory symptoms.
- Panniculitis in adults.

Management - Conventional

- Liver: No specific therapy, except supportive care and liver transplantation.
  - Fat soluble vitamins if cholestatic.
  - Provision of adequate nutrition.
  - Management of cirrhosis and portal hypertension.
  - Avoid obesity and limit alcohol, as per AASLD guide.
  - Liver transplant (no longer deficient).

- Lung: Protein replacement and general care. Has no benefit to the liver.

Management - Conventional

- Genetic counseling should be offered to all patients and families.
- Alpha-1 Foundation genetic counseling line: 1-800-785-3177
- Excellent layman literature available
- Prenatal diagnosis is available.

Therapy: Under Investigation

- Several approaches to liver disease treatment are being investigated.
  - *Increased* accumulation in the liver is likely to be detrimental.
  - *Decreased* accumulation in the liver is likely to be therapeutic. ? Other mechanisms, too?

- To date, no specific drug therapy can be recommended outside of clinical trials.

Therapy: Ursodeoxycholic Acid

- In vitro studies suggest possible theoretical benefit.
- Uncontrolled human use reports inconclusive.
- Commonly used during cholestasis but not supported by data.

Therapy: 4-Phenylbutyrate

- In vitro and animal studies suggest benefit.
- Not effective in human studies due to intolerable side effects before therapeutic level reached.
- Not recommended at this time outside of trials.

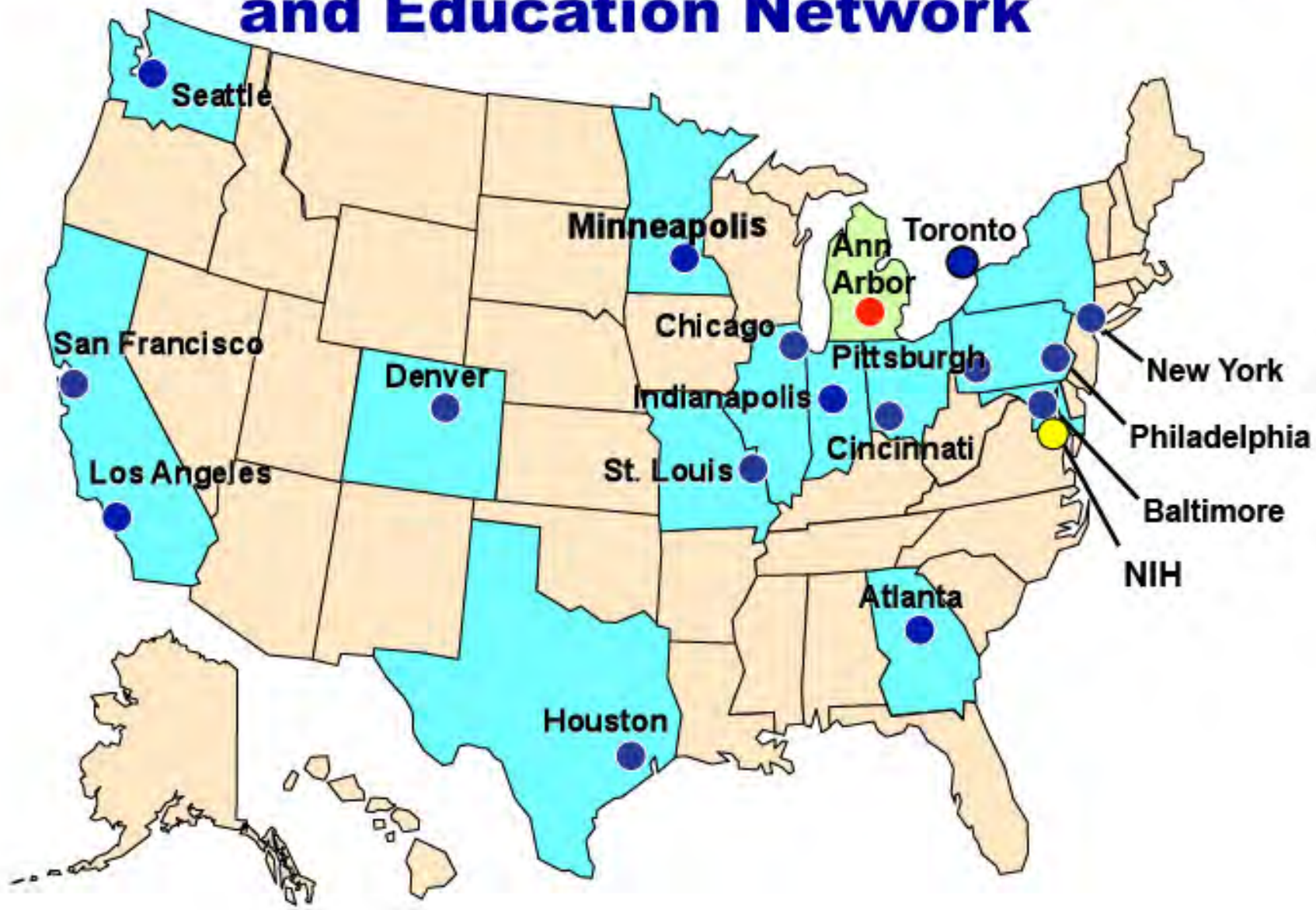
Therapy: norUDCA, Sirolimus and Carbamazepine

- In vitro and animal studies suggest benefit via increased intrahepatic degradation.
- Only one limited human study (suspended).
- Not recommended at this time outside of trials.

Observational Studies

- The Childhood Liver Disease Research and Education Network (ChiLDREN) is an NIH-sponsored consortium focused on the study of pediatric liver diseases
- 16 North American tertiary care centers
- The study enrolls patients with many conditions, including A1AT

Childhood Liver Disease Research and Education Network



Observational Studies

- Adult Alpha-1 Liver Disease Study.
  - Saint Louis University, Boston U, UCSD.
  - 5 year, prospective analysis of adult liver disease.
  - Contact: Jeff.Teckman@health.slu.edu
- Also U of Florida single center study.
- Studies in France and Germany

Observational Studies and Advocacy

- Alpha-1 Registry. A self-report patient data-base and contact registry.
  - www.alphaoneregistry.org,
  - email alphaone@musc.edu
  - 1-877-886-2383.

- Alpha-1 Foundation AlphaNet (lung Rx)
- AIR Lung Registry (Europe)

Summary of A1AT Deficiency

- Complex genetic disease of North America and Europe resulting from a point mutation.
- Multiple ages and organs involved, patients contact the medical system in multiple ways, but the disease community is cohesive.
- Disease modifiers are important, but are poorly understood.
- Treatment options are lacking for the liver.
- New trials and therapies will likely drive diagnosis.

Considerations

- The “Alpha-1 Community” is highly organized, motivated, and newly focused on liver.
- US and European registries exist.
- In other liver diseases in which cirrhosis was formerly seen as death or transplant (Hepatitis B and C infection) cure with new technology has now shown ***reversal*** of cirrhosis.
- This may be a good time to apply new technology to a fairly common, “rare” disease.

Arrowhead Alpha-1 Program
Bruce Given, M.D.

Alpha-1 Antitrypsin Deficiency

- AATD is a large scale orphan disease
  - Alpha-1 foundation estimates ~100,000 in the US
  - Approximately 100,000+ in Europe
- Mutation in AAT gene (Z-AAT) leads to mis-folding of the protein and poor export from hepatocytes: low levels in circulation and accumulation in liver

Pathophysiology

Lung

Tissues susceptible to damage by neutrophil proteases: COPD

Treated with AAT enzyme replacement therapy today, ?gene therapy in the future

Liver

Accumulation of mutant Z protein causes clinical liver disease

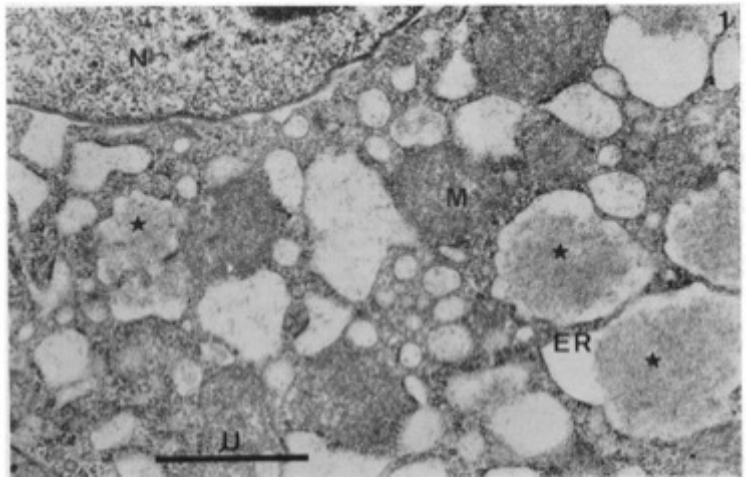
No current treatment

ARO-AAT Mechanism of Action

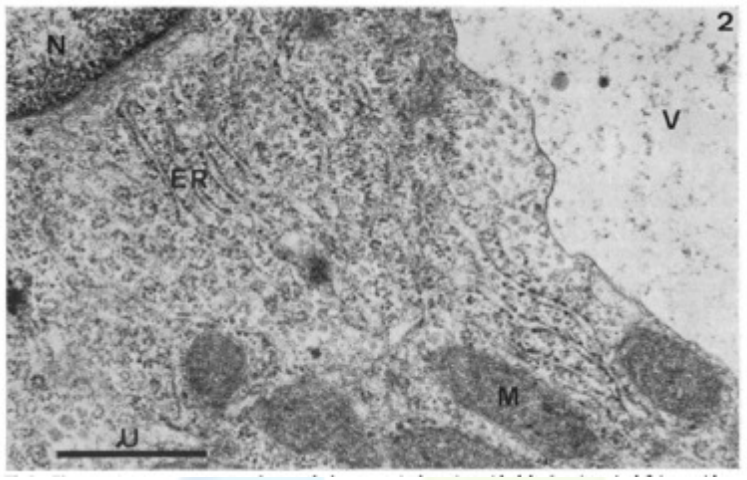
ARO-AAT designed to stop Z-AAT production by silencing AAT gene to:

- Prevent liver accumulation
- Allow clearance of accumulated protein
- Prevent cycles of cellular damage
- Prevent/Reverse progression of liver fibrosis

PiZZ phenotype (diseased)



Pi null phenotype (normal)

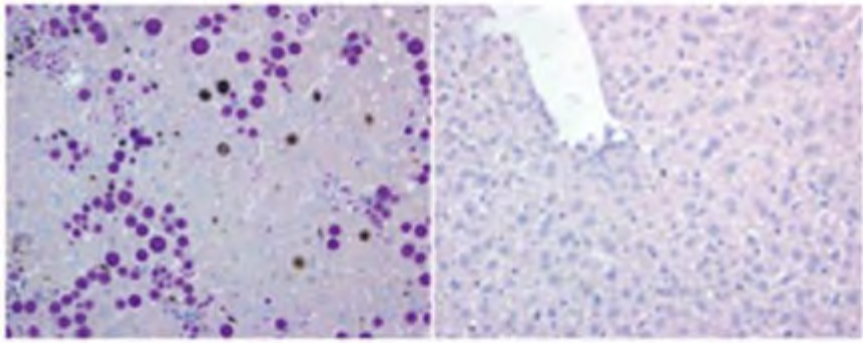


Feldmann G et al., *Gut* 1975

AAT Deficiency Liver Disease Mouse Model

The transgenic PiZ mouse model expressing the human Z-mutant AAT gene (Z-hAAT) recapitulates the human phenotype:

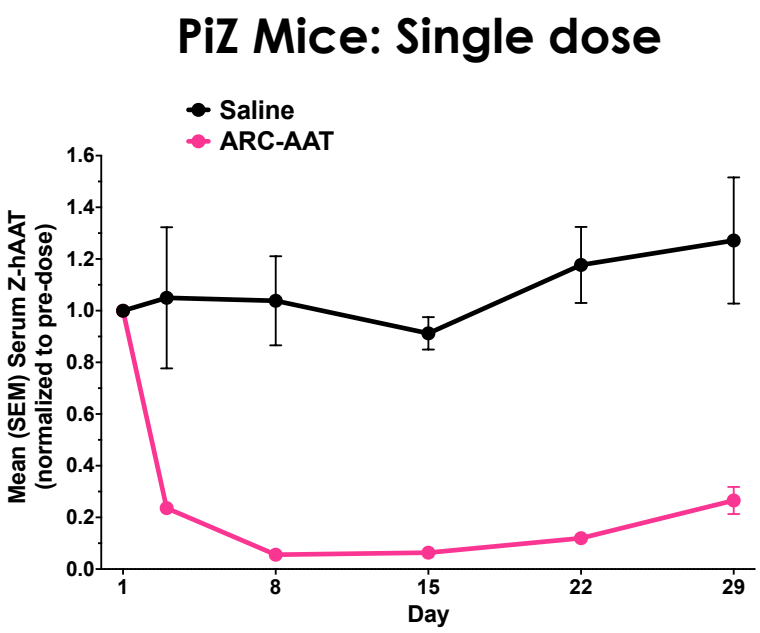
- Hepatocytes produce high levels of human Z-hAAT
- Z-hAAT forms polymers that accumulate in "globules" within the hepatocytes
- Presence of polymer stresses hepatocytes, eventually leading to HCC
- Liver phenotype worsens with age

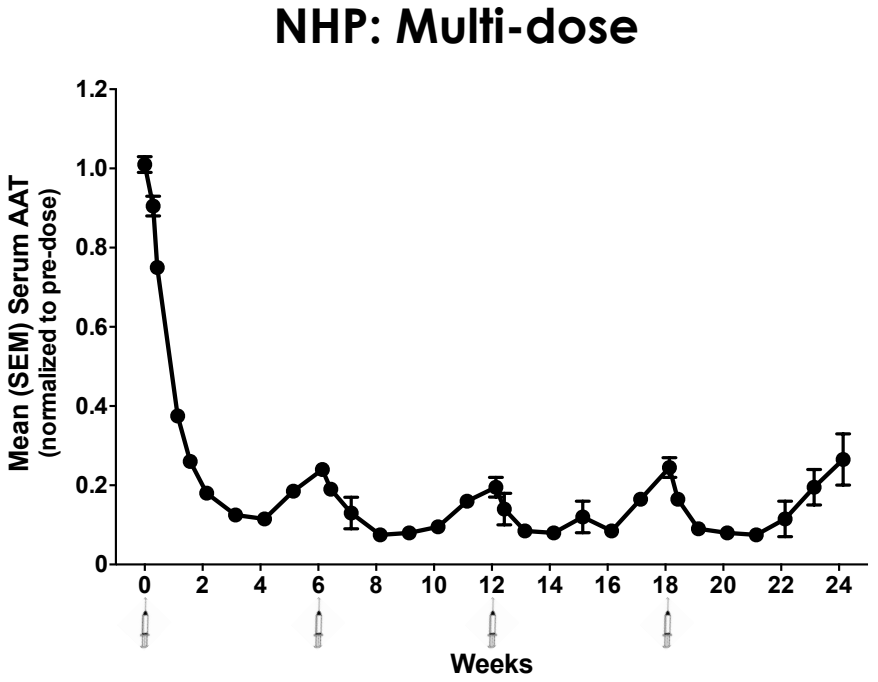


PiZZ **Wild Type**

Rudnick DA et al., *Hepatology*. 2004

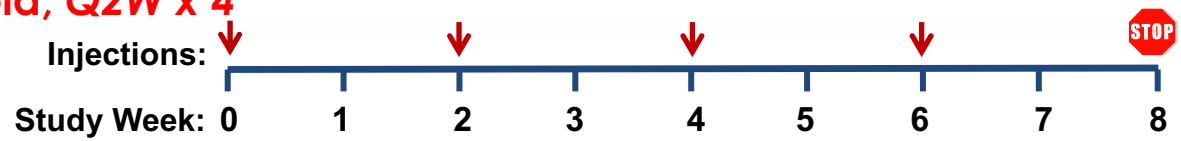
First Generation, ARC-AAT, Produces Deep AAT Knockdown: PiZ Mice and NHP

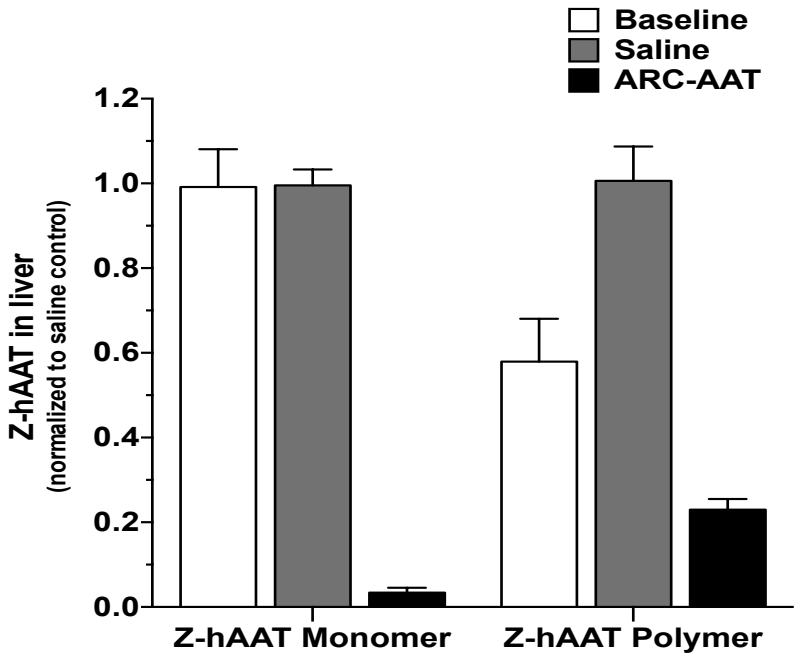




ARC-AAT Prevents Progression of Liver Disease in Young PiZ Mice: Liver Z-hAAT

5 weeks old; Q2W x 4





97% less soluble (monomer) Z-hAAT

77% less insoluble (polymer) Z-hAAT

ARC-AAT (8mg/kg API + 8 mg/kg EX1)

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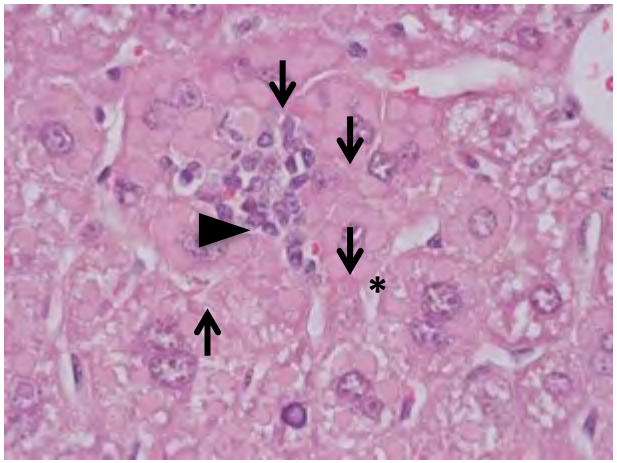
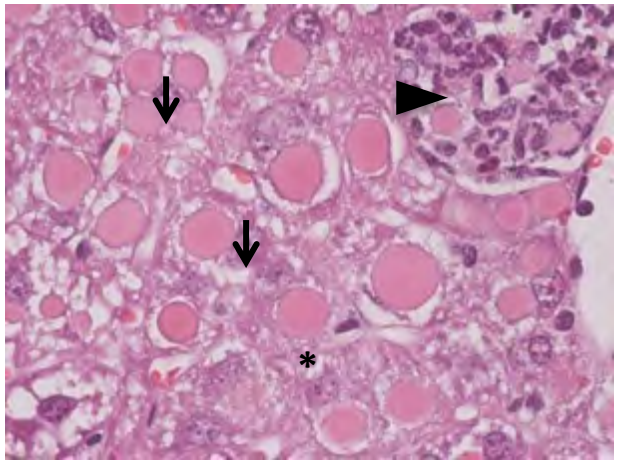
ARC-AAT Improves Liver Disease Phenotype in PiZ Mice with Established Disease: liver histology

11-17 weeks old; *Q2W x 16*



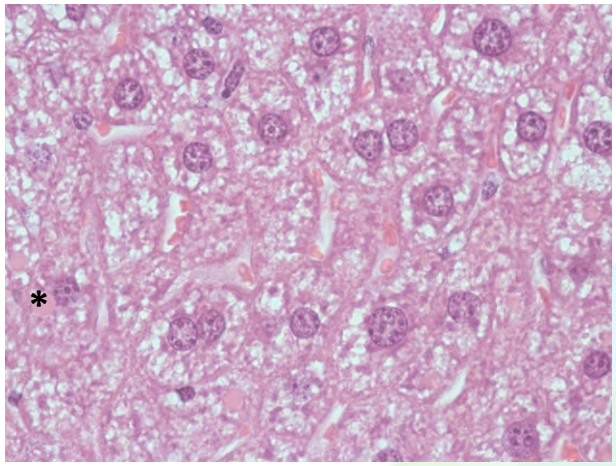
Baseline (11-17 weeks old)

- Significant globule accumulation (*);
- compressed nuclei (black arrows);
- apoptosis & inflammatory cells (arrowhead)



Saline control

- Significant globule accumulation (*), size 25-35 µm;
- compressed nuclei (black arrows);
- inflammatory cells (arrowhead)

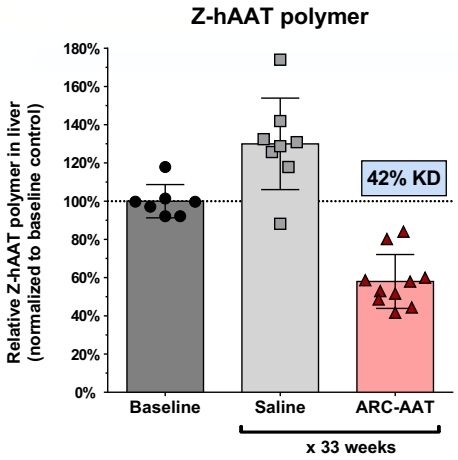


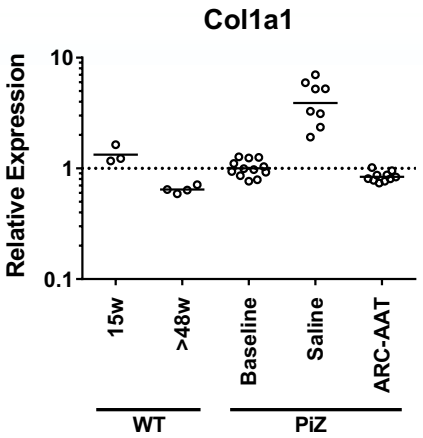
ARC-AAT

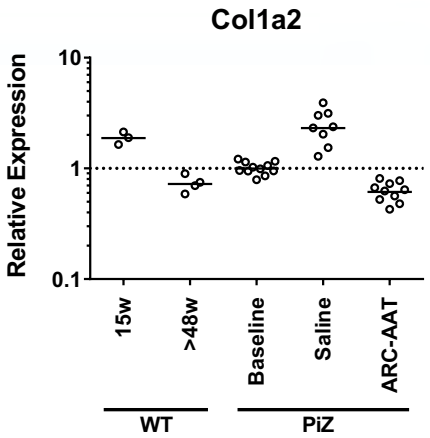
- Minimal to moderate globule accumulation (*), size 7-10 µm; no compressed nuclei,
- no inflammatory cells

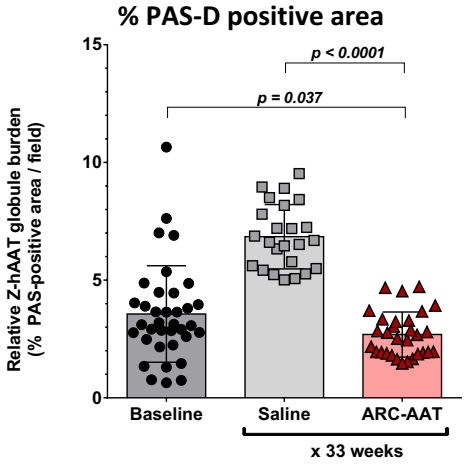
ARC-AAT treatment improves liver physiology and prevents further damage

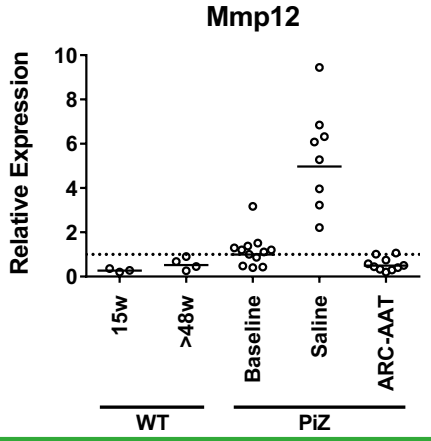
ARC-AAT Improves Liver Disease Phenotype in PiZ Mice with Established Disease

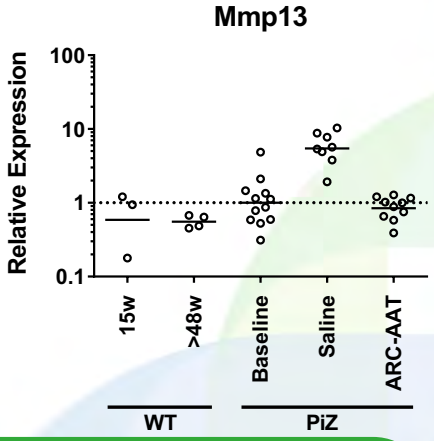










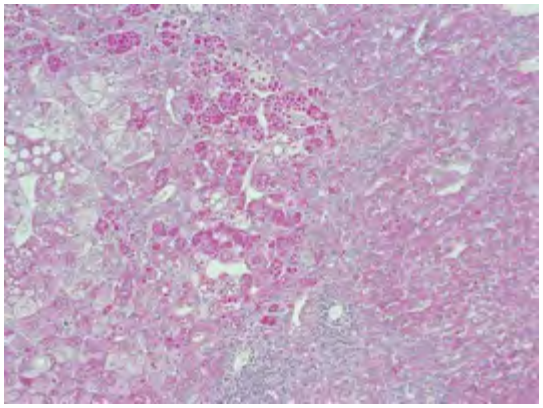


Prevention and reversal of the polymer and globular accumulation
Prevents the increase in fibrosis gene expression

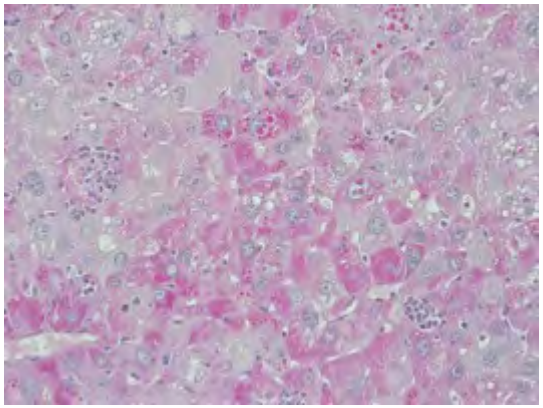
arrowhead pharmaceuticals

ARC-AAT Prevents Liver Tumors in Old PiZ Mice

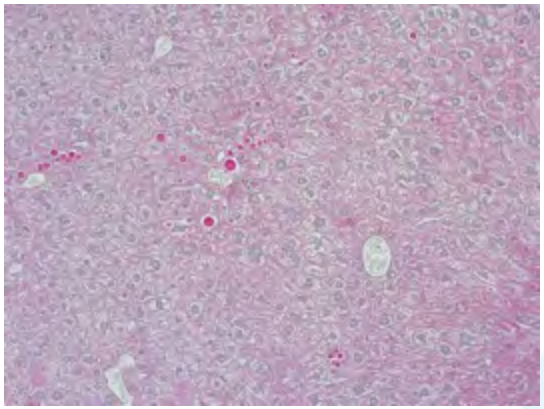
15-16 months old; Q2W x 16



Baseline (15-16 months old)
PAS-D globules, inflammation, neoplastic hepatocytes in some mice



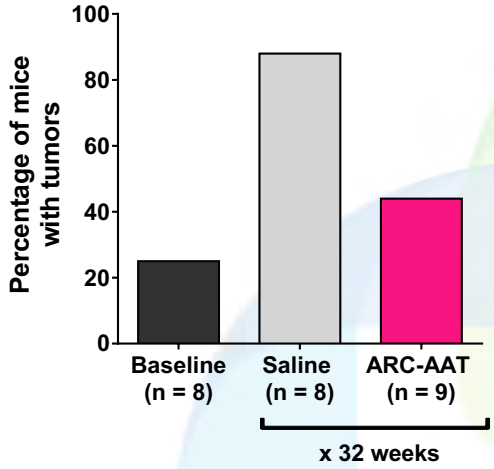
Saline x 32 weeks
PAS-D globules, inflammation, neoplastic hepatocytes, tumors



ARC-AAT x 32 weeks
Rare PAS-D globules, normal morphology

Some mice had tumors and/or neoplastic hepatocytes at baseline

ARC-AAT reduced tumor incidence over the treatment period



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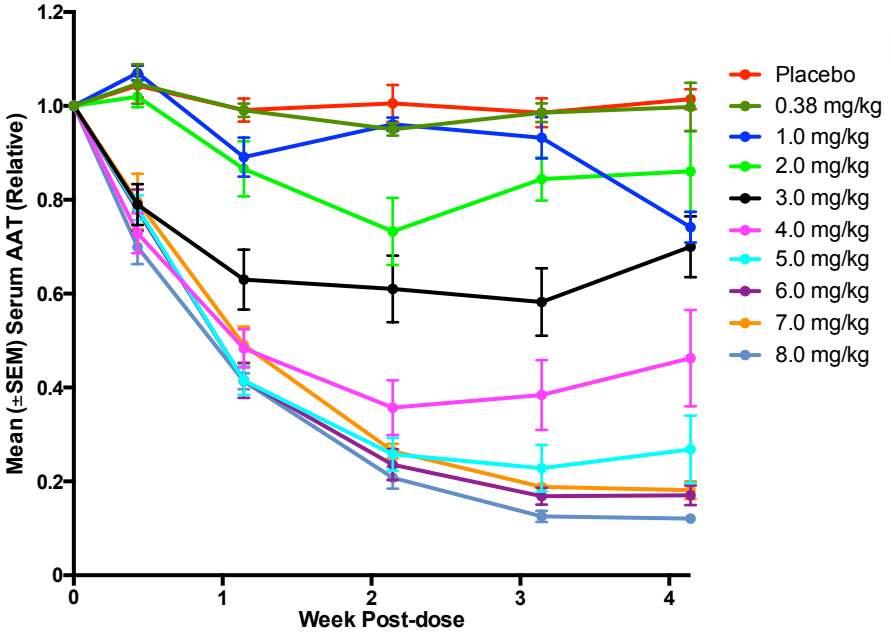
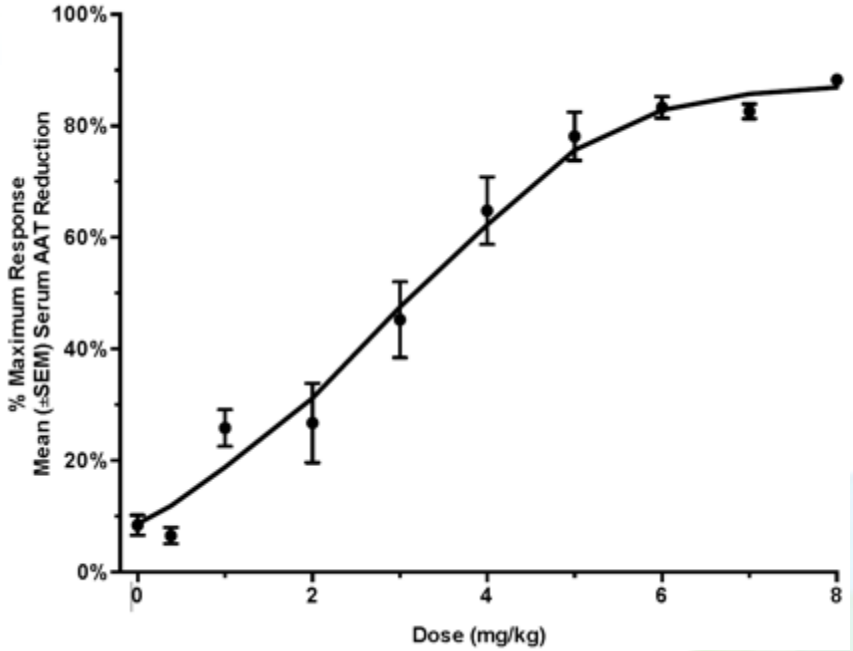
Dose Response in Healthy Volunteers with Single-dose ARC-AAT

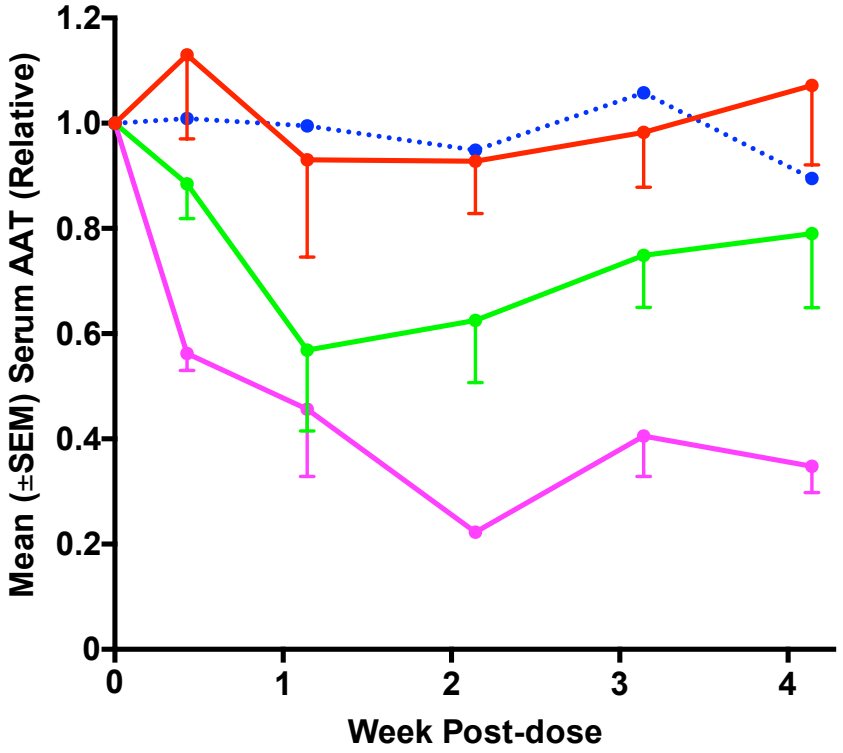




Dose Level (mg/kg)	PBO (n=18)	0.38 (n=4)	1 (n=4)	2 (n=4)	3 (n=4)	4 (n=4)	5 (n=4)	6 (n=4)	7 (n=3)	8 (n=3)
Max KD	24.8%	9.3%	31.9%	36.3%	61.0%	76.1%	86.7%	87.1%	85.1%	89.8%
Mean Max	8.4%	6.6%	25.9%	26.7%	45.3%	64.8%	78.1%	83.3%	82.6%	88.3%
P value	N/A	0.6363	0.0004	0.0014	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

89.9 % maximum serum AAT knockdown achieved in healthy volunteers

Dose Response in ZZ Patients with Single-dose ARC-AAT



Dose Level (mg/kg)	PBO (n=4)	2 (n=3)	4 (n=3)
Max KD	46.6%	73.7%	78.8%
Mean Max KD ± SEM	21.9% 9.80%	44.1% 15.00%	78.1% 0.48%
P value	N/A	0.2524	0.0047

78.8 % maximum serum AAT knockdown achieved at 4 mg/kg

Largely consistent with results in healthy volunteers

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ARO-AAT

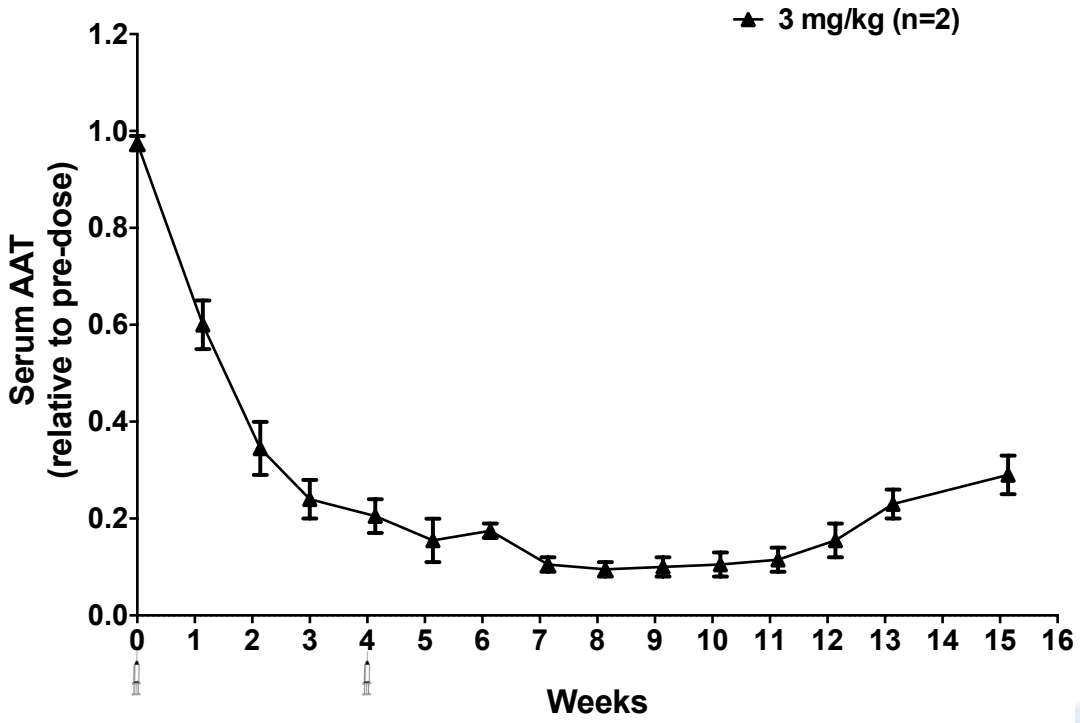
ARO-AAT: Key Design Elements Expected for the Next Generation

The Wish List:

- Subcutaneous dosing, monthly or less frequent
- No need for endosomal escape agent
- Full suppression of liver AAT production
  - Deep and prolonged KD of plasma AAT levels
- Expectation of wide therapeutic index
- Good tolerability in humans

ARO-AAT Provides Durable AAT knockdown:
Multi-dose in NHP, dosed subcutaneously

- 92% maximum serum AAT knockdown achieved
- Knockdown sustained for 7+ weeks following second dose



Durable knockdown supports once monthly or less frequent dosing

ARO-AAT Preliminary Safety Evaluation

- Based on clinical observations, clinical pathology and limited histopathology evaluations, ARO-AAT was well tolerated in the following non-GLP exploratory toxicity studies:
  - A repeated dose study in rats administered 3 weekly subcutaneous doses at dose levels of 30, 60, 120, and 300 mg/kg
  - An escalating dose study in two cynomolgus monkeys dosed weekly subcutaneously at doses up to and including 300 mg/kg

ARO-AAT: Key Design Elements Expected for the Next Generation

The Wish List:

- ✓ Subcutaneous dosing, monthly or less frequent
- ✓ No need for endosomal escape agent
- ✓ Full suppression of liver AAT production
  - ✓ Deep and prolonged KD of plasma AAT levels
- ✓ Expectation of wide therapeutic index

Good tolerability in humans (pending)

CTA planned for Q1 2018 pending completion of GLP tox

Hypertriglyceridemia

Ira Goldberg, M.D.

Director, Division of Endocrinology, Diabetes, and Metabolism,
NYU Langone Medical Center

Hypertriglyceridemia: Acute and Chronic Disease

Ira J. Goldberg
Clarissa and Edgar Bronfman Professor
Director, Division of Endocrinology, Diabetes and Metabolism
New York University School of Medicine

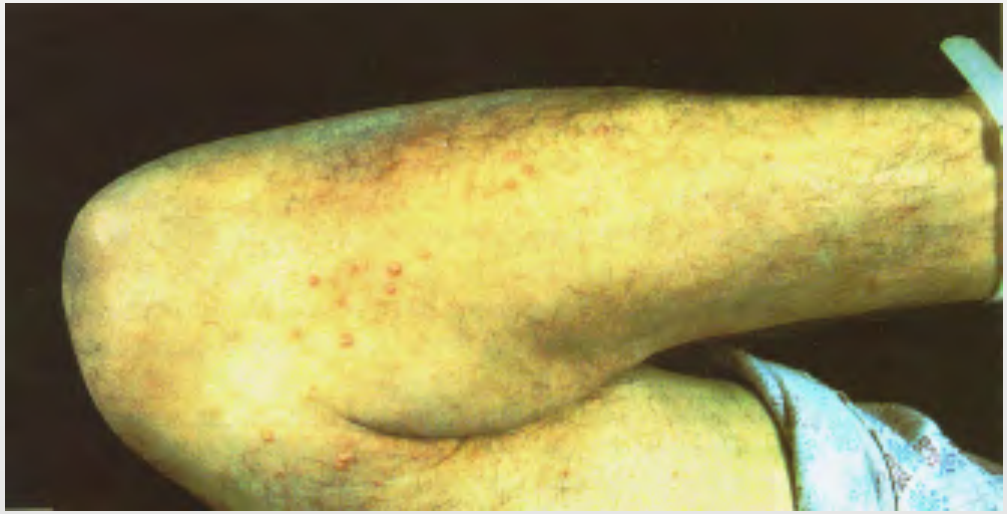
- Describe the causes of severe hypertriglyceridemia
- Explain the evidence linking hypertriglyceridemia with acute and chronic disease
- Outline the need for novel pharmacologic targets for the treatment of hypertriglyceridemia

Describe the causes of severe hypertriglyceridemia

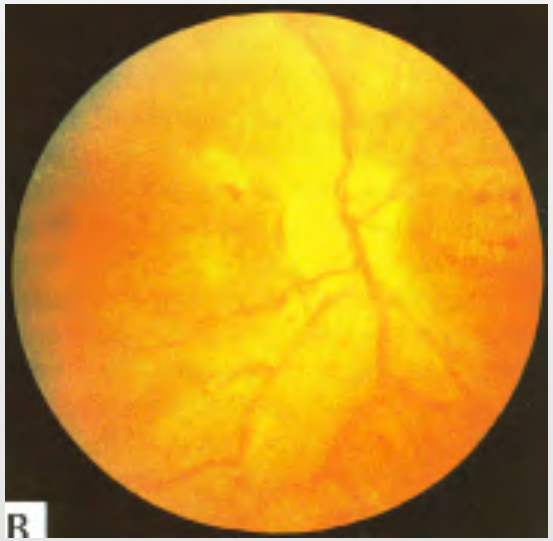
Explain the evidence linking hypertriglyceridemia with acute and chronic disease

Outline the need for novel pharmacologic targets for the treatment of hypertriglyceridemia

Clinical signs of severe hypertriglyceridemia

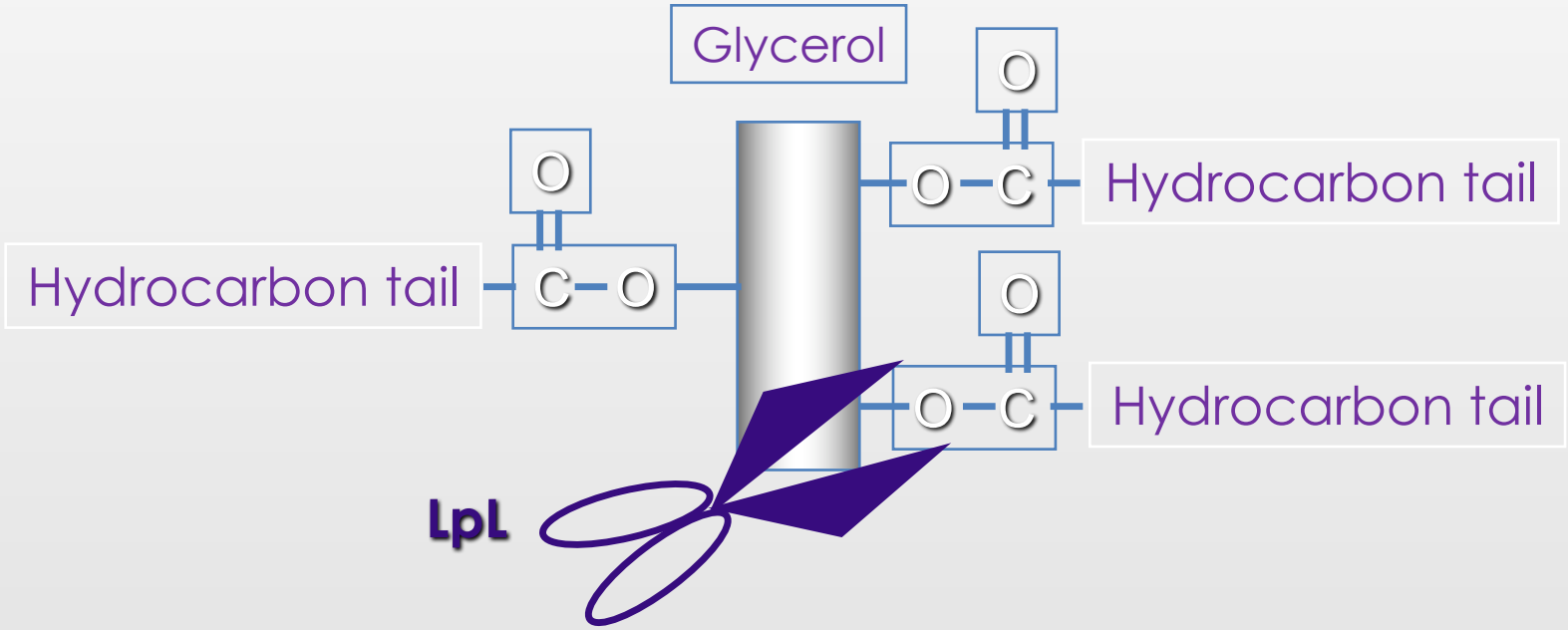


Eruptive xanthomas



Lipemia Retinalis

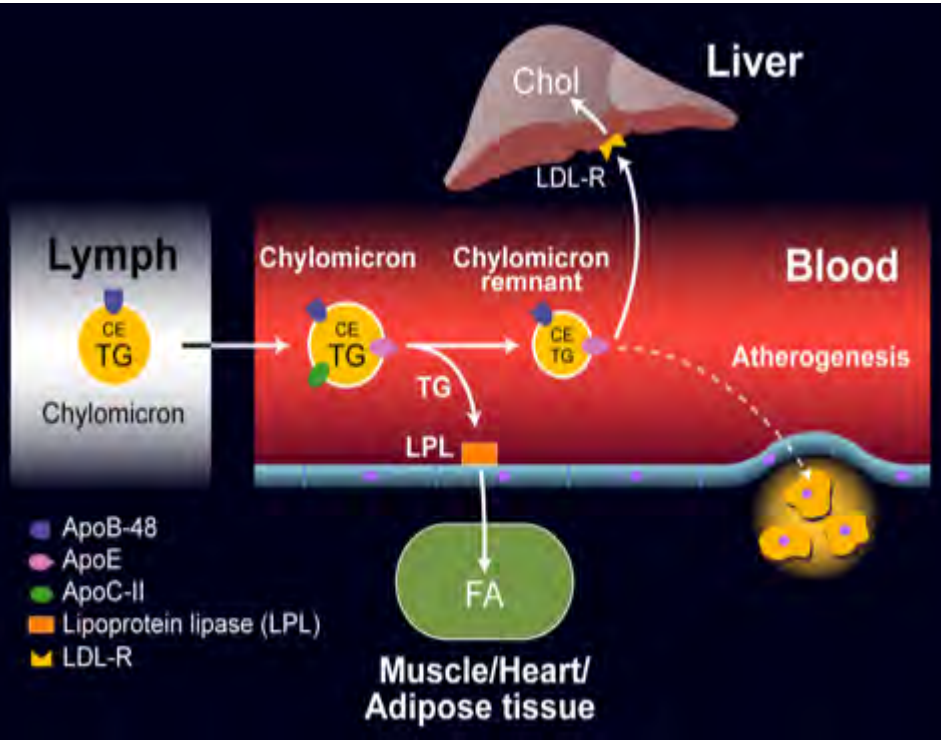
Triglyceride (TG) and Lipoprotein Lipase (LpL)

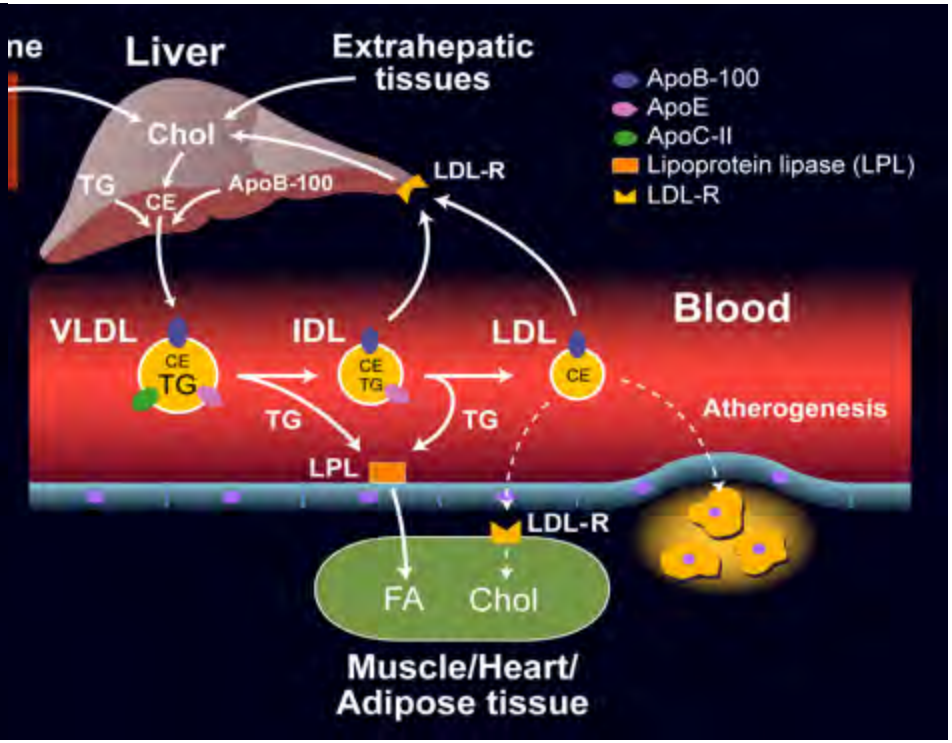


TG from liver and gut use LpL

Chylomicron Transport

Endogenous Pathway





What regulates lipolysis?

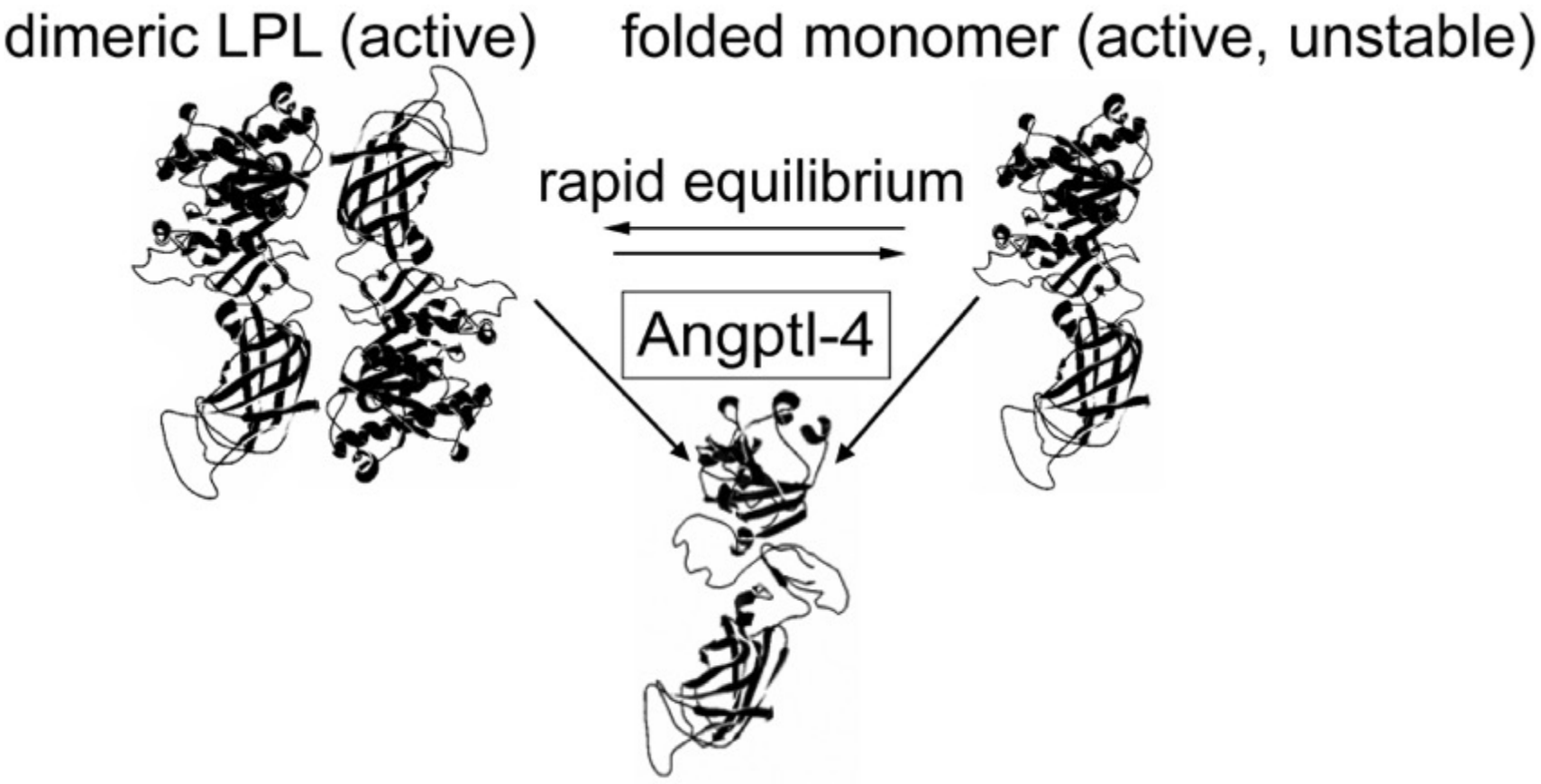
Activators

- ApoC-II (activator)
- GPIHBP1 (endothelial cell binding site)
- Lipase maturation factor (LMF, intracellular production)
- ApoA-V (increases binding to endothelial cells)

Inhibitors

- ApoC-III
- Angiopoietin-like proteins 3,4,8

Novel Regulators of Lipoprotein Lipase Activity



Angiopoietin-like proteins 3, 4, 8

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BRIEF REPORT

Exome Sequencing, *ANGPTL3* Mutations, and Familial Combined Hypolipidemia

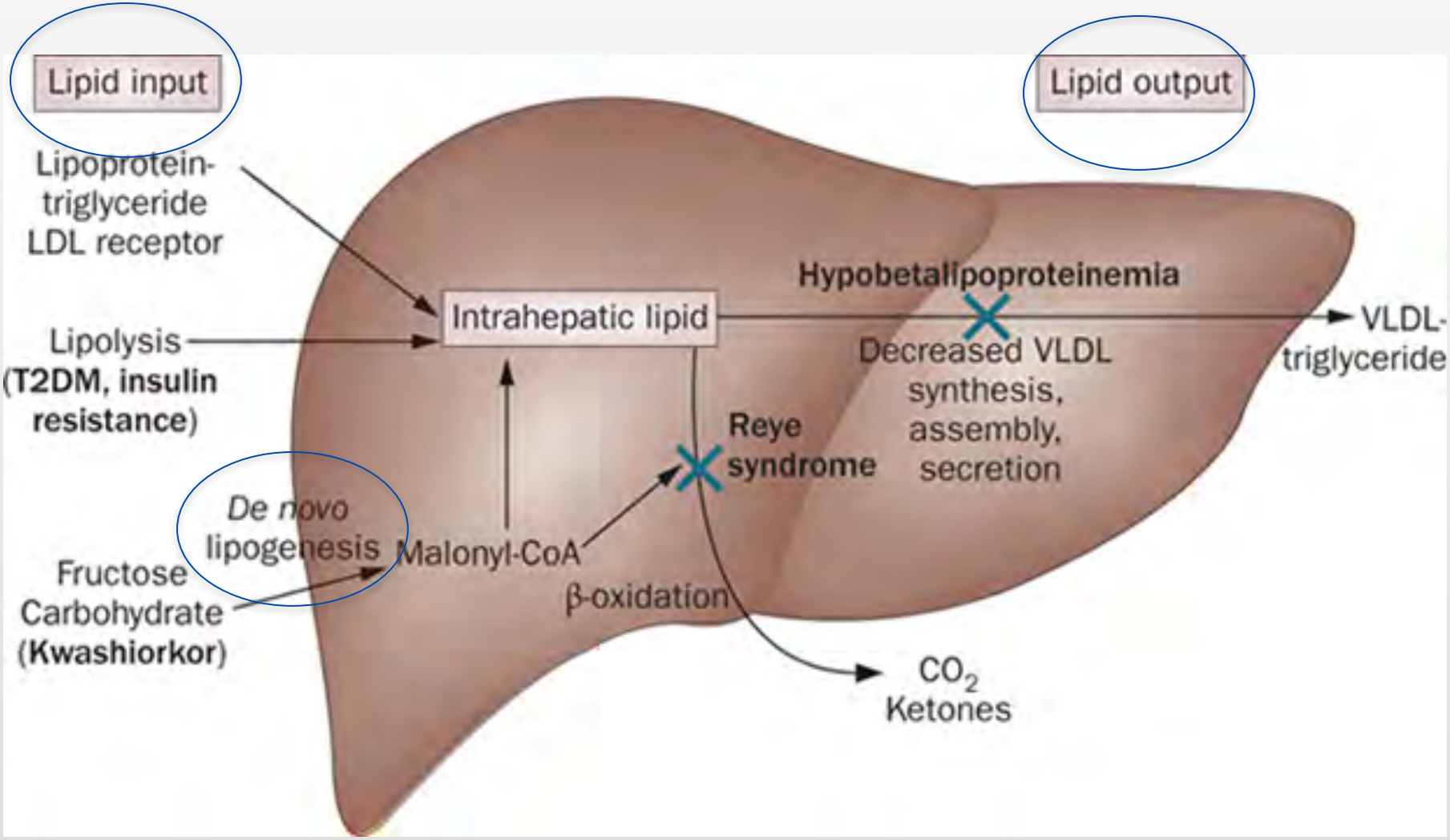
Kiran Musunuru, M.D., Ph.D., M.P.H., James P. Pirruccello, B.S., Ron Do, M.S., Gina M. Peloso, M.S., Candace Guiducci, B.S., Carrie Sougnez, B.S., Kiran V. Garimella, M.S., Sheila Fisher, M.L.A., Justin Abreu, M.S., Andrew J. Barry, B.S., Tim Fennell, B.S., Eric Banks, Ph.D., Lauren Ambrogio, B.S., Kristian Cibulskis, B.S., Andrew Kernytsky, Ph.D., Elena Gonzalez, B.S., Nicholas Rudzicz, M.S., James C. Engert, Ph.D., Mark A. DePristo, Ph.D., Mark J. Daly, Ph.D., Jonathan C. Cohen, Ph.D., Helen H. Hobbs, M.D., David Altshuler, M.D., Ph.D., Gustav Schonfeld, M.D., Stacey B. Gabriel, Ph.D., Pin Yue, Ph.D., and Sekar Kathiresan, M.D.

SUMMARY

We sequenced all protein-coding regions of the genome (the "exome") in two family members with combined hypolipidemia, marked by extremely low plasma levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. These two participants were compound heterozygotes for

N Engl J Med 2010;363:2220-7.

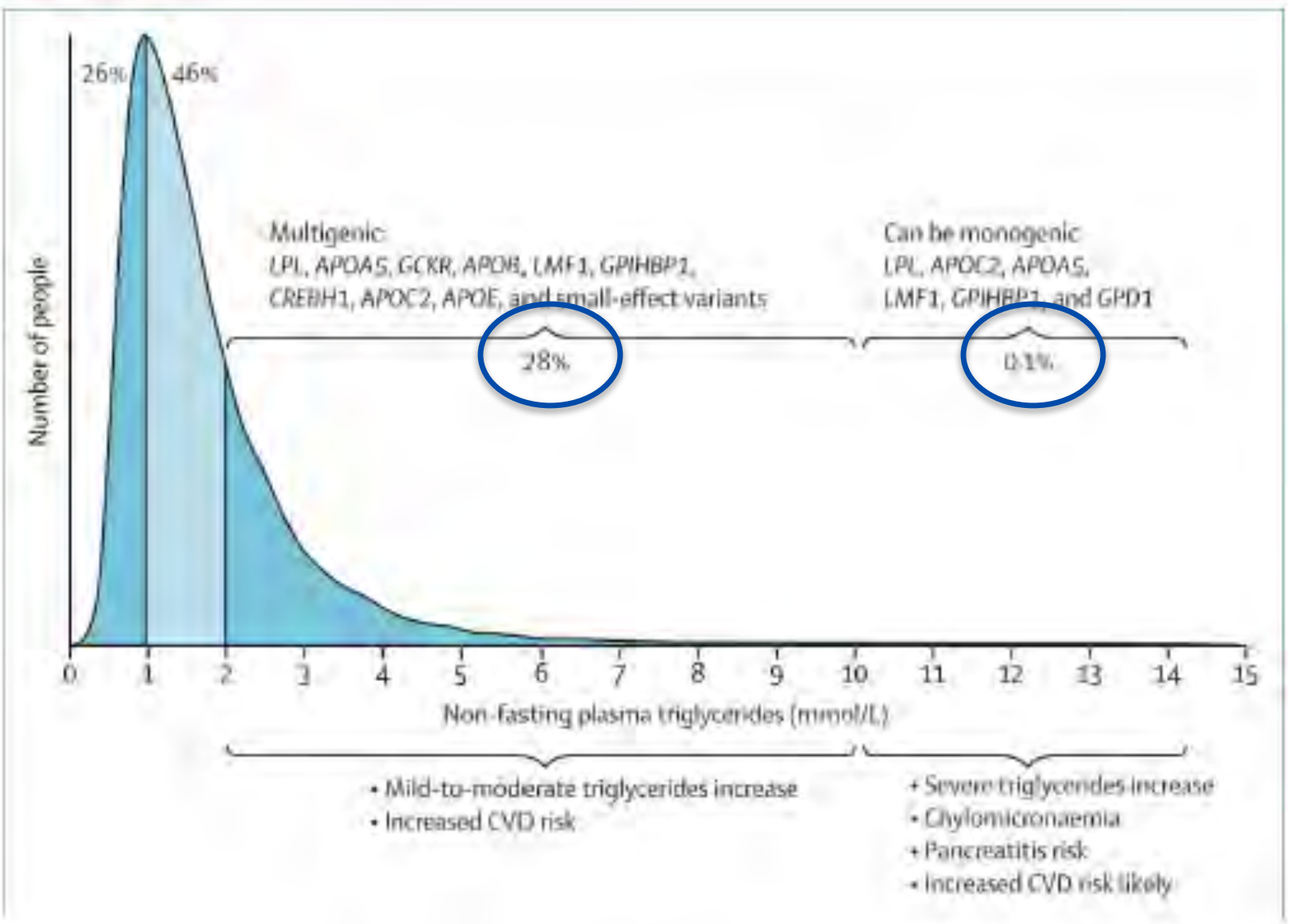
Most liver TG is recycled.



Medications causing HyperTG

- **Estrogen**
- Anti-hypertensives – thiazides, beta blockers
- Protease inhibitors
- Glucocorticoids
- **Alcohol**
- Retinoids
- Atyp. antipsychotics

Increased TG as a function of genetics



Hegele et al. Lancet Diabetes Endocrinol. 2014 Aug;2(8):655-66.

How common and what are the risk factors for hyperTG pancreatitis

Review of Kaiser Permanente, S. California

Triglyceride over 1000 mg/dL (11 mMol)

5,550 patients/2.3x10^6 total. ~0.2%

301 (5.4%) with pancreatitis during the 12 month follow up

42.1% with diagnosis of unspecified hyperlipidemia (so most not with hyperTG)

Pancreatitis group average TG 2,148 mg/dL

Co-morbidities included younger age, alcohol, prior history, hypertension, renal disease.

Rashid et al. 2016. al. J Clin Lipidol 10, 880

- Describe the causes of severe hypertriglyceridemia
- Explain the evidence linking hypertriglyceridemia with acute and chronic disease
- Outline the need for novel pharmacologic targets for the treatment of hypertriglyceridemia

Why does hyperchylomicronemia cause pancreatitis?

I don’t know!

Most hypertriglyceridemia is not a pancreatitis risk

Does it cause heart disease?

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J Clin Invest. 1973 Jul;52(7):1533-43

Hyperlipidemia in Coronary Heart Disease

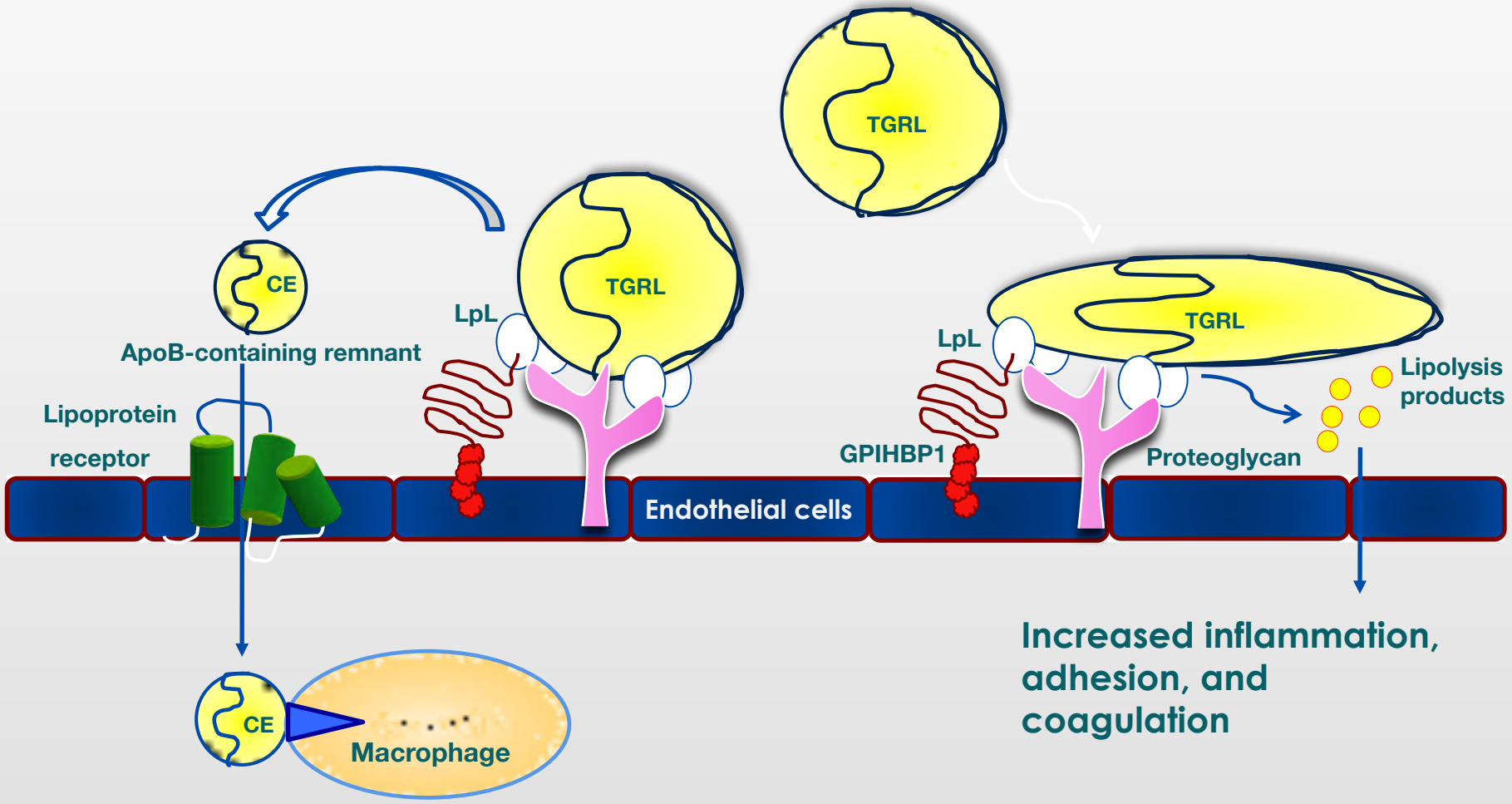
I. LIPID LEVELS IN 500 SURVIVORS OF MYOCARDIAL INFARCTION

JOSEPH L. GOLDSTEIN, WILLIAM R. HAZZARD, HELMUT G. SCHROTT, EDWIN L. BIERMAN, and ARNO G. MOTULSKY with the assistance of MARY JO LEVINSKI and ELLEN D. CAMPBELL

From the Departments of Medicine (Division of Medical Genetics, University Hospital, and Division of Metabolism and Gerontology, Veterans Administration Hospital) and Genetics, University of Washington, Seattle, Washington 98195

"These results raise the possibility that hypertriglyceridemia may be as an important a risk factor for coronary atherosclerosis as hypercholesterolemia."

Atherogenicity of Triglyceride-Rich Lipoproteins (TGRL)



Triglycerides and heart disease, still a hypothesis?
Goldberg, McPherson, Eckel, ATVB 2011, 31:1716-25

Genetics affecting Triglyceride Levels Correlate with CVD Risk

- Coding Variation in **ANGPTL4, LPL**, and SVEP1 and the Risk of Coronary Disease Myocardial Infarction Genetics and CARDIoGRAM Exome Consortia Investigators. N Engl J Med. 2016 374(12):1134-44..
- Inactivating Variants in **ANGPTL4** and Risk of Coronary Artery Disease. Dewey FE, Gusarova V,…….....Shuldiner AR. N Engl J Med. 2016 Mar 24;374(:1123-33.

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Atherogenicity of TG/FFA

Epidemiology but NO CLINICAL TRIAL DATA?

Comparison of ACCORD Subgroup Results With Those From Prior Fibrate Studies

Trial (Drug)	Primary Endpoint: Entire Cohort (P-value)	Lipid Subgroup Criterion	Primary Endpoint: Subgroup
HHS (Gemfibrozil)	-34% (0.02)	TG > 200 mg/dl LDL-C/HDL-C > 5.0	-71% (0.005)
BIP (Bezafibrate)	-7.3% (0.24)	TG ≥ 200 mg/dl	-39.5% (0.02)
FIELD (Fenofibrate)	-11% (0.16)	TG ≥ 204 mg/dl HDL-C < 42 mg/dl	-27% (0.005)
ACCORD (Fenofibrate)	-8% (0.32)	TG ≥ 204 mg/dl HDL-C ≤ 34 mg/dl	-31%

Learning Objectives

- Describe the causes of severe hypertriglyceridemia
- Explain the evidence linking hypertriglyceridemia with acute and chronic disease
- Outline the need for novel pharmacologic targets for the treatment of hypertriglyceridemia

Pharmacologic Treatments to lower TG

- Fibric acids (fenofibrate)
- Omega 3 fatty acids
- Niacin
- Statins
- Orlistat
- Block lipoprotein production (Lomitapide, Mipomersin)
- **Future:**
  - Block apoC-III production
  - apoC-II mimetics
  - Antibodies to or RNA inhibitors of angiopoietin-like proteins 3, 4, 8

NYU

A Null Mutation in Human *APOC3* Confers a Favorable Plasma Lipid Profile and Apparent Cardioprotection

Toni I. Pollin,[1] Coleen M. Damcott,[1] Haiqing Shen,[1] Sandra H. Ott,[1] John Shelton,[1] Richard B. Horenstein,[1] Wendy Post,[2] John C. McLenithan,[1,3] Lawrence F. Bielak,[4] Patricia A. Peyser,[4] Braxton D. Mitchell,[1] Michael Miller,[1] Jeffrey R. O'Connell,[1] Alan R. Shuldiner[1,3]

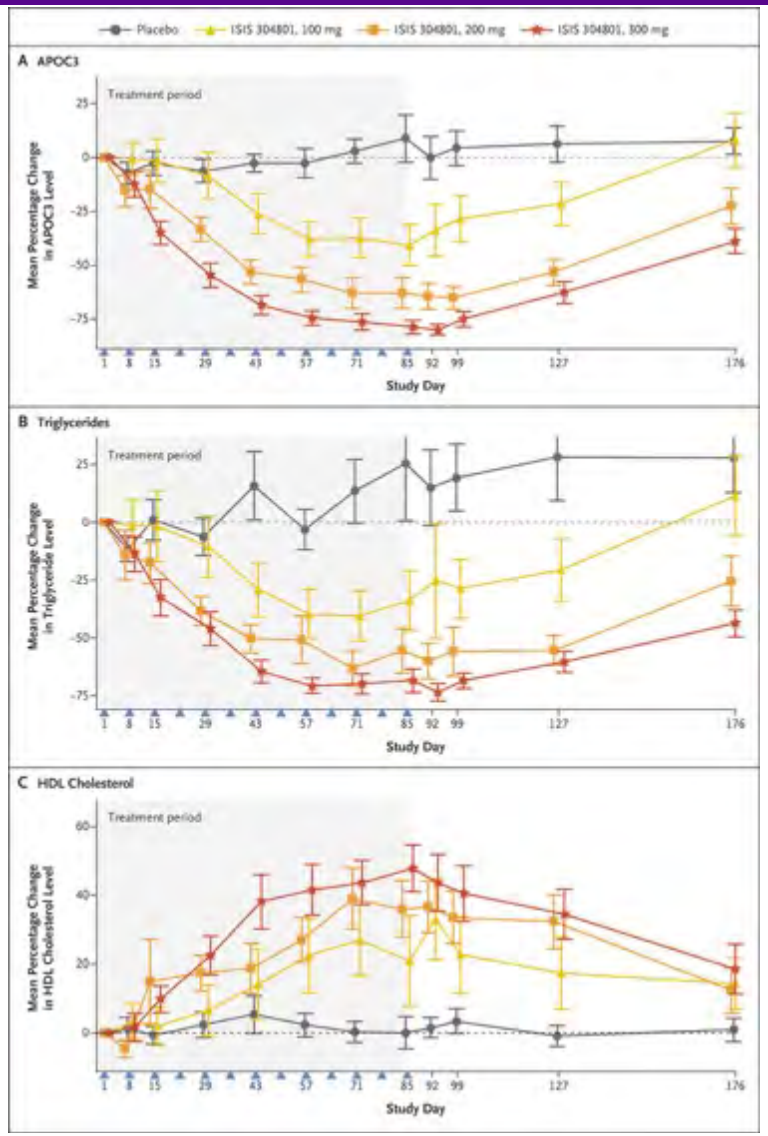
Apolipoprotein C-III (apoC-III) inhibits triglyceride hydrolysis and has been implicated in coronary artery disease. Through a genome-wide association study, we have found that about 5% of the Lancaster Amish are heterozygous carriers of a null mutation (R19X) in the gene encoding apoC-III (*APOC3*) and, as a result, express half the amount of apoC-III present in noncarriers. Mutation carriers compared with noncarriers had lower fasting and postprandial serum triglycerides, higher levels of HDL-cholesterol and lower levels of LDL-cholesterol. Subclinical atherosclerosis, as measured by coronary artery calcification, was less common in carriers than noncarriers, which suggests that lifelong deficiency of apoC-III has a cardioprotective effect.

ApoC-III ASO Reduces Triglycerides

ApoC-III

Triglycerides

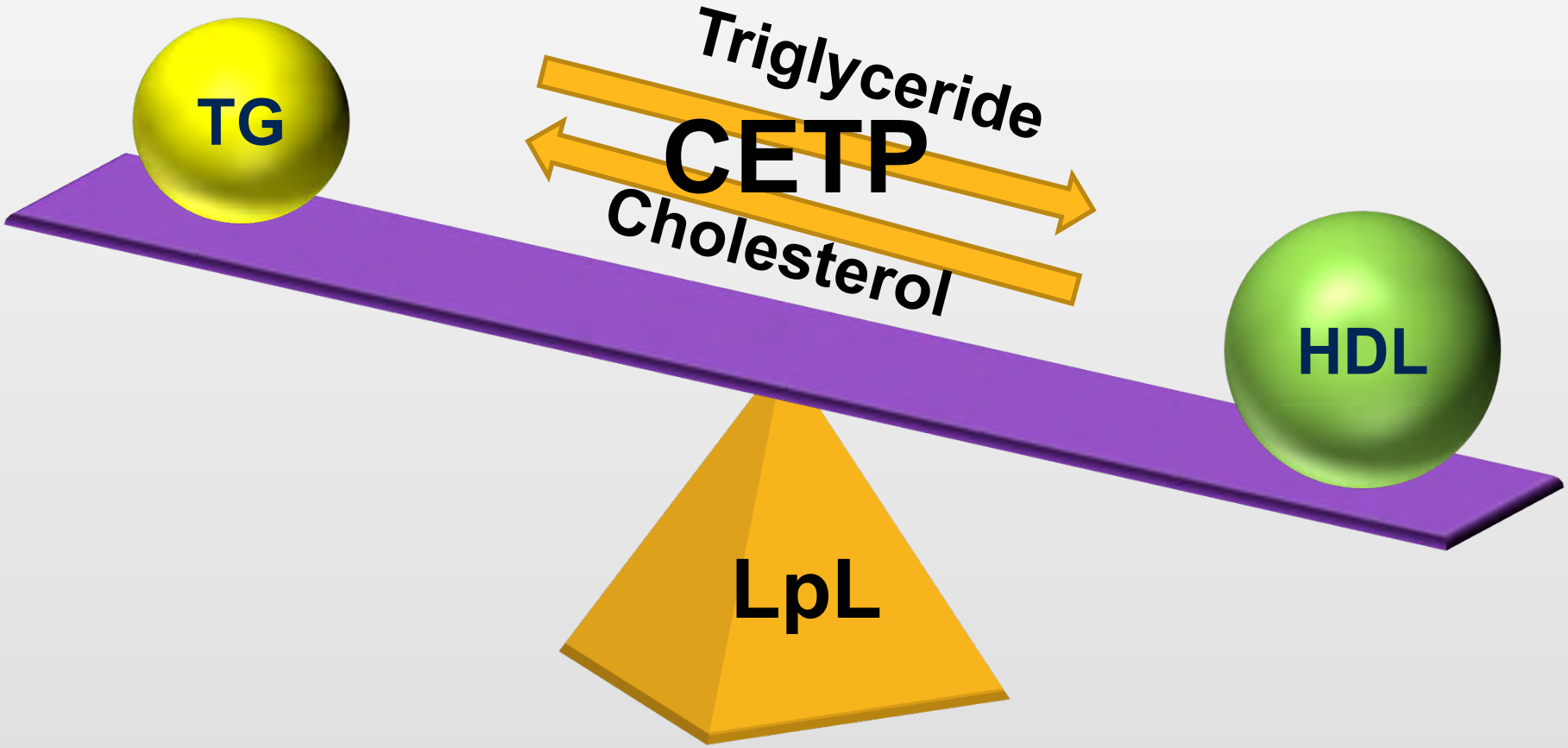
HDL



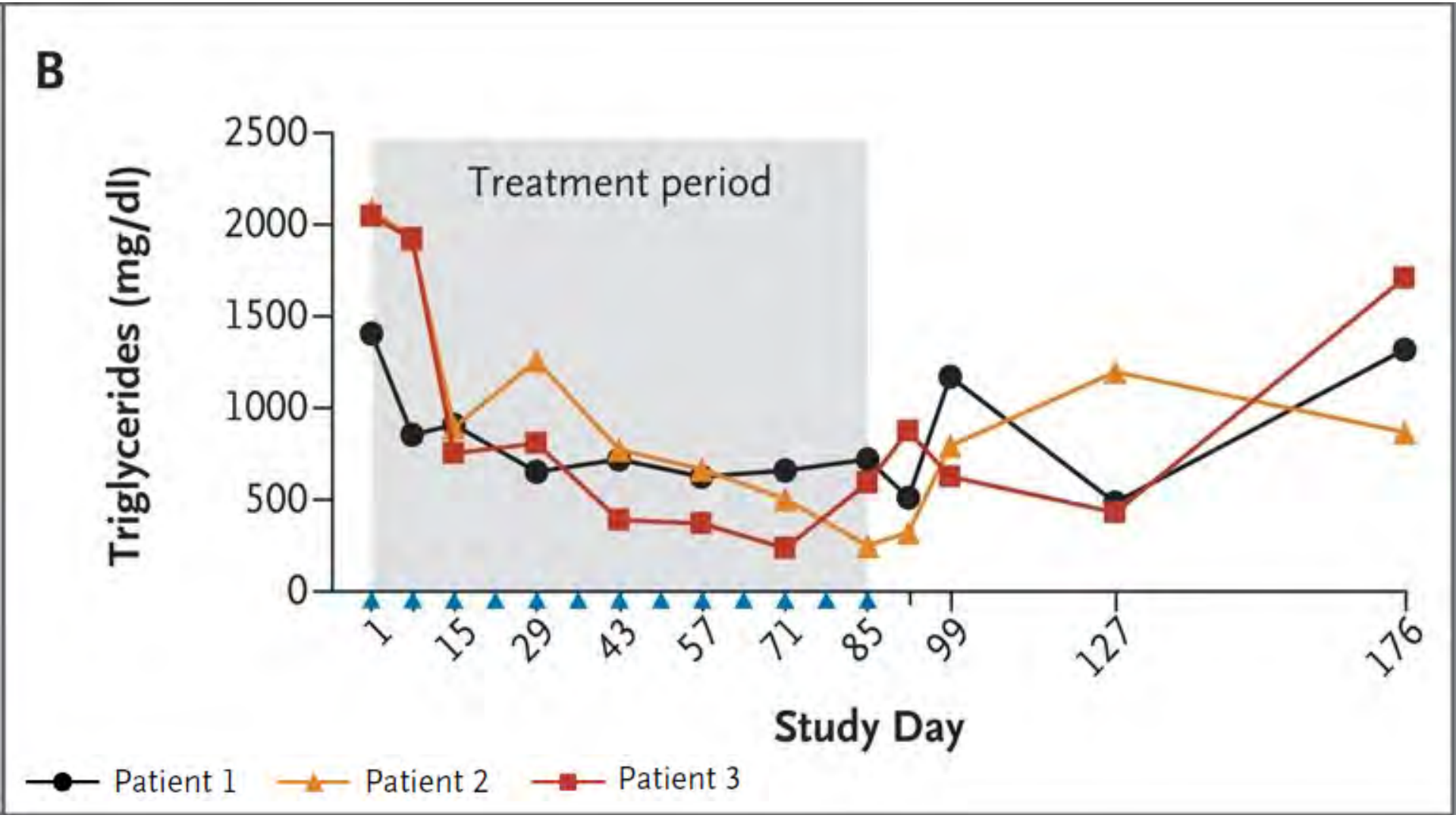
Gaudet D et al. N Engl J Med 2015;373:438-447

The NEW ENGLAND JOURNAL of MEDICINE

Why is HDL increased with apoC-III ASO?



ApoC-III ASO Reduced TG in LPL Deficiency



Gaudet D et al. N Engl J Med 2014;371:2200-2206

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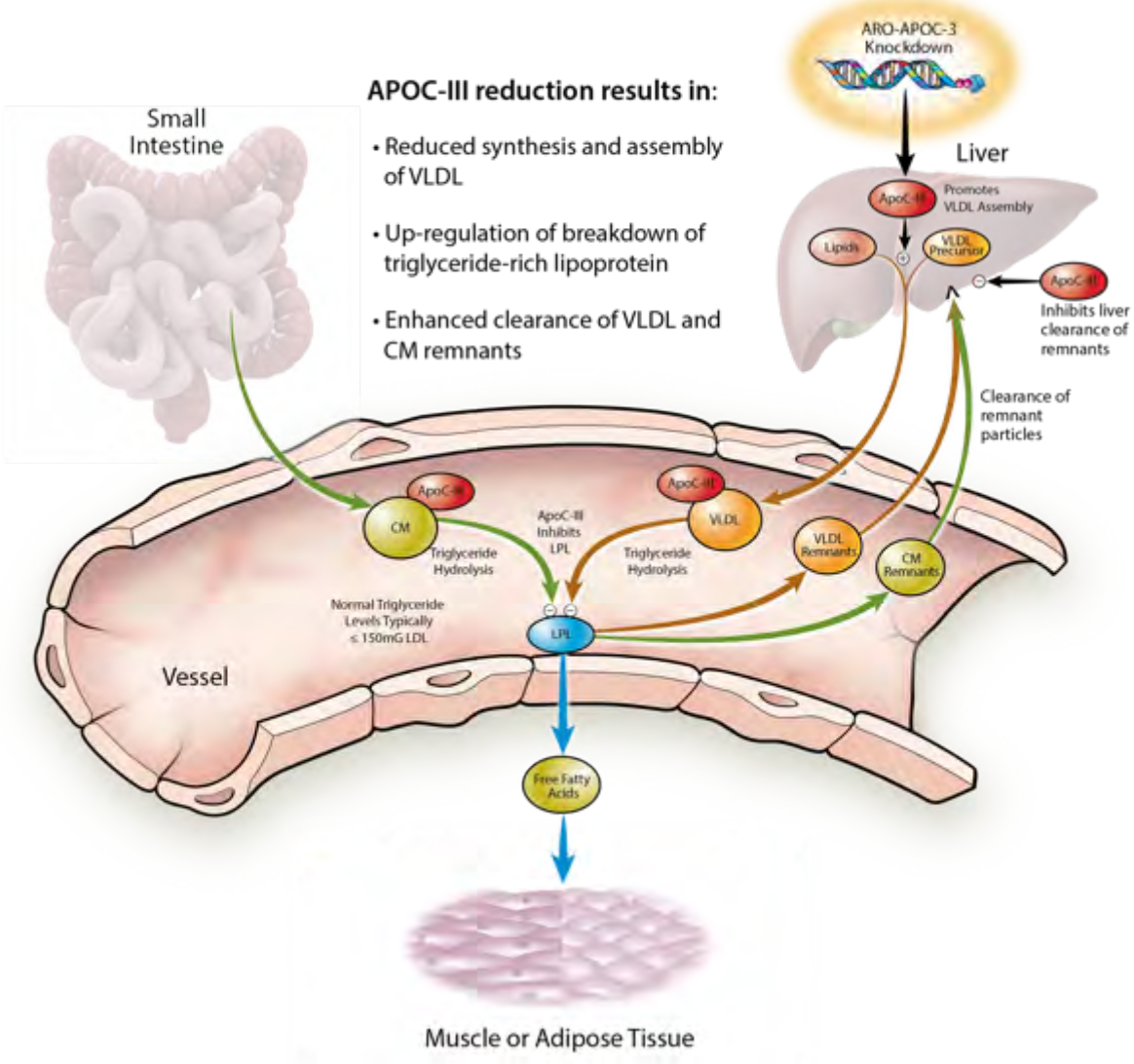
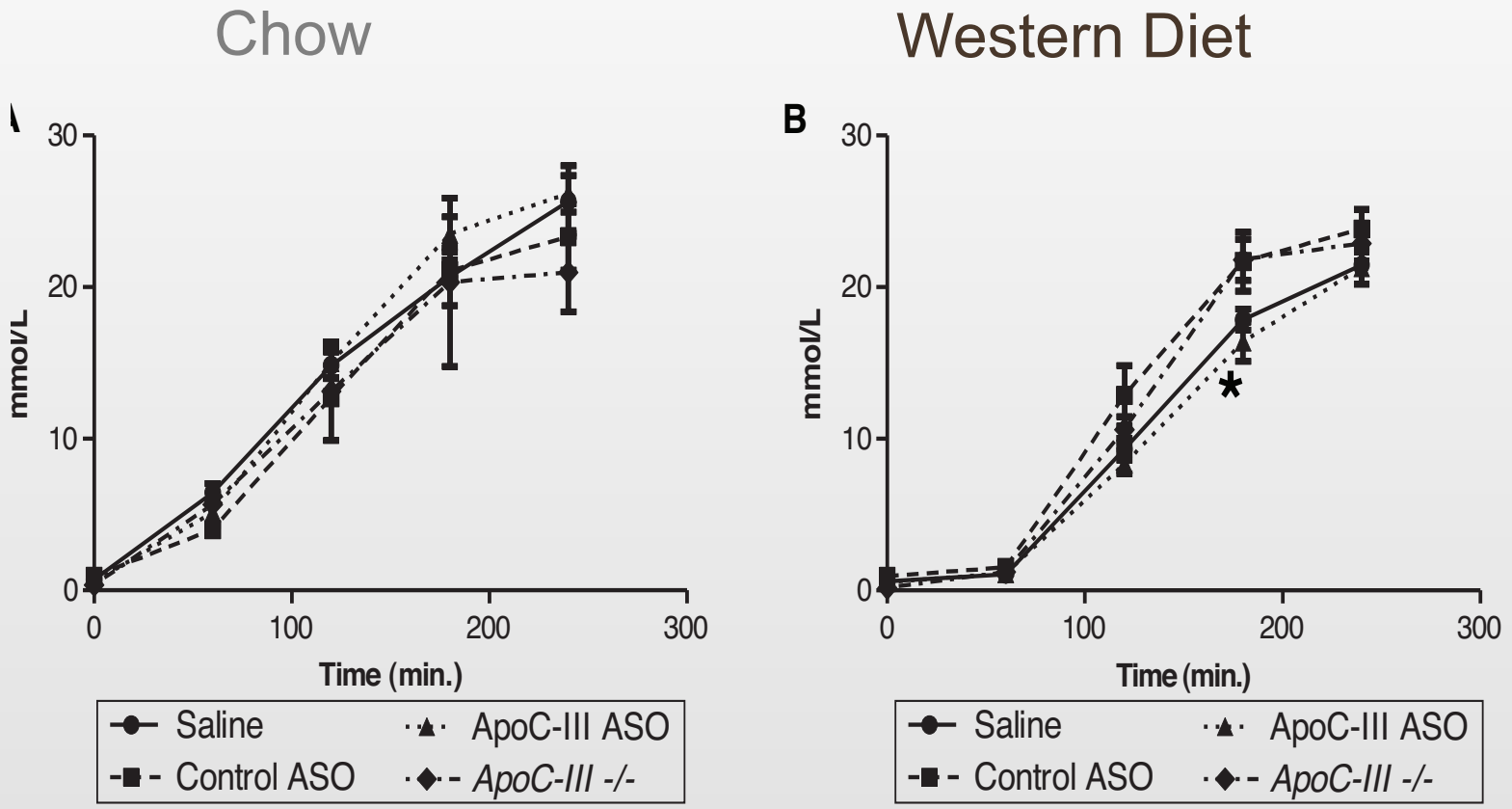
If apoC-III is an inhibitor of lipoprotein lipase, how does it lower TG in LpL deficiency?



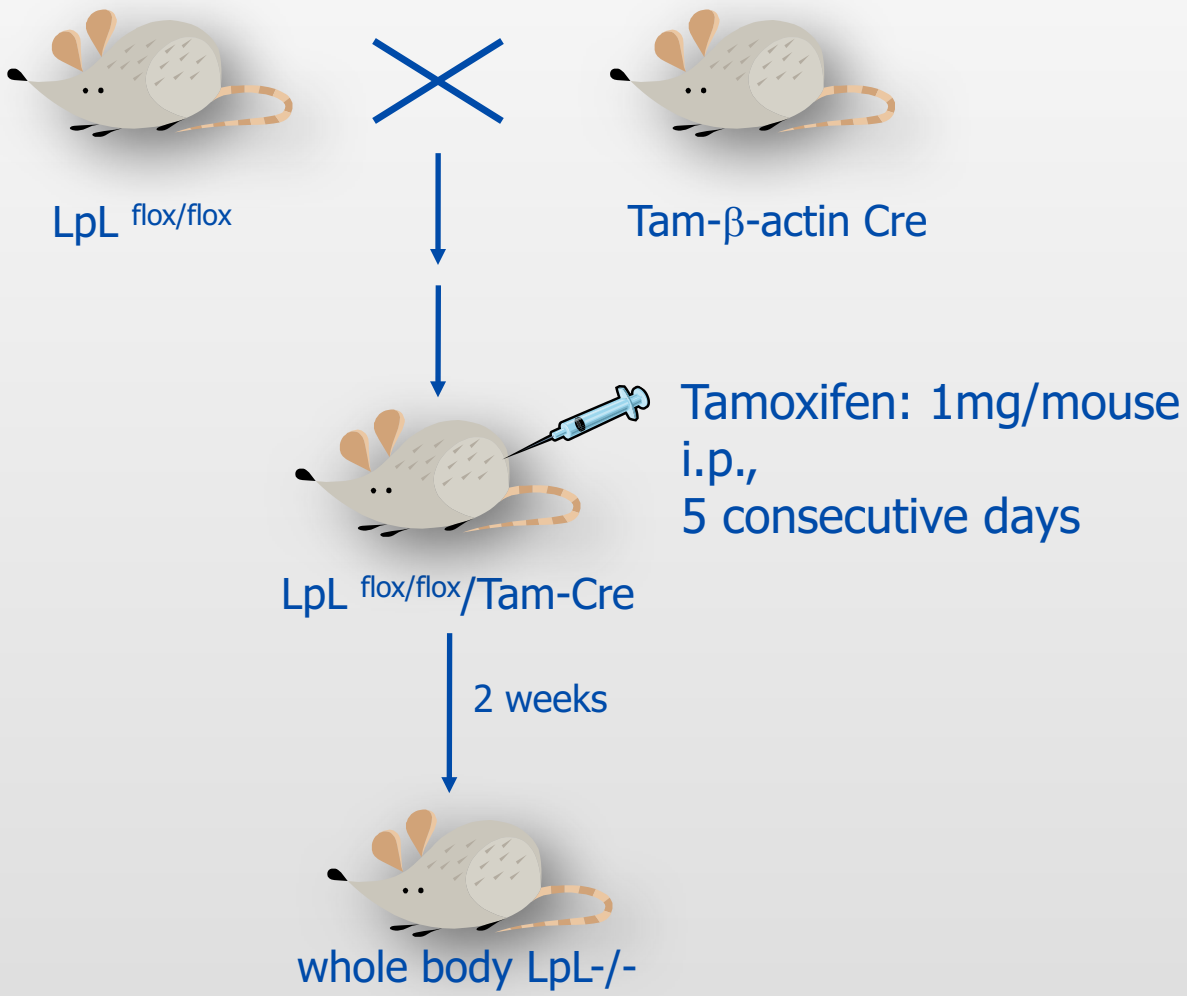
Hepatic TG Secretion and Content were not Affected in ApoC-III ASO Treated C57BL/6 Mice



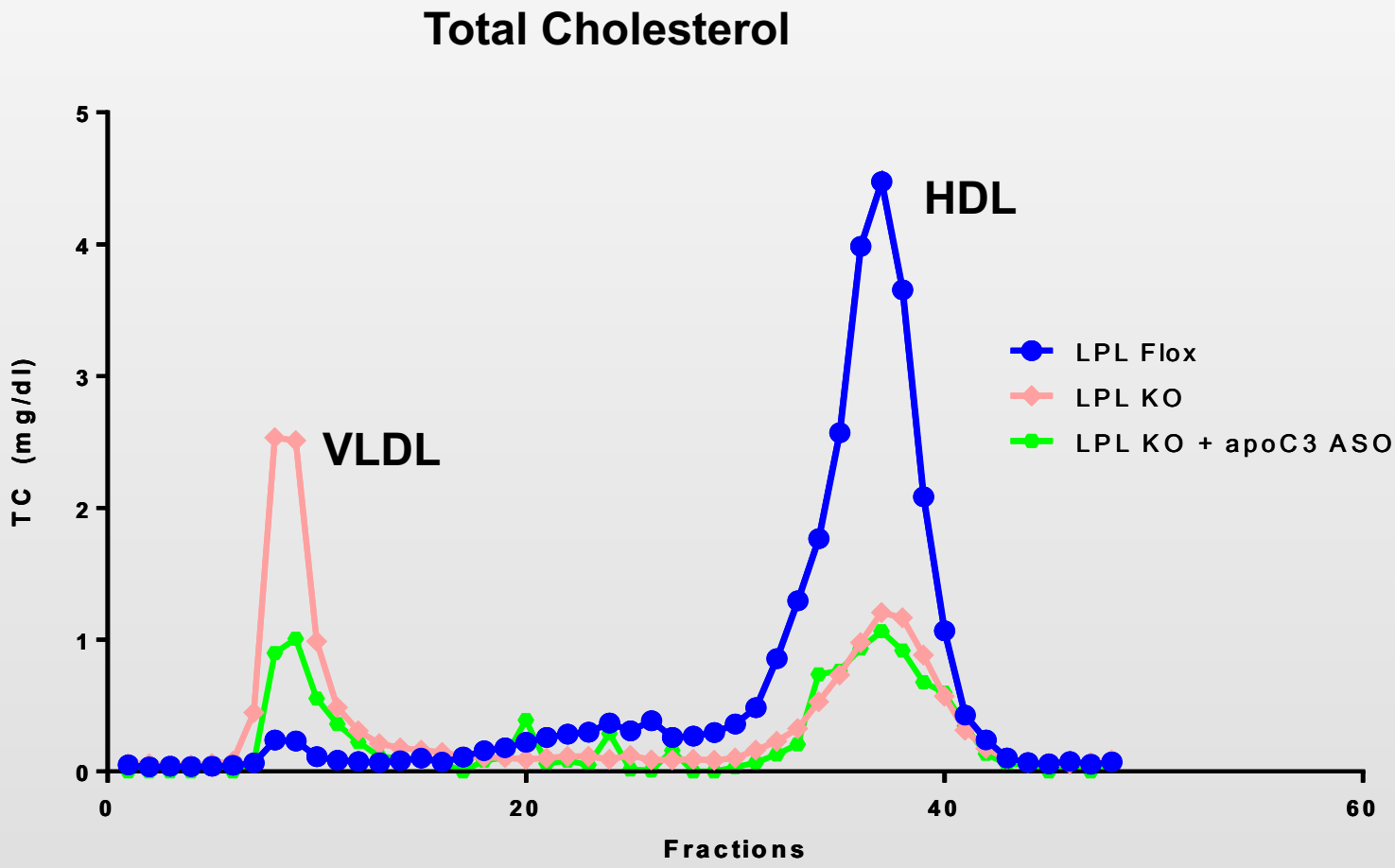
Graham et al., Circ Res. 2013. 112:1479-90

Generation of Inducible LpL Knockout

Son et al.



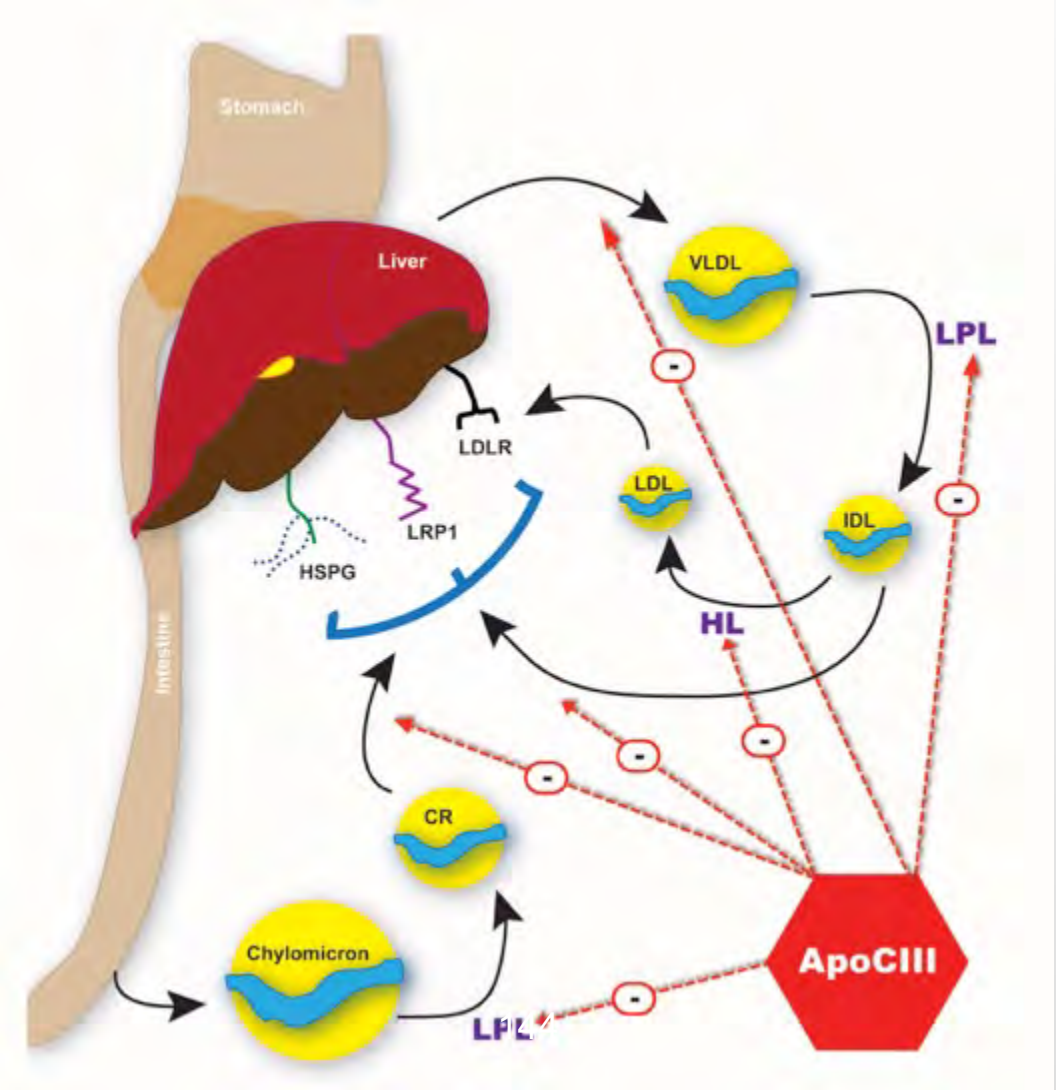
Antisense Oligonucleotide (ASO) Reduced TG but Did Not Increase HDL



Basu in Gordts, et al. J Clin Invest. 2016 126: 2855-2866

Does ApoC-III Modulate TRL Clearance via LDLR/LRP1 or HSPGs?

Jeff Esko/Philip Gordts - UCSD



Take Home Message

- Rare recessive genetic diseases lead to severe hypertriglyceridemia and pancreatitis.
- But this can occur in patients with a single mutations and a second insult: estrogen, alcohol, diabetes.
- Triglyceride and HDL levels are usually inversely correlated.
- Data on treatment of triglyceride to reduce CVD is inconclusive.
- Newer drugs (inhibitors of ApoC-III and Angplt3) will hopefully prevent hypertriglyceridemic pancreatitis and might also reduce CVD

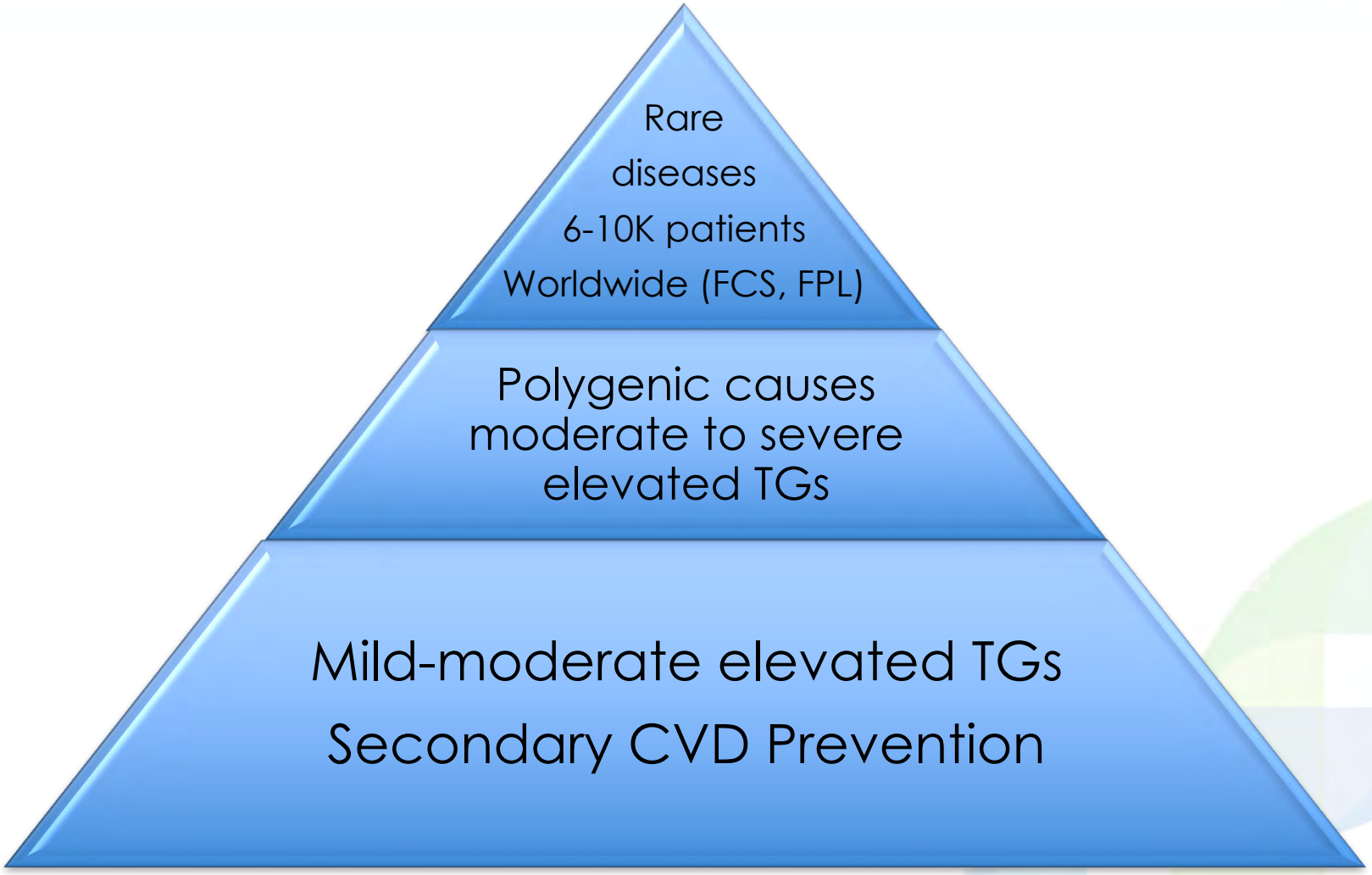
Arrowhead Hypertriglyceridemia Program
Bruce Given, M.D.

Clinical Indications Related to High Triglycerides

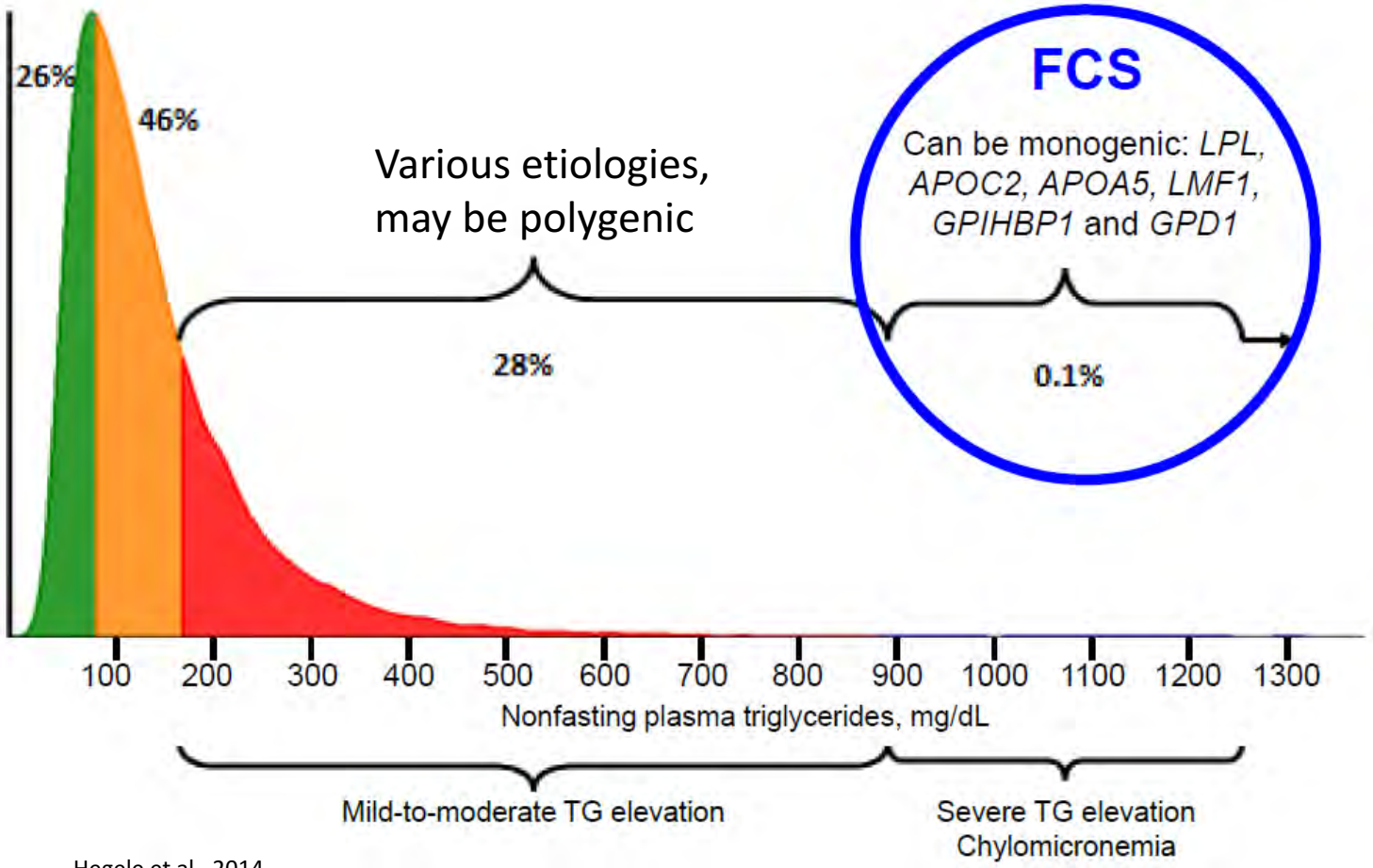
Two primary indications to lower TGs with pharmacotherapy

1. Reduce pancreatitis risk (TGs > ~900 mg/dL)
   - Goal is to get well below 500 mg/dL to prevent pancreatitis associated with 2-3X rise post ETOH/fatty meal
   - Drugs used in conjunction with exercise, strict diet (< 20 grams of fat per day)
2. Reduce CVD risk

Clinical Indications: Tiered by Size and Regulatory Complexity



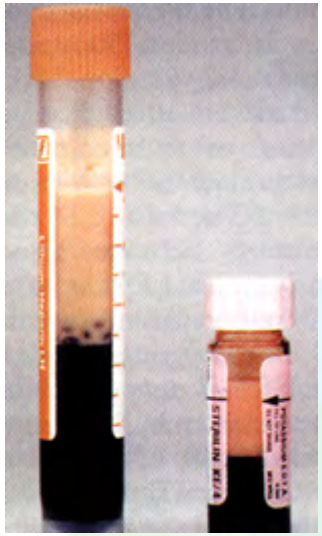
Clinical Indications: Moderate to Severe Hypertriglyceridemia



Hegele et al., 2014

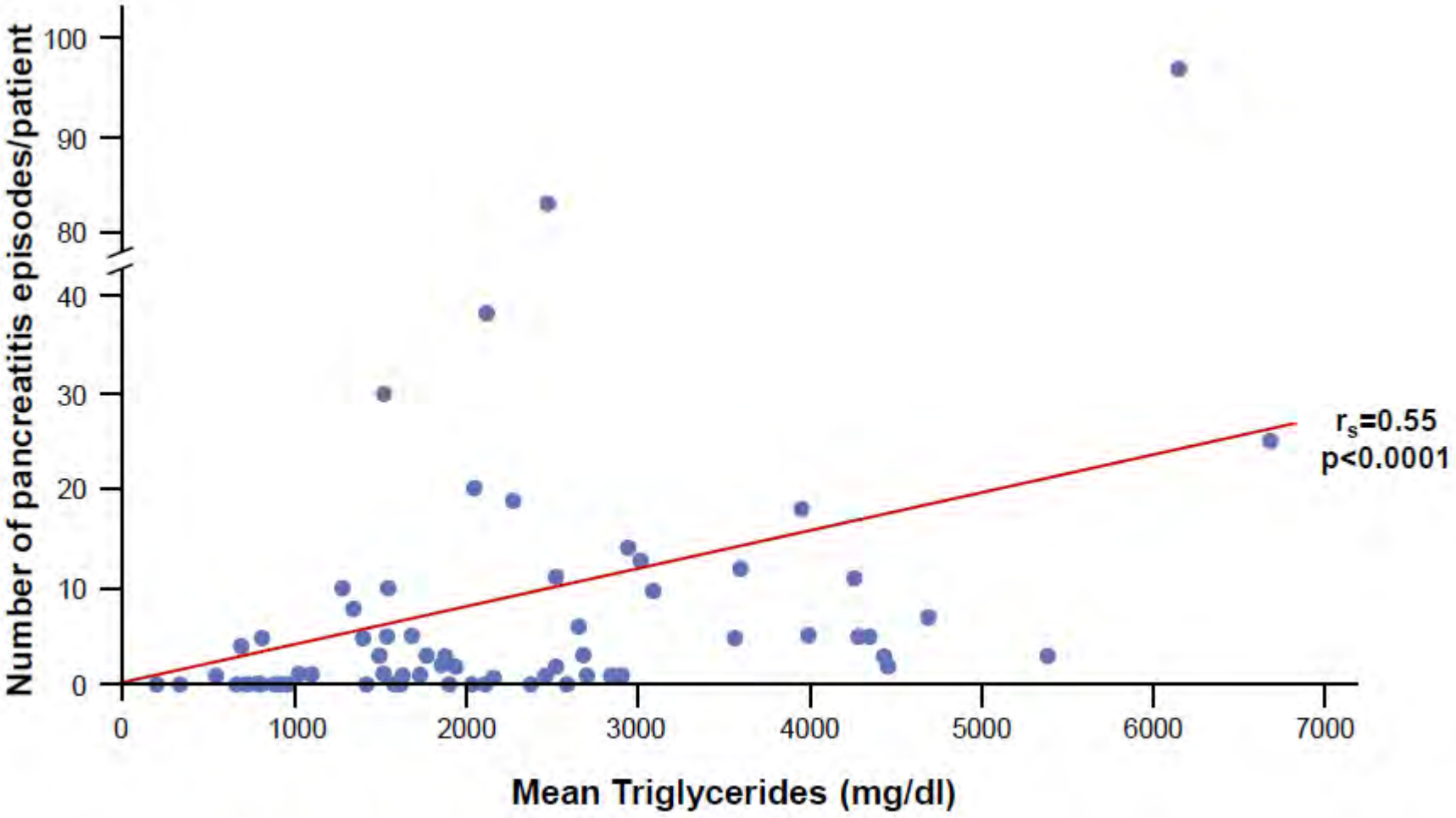
Familial Chylomicronemia Syndrome (FCS)

- FCS: Severely elevated triglycerides (often over 2,000 mg/dL)
  - Loss-of-function in gene(s) responsible for LPL dependent triglyceride clearance (LPL, APOC2, APOA5, LMF1)
  - Multiple systemic manifestations
    - Recurrent abdominal pain
    - Acute pancreatitis (admission, narcotics, 10% mortality)
    - Neurocognitive problems
    - Type 2 diabetes mellitus
    - Eruptive xanthomas



- Estimated 3,000-5,000 patients worldwide
- No effective available therapy
  - Available drugs (fibrates, fish oils, niacin) ineffective as they work through LPL dependent pathway
  - Currently managed by severe dietary restrictions (< 20 grams of daily fat)
    - Adherence difficult, doesn't normalize triglycerides, only reduces pancreatitis risk

Triglyceride Levels Correlate with Frequency of Pancreatitis Attacks



Familial Partial Lipodystrophy (FPL)

- FPL: mutations in genes responsible for efficient lipid storage in adipose tissue (e.g. *LNMA* gene, responsible for normal adipocyte development)
  - Multiple systemic manifestations
    - Very high triglycerides (>1000 mg/dL)
    - Pancreatitis
    - Insulin resistance
    - Hepatic steatosis
    - CVD
- Estimated 3,000-5,000 patients worldwide
- Very limited effective available therapy
  - Manage with low fat, high carbohydrate diet

Cardiovascular Disease

Plasma triglyceride levels are an independent risk factor for cardiovascular disease (Rosenson, ACC, 2014)

- Genetic studies support causal relationship
- Independent of LDL-C or HDL-C

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ORIGINAL ARTICLE

Loss-of-Function Mutations in *APOC3* and Risk of Ischemic Vascular Disease

Anders Berg Jørgensen, M.D., Ph.D., Ruth Frikke-Schmidt, M.D., D.M.Sc., Børge G. Nordestgaard, M.D., D.M.Sc., and Anne Tybjærg-Hansen, M.D., D.M.Sc.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Loss-of-Function Mutations in *APOC3*, Triglycerides, and Coronary Disease

The TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute*

Genetic Validation

Loss of function mutations in *APOC3* associated with lower TGs and reduced incidence of coronary artery disease

Mean changes in lipid parameters in heterozygotes and homozygotes for *APOC3* LOF mutations versus non-carriers (all ethnicities)

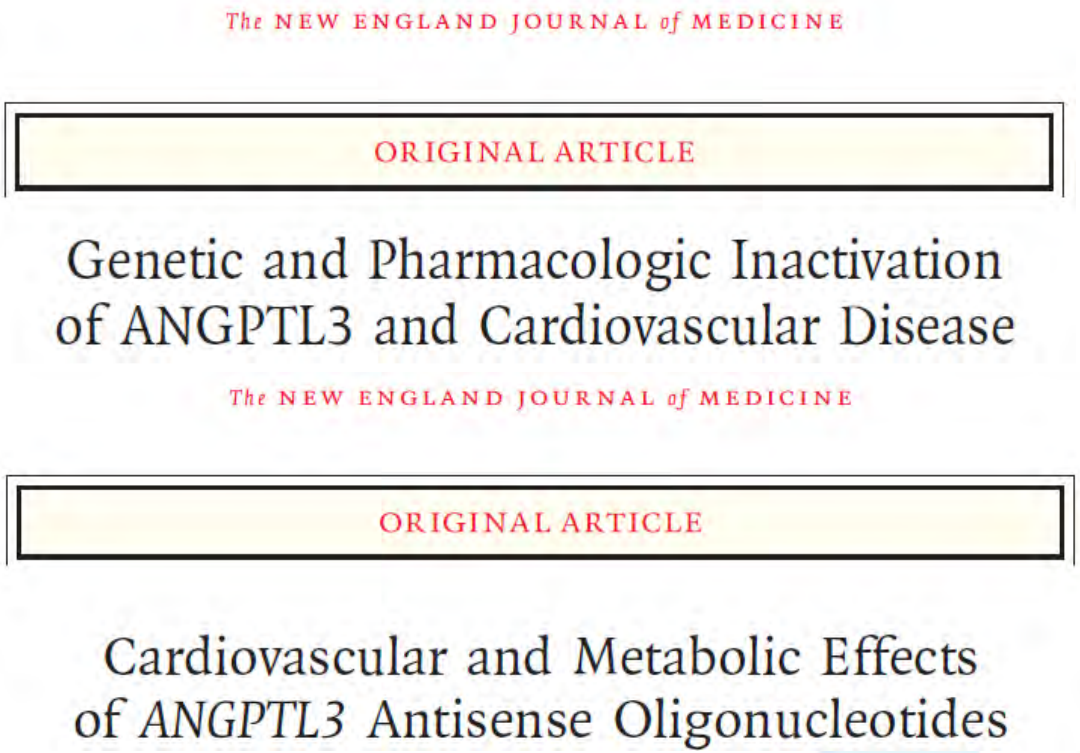
Serum Lipid Metric	***APOC3* deficient heterozygote** (TG working group, NEJM 2014)	***APOC3* deficient homozygote*** (Saleheen et al., 2016)
APOC3 levels	-46%	-89.4%
Triglycerides	-39%	-61.7%
LDL-C	-16%	Similar
HDL-C	+22%	+28%
CAD risk	-40%	Not reported
Adverse Phenotype	None based on genetic studies	None described

* Based on four human homozygotes

arrowhead pharmaceuticals

Other Lipid Targets of Interest

- ANGPTL3: liver synthesized inhibitor of lipoprotein lipase and endothelial lipase
  - Inhibition shown to lower serum LDL, serum and liver triglycerides
  - Early clinical and genetic validation as a novel target for CVD and possibly NASH



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ORIGINAL ARTICLE

Genetic and Pharmacologic Inactivation of ANGPTL3 and Cardiovascular Disease

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ORIGINAL ARTICLE

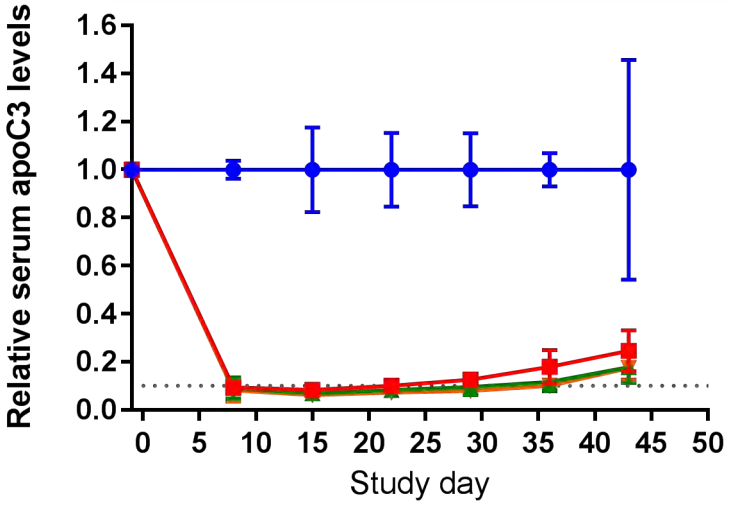
Cardiovascular and Metabolic Effects of *ANGPTL3* Antisense Oligonucleotides

ARO-APOC3 and ARO-ANG3

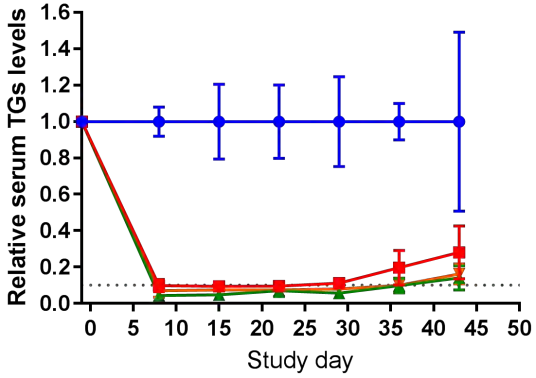
Single-dose Study in ApoC3 Transgenic Mice

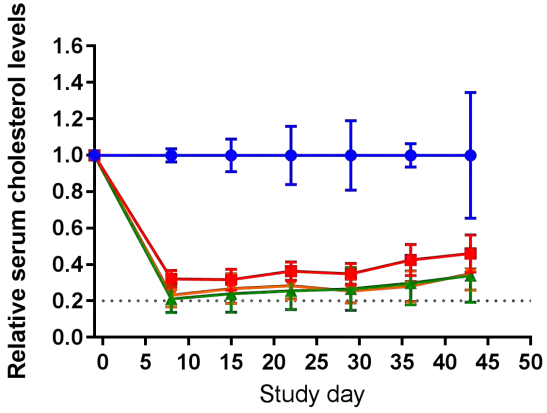
All dosed on study day 1 at 2 mpk

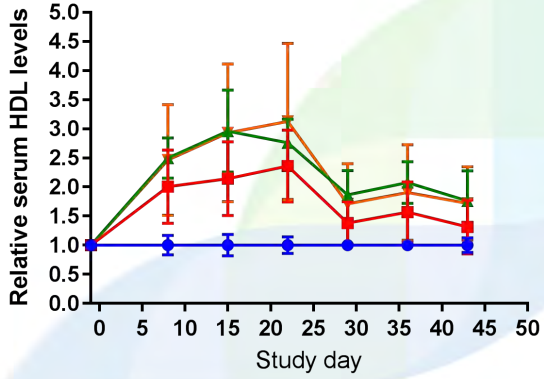
Data normalized to pre-dose and D5W control



- Deep KD after a single dose
- Max KD sustained for 3 weeks
- Expected effects on lipid profile



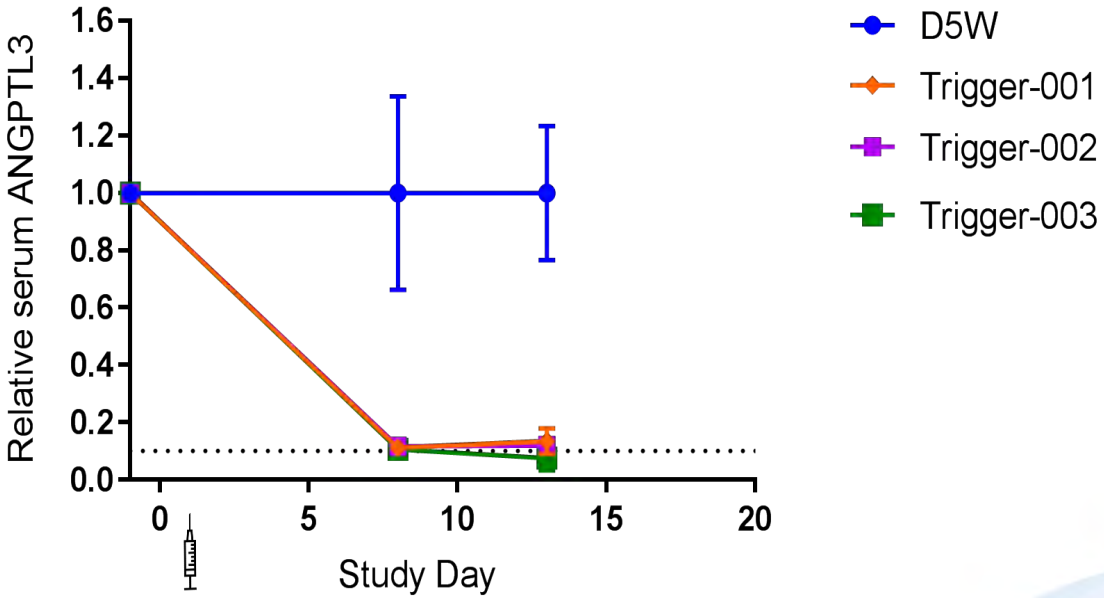




Fresh Data from our First AngPTL3 Mouse Study

All dosed on study day 1 at 3 mpk

Data normalized to pre-dose and D5W control



ARO-APOC3 and ARO-ANG3: Key Design Elements Expected

The Wish List:

- Subcutaneous dosing, monthly or less frequent
- No need for endosomal escape agent
- Full suppression of liver gene production
  - Deep and prolonged KD of triglyceride levels
  - Favorable effects on LDL
- Expectation of wide therapeutic index

CTA planned for one or both candidates by the end of 2018

Concluding Remarks
Chris Anzalone, Ph.D.

Value Proposition

All built on the TRiM™ Platform

- Modular
- Scalable
- Structurally simple
- Widely targetable

- **ARO-AAT and ARO-HBV in the clinic soon**
  - Potent in animal models
  - Wide safety margins expected
- **ARO-APOC3 and ARO-ANG3 are exciting additions to CV portfolio**
  - Orphan and large market opportunities
  - Wide safety margins expected
- **Using RNAi outside the liver is real now**
  - Tumor targeting has matured
  - Inhaled administration for lung delivery opens vast new opportunities

Pipeline

Drug	Indication	Pre-clinical	Pre-IND	Phase 1	Phase 2	Phase 3
ARO-AAT	Alpha-1 Antitrypsin Deficiency			CTA planned Q1 2018		
ARO-HBV	Hepatitis B			CTA planned Q2 2018		
ARO-APOC3	Hypertriglyceridemia		CTA planned Q4 2018			
ARO-ANG3	Hypertriglyceridemia		CTA planned Q4 2018			
ARO-Lung1	Undisclosed		CTA planned Q4 2018			
ARO-HIF2	Renal Cell Carcinoma		CTA planned 2019			
ARO-F12	Thrombosis/Hereditary Angioedema		Available for partnering			
ARO-LPA	Cardiovascular Disease		Partnered with Amgen			
ARO-AMG1	Cardiovascular Disease		Partnered with Amgen			

Q &A Session