Human Gene Protocol #1201-1144: *AAV8-mediated Low Density Lipoprotein Receptor Gene Replacement in Subjects with Homozygous Familial Hypercholesterolemia*

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RAC

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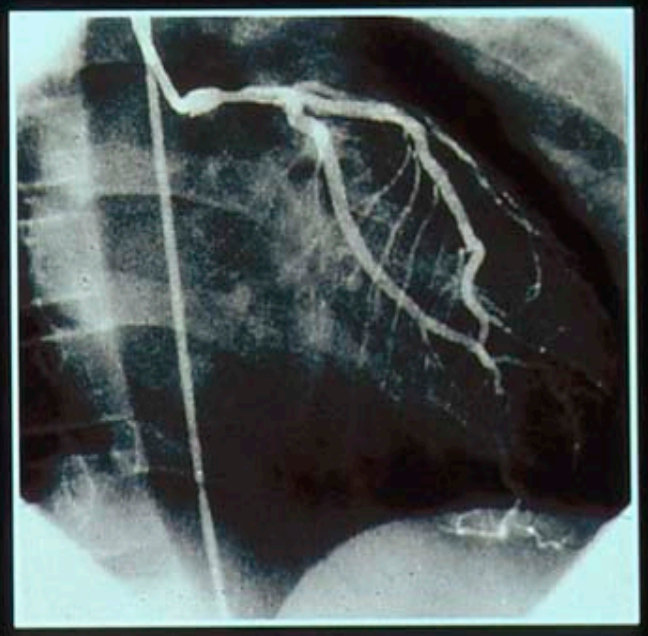
Familial Hypercholesterolemia

12 Y.O. Female

LDL cholesterol 760 mg/dL (normal < 130 mg/dL)



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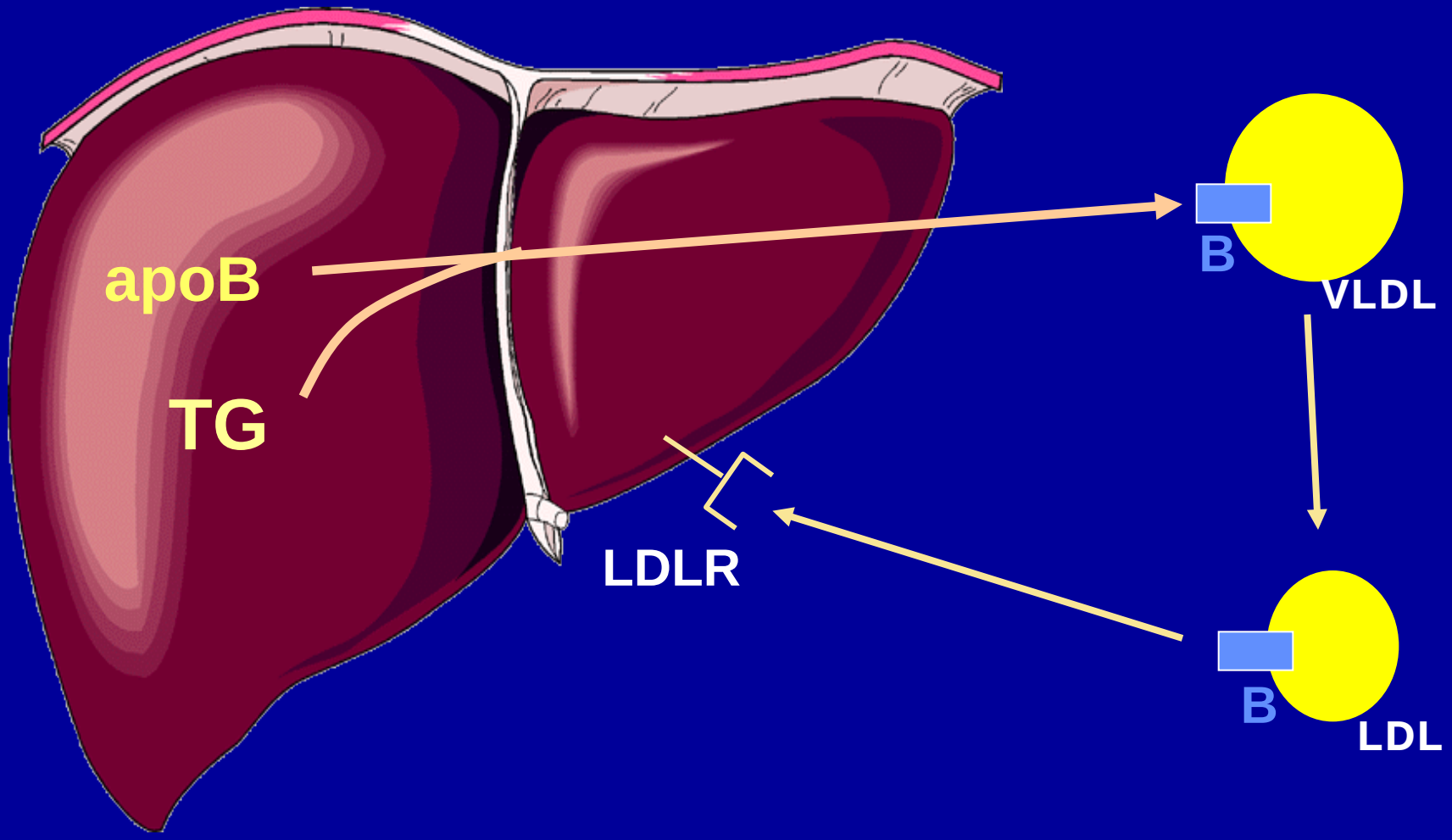
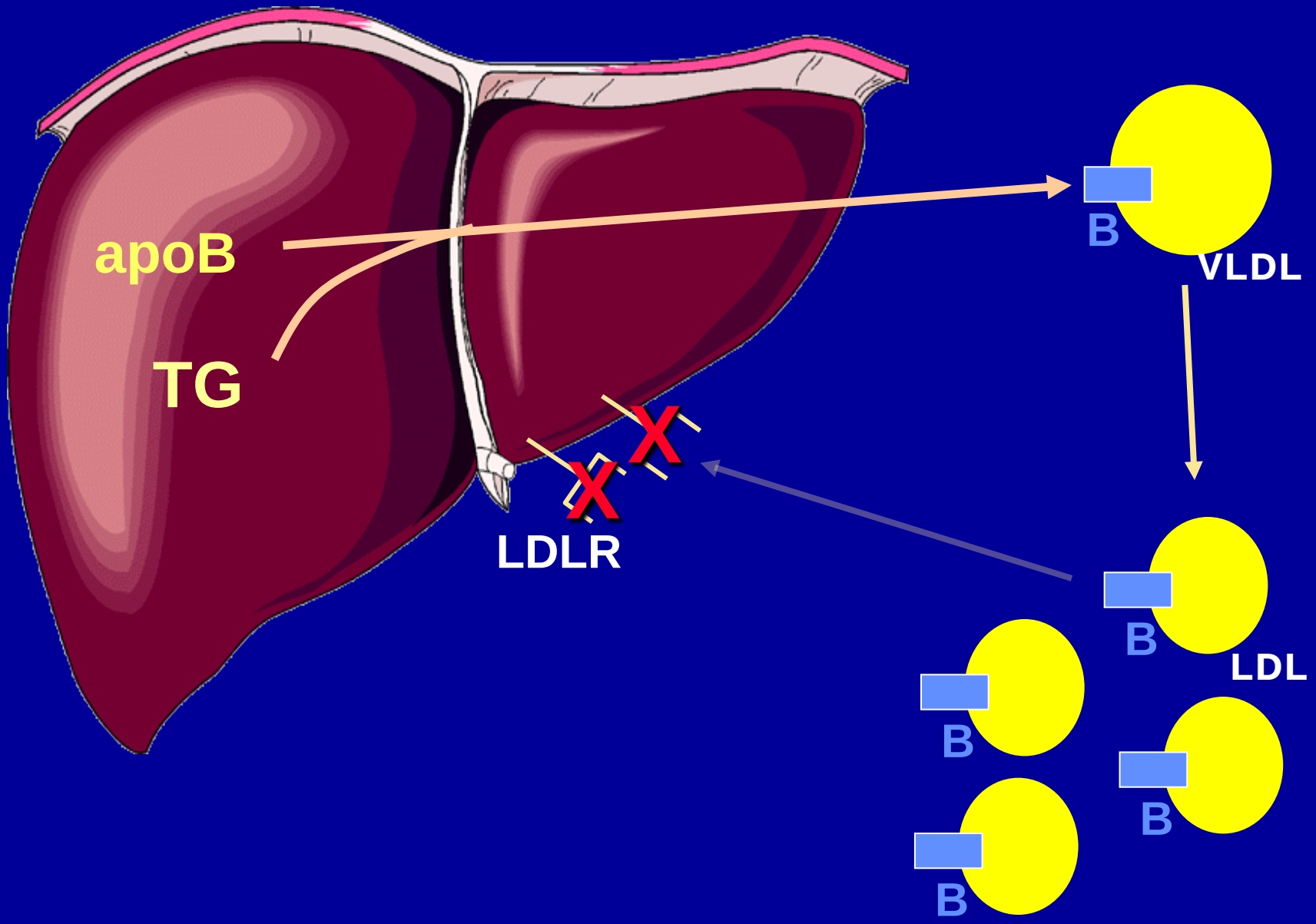
Regulation of LDL metabolism



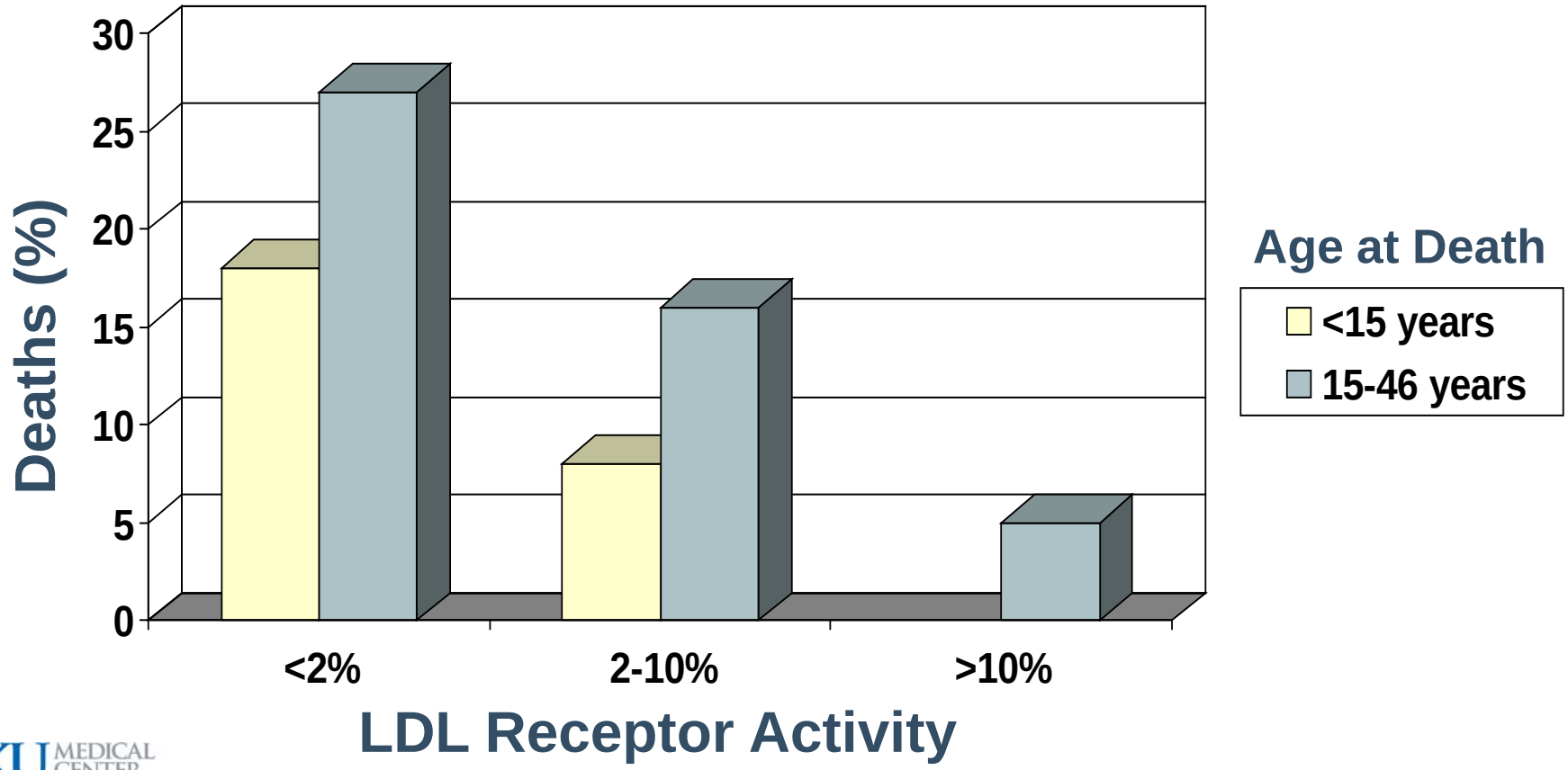
Impaired LDL catabolism in homozygous familial hypercholesterolemia (hoFH)



Homozygous FH

- **Loss of function mutations in both LDL receptor alleles**
- **Estimated prevalence 1:1 million**
- **> 1000 mutations in the LDL receptor reported to date**
- **Subtypes:**
  - Receptor negative: no functional LDLR activity
  - Receptor defective: up to 20% of normal LDLR activity

Mortality in Homozygous FH is influenced by LDL Receptor activity



Goldstein JL, Hobbes HH, Brown MS. Familial Hypercholesterolemia, 1993

LDL Receptor-Defective patients fare better than LDL Receptor-Negative patients

	LDLR Negative (n = 18)	LDLR Defective (n = 16)	p Value
Age at visit 1 (yrs)	11.5 (3.3–29)	28.1 (3.3–44.6)	0.0083
Age at first xanthomas (yrs)	2.0 (0.25–4)	7.0 (1–15)	0.0003
Age at FH diagnosis (yrs)	3.0 (0.5–7)	8.0 (2–17)	0.0005
Total cholesterol at diagnosis (mg/dl)	903 ± 187	715 ± 124	0.0019
Age at start of treatment (yrs)	5.0 (1.2–10)	16.0 (2–31)	0.0013
Age at CAD (yrs)	12.5 (6–16)	22.0 (16–37)	0.0039

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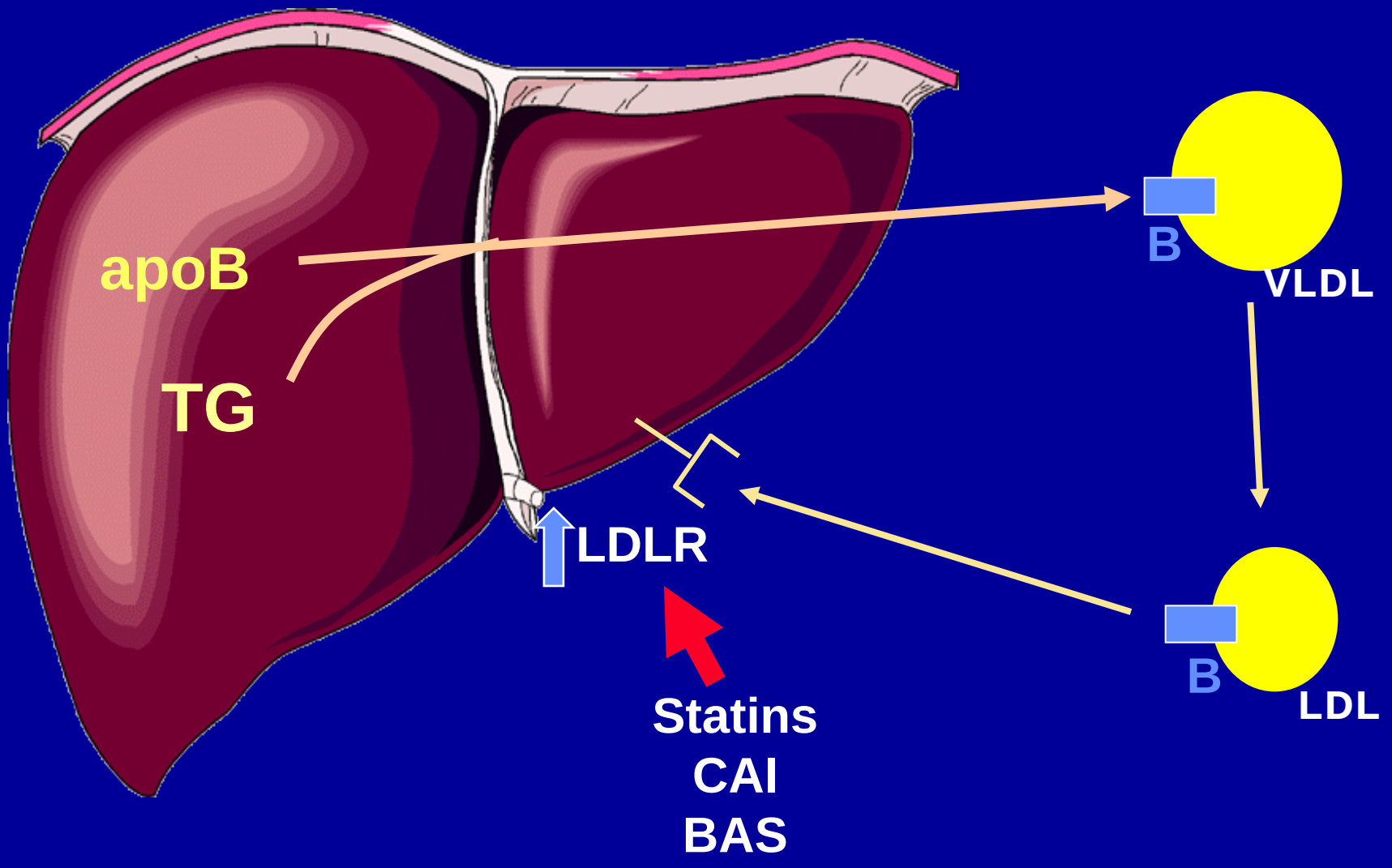
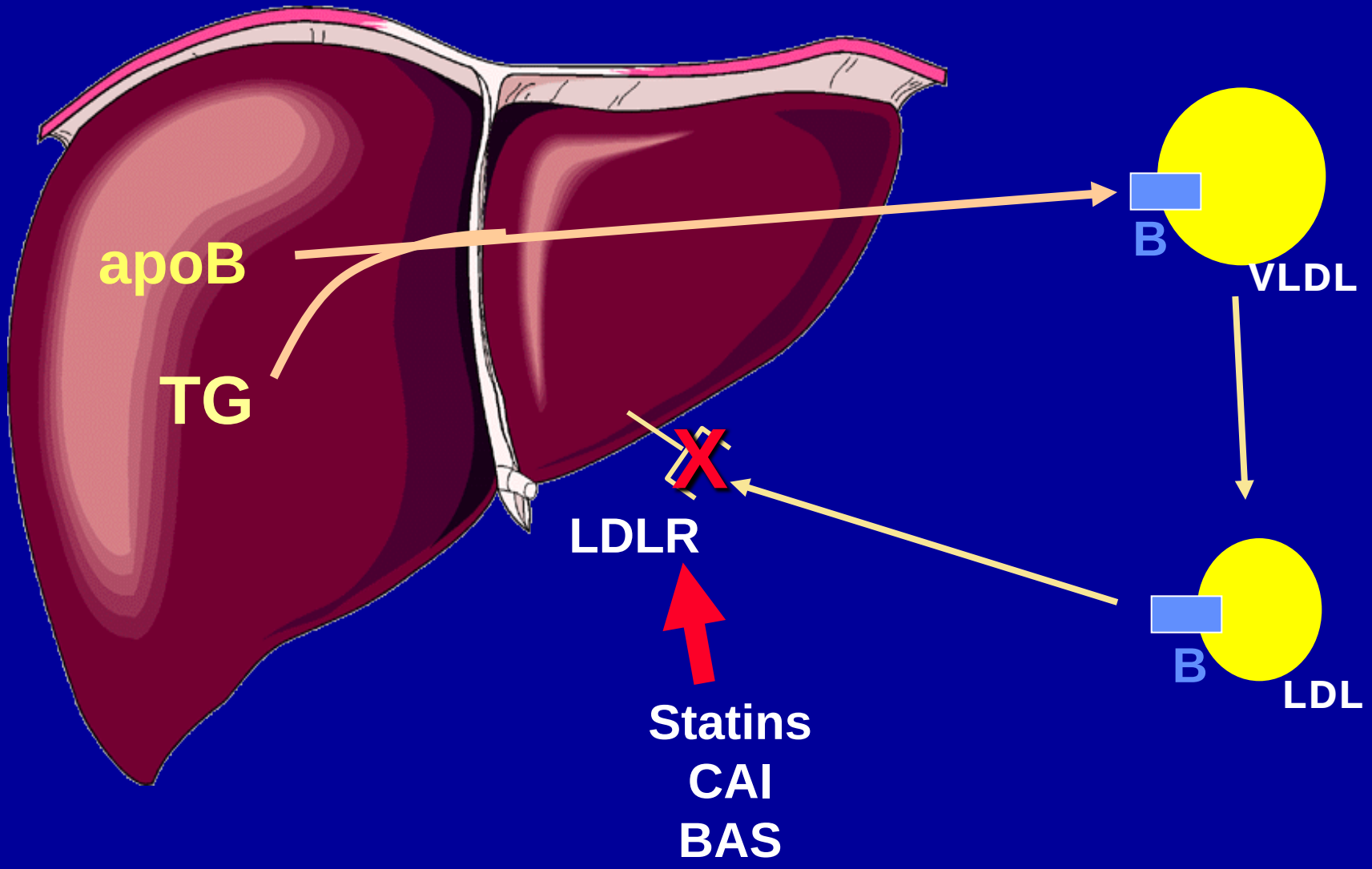
Kolansky, et al., Am J Cardiol, 102:1438-1443 (2008)

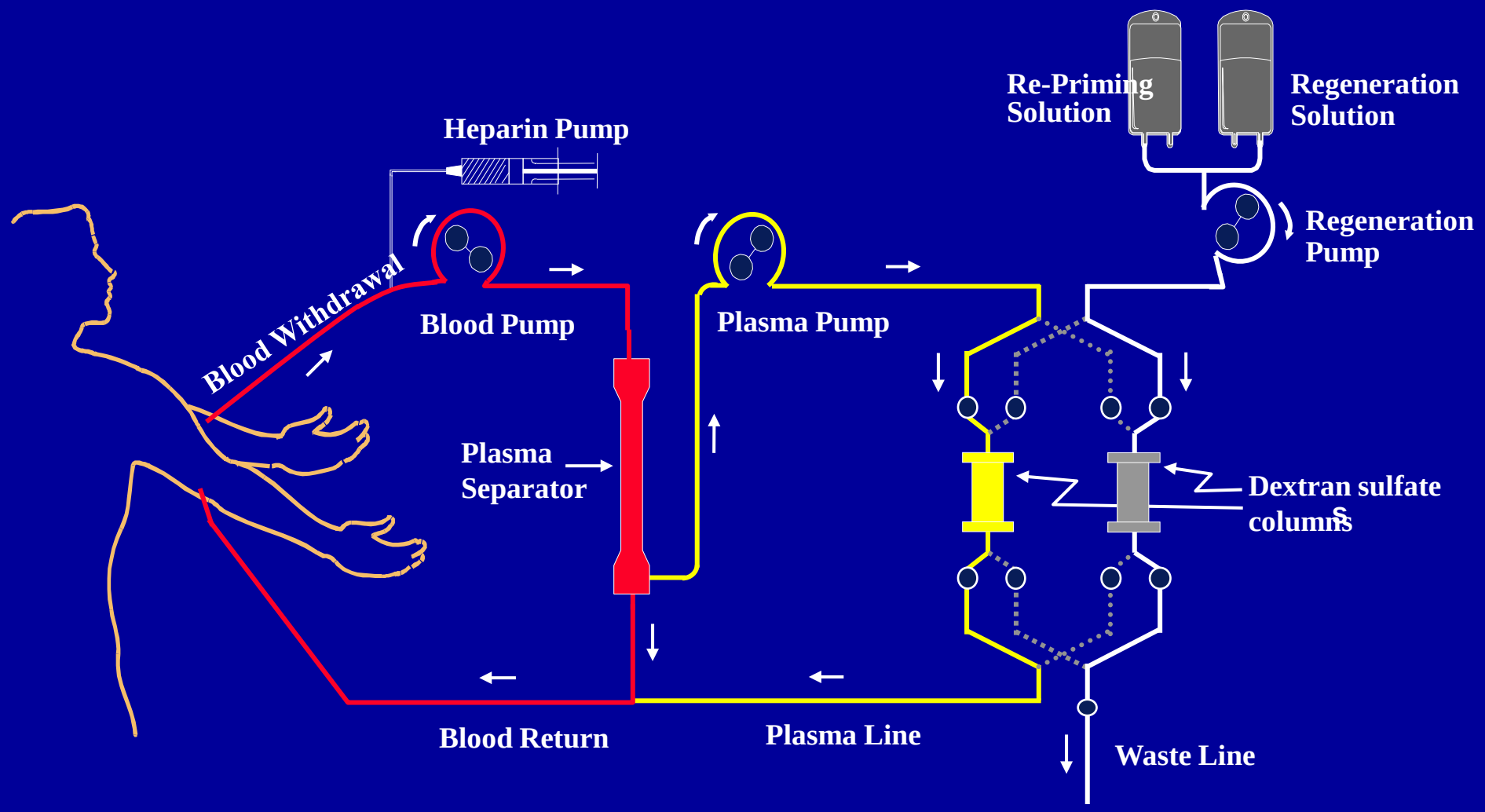
Current LDL-lowering therapies converge on upregulation of the hepatic LDL receptor



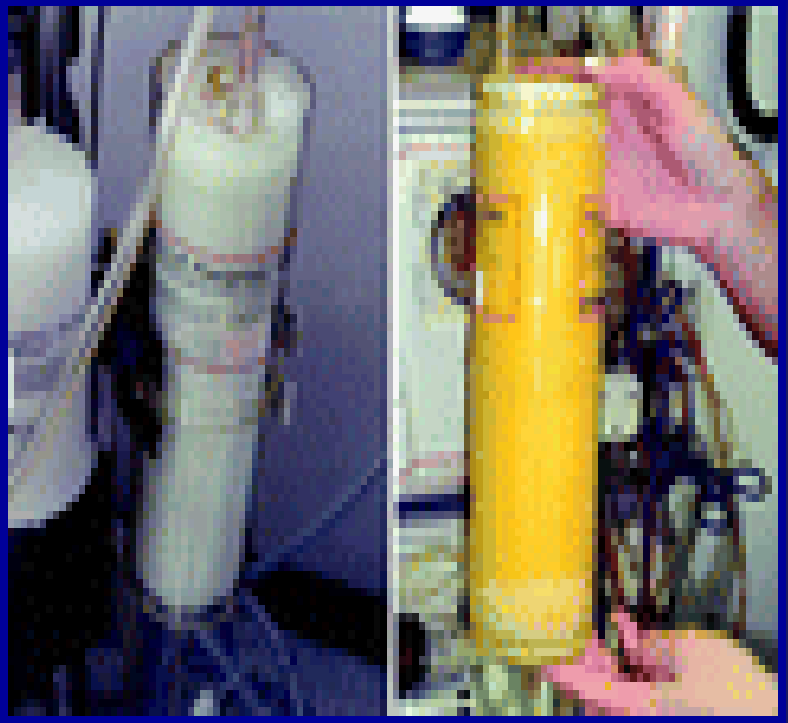
Patients without functional LDL receptors don't respond to drug therapy



LDL Apheresis



LDL apheresis purges the blood of LDL cholesterol



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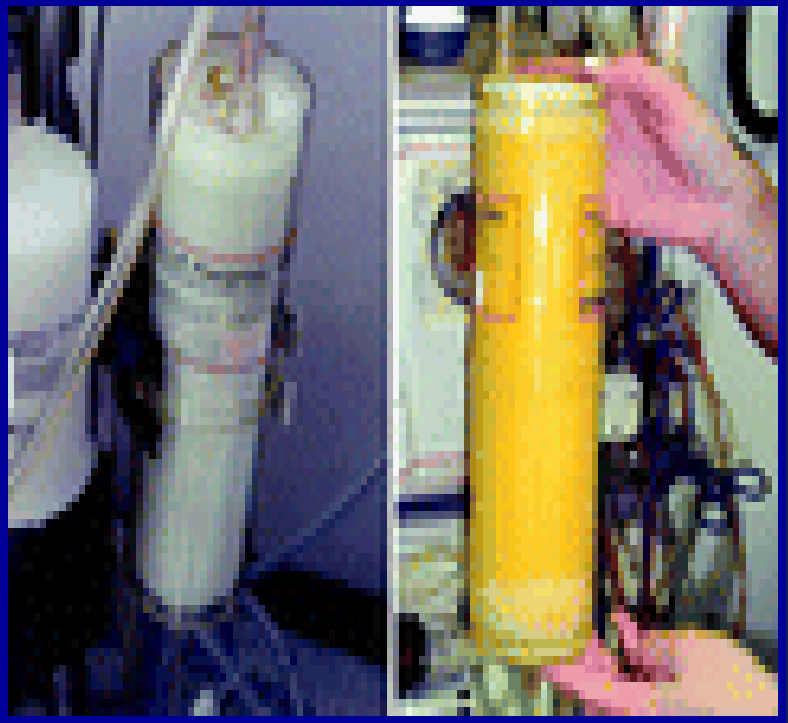
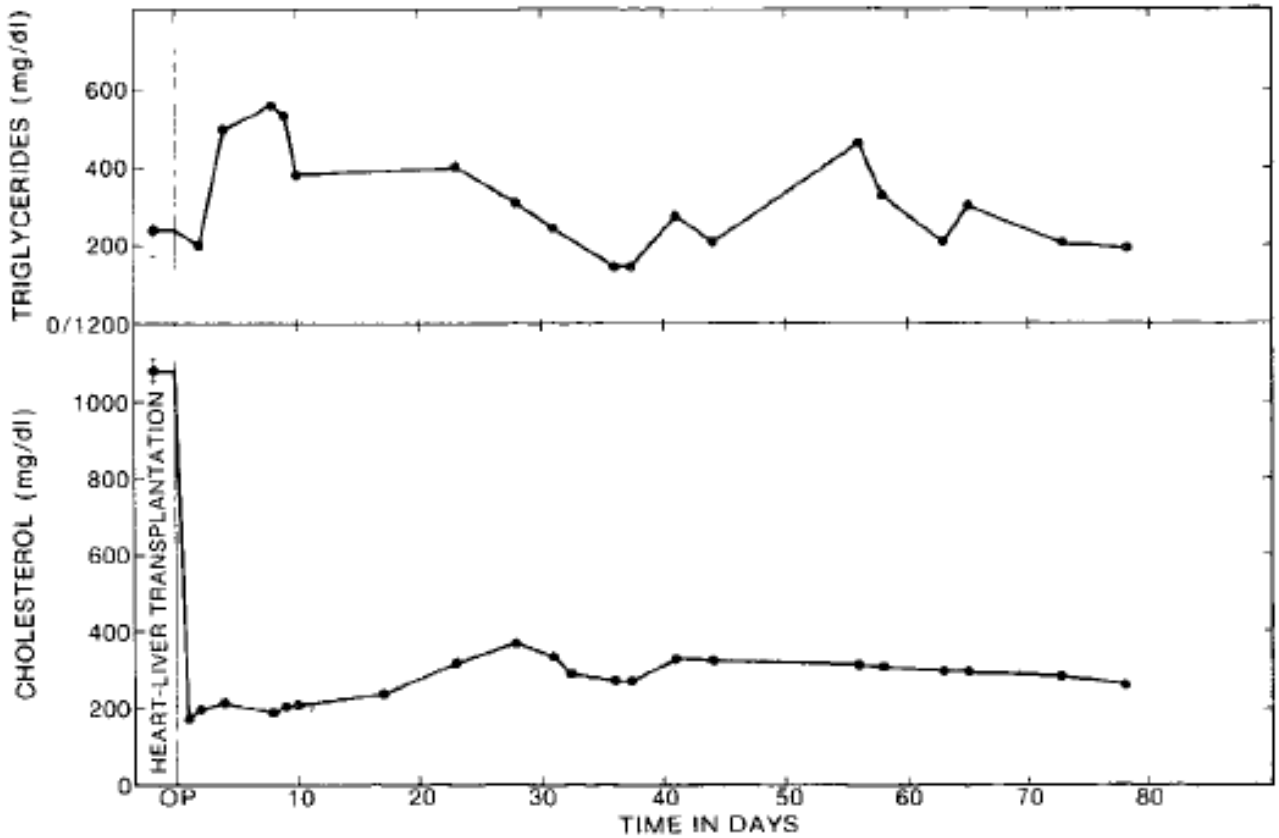


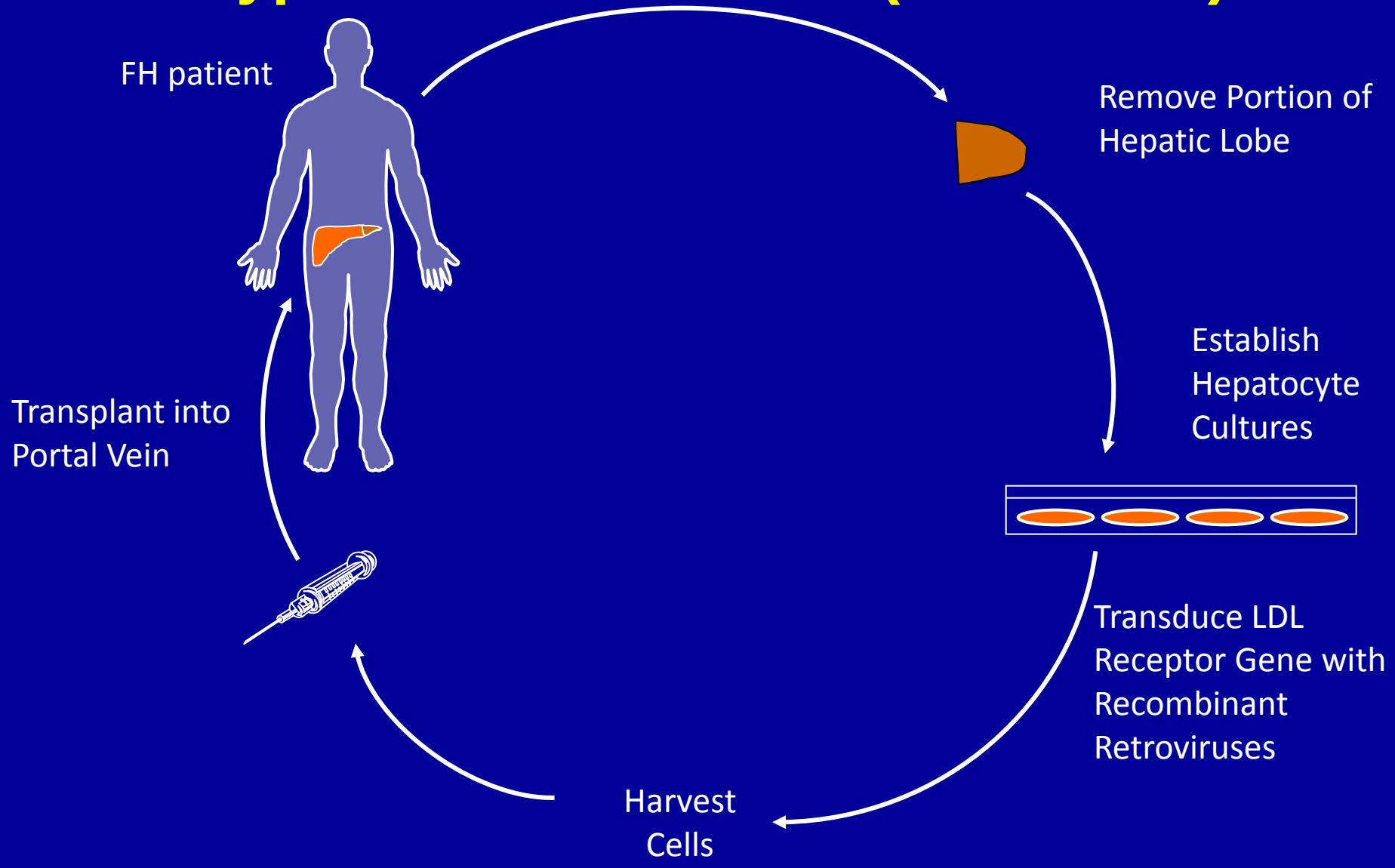
But LDL rebounds to baseline within 1-2 weeks

Liver transplantation markedly reduces LDL in patients with Familial Hypercholesterolaemia

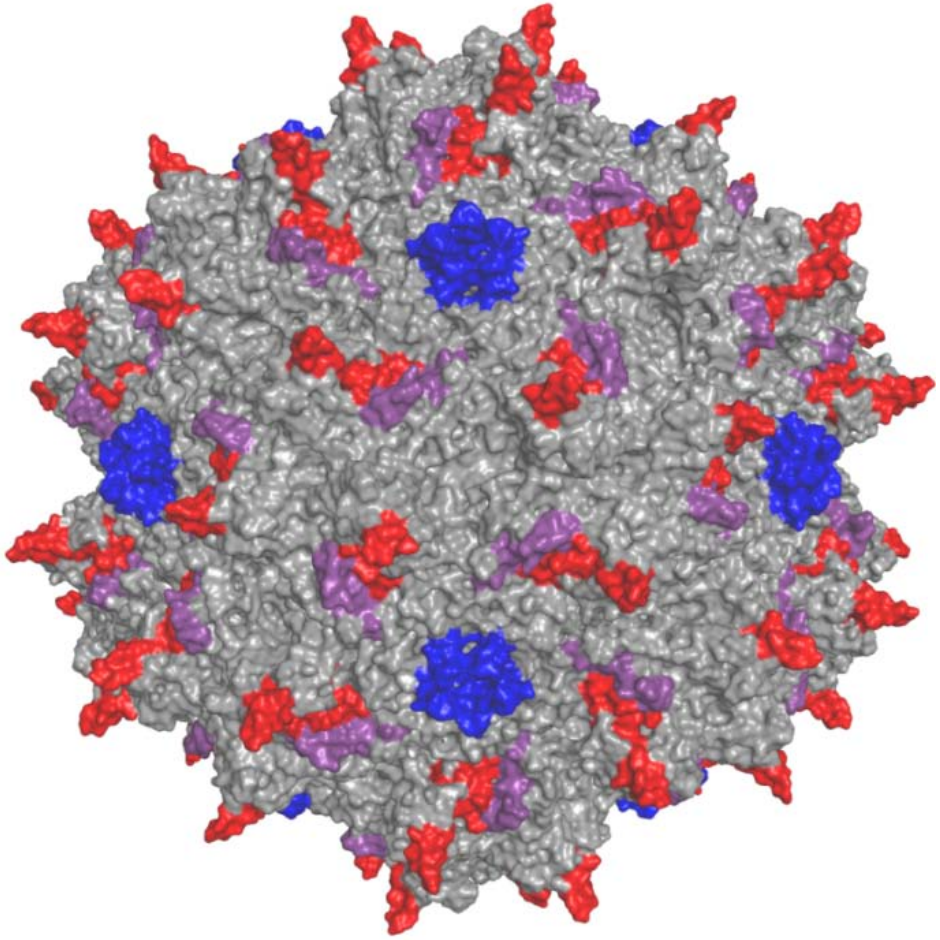


Plasma or serum cholesterol and triglyceride levels before and after liver-heart transplantation.

Ex Vivo Gene Therapy for Familial Hypercholesterolemia (1992-1995)



Adeno-associated viral vectors for in vivo liver-directed gene therapy



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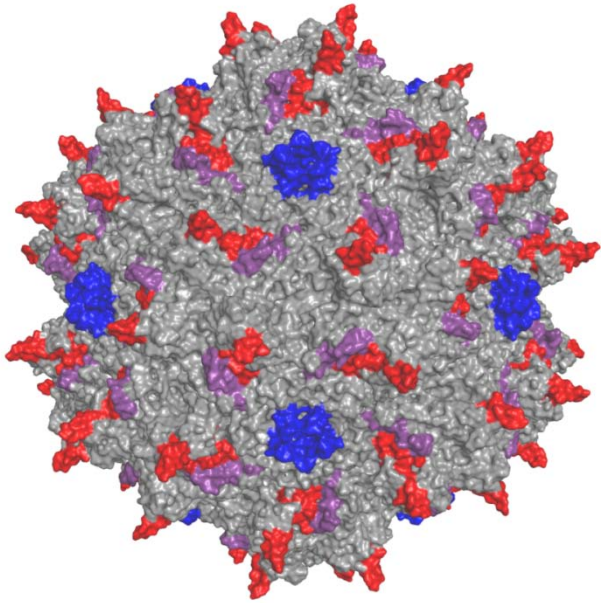
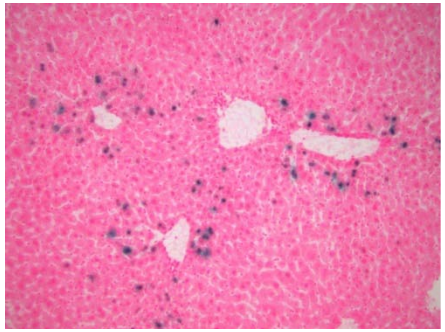
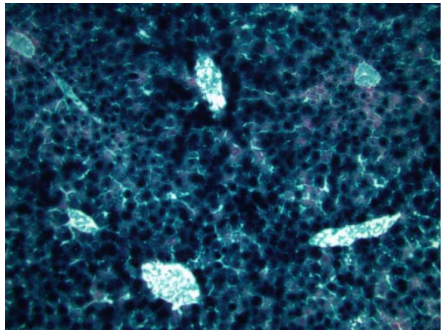
AAV8 is Vector of Choice in Liver



AAV2



AAV8



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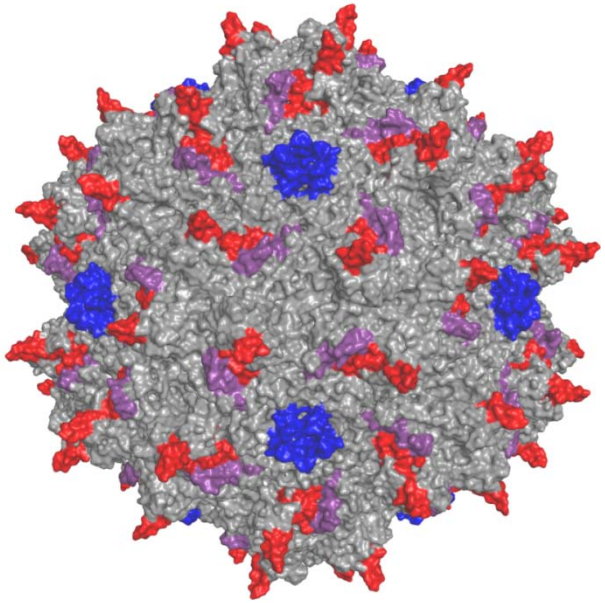
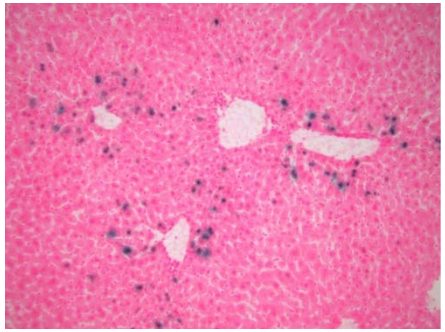
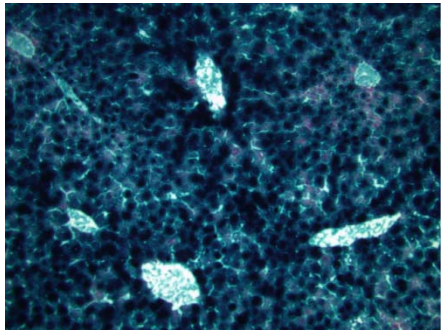
AAV8 – Vector of Choice in Liver



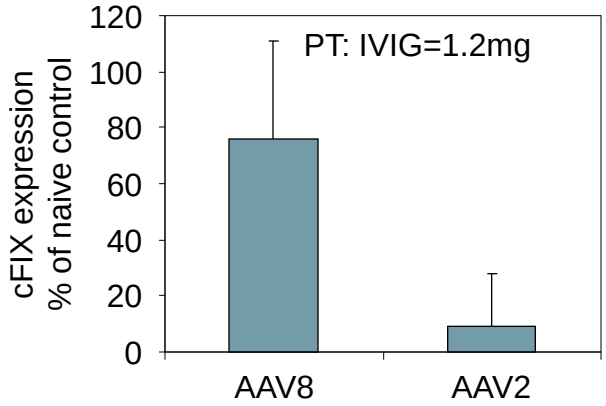
AAV2



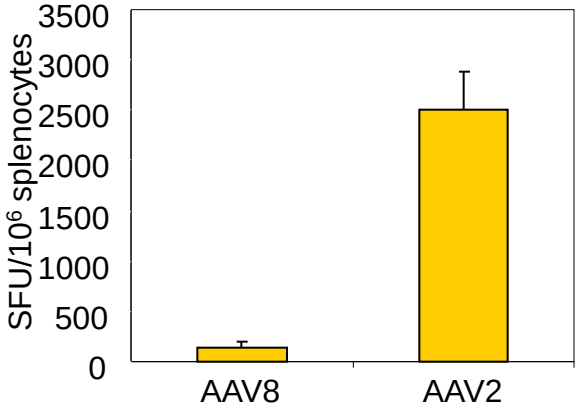
AAV8



NAb



Capsid T cell (d7)



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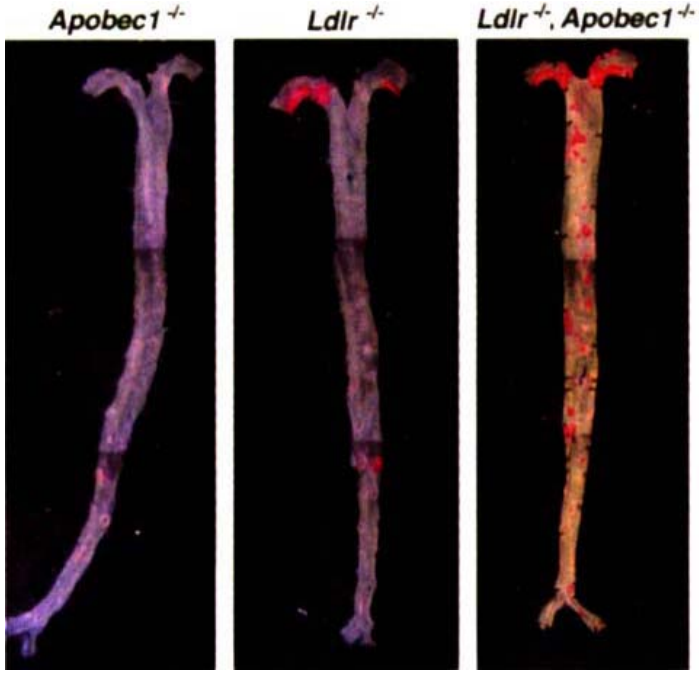
Murine model of homozygous FH: LDLR$^{-/-}$ Apobec1$^{-/-}$ (DKO) Mice

A mouse model of human familial hypercholesterolemia: Markedly elevated low density lipoprotein cholesterol levels and severe atherosclerosis on a low-fat chow diet

Lyn Powell-Braxton[1], Murielle Véniant[2], Richard D. Latvala[1], Ken-Ichi Hirano[3], Wesley B. Won[1], Jed Ross[1], Noel Dybdal[1], Constance H. Zlot[2], Stephen G. Young[2] & Nicholas O. Davidson[3,4]

Nature Medicine, 1998, p. 934-938



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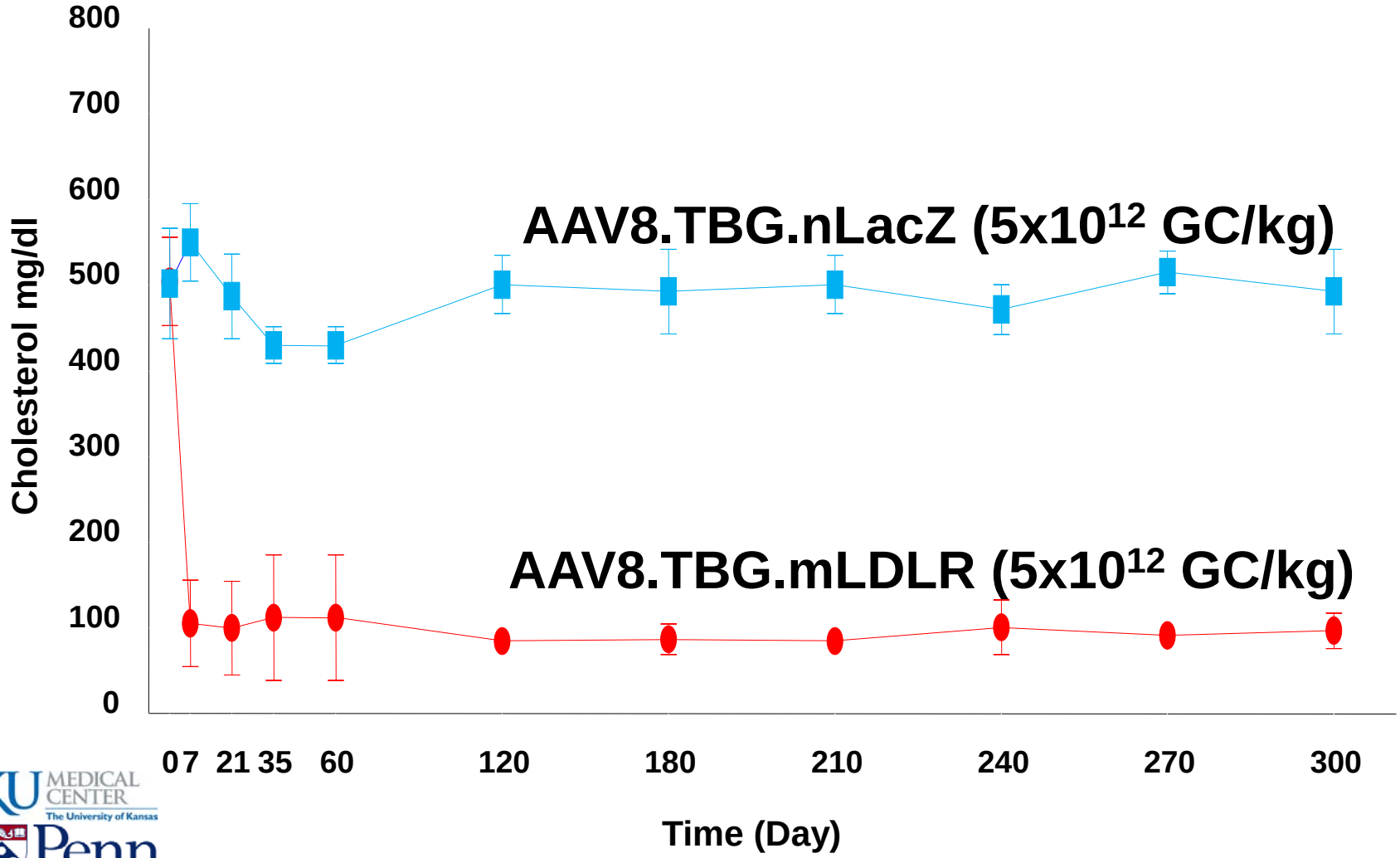
AAV8.TBG.mLDLR confers stable correction of cholesterol levels in LDLR$^{-/-}$ Apobec1$^{-/-}$ (hoFH) mice



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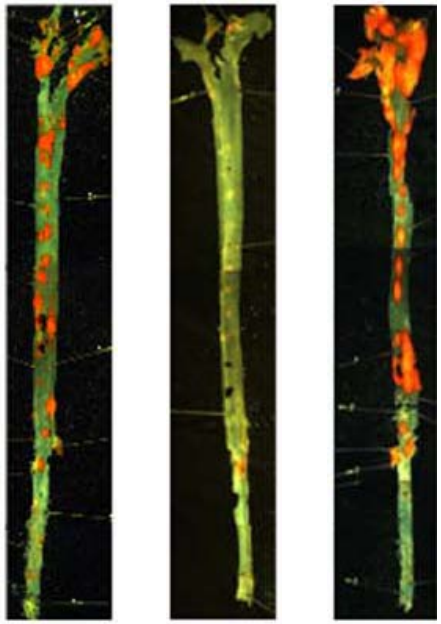
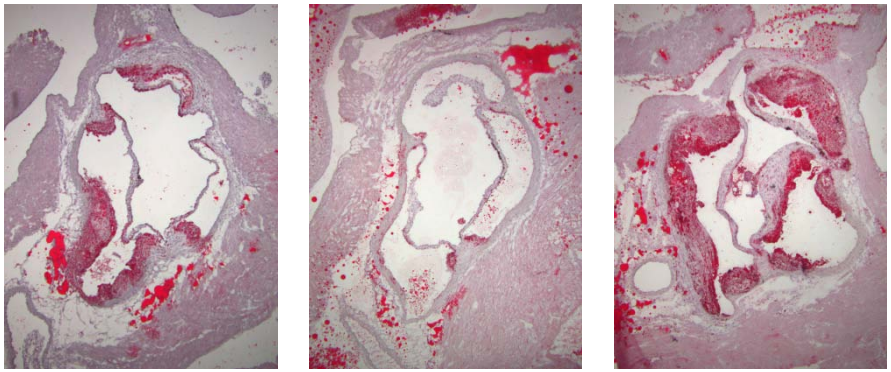
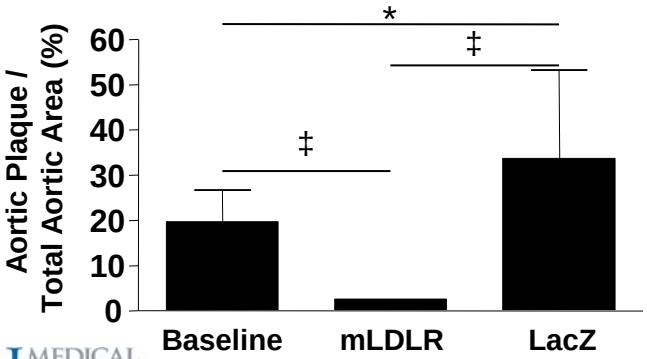
AAV8.TBG.mLDLR induces regression of atherosclerosis in LDLR$^{-/-}$ Apobec1$^{-/-}$ (hoFH) mice

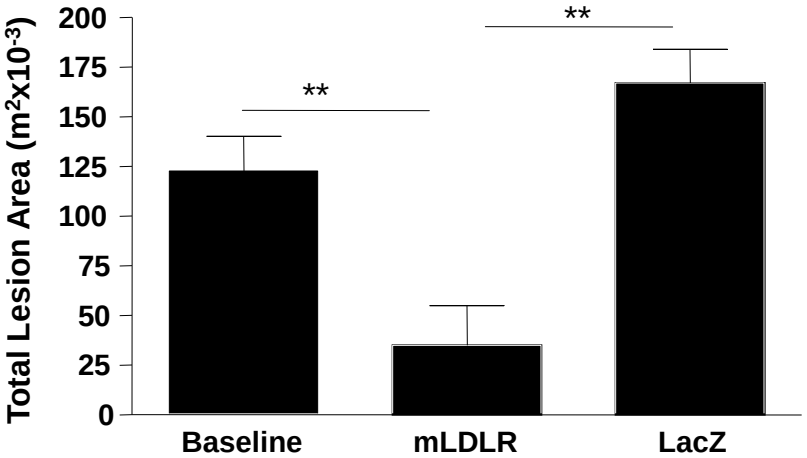


Baseline mLDLR LacZ



Baseline mLDLR LacZ





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Features of AAV8.TBG.hLDLR Phase I clinical trial in homozygous FH

1) Eligibility Criteria
   - Homozygous FH—clinical and molecular
   - Adults age ≥ 18
   - AAV8 NAb < 1:20
   - No cardiac event within 6 months

2) Design
   - Open label dose escalation (3+3 design)
   - Total subjects = 12 – 18
   - Primary endpoints – safety
   - Secondary endpoints – serum LDL and LDL turnover

3) Protocol
   - Screening ICD – remote
   - Vector infusion ICD – KUMC
     - Visit 1 : Time -1 month
       - Consent
       - Withdraw baseline therapy
     - Visit 2 : Time 0
       - Baseline LDL kinetic study
       - Dosing of vector
     - Visit 3 : Time +3 months
       - Kinetic study
       - Re-initiate baseline therapy

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Dosing for AAV8.TBG.hLDLR Phase I FH Clinical Trial

1) Preclinical Studies

   MTD > 10^{13} GC/kg

   MED = 0.5 to 1.5×10^{11} GC/kg

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Dosing for AAV8.TBG.hLDLR Phase I FH Clinical Trial

1) Preclinical Studies

   MTD > 10^{13} GC/kg

   MED = 0.5 to 1.5×10^{11} GC/kg

2) Human dosing

	FH	
	GC/kg	Particles/kg
Low	3×10^{11}	3×10^{11}
Medium	10^{12}	10^{12}
High	3×10^{12}	3×10^{12}

- Low dose is higher than preclinical MED
- High dose is lower than preclinical MTD

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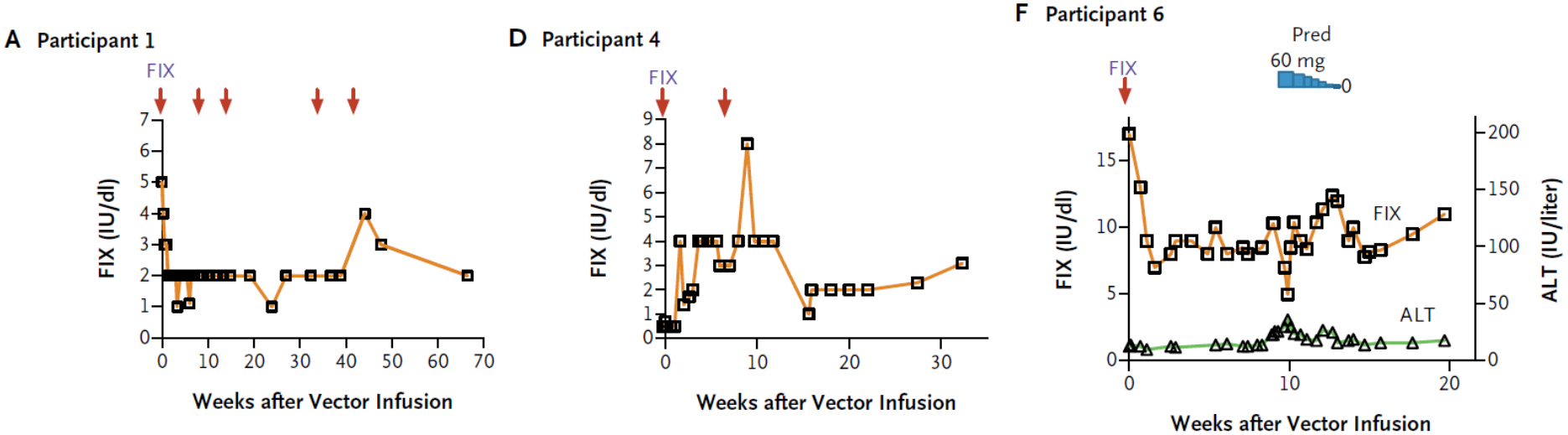
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adenovirus-Associated Virus Vector–Mediated Gene Transfer in Hemophilia B



Dose (GC/kg)	$2x10^{11}$	$6x10^{11}$	$2x10^{12}$
Capsid T cell	0/2	2/2	2/2
↑ LFTs	0/2	0/2	1/2

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Nathwani, et al., N Engl J Med 2011; 365:2357-2365.

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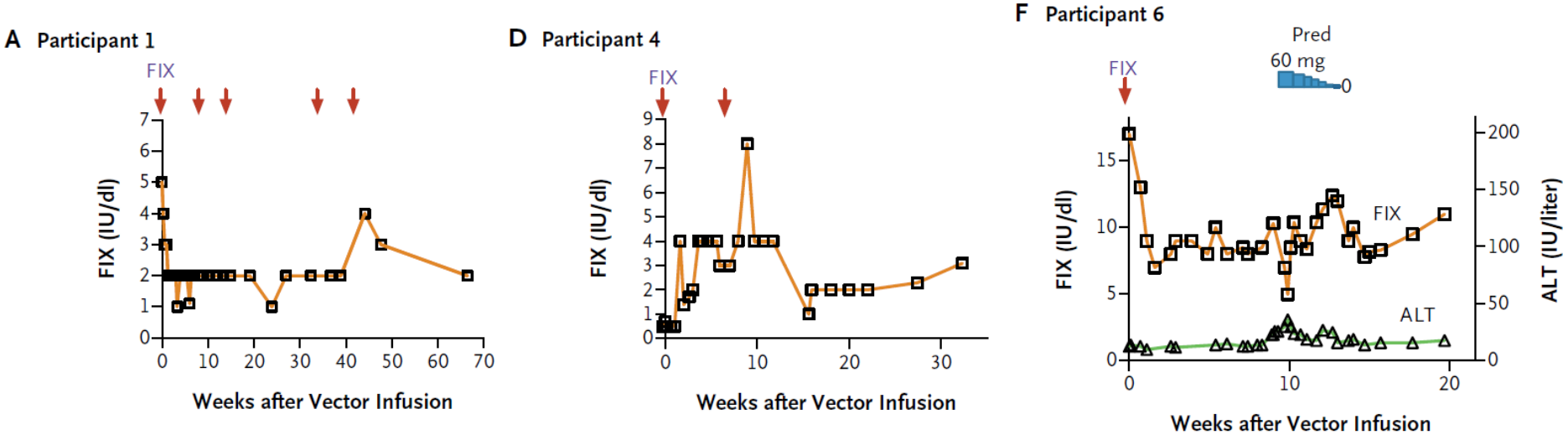

Particles/kg[1]	**10^{12}**	**$3x10^{12}$**	**10^{13}**
Dose (GC/kg)	$2x10^{11}$	$6x10^{11}$	$2x10^{12}$
Capsid T cell	0/2	2/2	2/2
↑ LFTs	0/2	0/2	1/2

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[1]Allay, J.A., et al., *Good manufacturing practice production of self-complementary serotype 8 adeno-associated viral vector for a hemophilia B clinical trial.* Hum Gene Ther, 2011. **22**(5): p. 595-604.

Dosing for AAV8.TBG.hLDLR Phase I FH Clinical Trial

1) Preclinical Studies

   MTD > 10^{13} GC/kg

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2) Human dosing

	FH		Hemophilia	
	GC/kg	Particles/kg	GC/kg	Particles/kg
Low	3×10^{11}	3×10^{11}	2×10^{11}	10^{12}
Medium	10^{12}	10^{12}	6×10^{11}	3×10^{12}
High	3×10^{12}	3×10^{12}	2×10^{12}	10^{13}

- Particle load in hemophilia study was 3-fold higher at each cohort than in planned FH study

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Dosing for AAV8.TBG.hLDLR Phase I FH Clinical Trial

1) Preclinical Studies

   MTD > 10^{13} GC/kg

   MED = 0.5 to 1.5×10^{11} GC/kg

2) Human dosing

	FH		Hemophilia	
	GC/kg	Particles/kg	GC/kg	Particles/kg
Low	3×10^{11}	3×10^{11}	2×10^{11}	10^{12}
Medium	10^{12}	10^{12}	6×10^{11}	**3×10^{12}**
High	3×10^{12}	**3×10^{12}**	2×10^{12}	10^{13}

- Particle load in medium dose in hemophilia study is similar to highest dose in planned FH study

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Questions

1) Are there potential clinical consequences of withdrawing lipid lowering therapies for 4 months?

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1) Immunotoxicity – capsid T cells
   - Will we detect pre-existing T cells to capsid?
   - If so, will this affect eligibility?
   - Do we expect to see capsid T cells following vector?
   - Do we think they will be pathogenic?
   - How will we treat toxicity?