Modifications in Mouse Models to Enhance Nephropathy/Neuropathy

- Increased oxidative stress

- Increased glucose metabolic flux or alteration in GLUT expression profiles that will lead to changes in glucose metabolism

AMDCC

GCLC +/- db/db C57BL/6J model

- γ-glutamate cysteine ligase heavy chain responsible for glutathione synthesis
- GCLC -/- embryonically lethal
- GCLC +/- mild oxidative stress
- GCLC +/- mice placed in db/db c57BL/6J background

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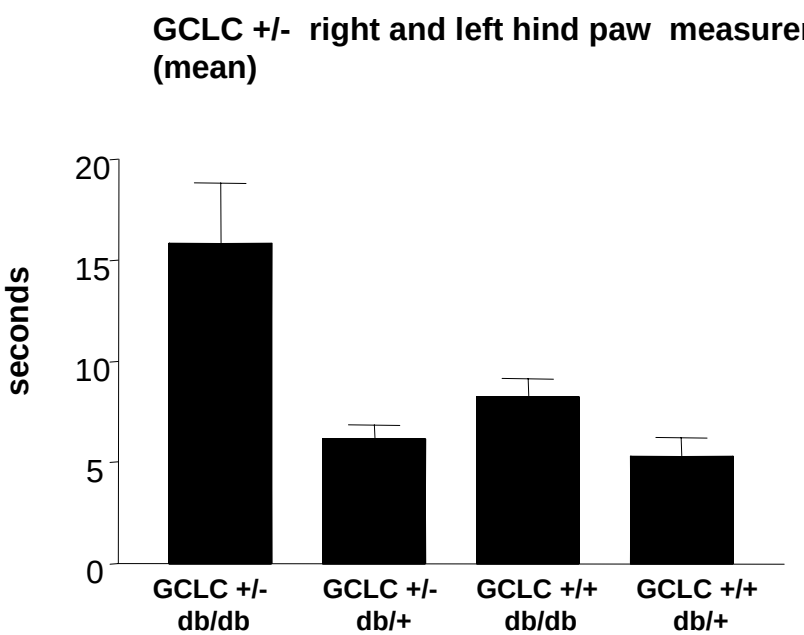
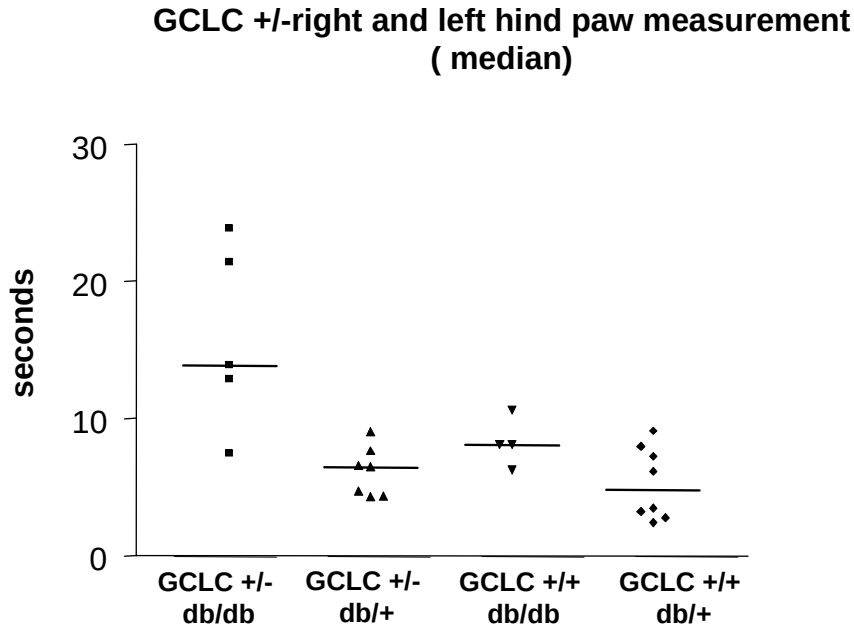
Neuropathy-GCLC db/db C57BL/6J model





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ARtg SOD2 +/- C57BL/6J model

- Aldose reductase (AR) implicated in diabetic complications
- ARtg mice have no increase neuropathy (Stevens, et al.)
- ARtg mice have decreased ROS and evidence of increased SOD activity

- Combined model (ARtg SOD2+/-) has relatively normal ROS levels

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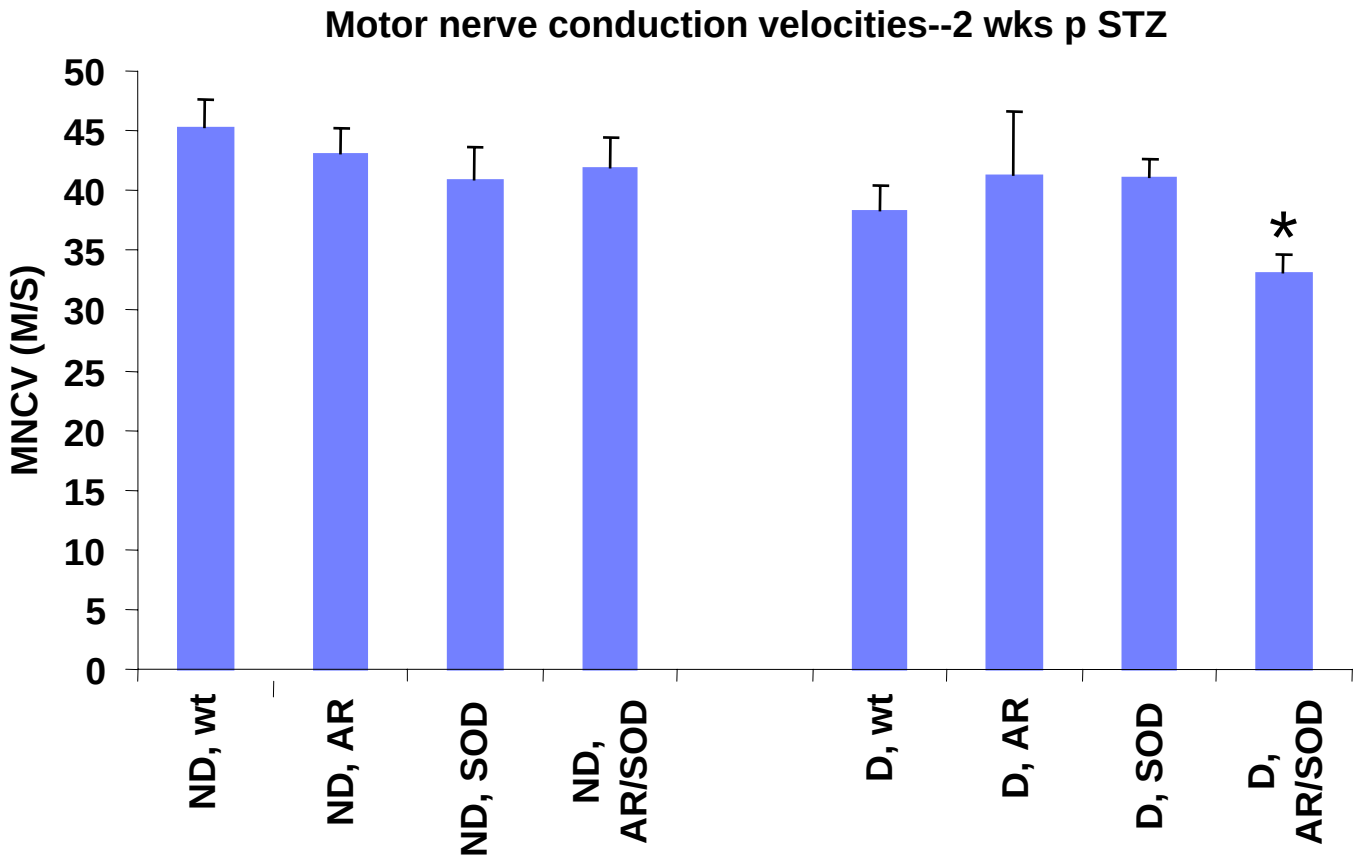
Neuropathy-ARtg SOD2 +/- STZ c57Bl/6J model



* p<0.05 vs. D, wt

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GLUT4 -/- C57BL/6J model

- GLUT4 -/- mice: insulin resistance but no overt diabetes, diminished fat stores and FFA levels.
- GLUT4 expressed in renal glomerular mesangial cells and podocytes.
- GLUT4 -/- led to proteinuria on mixed background. Pathogenesis unclear (increased GLUT1?)

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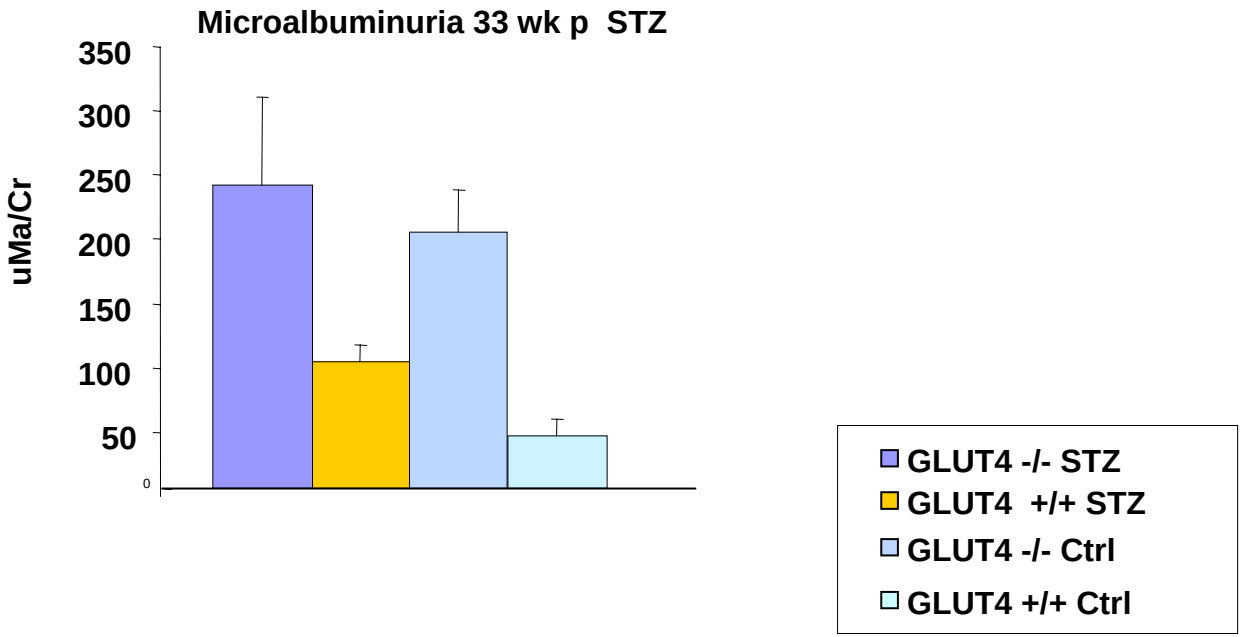
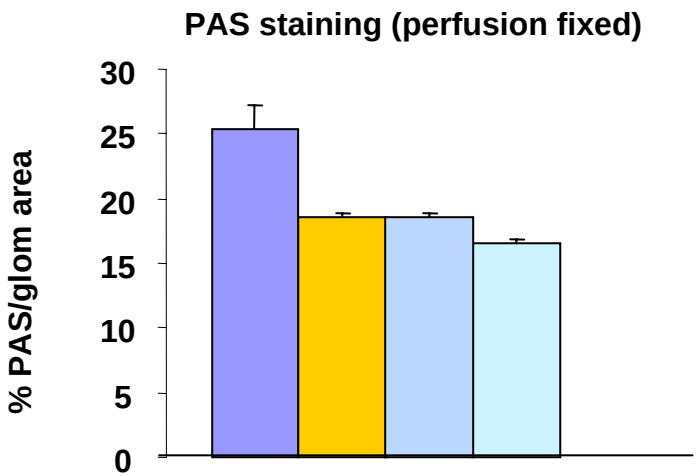
GLUT4 -/- STZ C57BL/6J model





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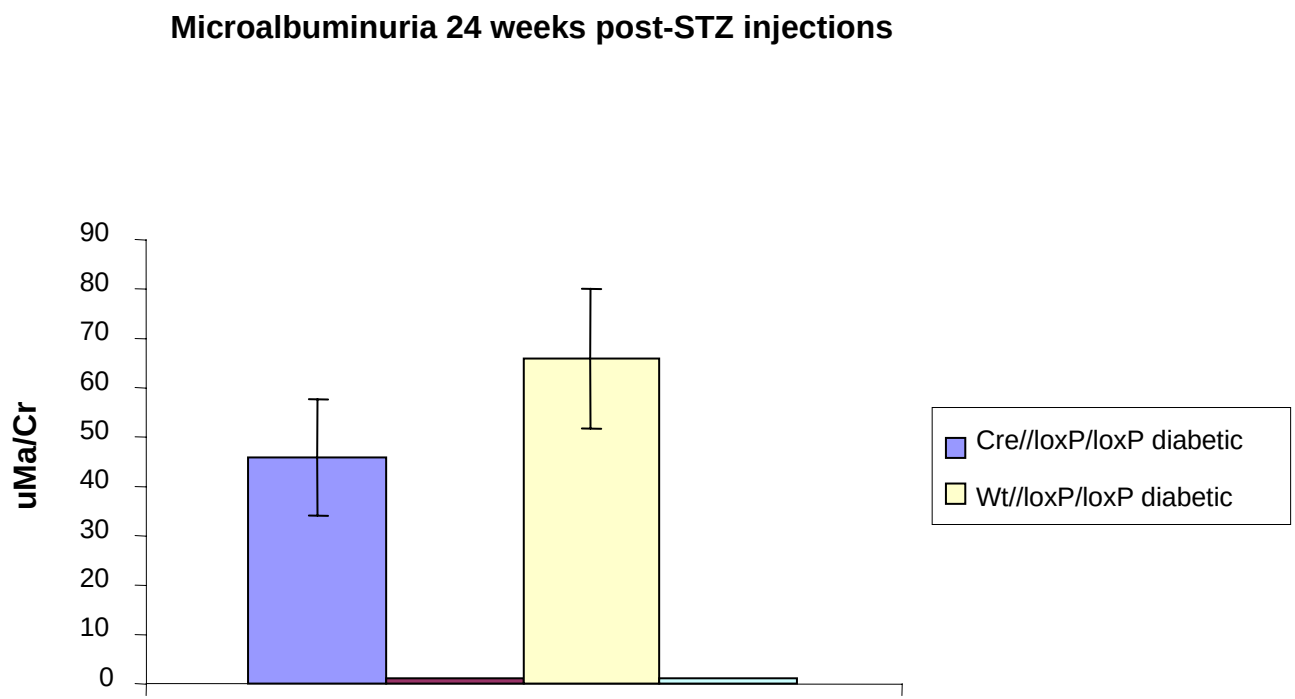
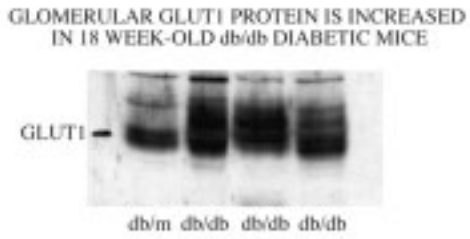
Nphs2 Cre GLUT4 loxP/loxP STZ mixed model



GLUT1tg C57Bl/6J model



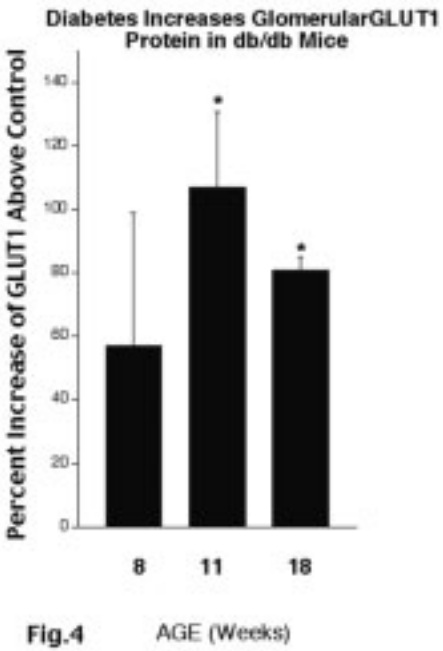


Fig.4

- GLUT1 is increased in glomerular cells in diabetes and in mesangial cells and podocytes cultured in high glucose
- GLUT1 leads to enhanced PKCα and AR activity, fibronectin synthesis
- Modified β-actin promoter drives GLUT1 in many tissues: high in mesangial cells

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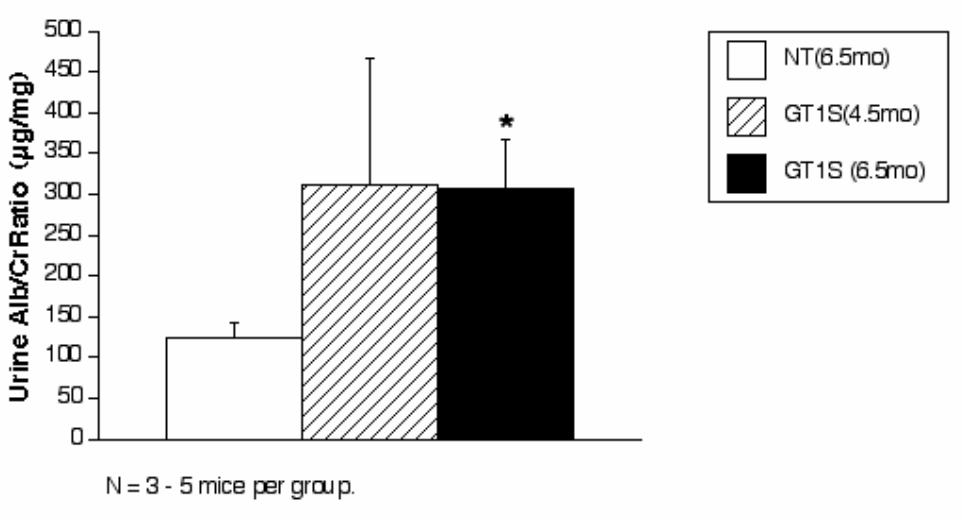
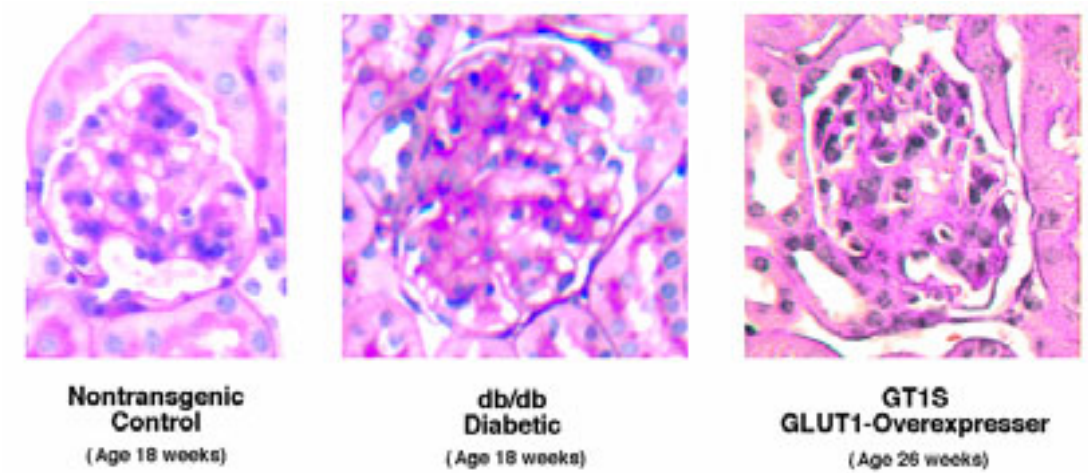
Nephropathy-GLUT1tg db/db C57BL/6J model

Albumin/Creatinine Ratios



PAS staining



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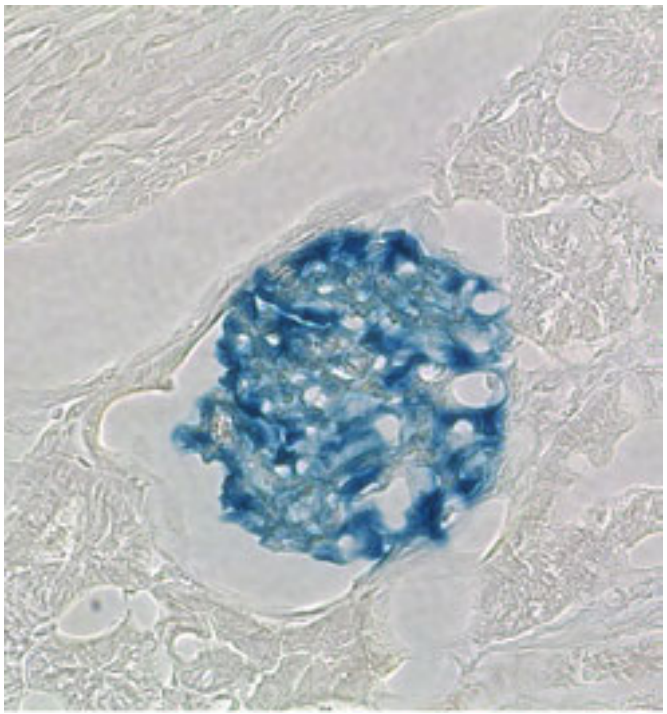
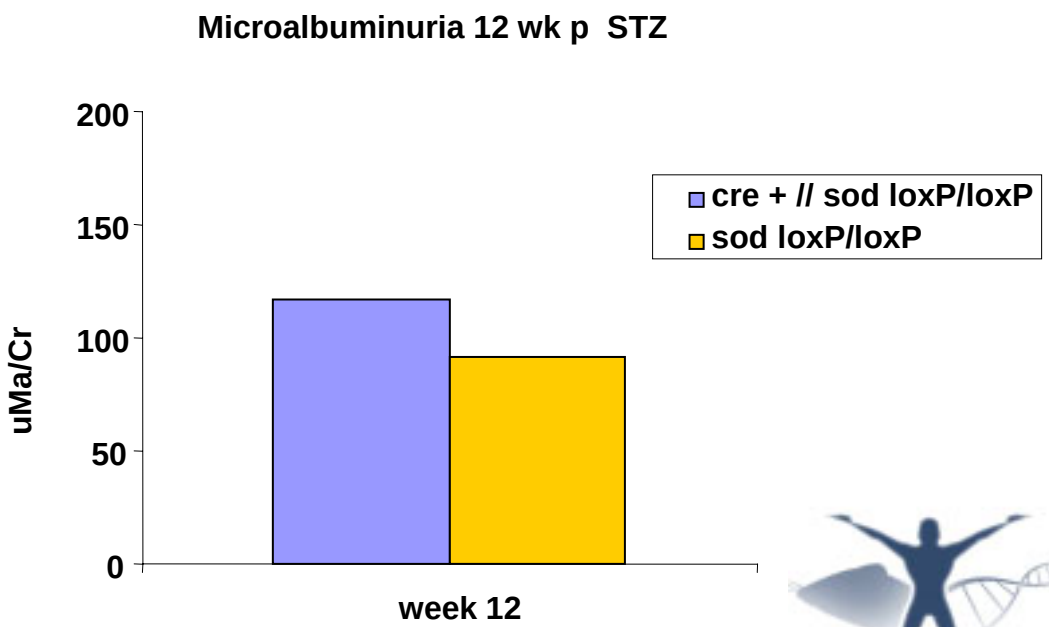
Nephropathy
Nphs2 Cre SOD2 loxP/loxP C57BL/6J model

nphs2 cre x Rosa26



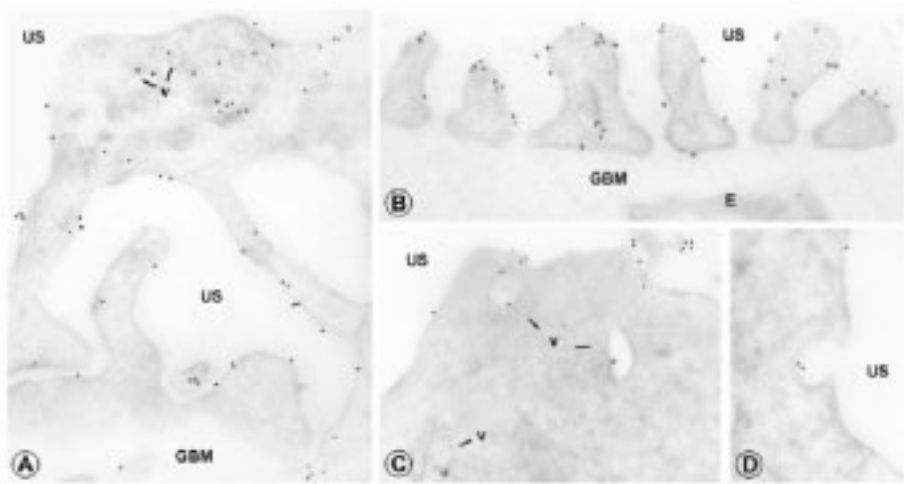


AMDCC

Nphs2 GLUT1tg db/db C57BKS 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 C57BKS model

Glomerular GLUT1 immunoblot