

Mouse Models of Diabetic Macrovascular Disease

RU/Columbia/NYU Group

- 1. “Create new mouse models of diabetes”
Markus Stoffel-RU**
- 2. “Create mouse models of diabetic
dyslipidemia” Ira Goldberg-Columbia**
- 3. “Effect of diabetes on atherosclerosis
progression” Jan Breslow-RU**
- 4. “Effects of diabetes on atherosclerosis
regression/remodeling” Ed Fisher-NYU**
- 5. “Effect of diabetes on arterial
injury/restenosis” Hayes Dansky-Columbia**

Major Goal: Create Mouse Model Diabetes Worsens Atherosclerosis

Strategy:

- 1. Create mice with diabetic dyslipidemia**
- 2. Cross with models of hyperglycemia,
insulin resistance or both**
- 3. Assess effects on atherosclerosis
progression, regression and response to
arterial injury**

Platform Model: C57BL/6J LDLR-/- Mouse

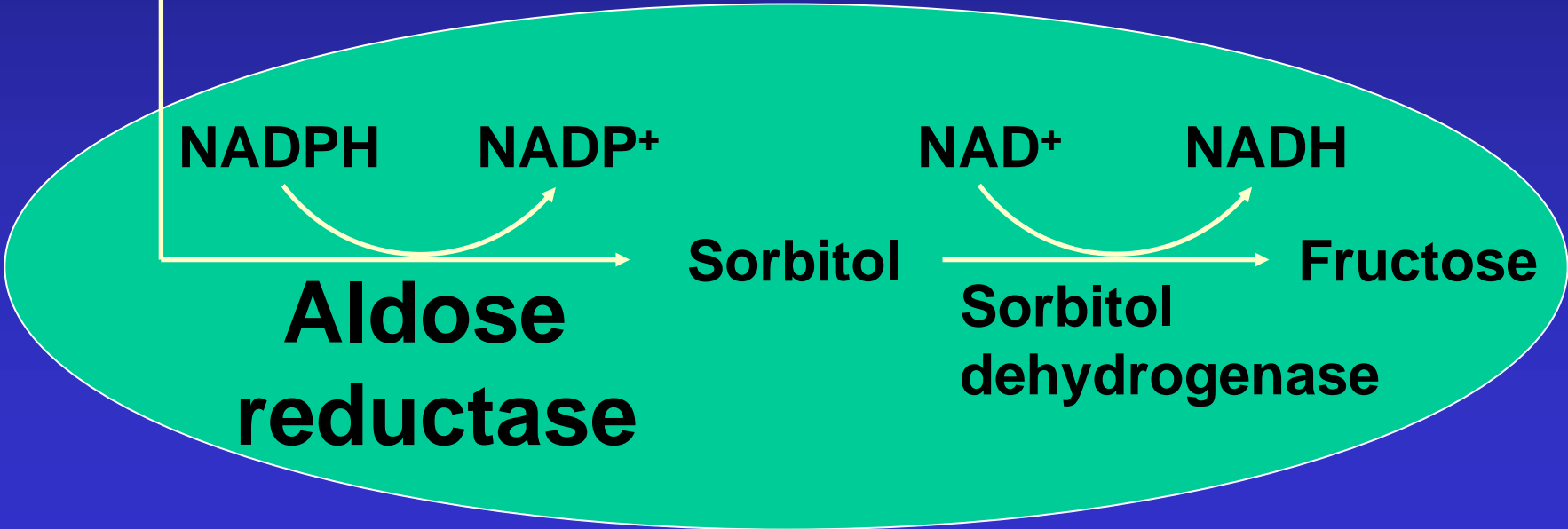
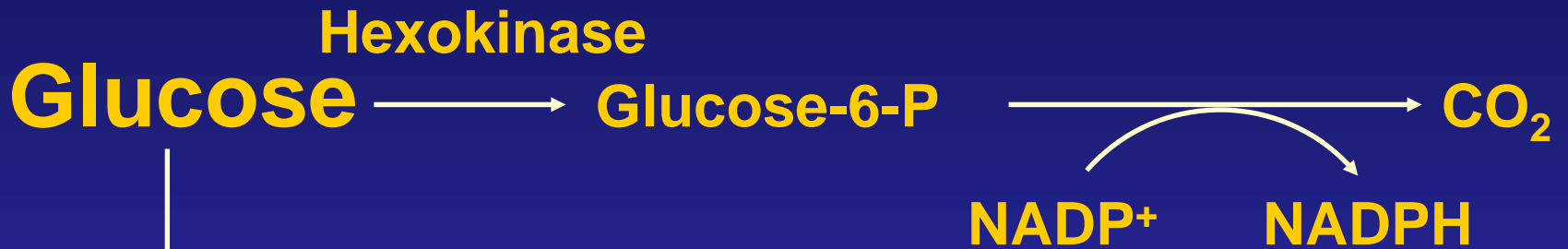
- **Hyperglycemia: STZ; Pdx1+/-**
- **Insulin Resistance: Akt2-/-; Foxa2T156A-DN**
- **Combination: Ob/Ob**
- **Sensitizer: HuARTg (Japan to Michigan)**

Standardization of dietary approach and lesion analysis

- **Effects of low-fat, semisynthetic diets containing increasing amounts of cholesterol in C57BL/6J and FVB/N LDLR^{-/-} mice**
- **Compare lesion development in aortic root, BCA and whole aorta (en face)**
- **Conclusions: Lesion acceleration on low fat diet without complications of weight gain from high fat diet and best site for routine lesion quantitation is the aortic root**

Diabetic Dyslipidemia

- **Diabetic dyslipidemia mimicked by: LDLR-/-, LDLR-/-apoAI-/-, HuBTg, HuCETPTg, LPL+/- and high fat-high cholesterol diets**
- **Mice made hyperglycemic with low dose STZ protocol**
- **No evidence of diabetes effect on atherosclerosis progression, exclusive of lipid abnormalities**
- **Hypothesis: A gene present in humans but not mice mediates toxic effect of diabetes/hyperglycemia**



Human Aldose Reductase Transgene: Expression Restorative Not Pharmacological

Heart mRNA Northern Blot



Study Design (in progress)

LDLR^{-/-} mice X HuARTg mice

LDLR^{-/-}-HuARTg vs. LDLR^{-/-}
Con & STZ

LDLR^{+/-}-HuARTg vs. LDLR^{+/-}
Con & STZ

0.5% cholesterol diet

0.02% Chol

Chow diet

Paigen diet

6 wks

8 wks

12 wks

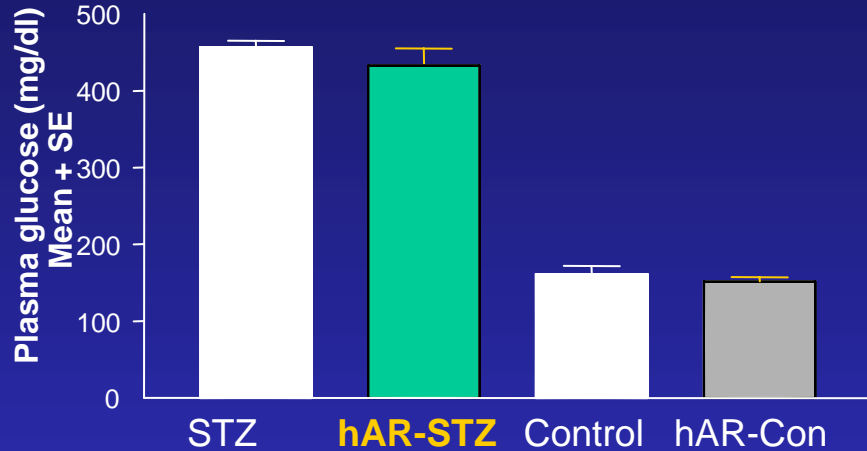
12 wks

12 wks

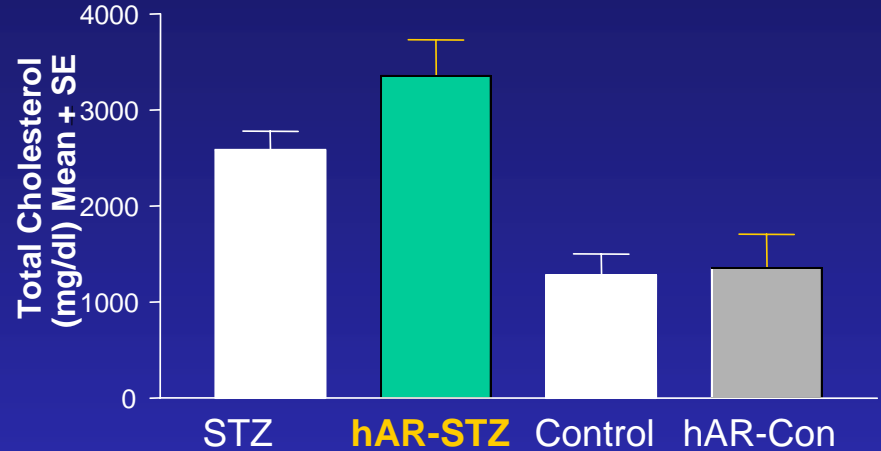
12 wks

Plasma glucose and lipids after 6 weeks on 0.5% cholesterol diet – all LDLR-/-

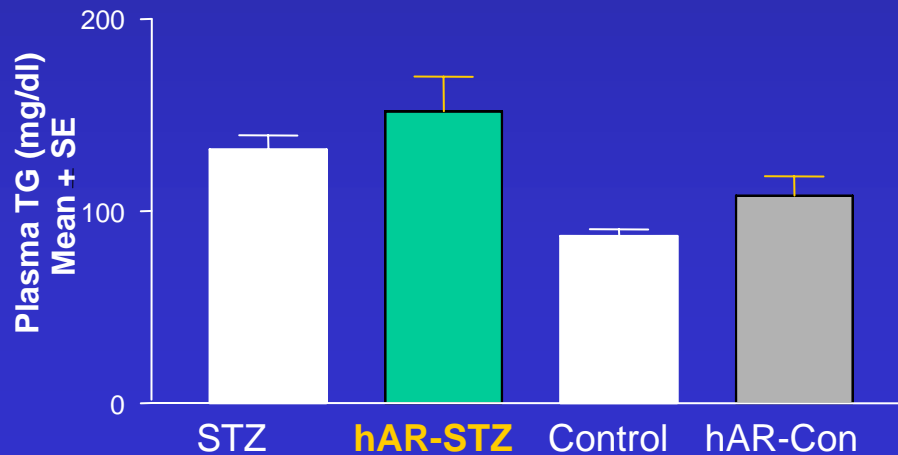
Plasma glucose



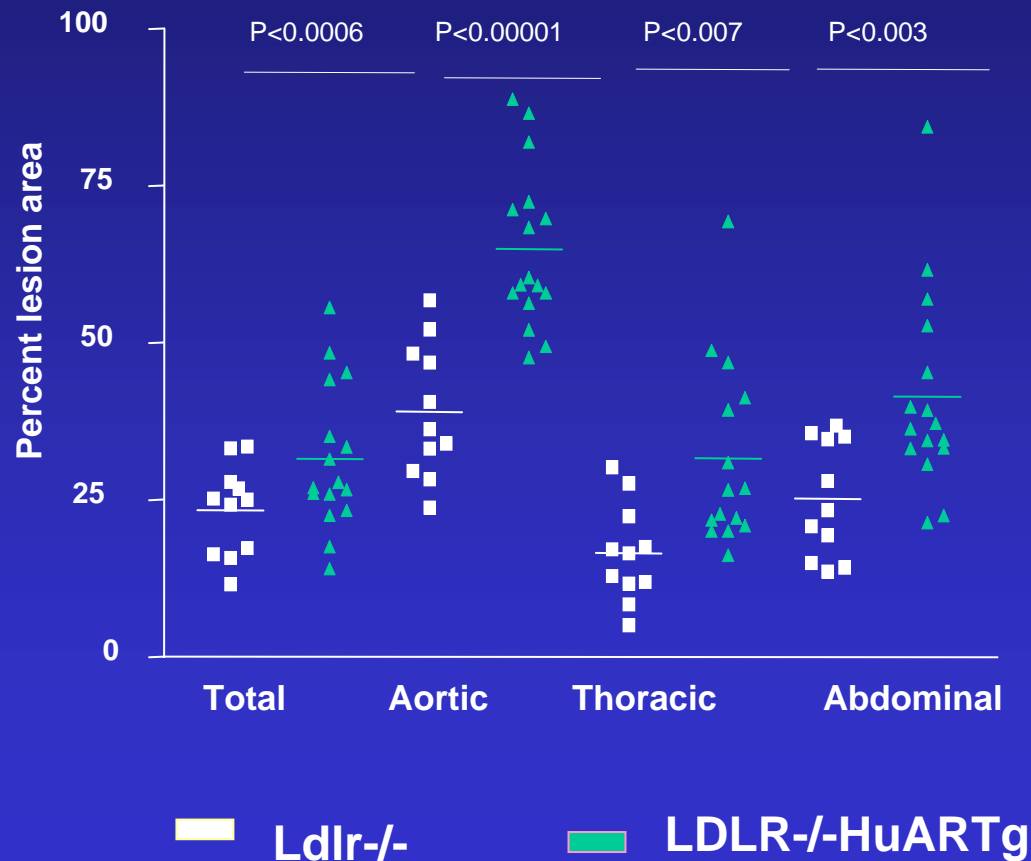
Total cholesterol



Triglyceride



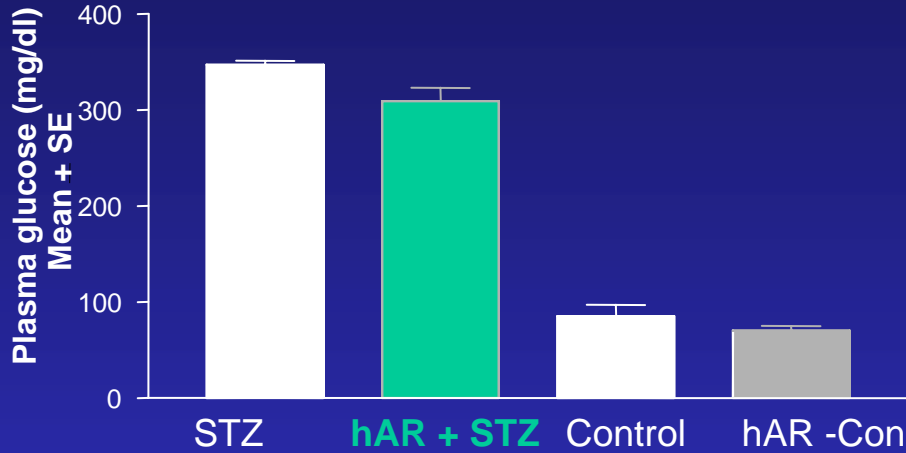
LDLR^{-/-} mice without or with HuARTg STZ diabetes fed 0.5% chol diet (6 wks) En Face Lesion Area



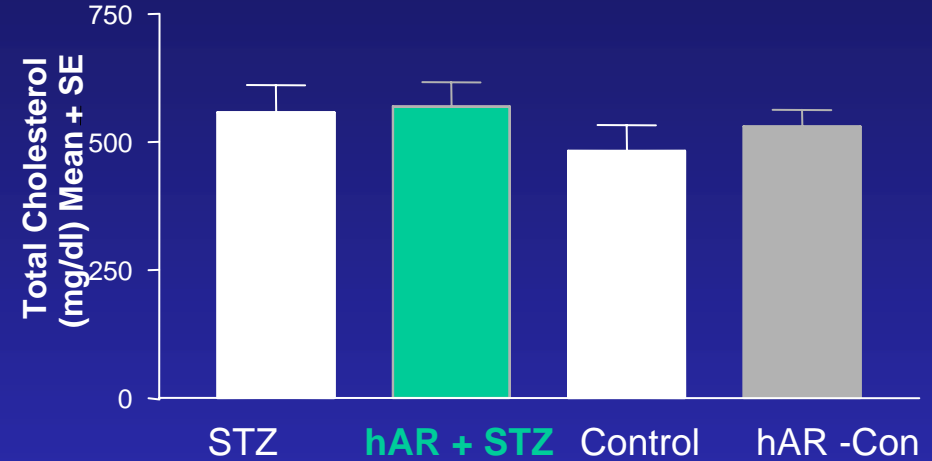
Plasma glucose and lipids after 12 weeks on Paigen diet

All mice are LDLR+/-

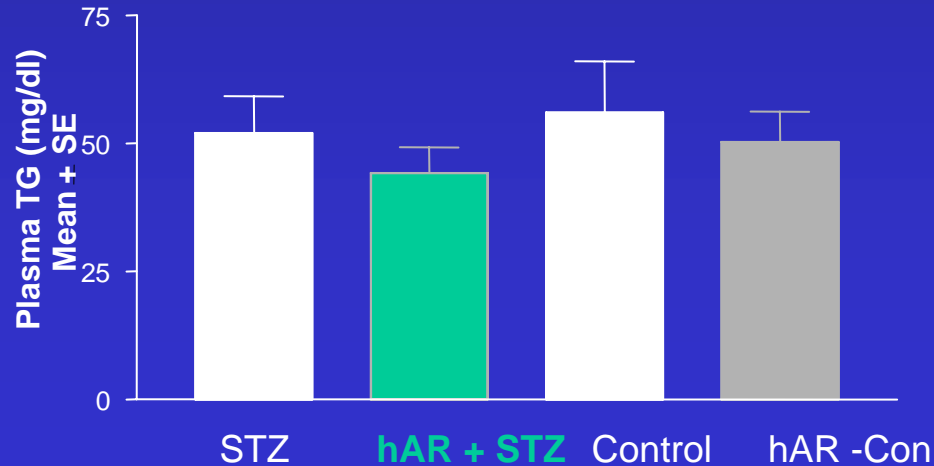
Plasma glucose



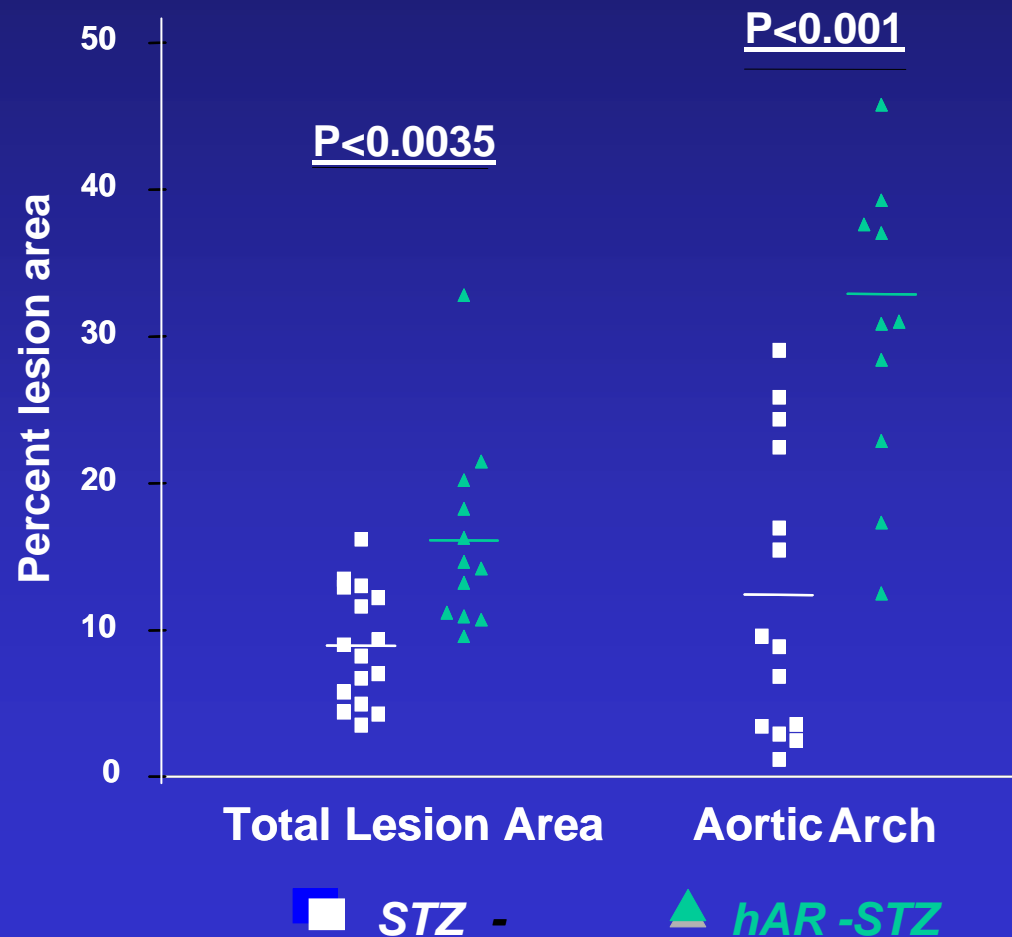
Total cholesterol



Triglyceride



LDLR+/- mice without or with HuARTg STZ diabetes fed Paigen diet (12 wks) En Face Lesion Area



C57BL/6J LDLR^{-/-} HuARTg mice made diabetic with STZ have enhanced en face lesion area

Plan:

1. STZ-induced hyperglycemia studies: optimize diet and duration and extend analysis to aortic root and BCA
2. Extend model to Pdx1^{+/-} induced hyperglycemia:
LDLR^{-/-}-Pdx1^{+/-} X LDLR^{-/-}-HuARTg
LDLR^{-/-}; LDLR^{-/-}-Pdx1^{+/-}; LDLR^{-/-}-HuARTg; LDLR^{-/-}-Pdx1^{+/-}-HuARTg
3. Atherosclerosis: Quantitation Aortic Root, BCA; Assessment of plaque vulnerability phenotypes
4. Tissues distributed to AMDCC core laboratories for assessment of nephropathy, retinopathy, neuropathy, uropathy
5. Extra mice bred for shipment to AMDCC core laboratories for functional studies (neuropathy, uropathy, cardiomyopathy)

C57BL/6J LDLR^{-/-} Pdx1^{+/-} Mice

Effect on Atherosclerosis

Females

	Pdx ^{+/+}	Pdx ^{+/-}	Signif t-test
Aortic Root $\mu\text{m}^2(\times 10^{-4})$	34.4 \pm 8.0	23.9 \pm 8.3	p=0.0037
Body Weight g	20.1 \pm 1.5	20.3 \pm 1.8	p=0.7707
Fasting Gluc mg/dl	130 \pm 16	181 \pm 27	p=0.0000
IPGTT Gluc(30M)mg/dl	320 \pm 62	513 \pm 78	p=0.0000
Cholesterol mg/dl	470 \pm 134	387 \pm 117	p=0.1567
HDL Chol mg/dl	28 \pm 10	33 \pm 10	p=0.2296
Triglycerides mg/dl	96 \pm 40	81 \pm 27	p=0.3502

C57BL/6J LDLR-/- Pdx1+/- Mice

Effect on Atherosclerosis

Males

	Pdx+/+	Pdx+/-	Signif t-test
Aortic Root $\mu\text{m}^2(\times 10^{-4})$	12.2 \pm 6.8	16.6 \pm 13.1	p=0.2717
Body Weight g	27.7 \pm 2.4	27.4 \pm 1.6	p=0.6828
Fasting Gluc mg/dl	139 \pm 16	214 \pm 41	p=0.0000
IPGTT Gluc(30M)mg/dl	341 \pm 68	523 \pm 50	p=0.0000
Cholesterol mg/dl	447 \pm 151	352 \pm 89	p=0.0480
HDL Chol mg/dl	43 \pm 8	44 \pm 10	p=0.8000
Triglycerides mg/dl	109 \pm 36	73 \pm 17	p=0.0020

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