



AMDCC

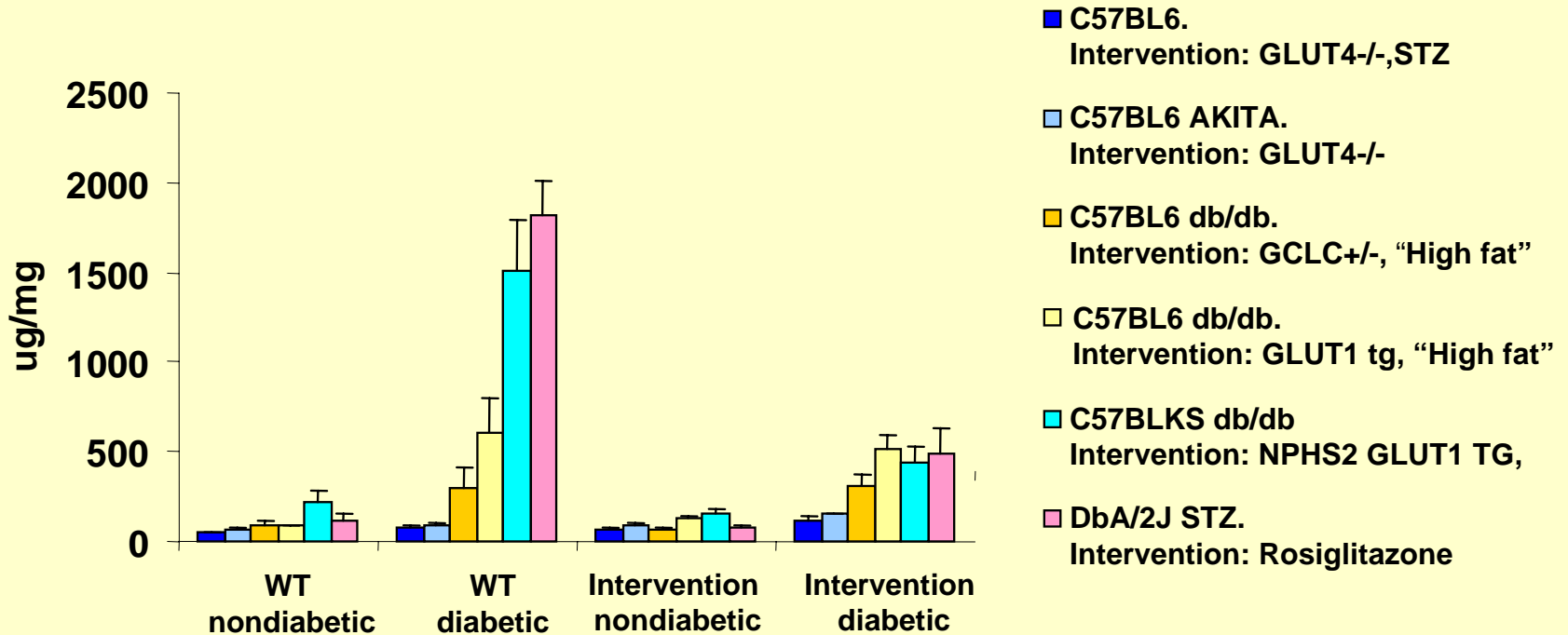
THE ANIMAL MODELS OF DIABETIC
COMPLICATIONS CONSORTIUM

Michigan/Chicago unit

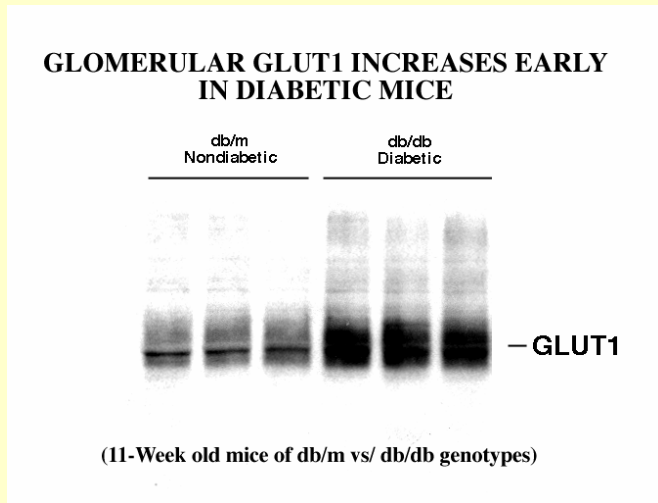
Modifications in Mouse Models to Enhance Nephropathy/Neuropathy- GLUT1 overexpression

- Increased oxidative stress
- Increased glucose metabolic flux or alteration in GLUT expression profiles that will lead to changes in glucose metabolism
- Altered signaling that may enhance glucose toxicity

Five Models: ACR at Termination



GLUT1tg C57Bl/6J model (GT1S)

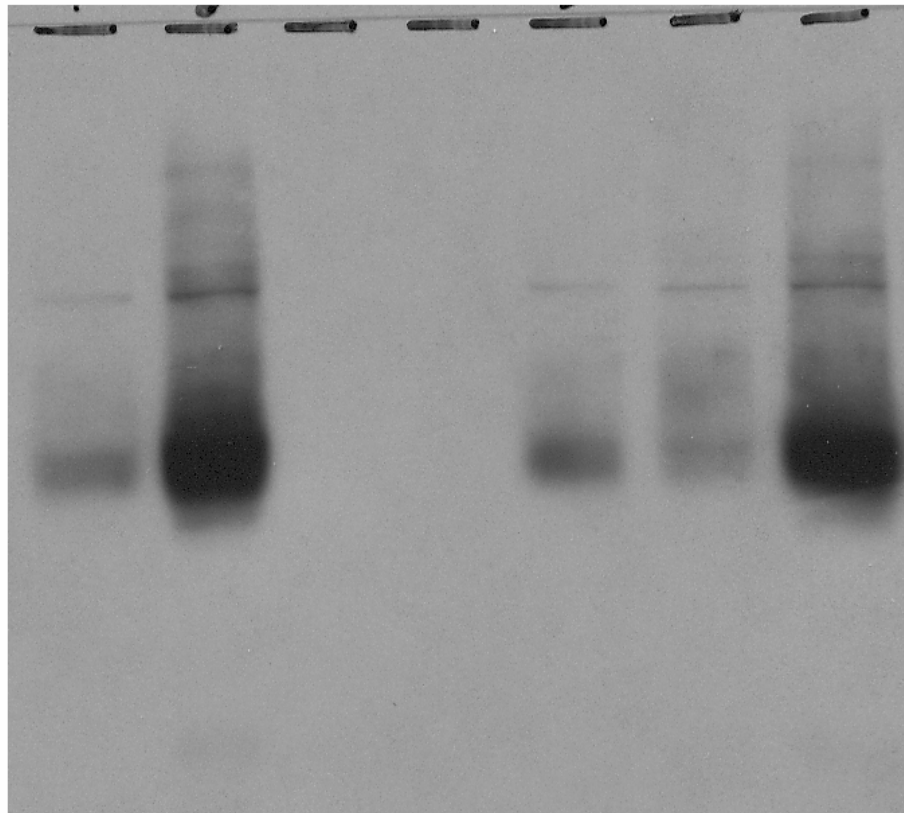


- GLUT1 is increased in glomerular cells in diabetes
- GLUT1 leads to enhanced PKC α and AR activity, fibronectin synthesis
- Modified β -actin promoter drives GLUT1 in many tissues: high in mesangial cells
- Bred onto db/db C57BL/6J
- Effect of “high fat” feeding (breeder chow; ca 7% fat)

Glomerular GLUT1 Protein is Increased in Both GT1S Transgenic Mice and Type 2 Diabetic Mice

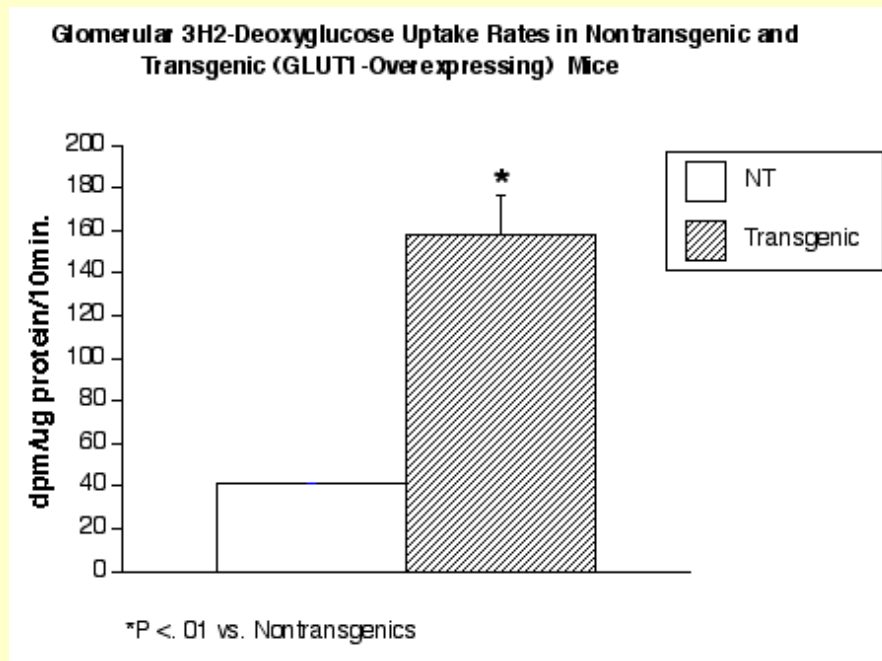
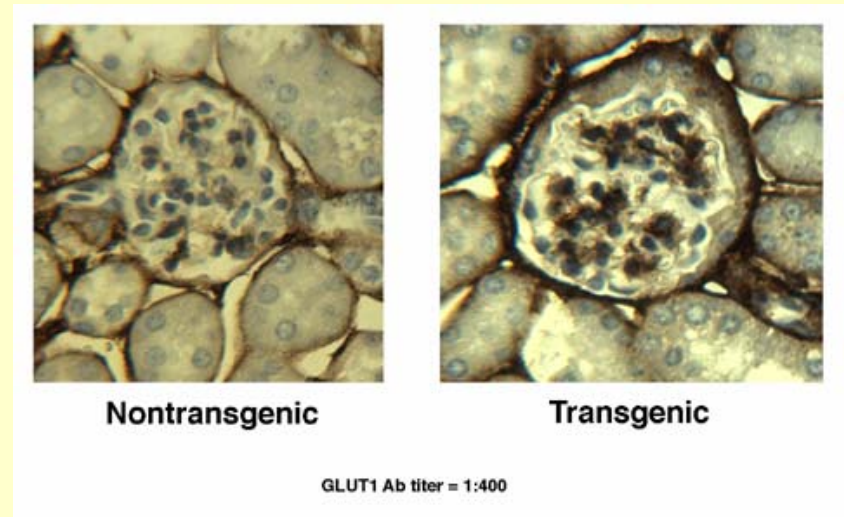
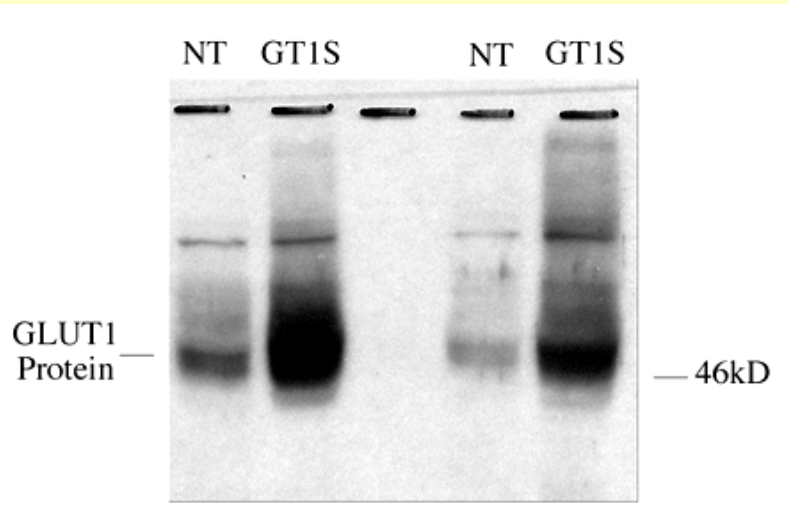
NT GT1S

db/m db/m db/db

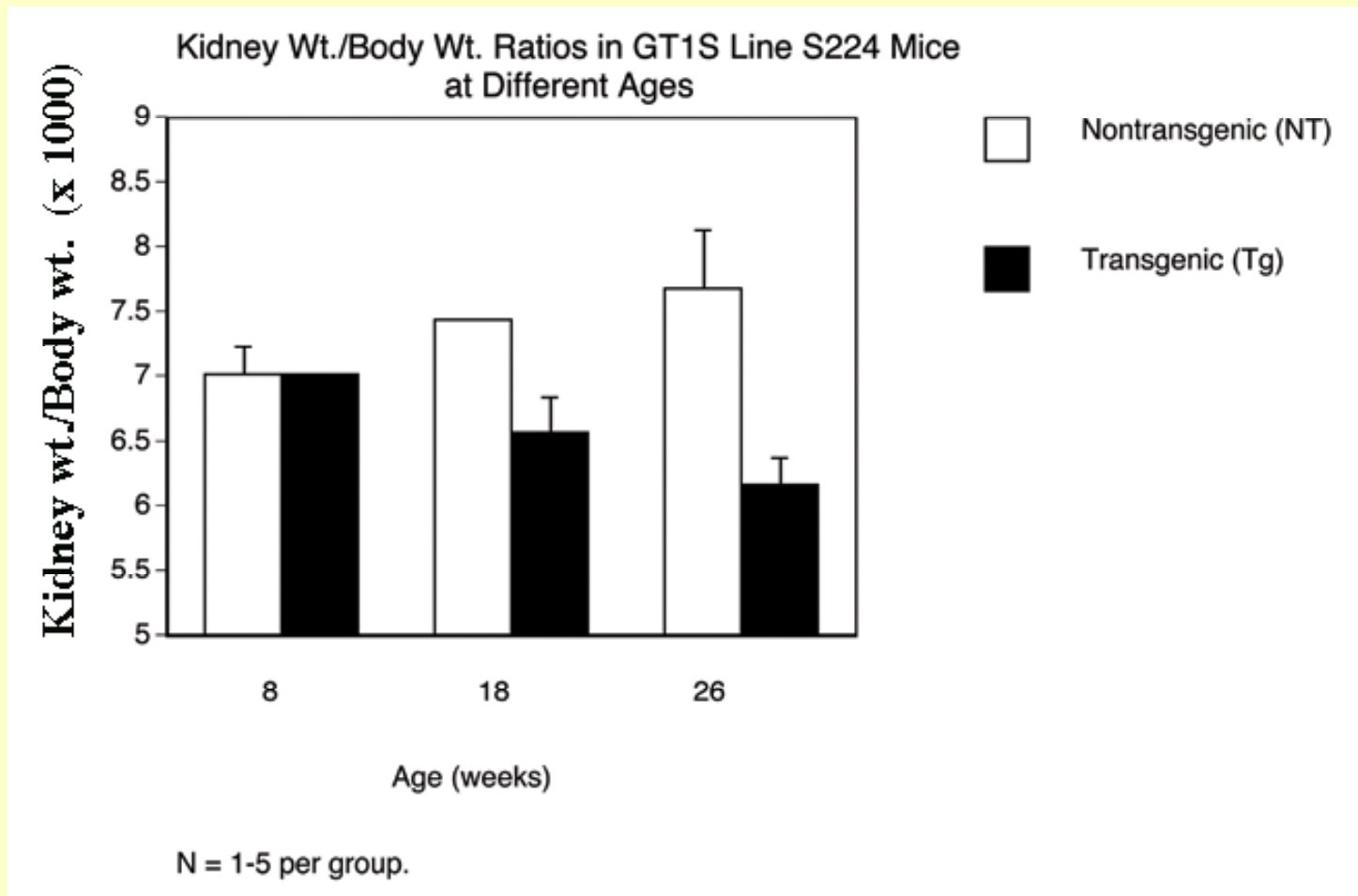


— GLUT1

GLUT1tg C57BL/6J (GT1S) model

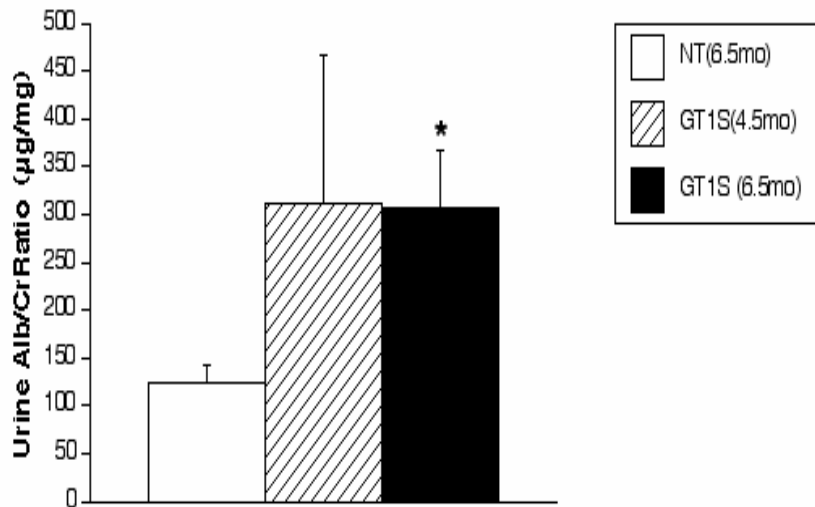


Kidney Wt./ Body Wt. Ratios



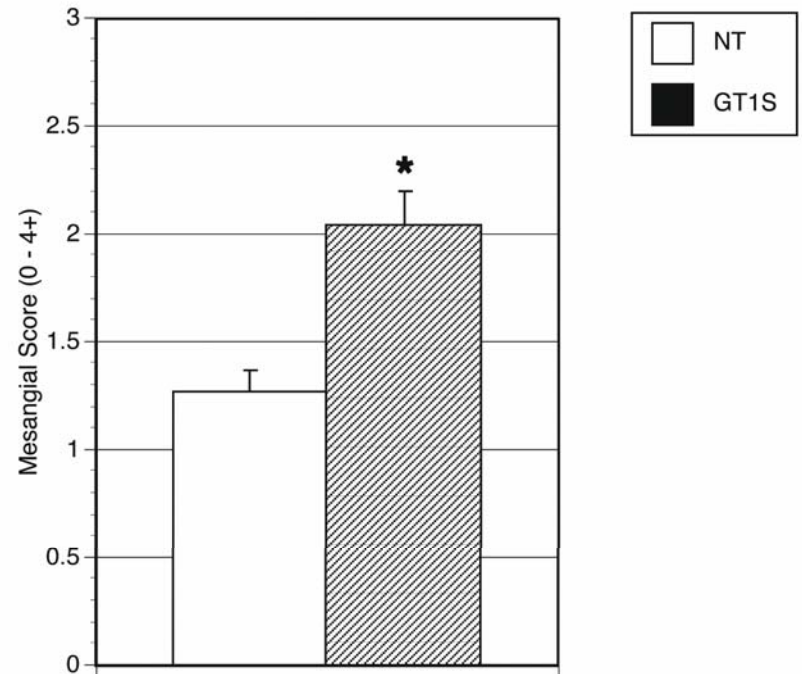
GLUT1tg C57BL/6J (GT1S) model—26 wks

Urinary Albumin/Cr Ratios for GT1S Line Mice



N = 3 - 5 mice per group.

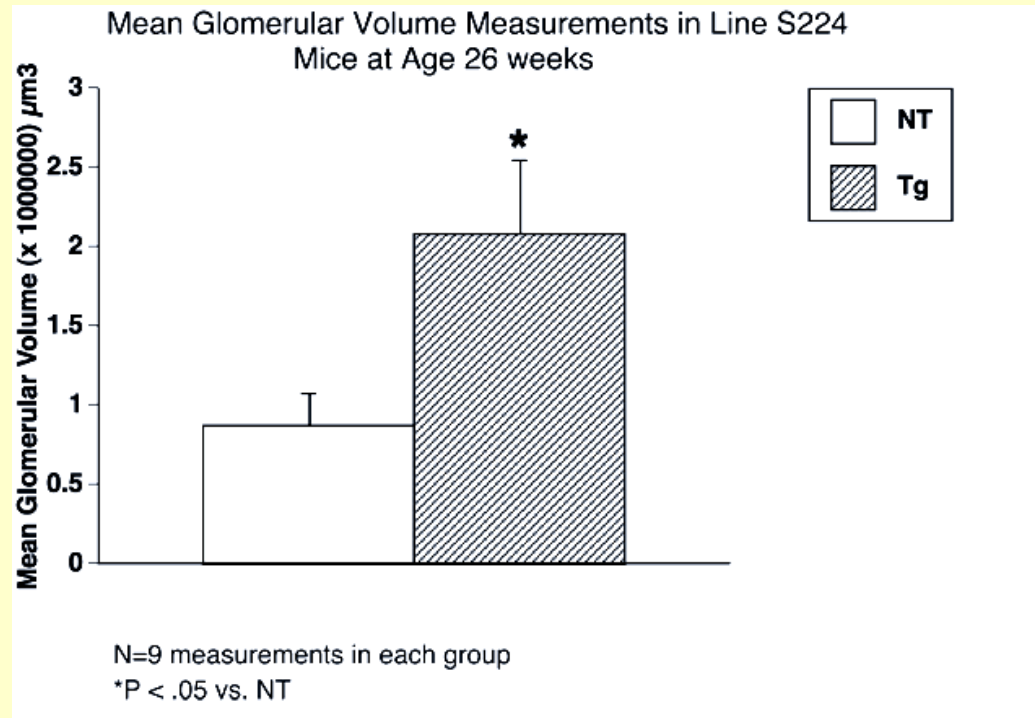
Mesangial score



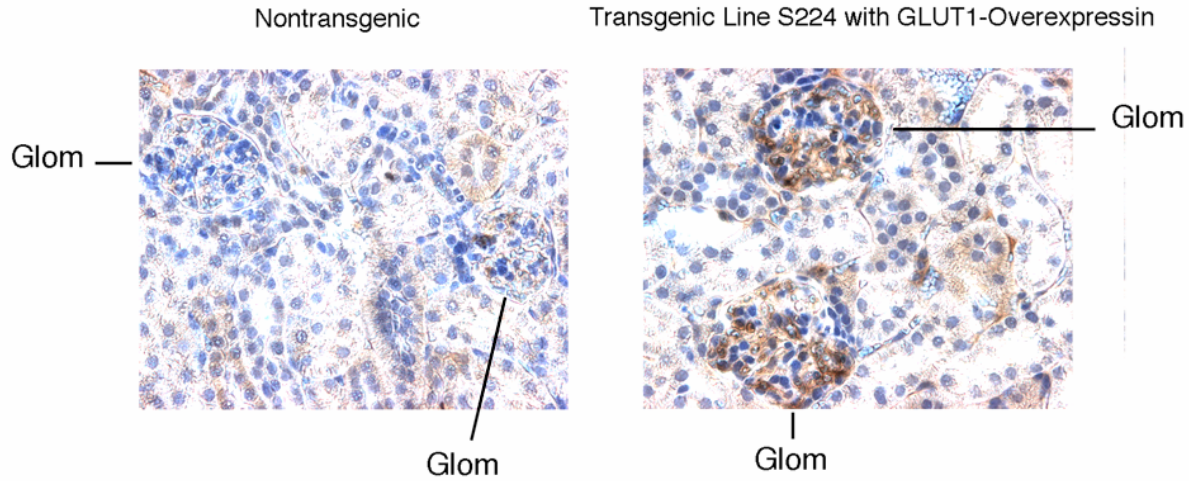
N = 22 - 25 measurements in each group.

*P < .001 vs. NT

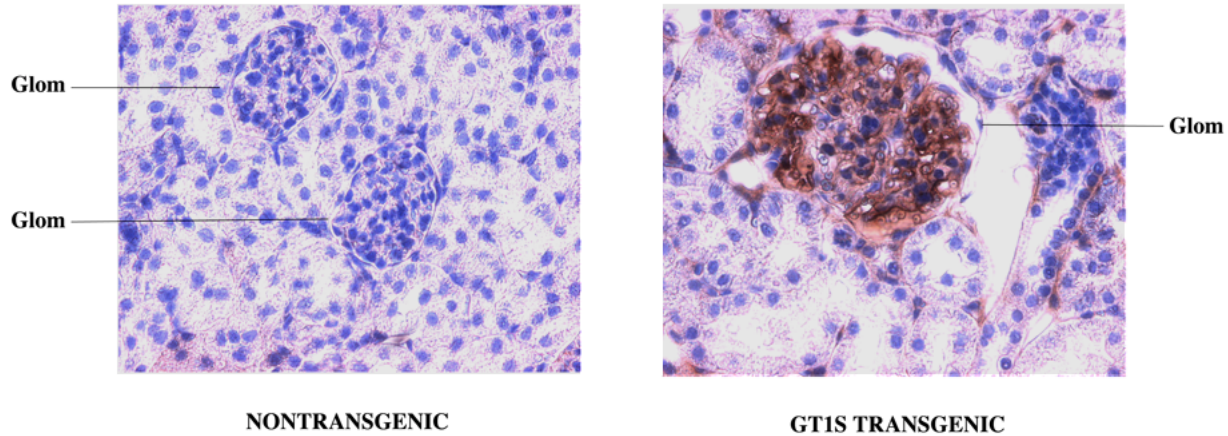
GLUT1tg C57BL/6J (GT1S) model—26 wks



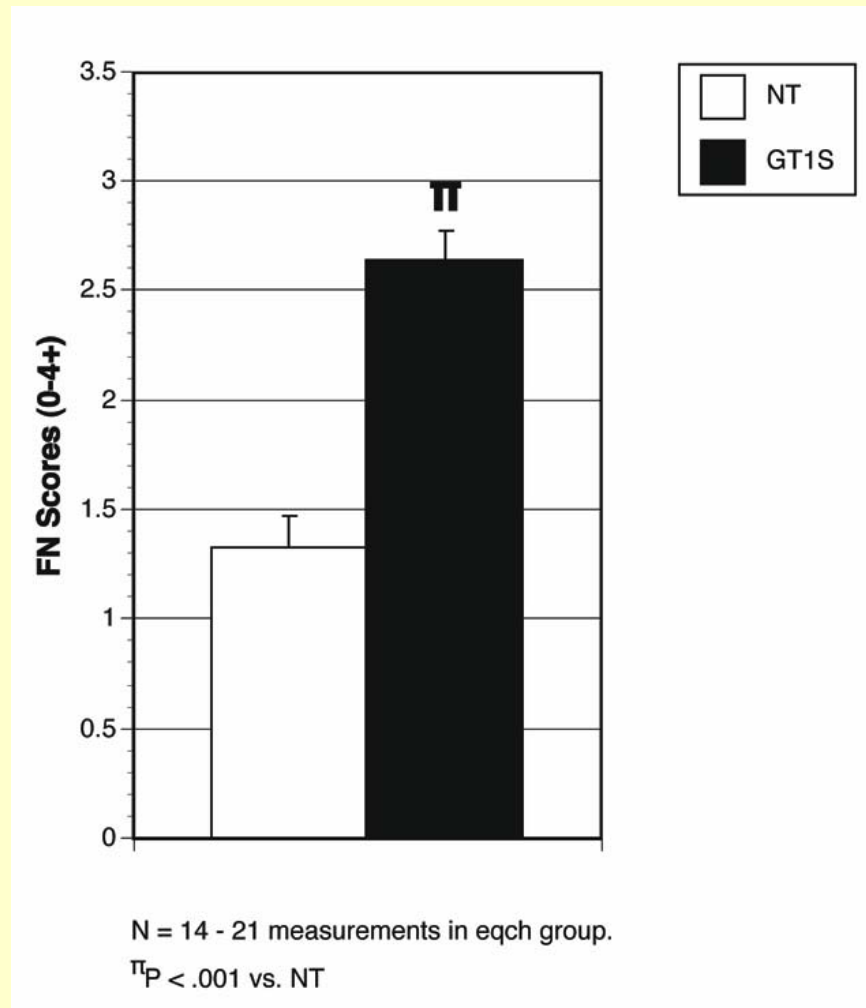
Immunolabelling of Type IV Collagen in Nontransgenic and Transgenic
Line S224 GLUT1-Overexpressing Mice Age 26 Weeks



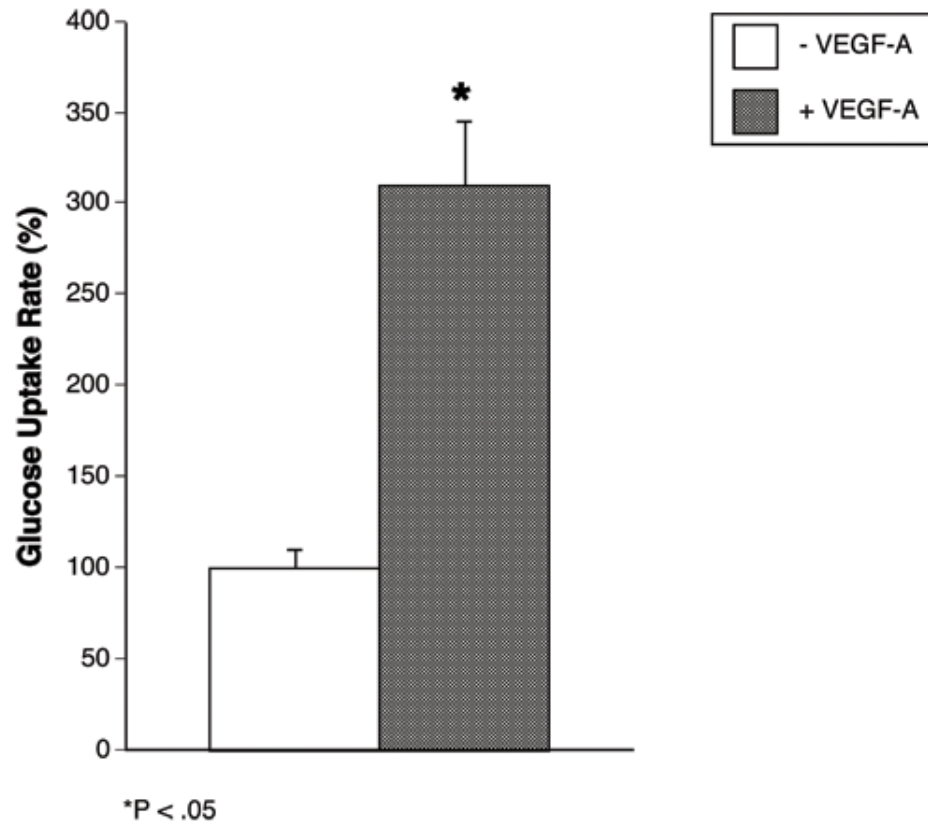
**Glomerular Fibronectin in Nontransgenic and Line 224
GT1S Transgenic Mice at Age 26 Weeks**



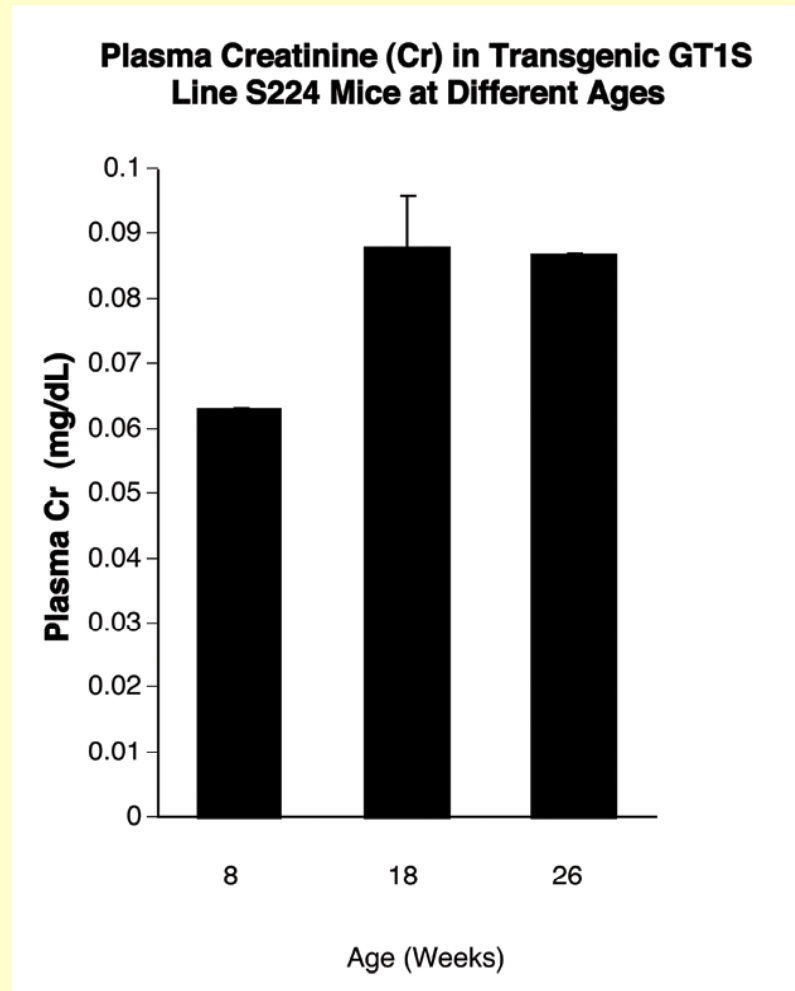
FN Staining Scores in Nontransgenic and GT1S Transgenic Glomeruli at Age 26 Weeks



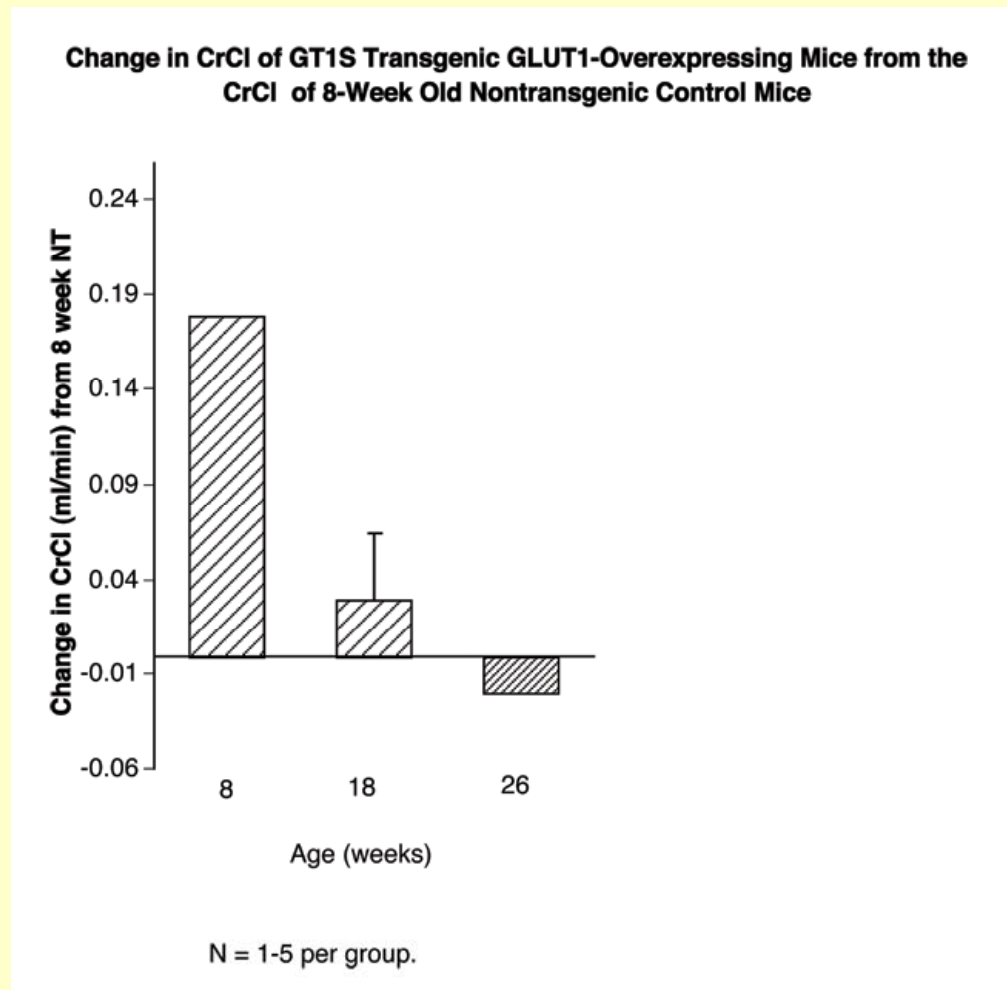
VEGF-A Stimulates Glucose Uptake in Cultured MC's



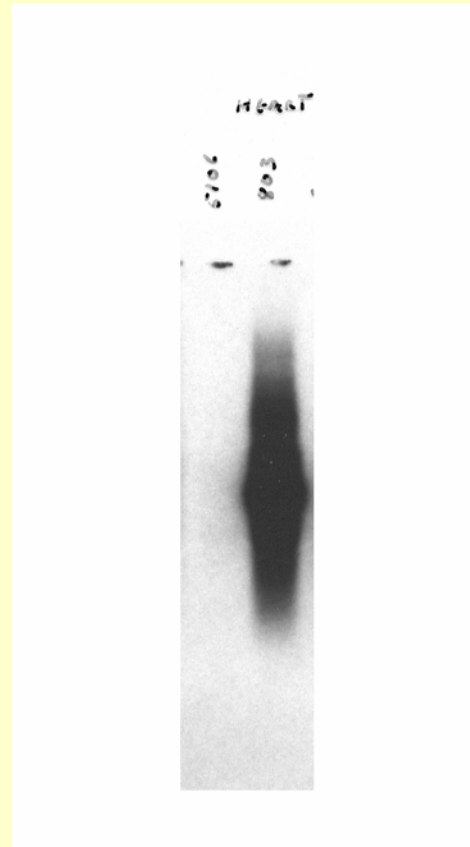
Serum Creatinine Increased in GT1S Transgenic Mice



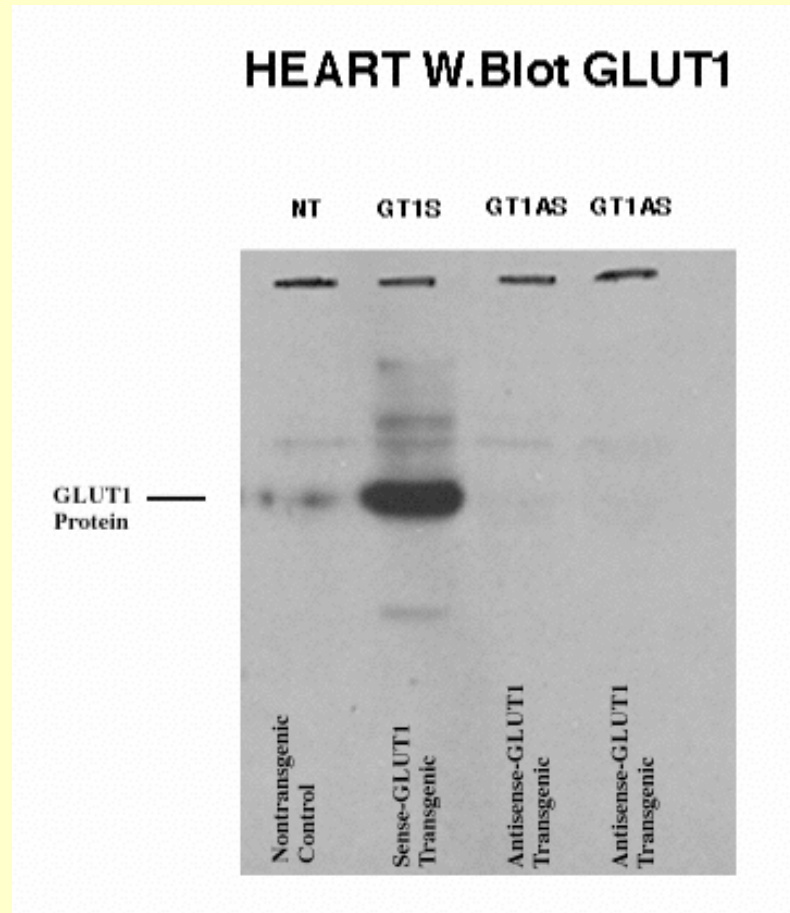
Change in CrCl from Control Over Time



GLUT1 mRNA is Increased in the Hearts of GT1S Transgenic Mice



GLUT1 Protein is Increased Approximately 7-Fold in the Hearts of GT1S Transgenic Mice



Nontransgenic Heart at Age 16 weeks

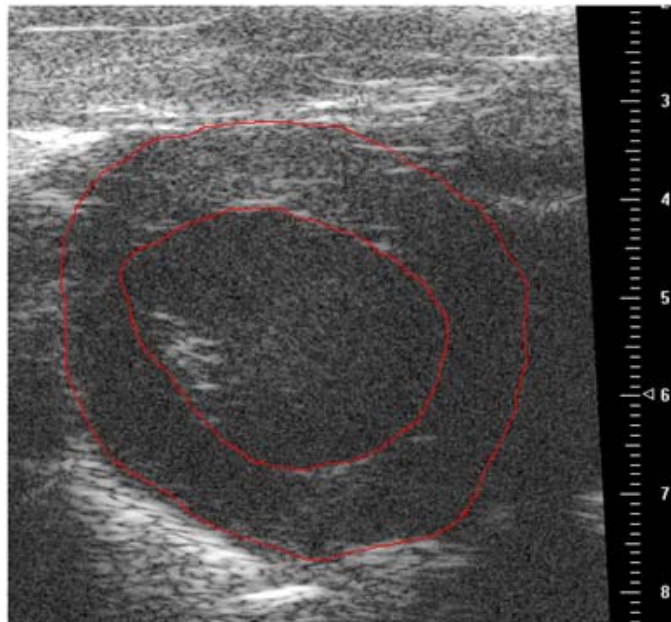
QuickTime™ and a
Microsoft Video 1 decompressor
are needed to see this picture.

GT1S Transgenic Heart at Age 16 Weeks

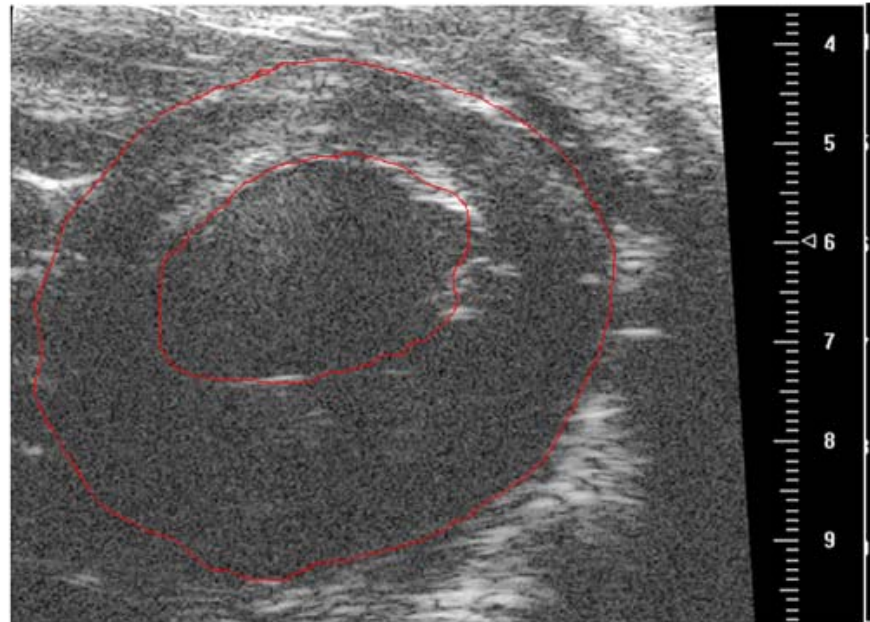
QuickTime™ and a
Microsoft Video 1 decompressor
are needed to see this picture.

Cardiac Hypertrophy Shown in Diastole in GT1S Transgenic Mice, in the Absence of Hypertension

Short Axis Echo Images of the Left Ventricle in Nontransgenic and GT1S Transgenic Mice

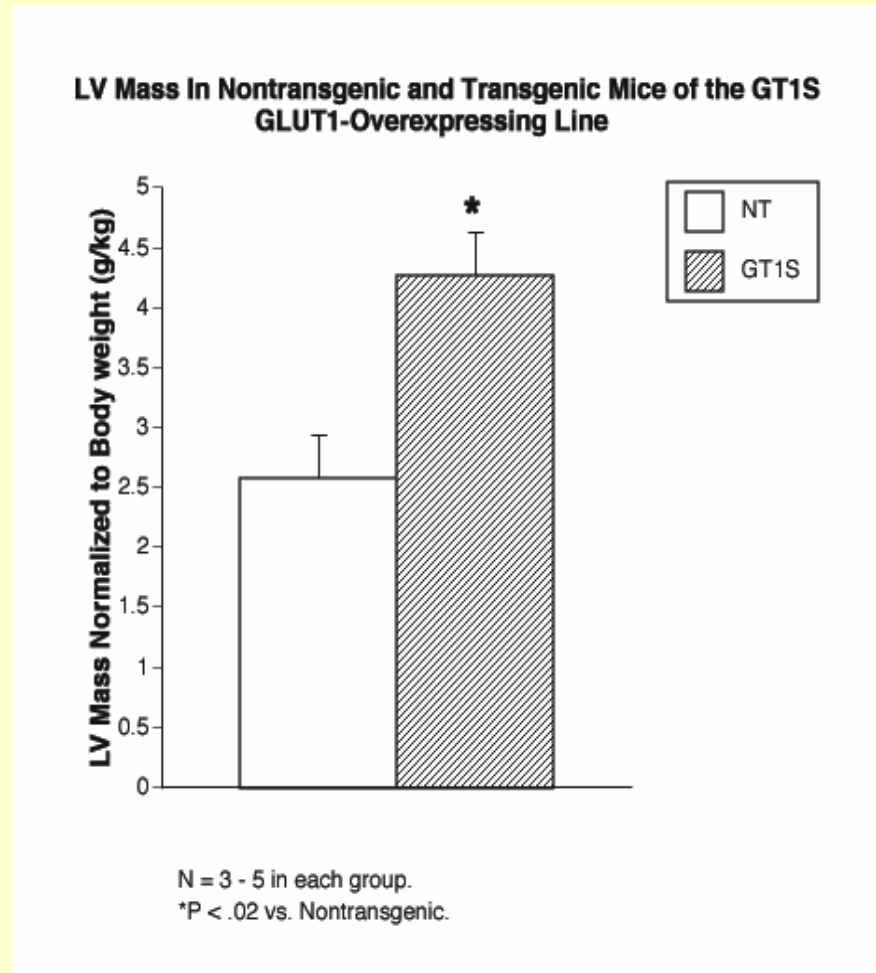


Nontransgenic



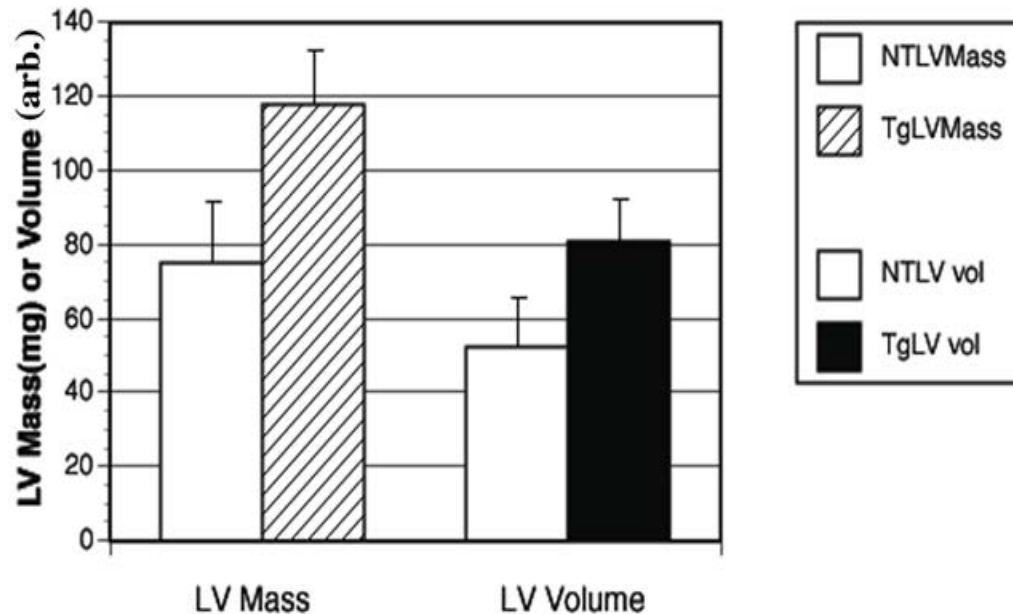
Transgenic

LV Mass Measurements in Nontransgenic & Transgenic Mice of the GT1S GLUT1-Overexpressing Line



Increased LV Mass and Volume in GT1S Transgenic Hearts

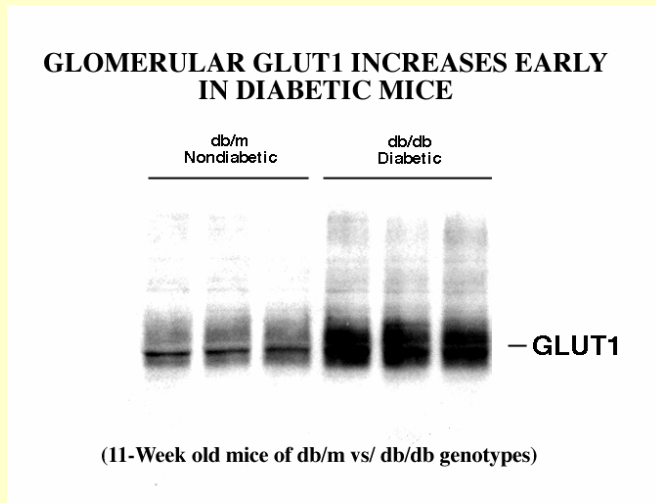
Assessments of LV Mass and Volume in Nontransgenic and Transgenic GLUT1-Overexpressing Mice by Transthoracic Echocardiography



NT = Nontransgenic Mice

Tg = Line S224 GLUT1-Overexpressing

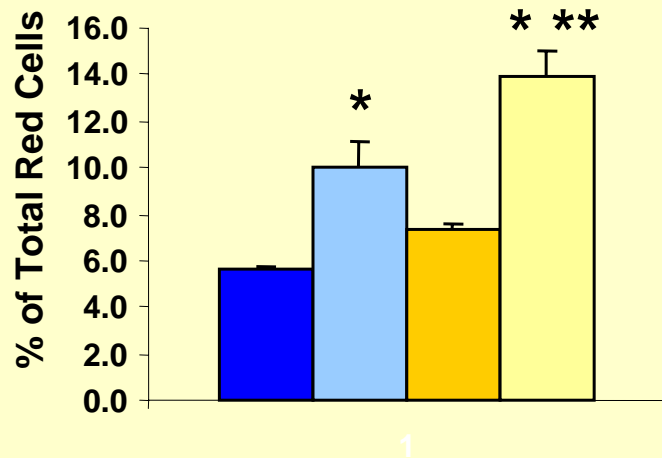
GLUT1tg C57Bl/6J db/db model (GT1S)



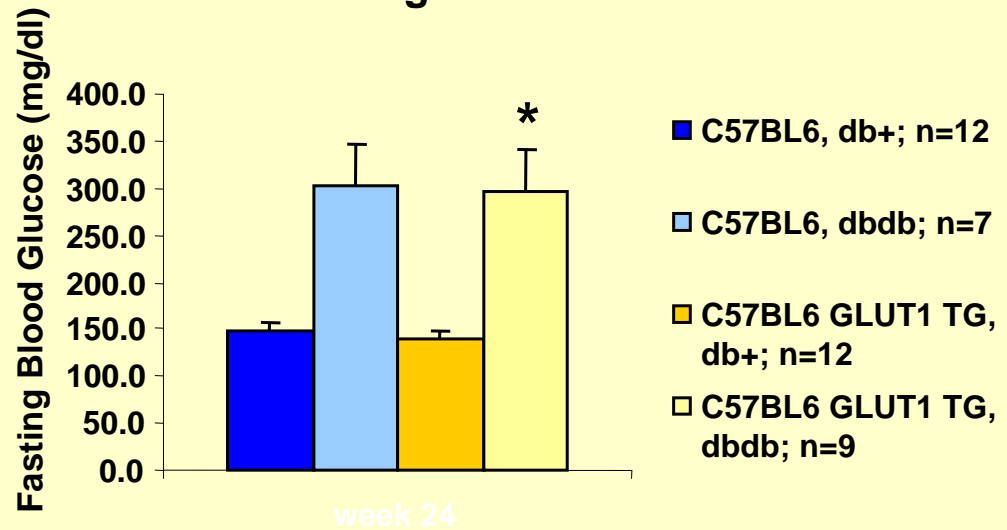
- GLUT1 is increased in glomerular cells in diabetes
- GLUT1 leads to enhanced PKC α and AR activity, fibronectin synthesis
- Modified β -actin promoter drives GLUT1 in many tissues: high in mesangial cells
- Bred onto db/db C57BL/6J
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Fasting blood sugar GLUT1 tg C57BL/6J db/db model

24 week Glycated Hemoglobin



Fasting Blood Glucose



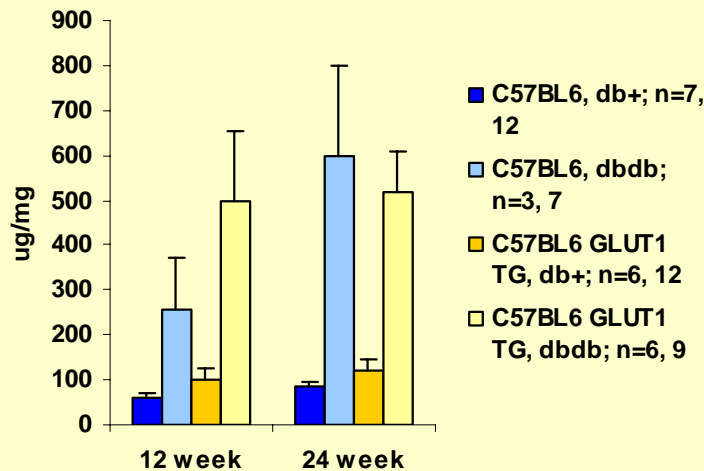
* vs. control, $p < 0.03$

** vs. C57BL6, dbdb; $p = 0.0083$

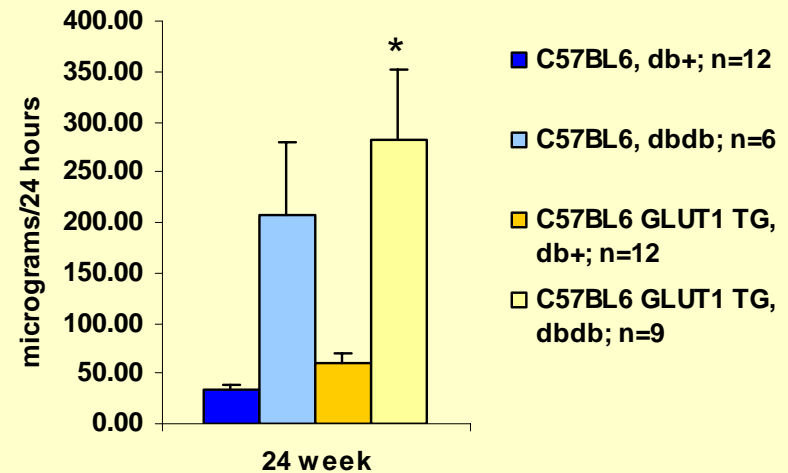
Albuminuria

GLUT1 tg C57BL/6J db/db model-24 wk

Urinary Albumin Creatinine Ratio



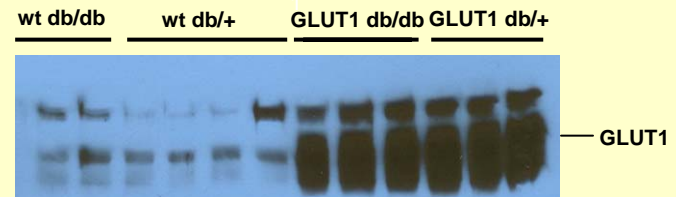
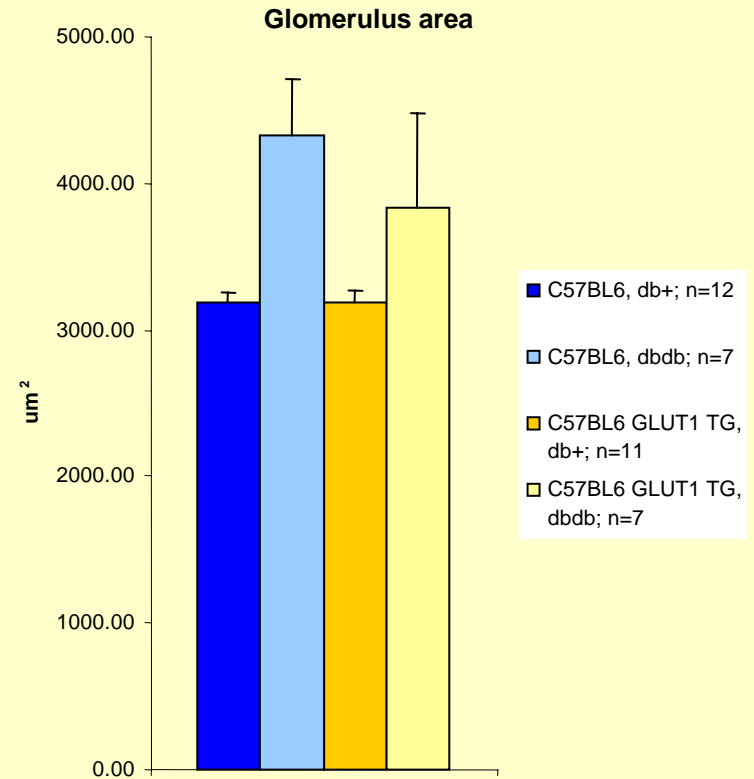
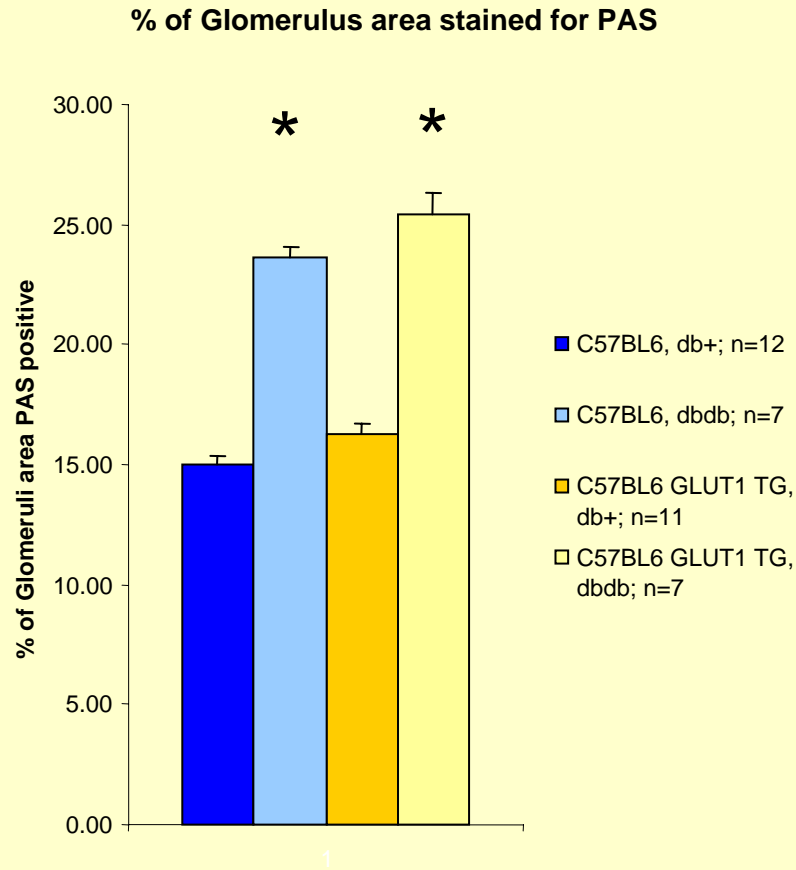
Total Urinary Albumin



* vs. control, $p < 0.02$

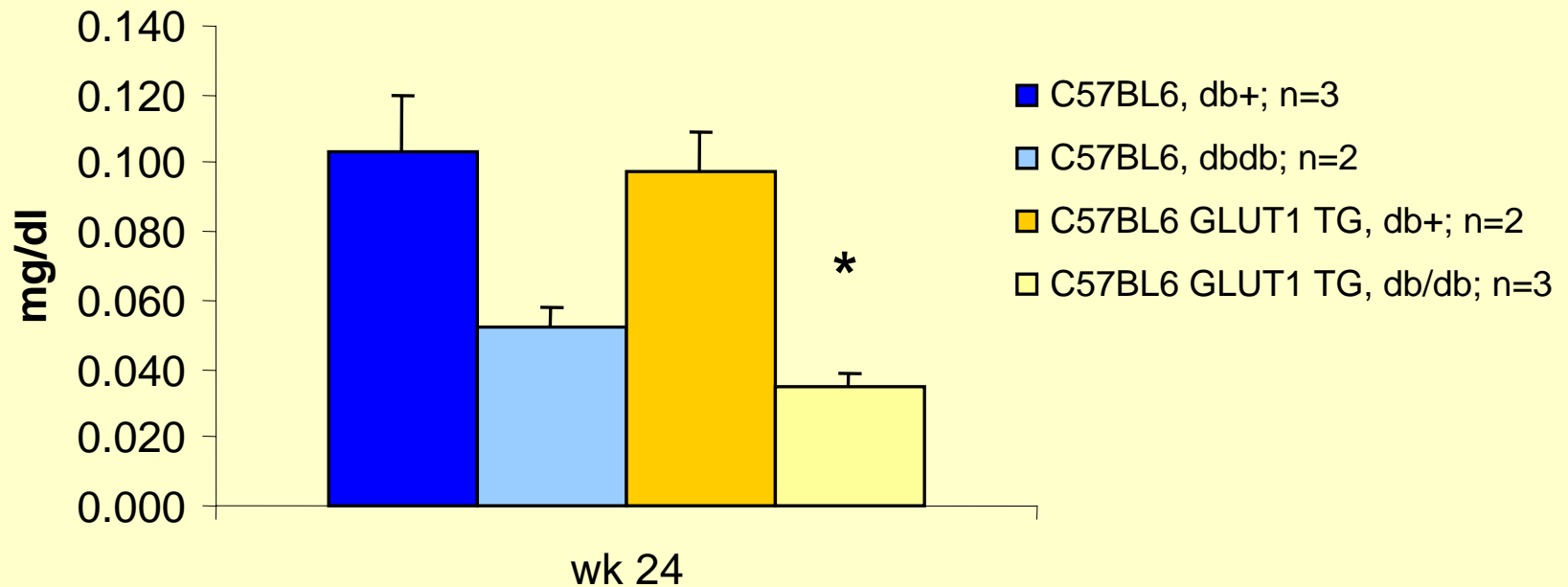
PAS expansion

GLUT1 tg C57BL/6J db/db model-24 wk



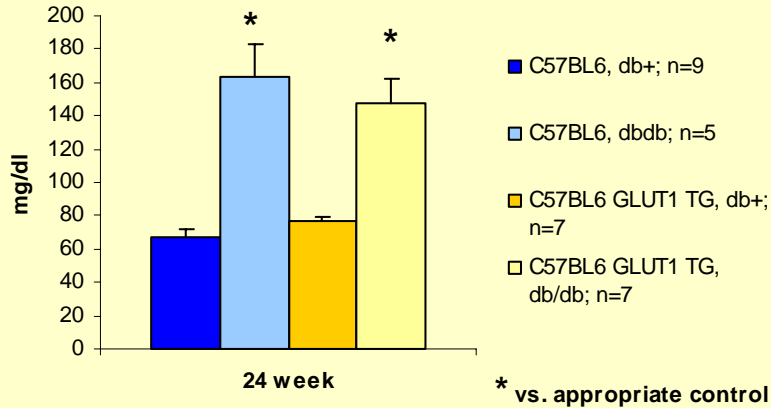
* vs. control, p<0.0001

HPLC Serum Creatinine 24 weeks GLUT1 tg C57BL/6J db/db model-24 wk

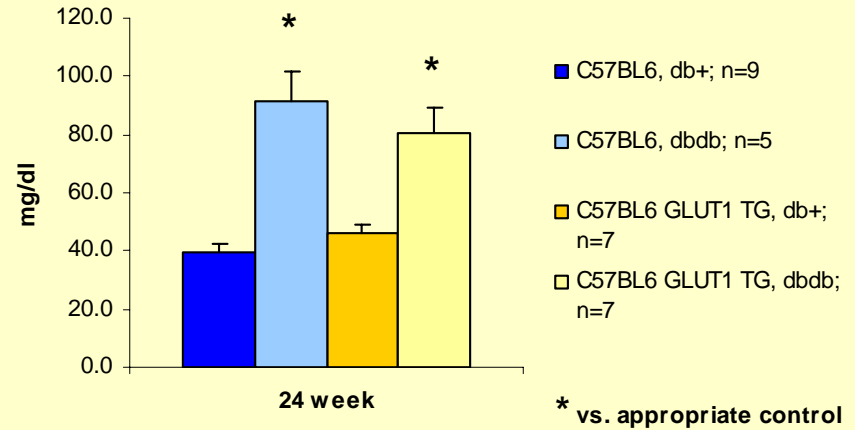


GLUT1 TG, High Fat Chow

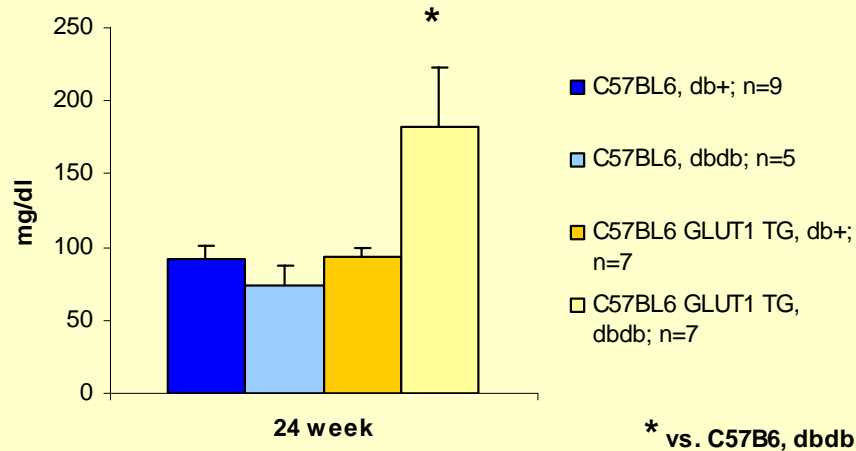
Serum Total Cholesterol



Serum HDL



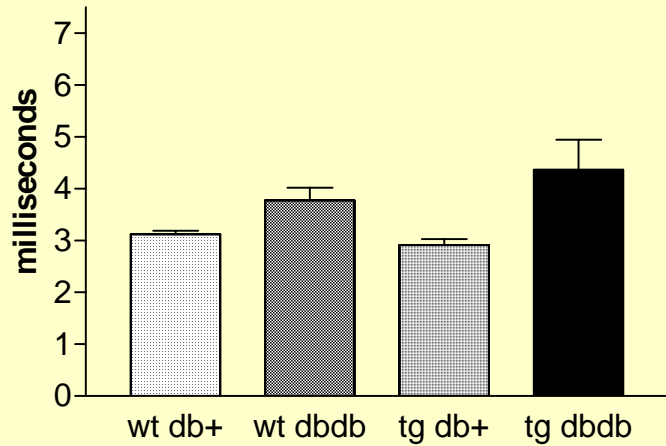
Serum Triglycerides



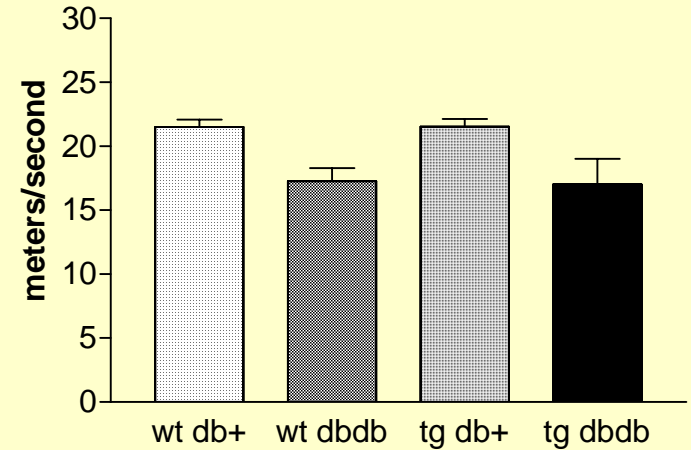
Nerve Conduction Velocity

GLUT1tg C57Bl/6J dbdb Mice

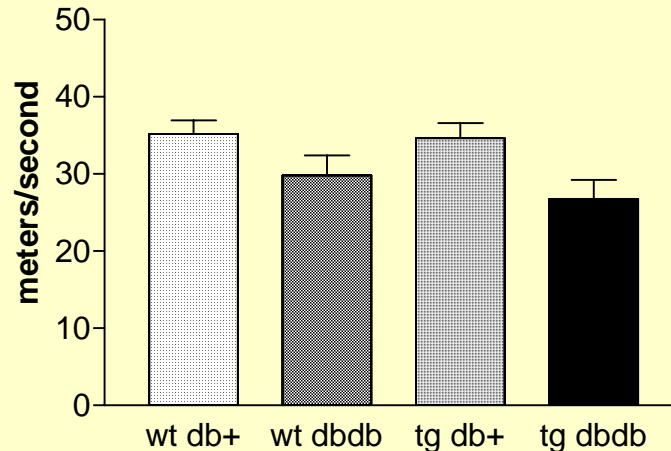
TDML



TSNCV



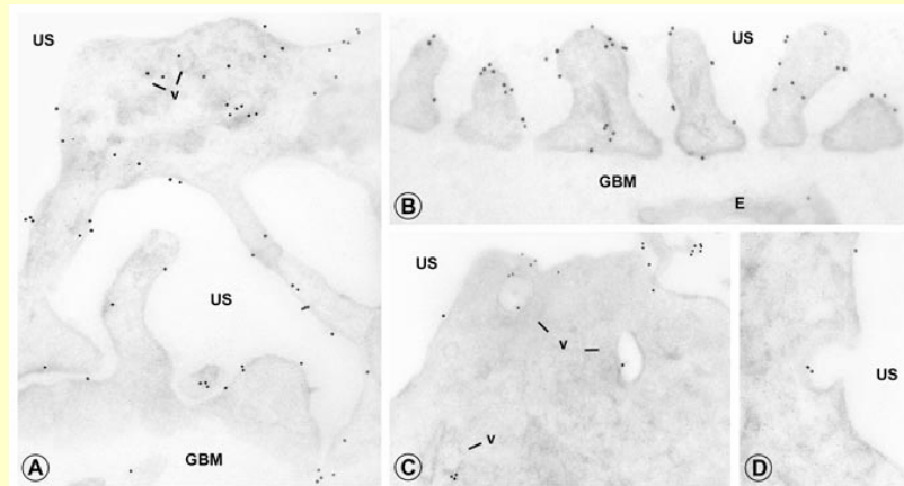
SMNCV



Nphs2 GLUT1tg db/db C57BLKS model

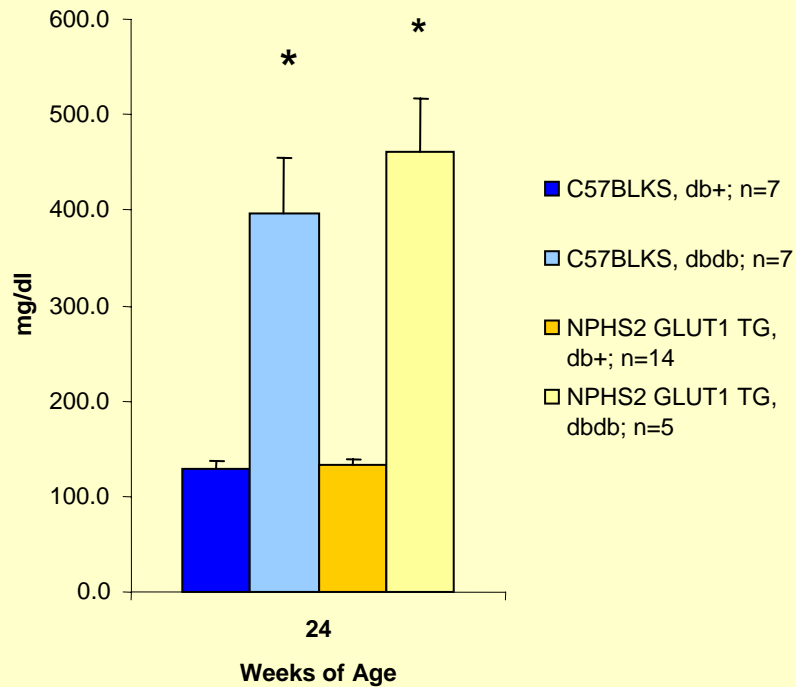
- GLUT1 is highly expressed in podocytes
- High glucose and diabetes in humans and rodents lead to podocyte loss
- Nphs2 promoter drives GLUT1 in podocytes
- db/m C57BKS eggs injected to allow direct examination on diabetic background

GLUT1 in human kidney podocytes



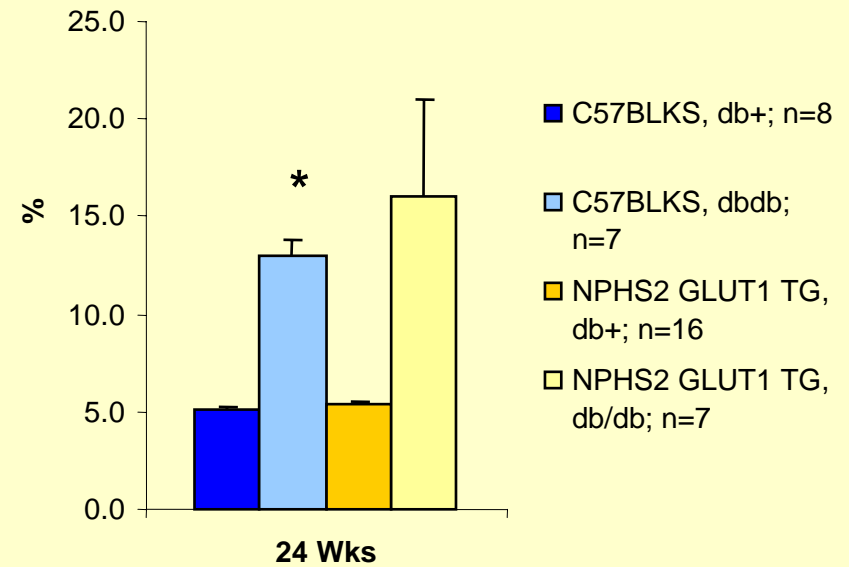
Nphs2 GLUT1tg db/db C57BLKS model

Fasting blood sugar



* vs. control, p<0.0001

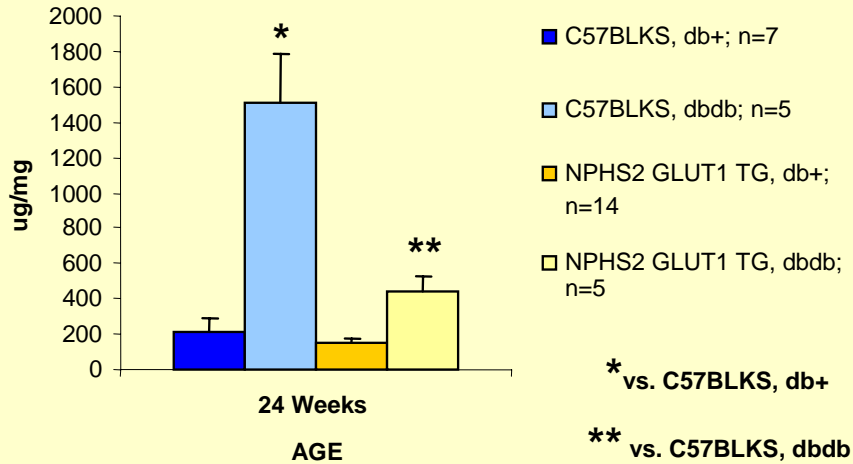
Glycated Hemoglobin



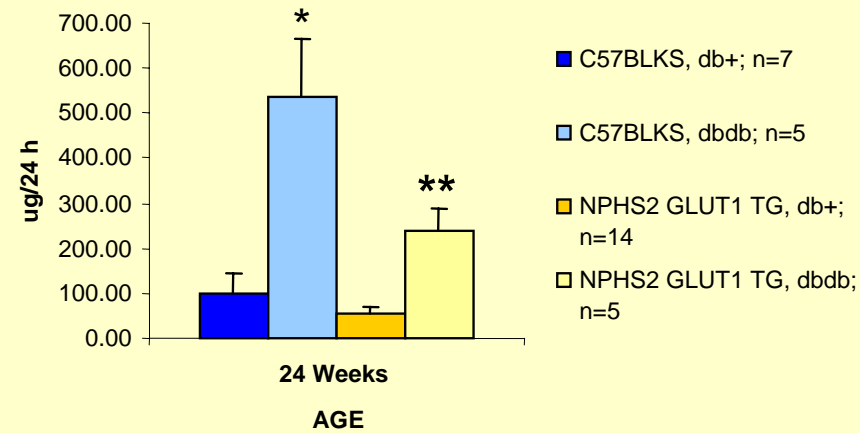
* vs. controls, p<0.0001

Nphs2 GLUT1tg db/db C57BLKS model

Urinary Albumin Creatinine Ratio

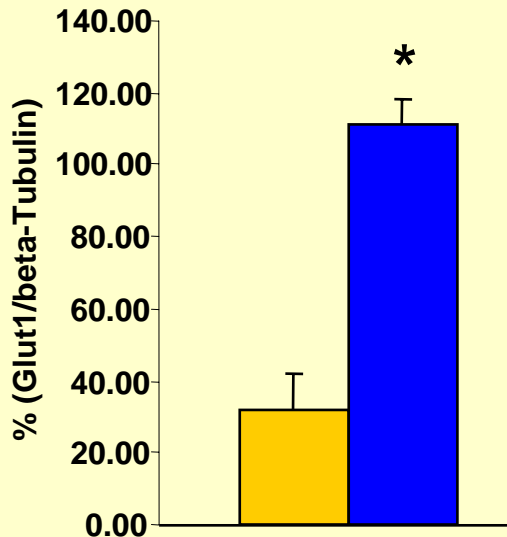


Urinary Total Albumin

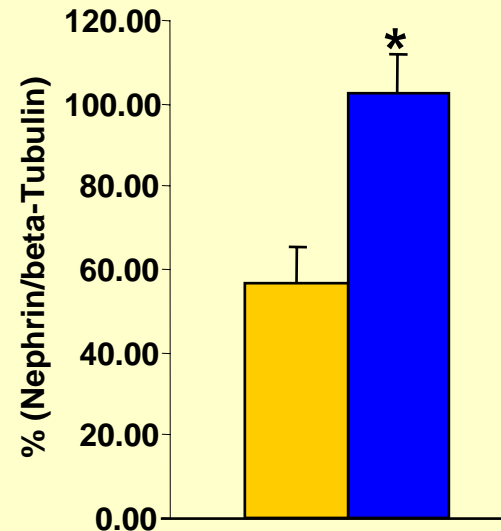


GLUT1 and nephrin expression- 6-8 wk Nphs2 GLUT1tg db/db C57BLKS model

Isolated Glomerular GLUT1 expression



Isolated Glomerular Nephrin Expression



*p<0.05 vs. C57BL6

■ C57BL/6, n=9
■ Nphs2 GLUT1 tg db/db, n=8

Summary

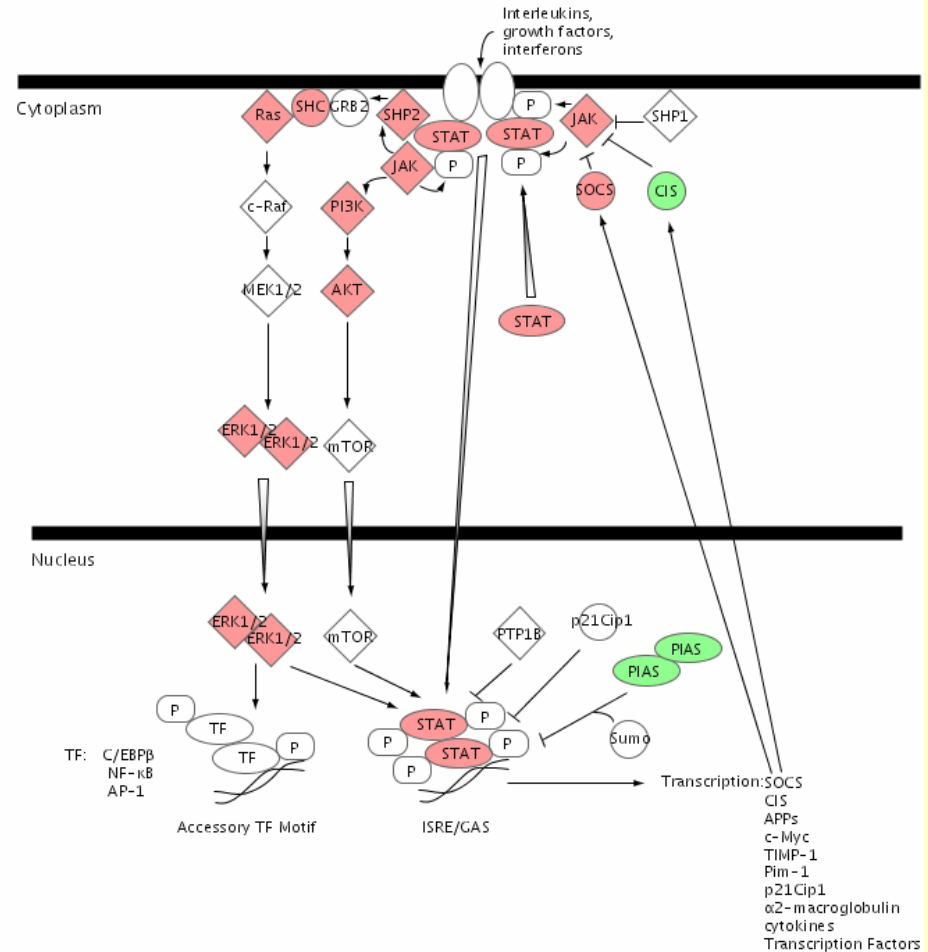
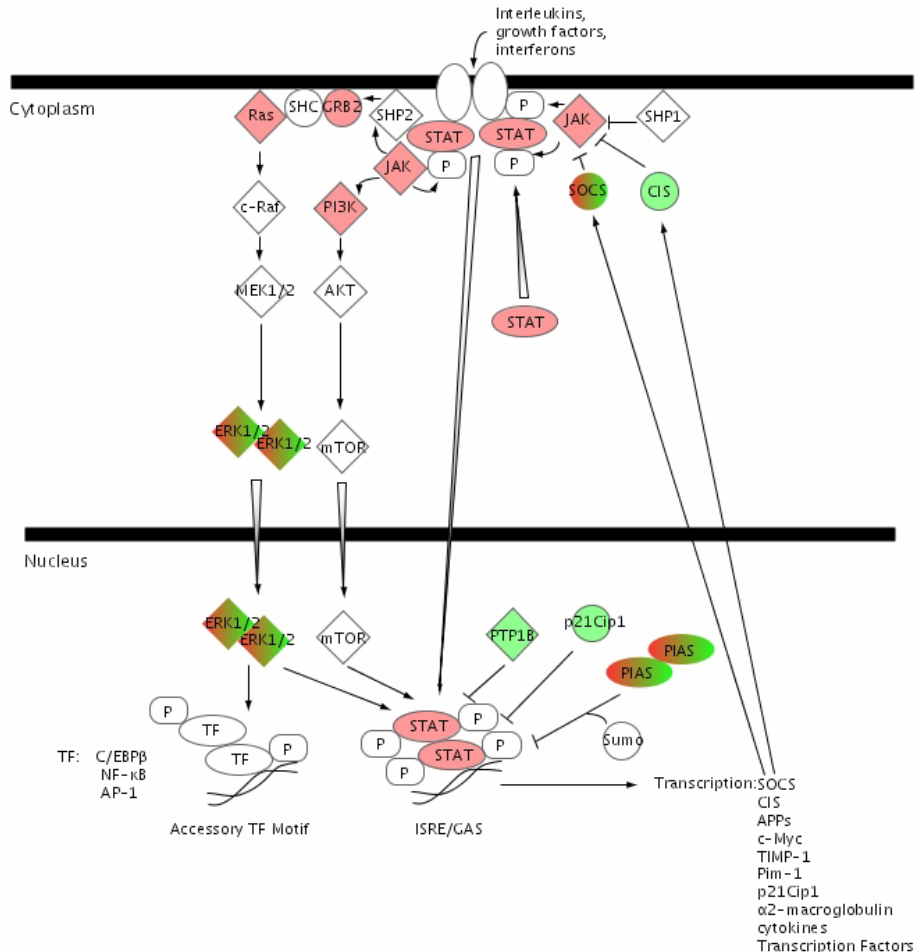
- GLUT1 tg in nondiabetic C57BL6 mice results in enlarged glomeruli, increased proteinuria and mesangial matrix expansion.
- GLUT1 tg in nondiabetic C57BL6 mice have LV hypertrophy and LV volume in the absence of hypertension.
- GLUT1 tg in C57BL6 db/db diabetic mice fed with higher fat chow fails to increase proteinuria and mesangial matrix expansion significantly by 6 months of age.
- “High fat” feeding in C57BL/6 db/db mice leads to sustained hyperglycemia and more robust nephropathy than in mice fed a normal fat chow.
- Podocyte specific GLUT1 overexpression unexpectedly leads to reduced proteinuria in C57BLKS db/db mice
- So what now?

Human Diabetic Nephropathy

JAK/STAT Pathways

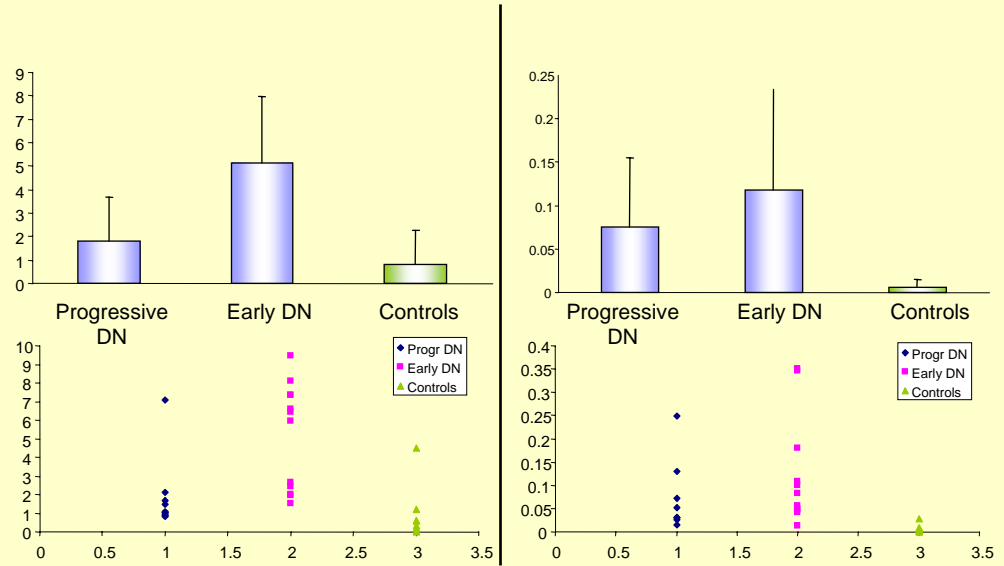
Early DN- Glomerular

Progressive DN- Tubulointerstitial

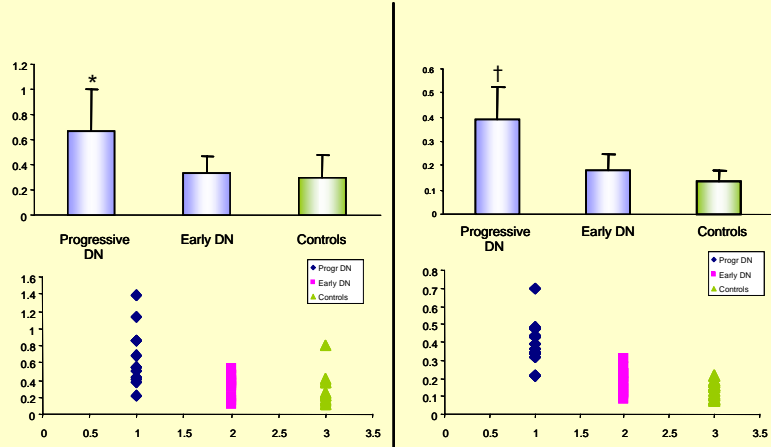


Human type 2 model

Jak2 Glomeruli



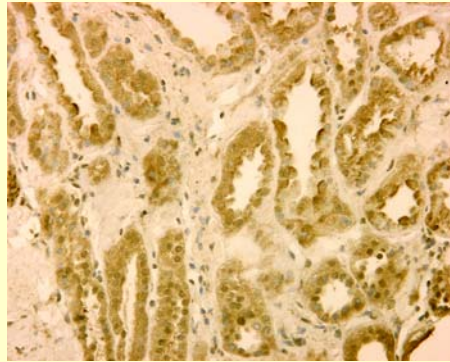
Jak2-Tubulointerstitium



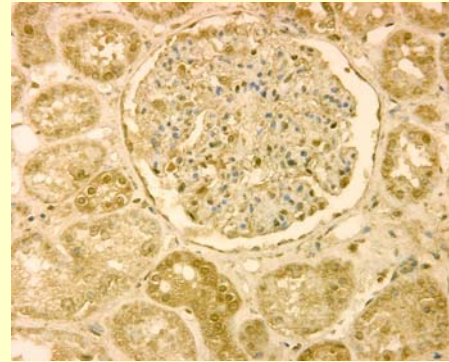
Human type 2 model

Jak2

Diabetic

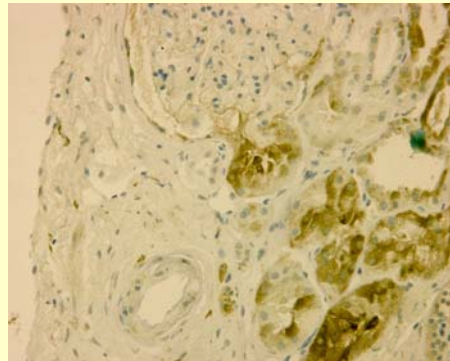


Normal

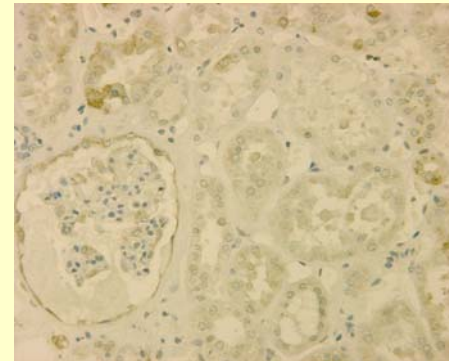


Jak3

Diabetic



Normal



db/db C57BL/6J model Jak2 expression

