# AMDCC Progress Report
# Duke/UNC/Stanford Unit

Program Director
Thomas M. Coffman, MD

AMDCC

Susceptibility Mutation ← *Model Development*

+ ApoE-/-

+STZ

**Kidney Phenotype Screen**

**Vascular & Kidney Phenotype Screen**

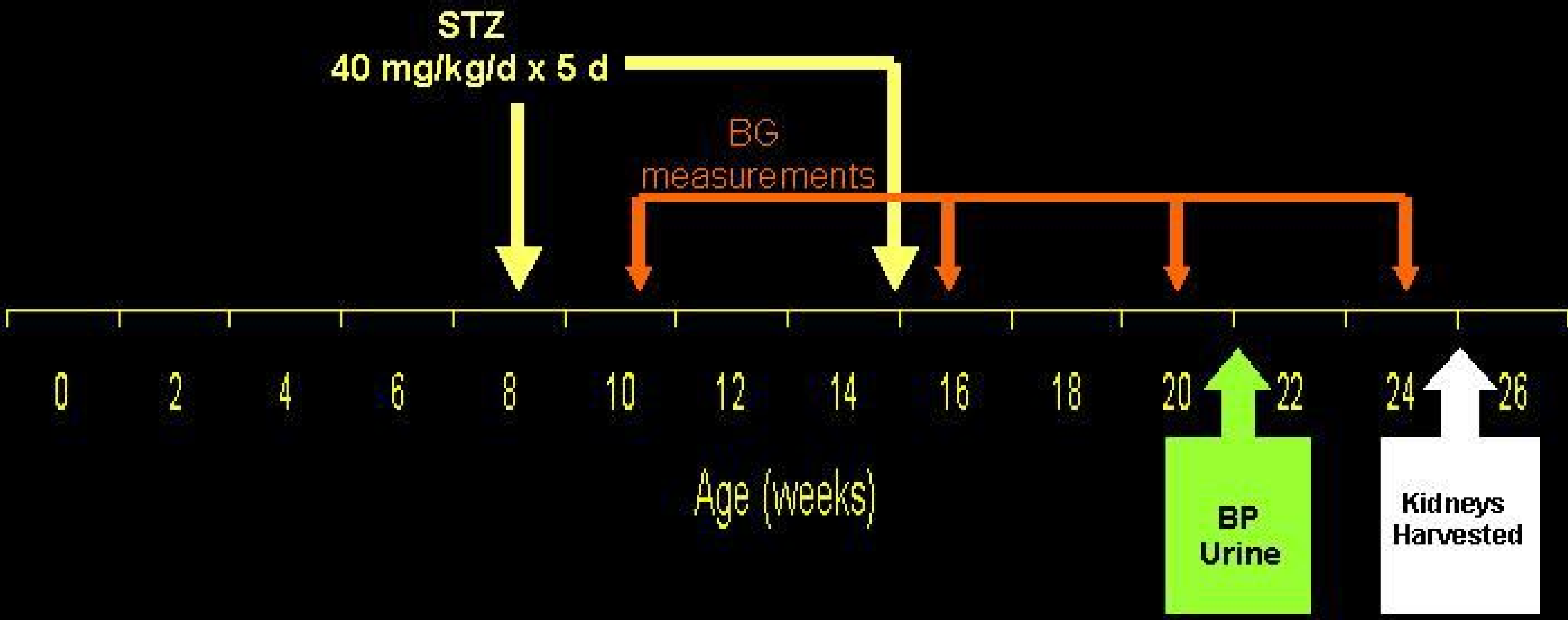
**Transfer mutations to diabetic backgrounds**

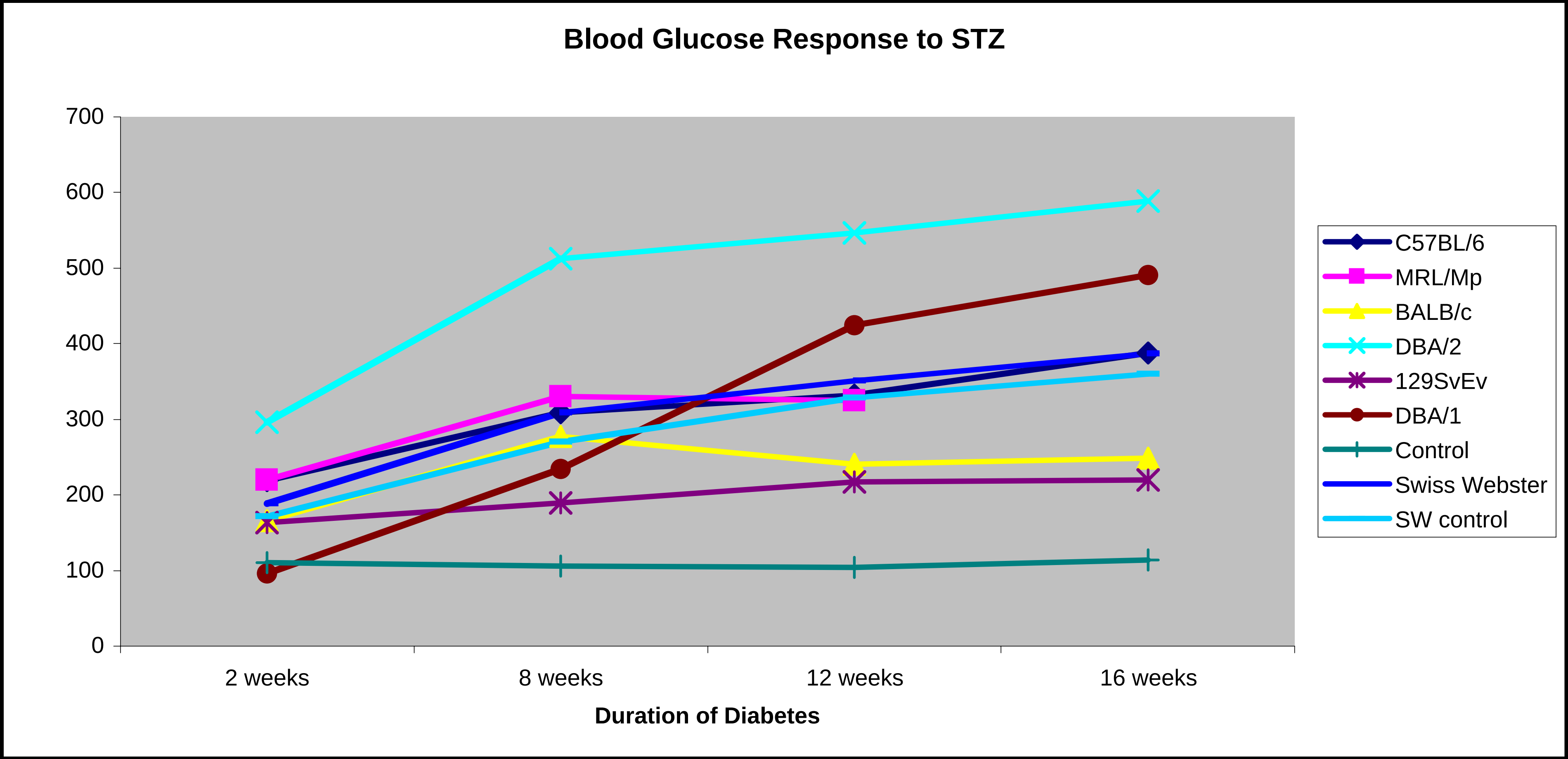
*Generate ES Cell Lines From Diabetic Mice* →

# STZ Strain Comparison

- Added DBA/1 and Swiss Webster
- Total of 7 strains screened

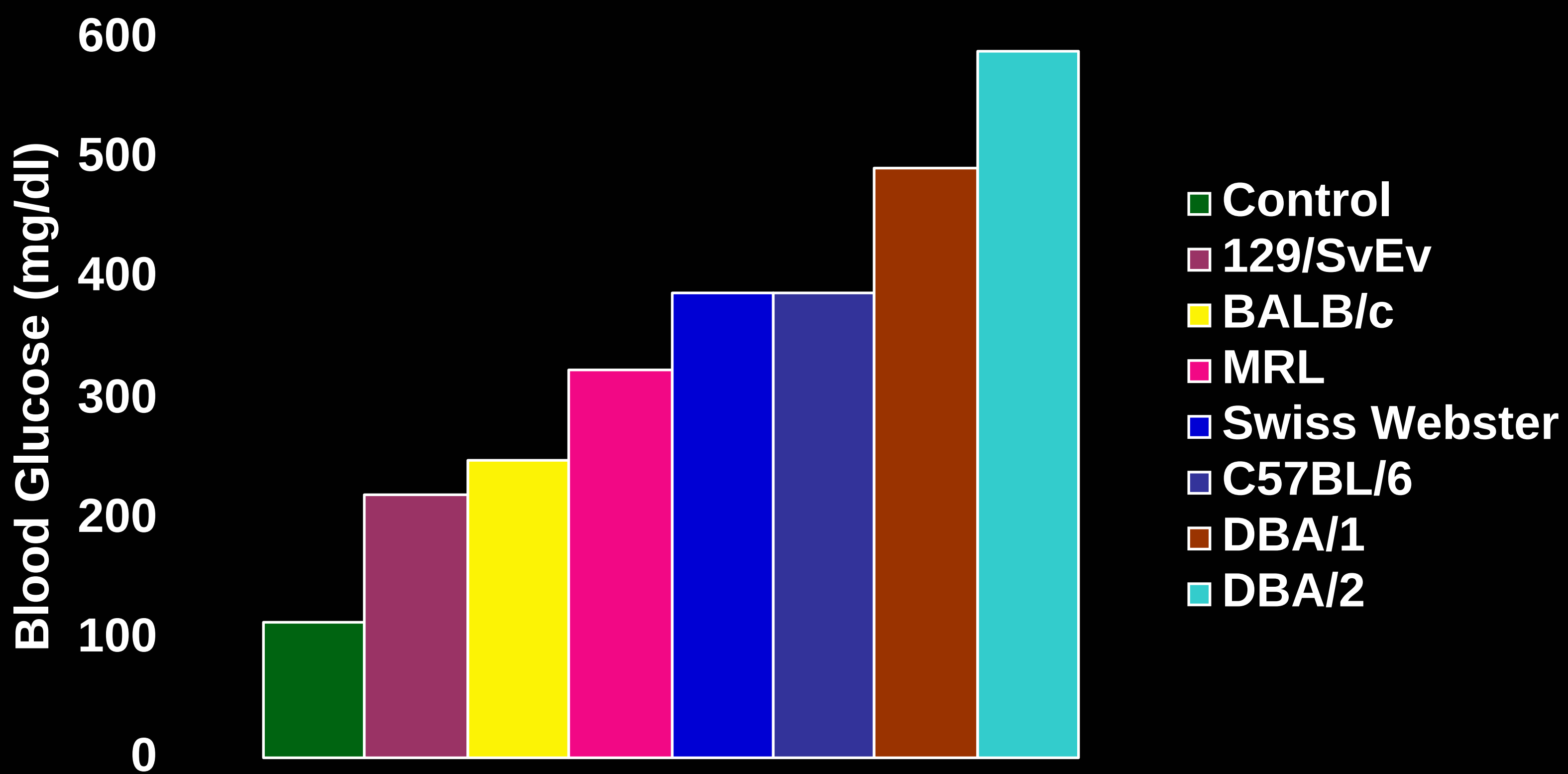
# Strain Comparison Protocol



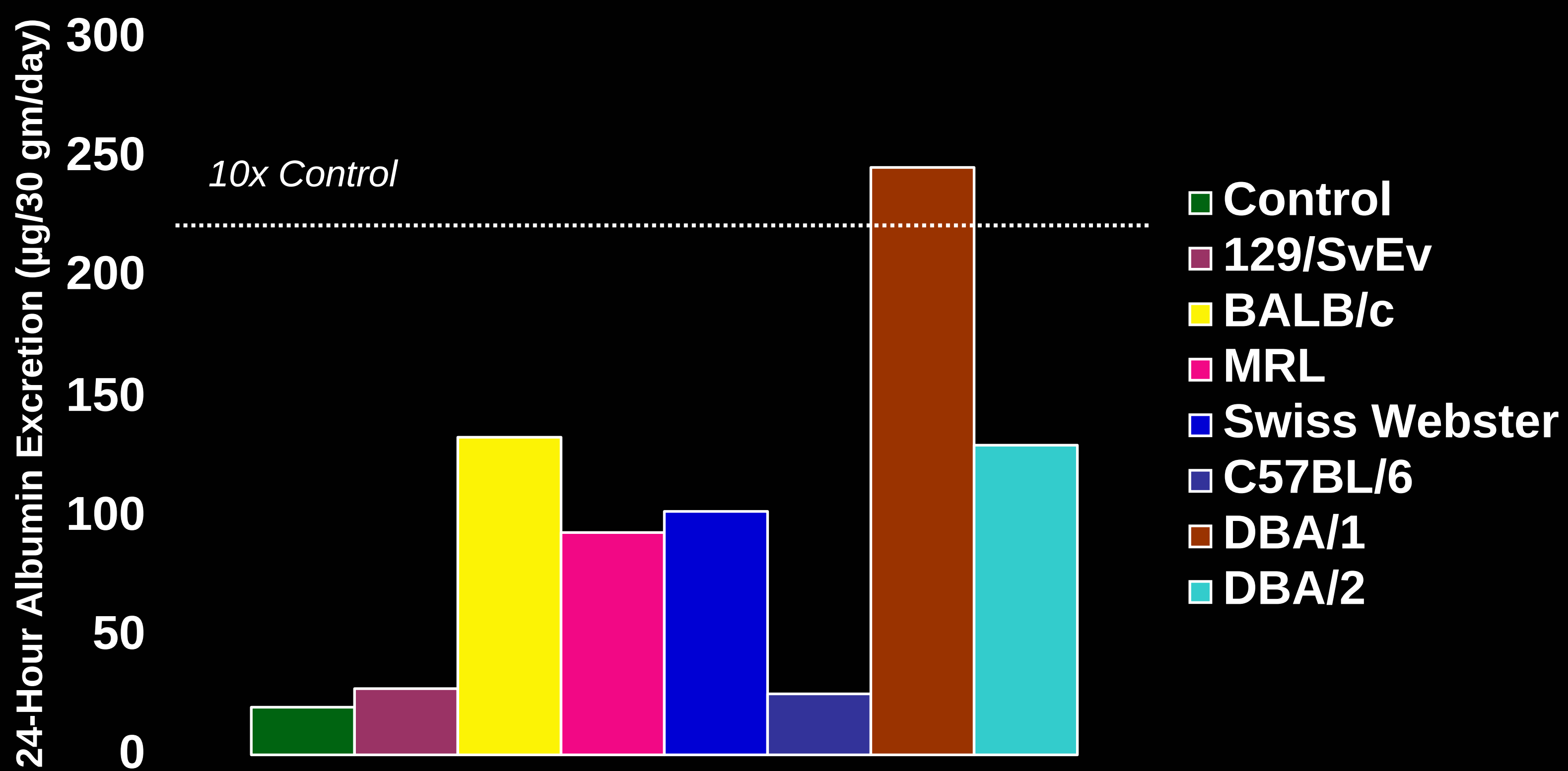


Blood Glucose Response to STZ
700
600
500
400
300
200
100
0
2 weeks
8 weeks
12 weeks
16 weeks
Duration of Diabetes
C57BL/6
MRL/Mp
BALB/c
DBA/2
129SvEv
DBA/1
Control
Swiss Webster
SW control

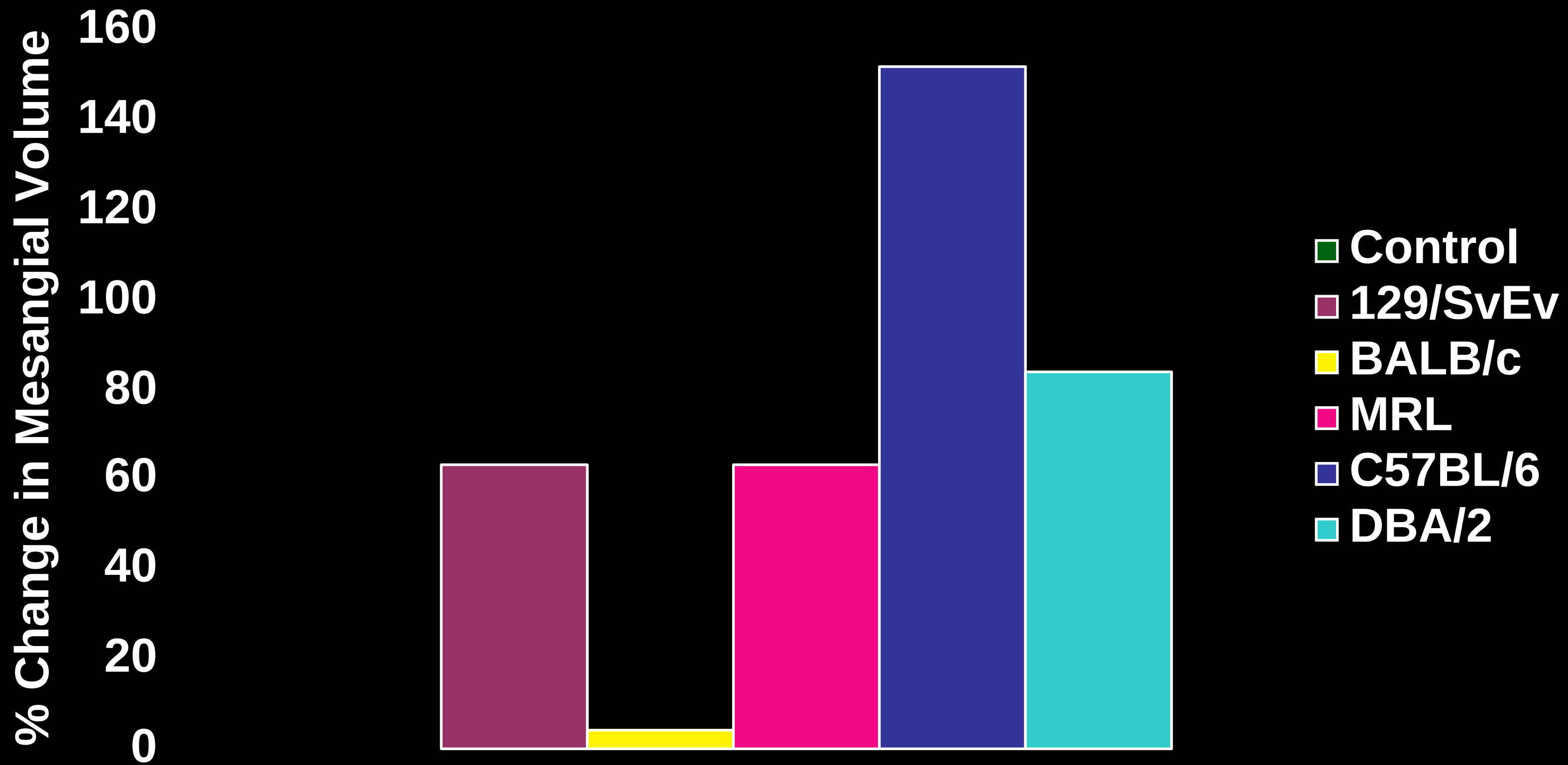
# Blood Glucose 16 Weeks After STZ



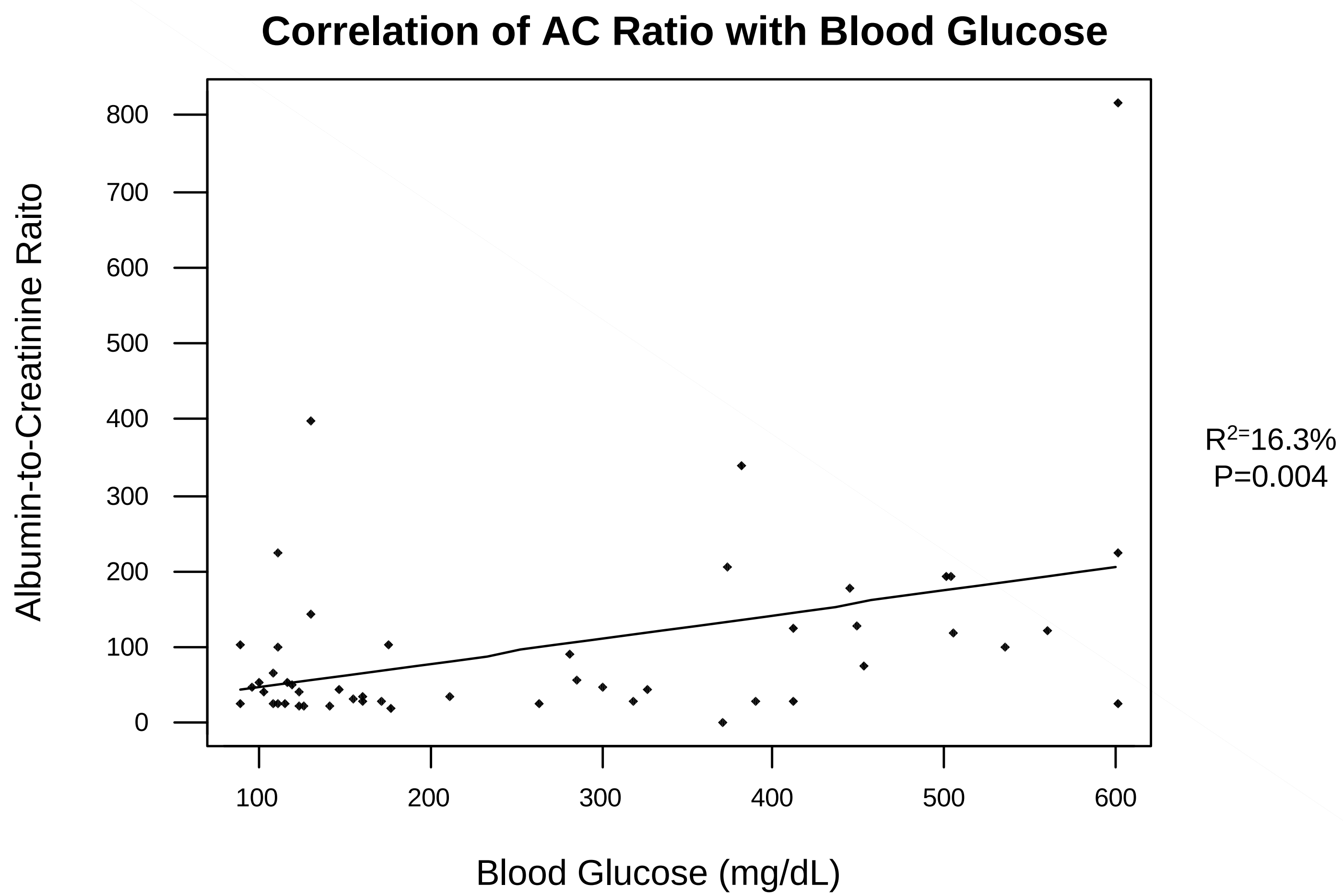
# 24-Hour Albumin Excretion 16 Weeks After STZ



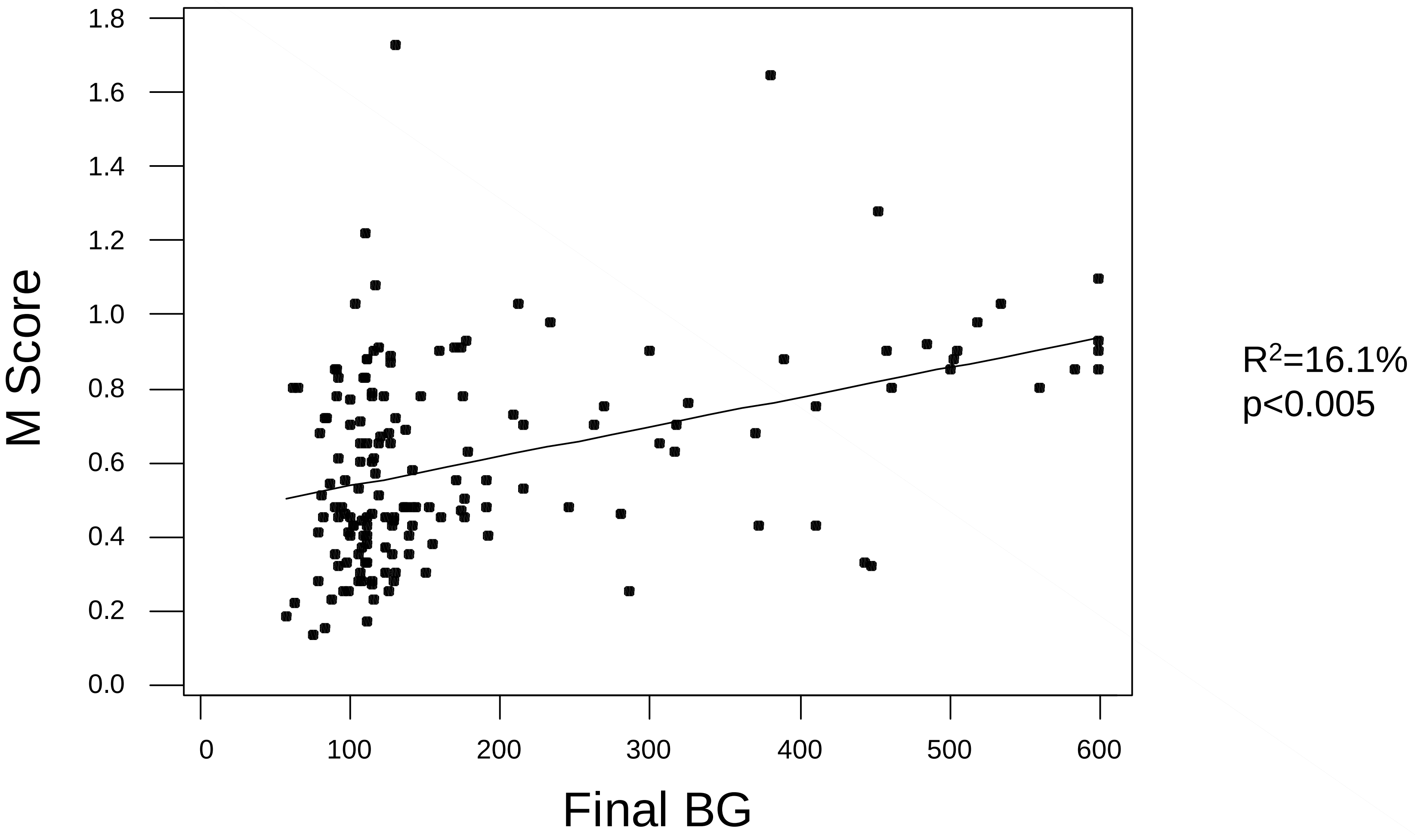
# Mesangial Expansion 16 Weeks After STZ




*There was no significant increase in glomerular volume (Vg) in any group.*



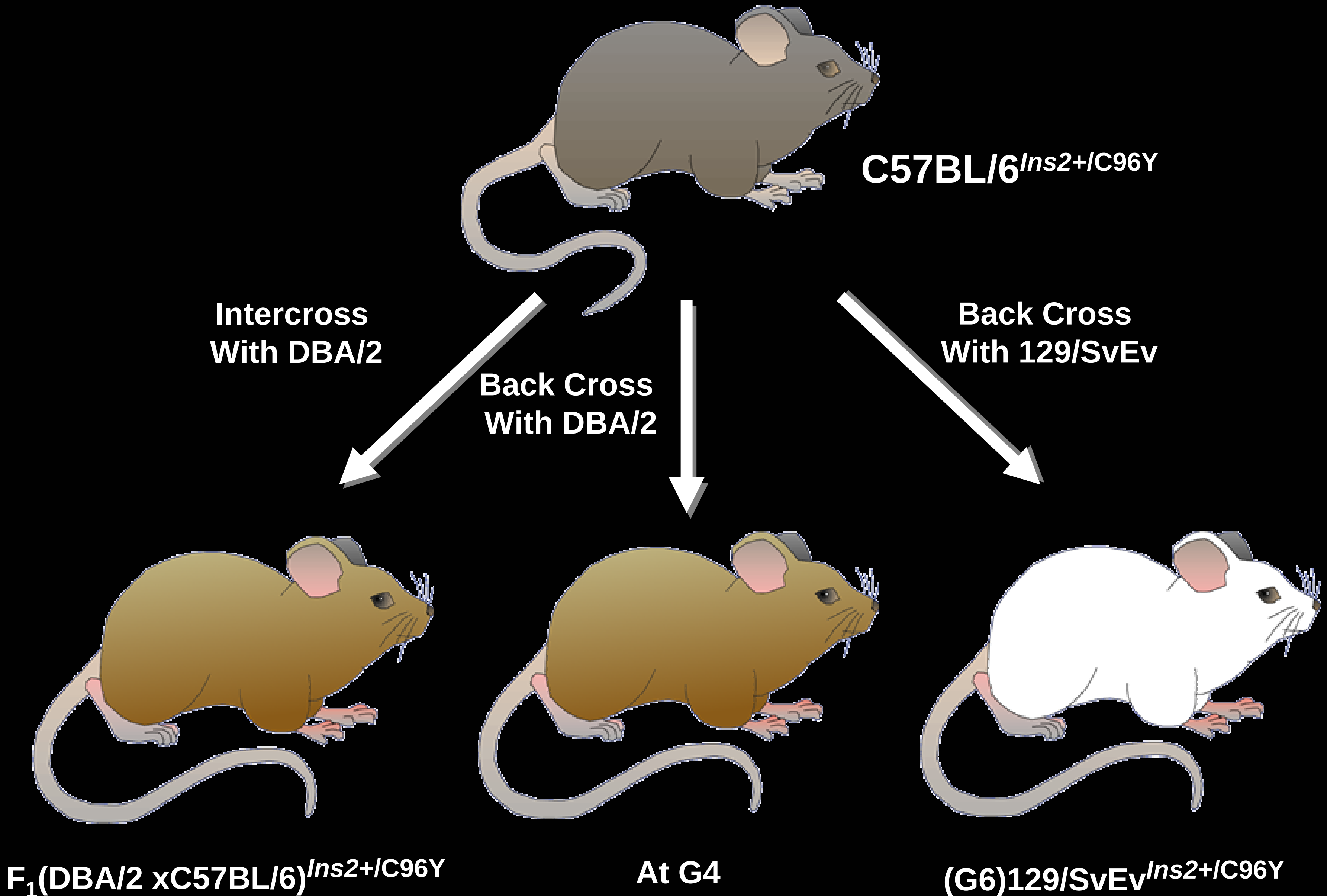
Correlation of AC Ratio with Blood Glucose
Albumin-to-Creatinine Raito
0
100
200
300
400
500
600
700
800
100
200
300
400
500
600
Blood Glucose (mg/dL)
R2=16.3%
P=0.004

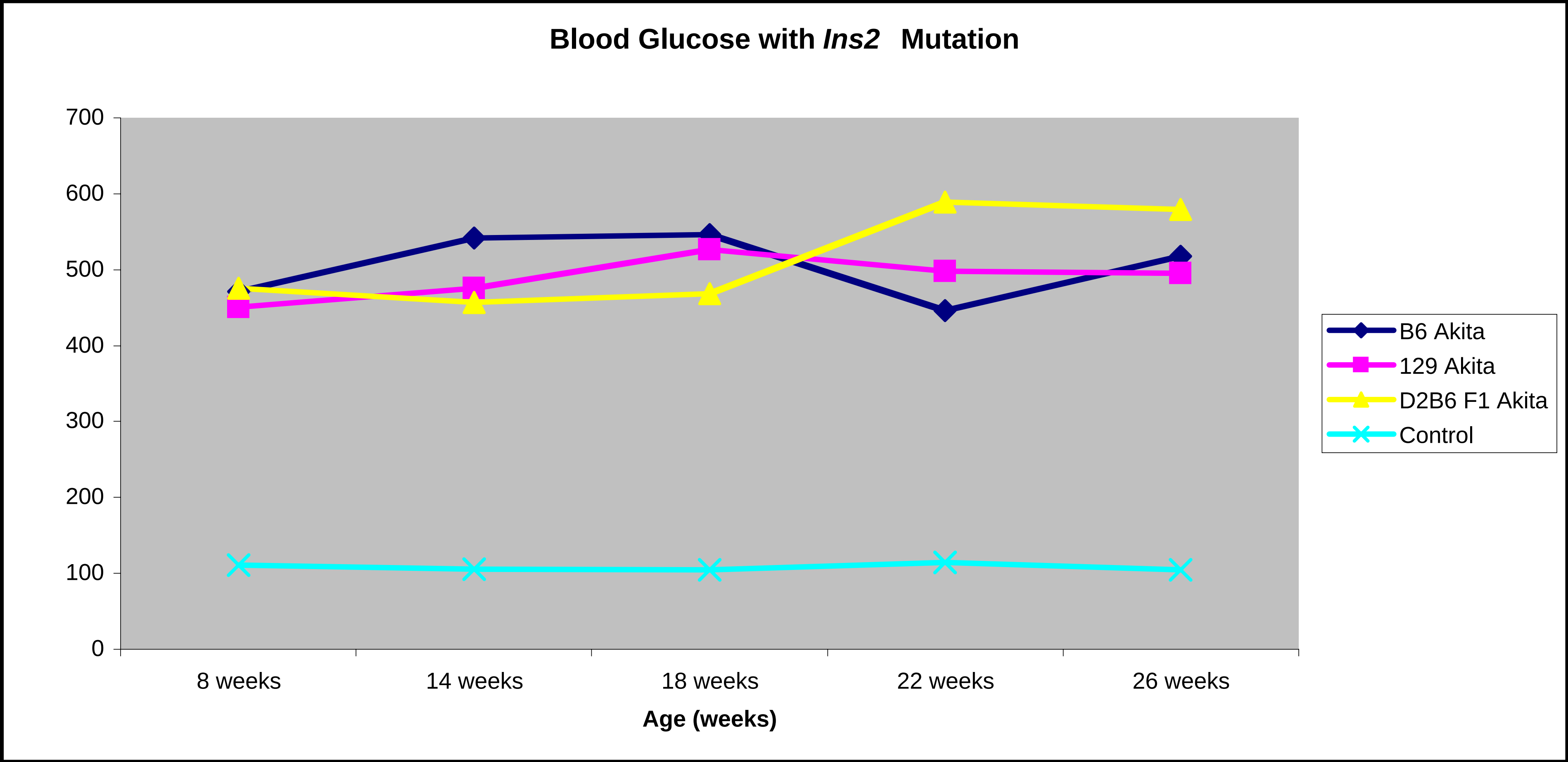


M Score
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
500
600
Final BG
R2=16.1%
p<0.005

# Strain Effects in the Akita (*Ins2*$^{+/C96Y}$) model

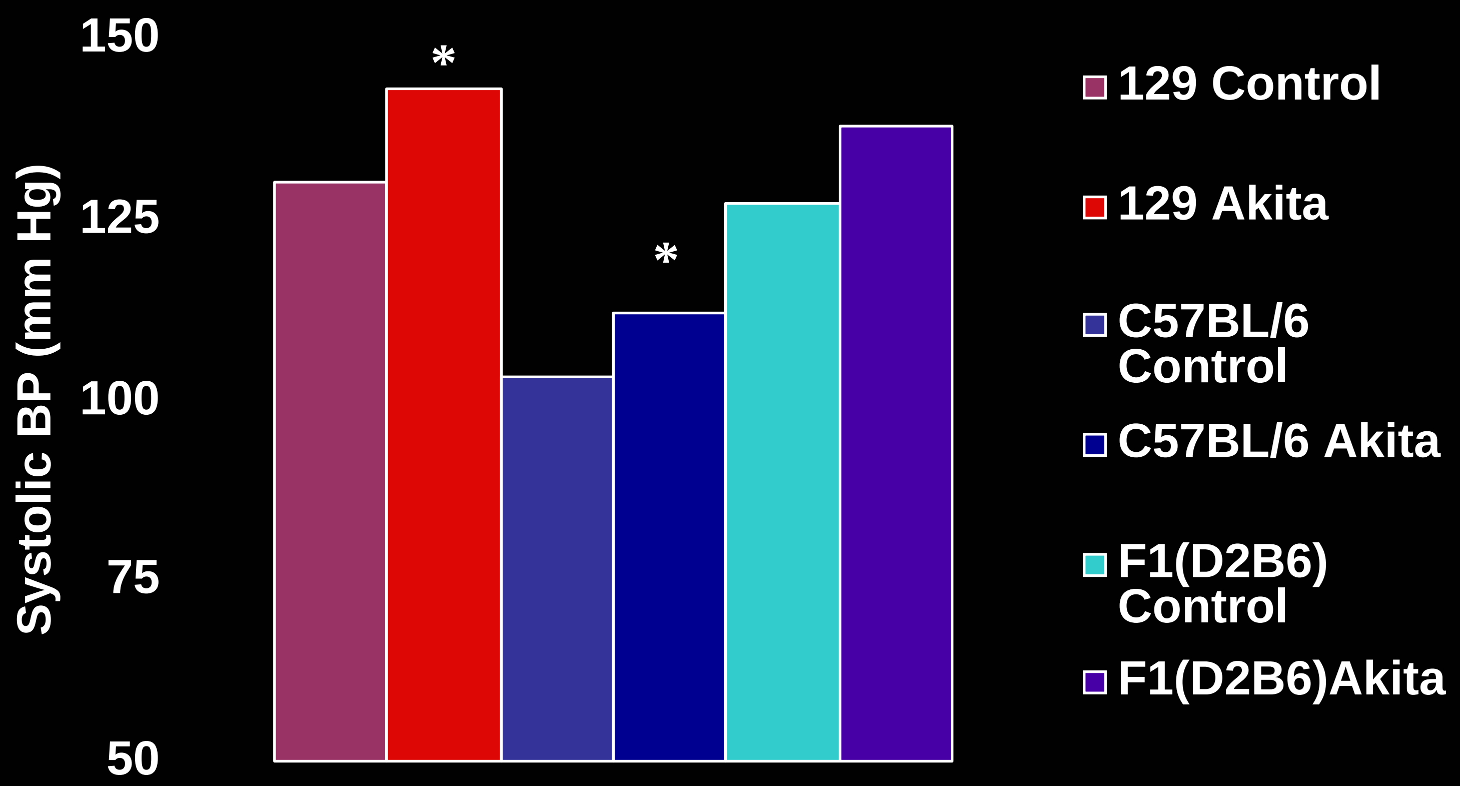
# Generating Inbred *Ins2*$^{+/C96Y}$ Lines



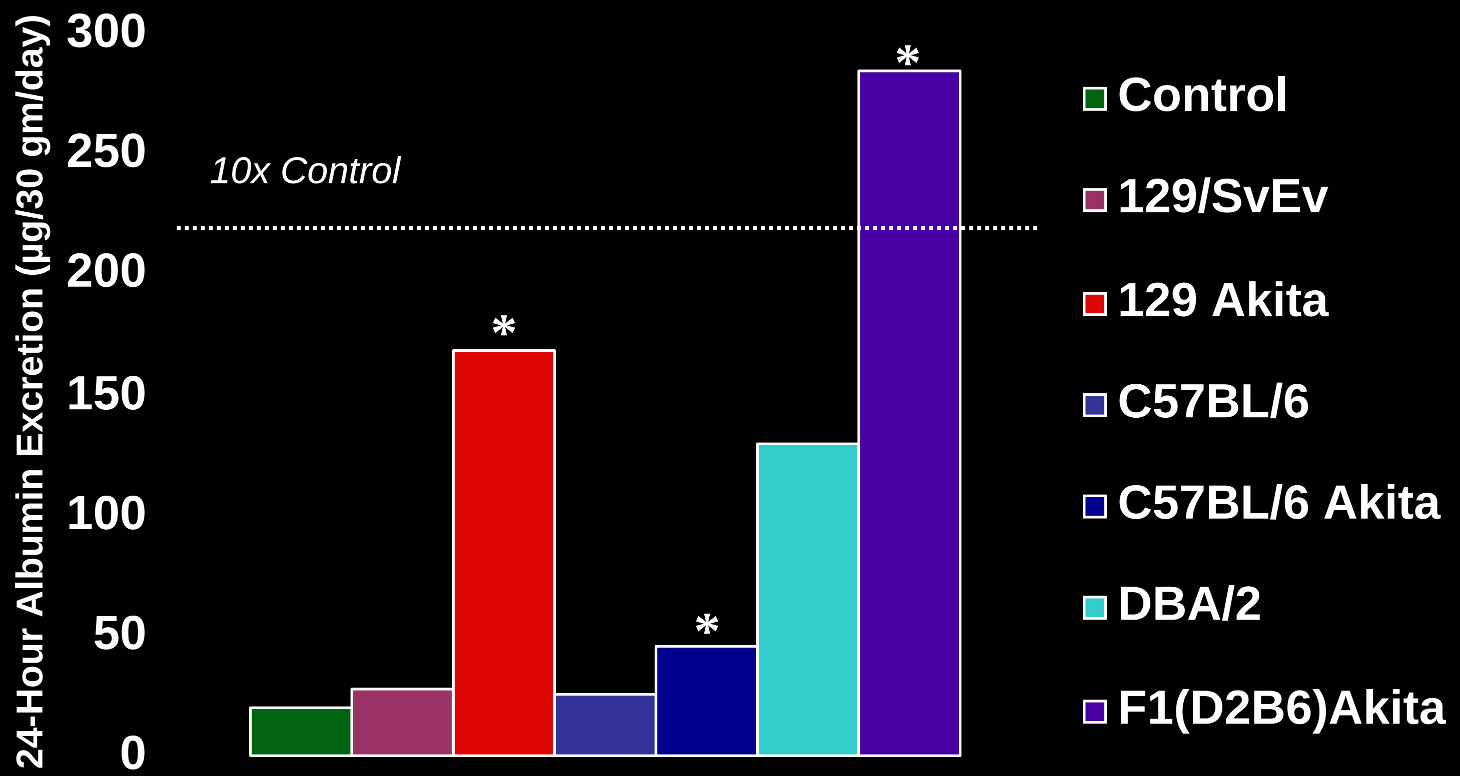


Blood Glucose with *Ins2* Mutation
700
600
500
400
300
200
100
0
8 weeks
14 weeks
18 weeks
22 weeks
26 weeks
Age (weeks)
B6 Akita
129 Akita
D2B6 F1 Akita
Control

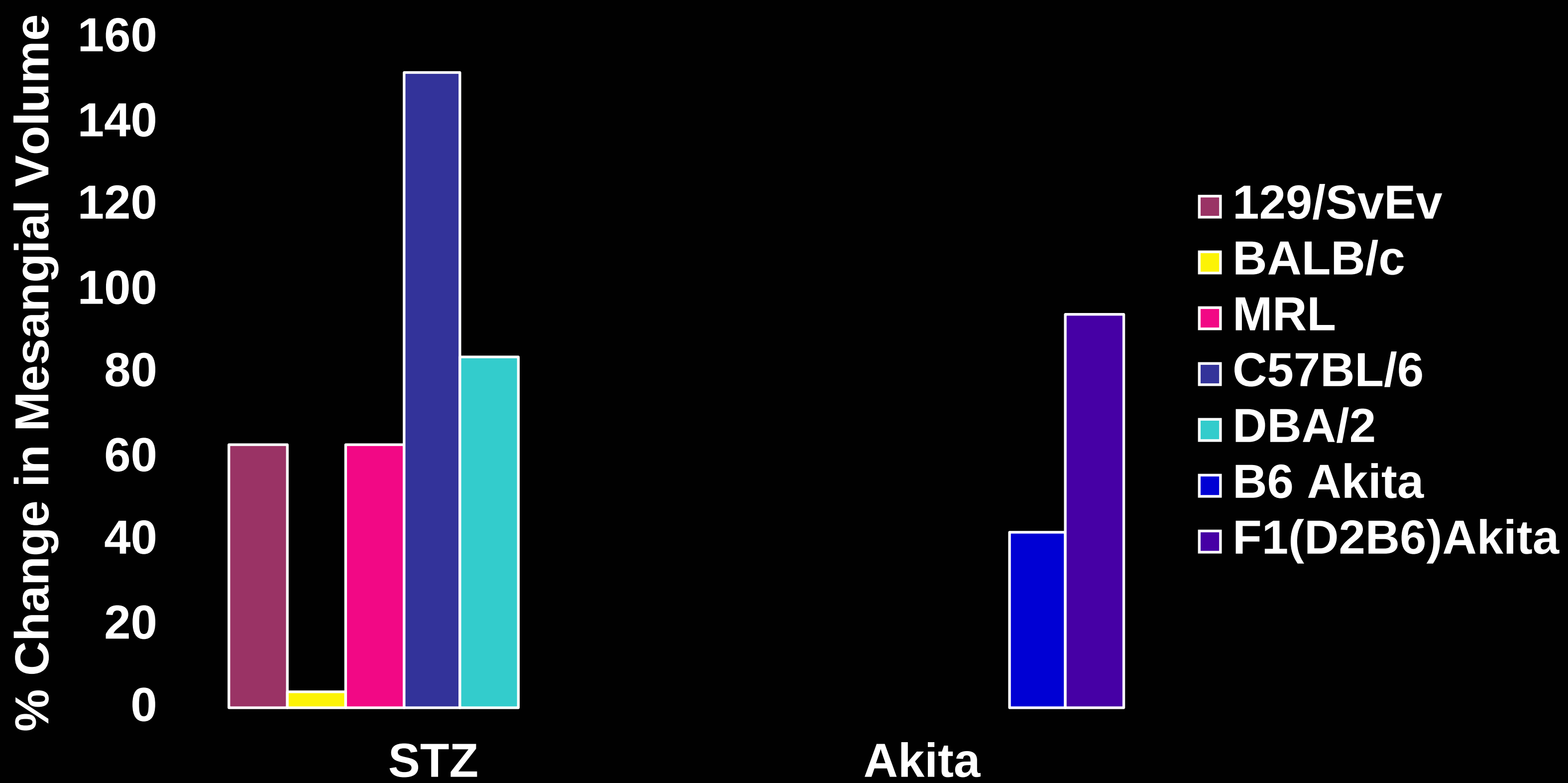
# Systolic Blood Pressures in 6-Month Old Mice



# 24-Hour Albumin Excretion in STZ and Akita Mice

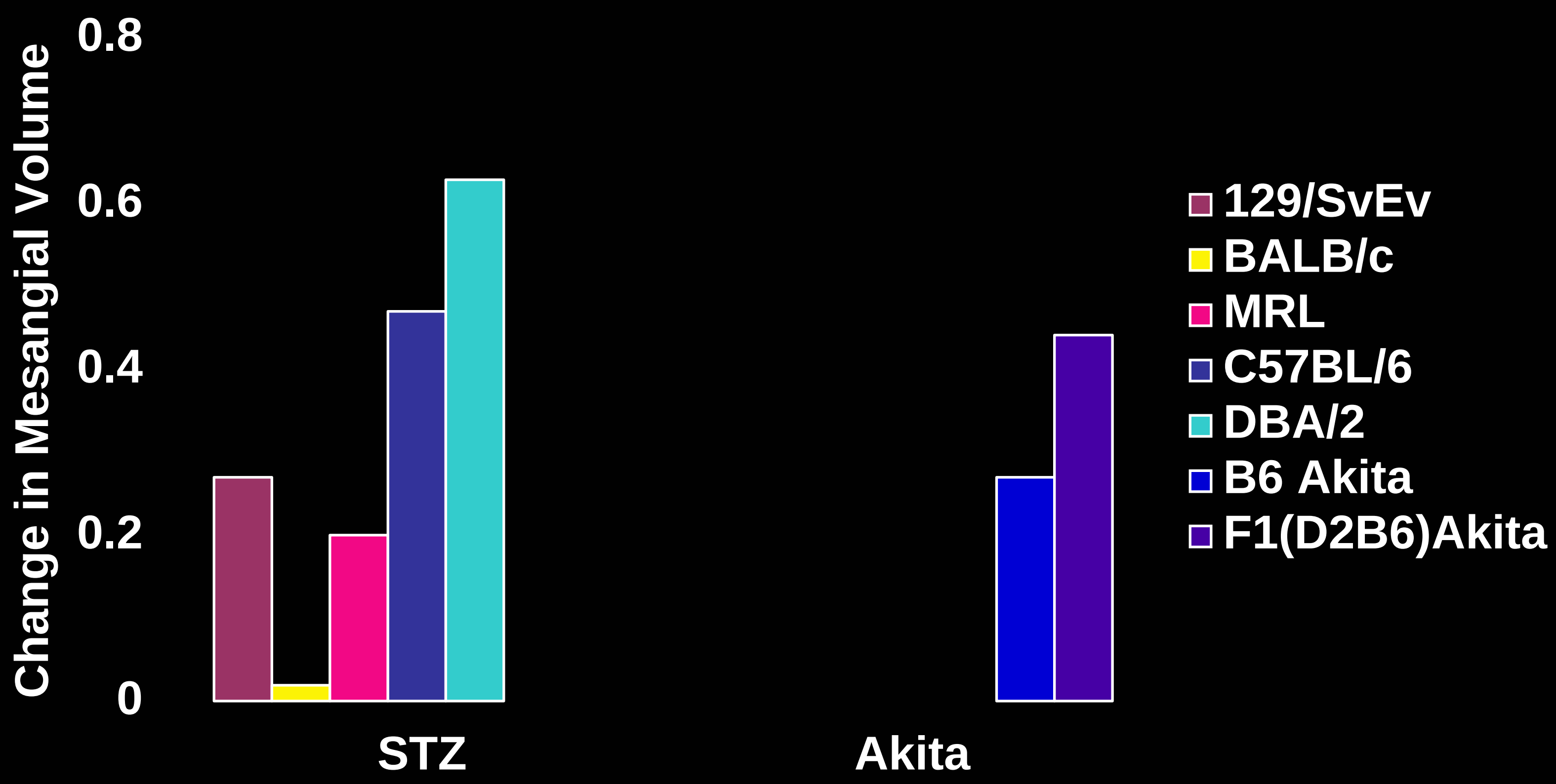


# Mesangial Expansion in Diabetic Mice

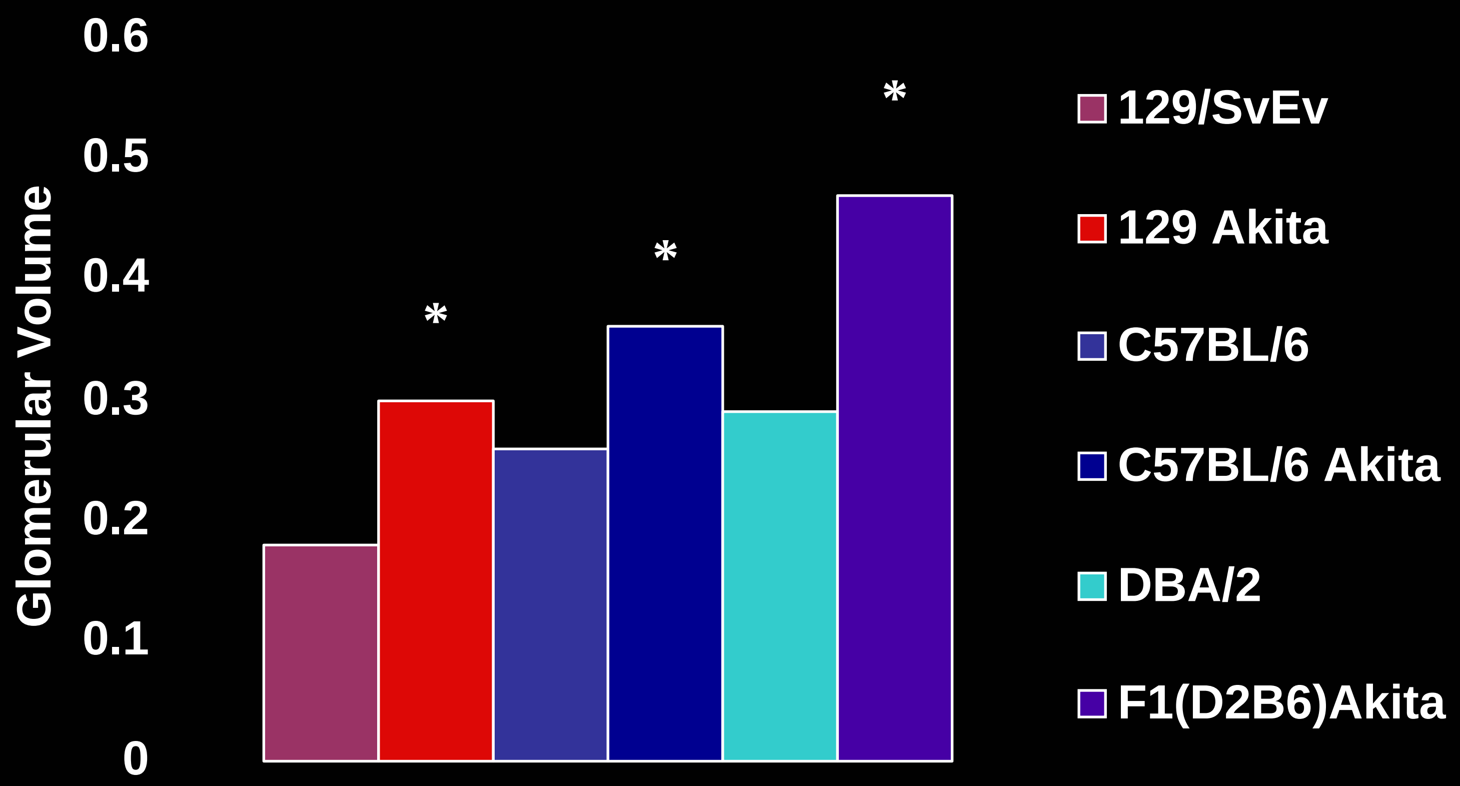


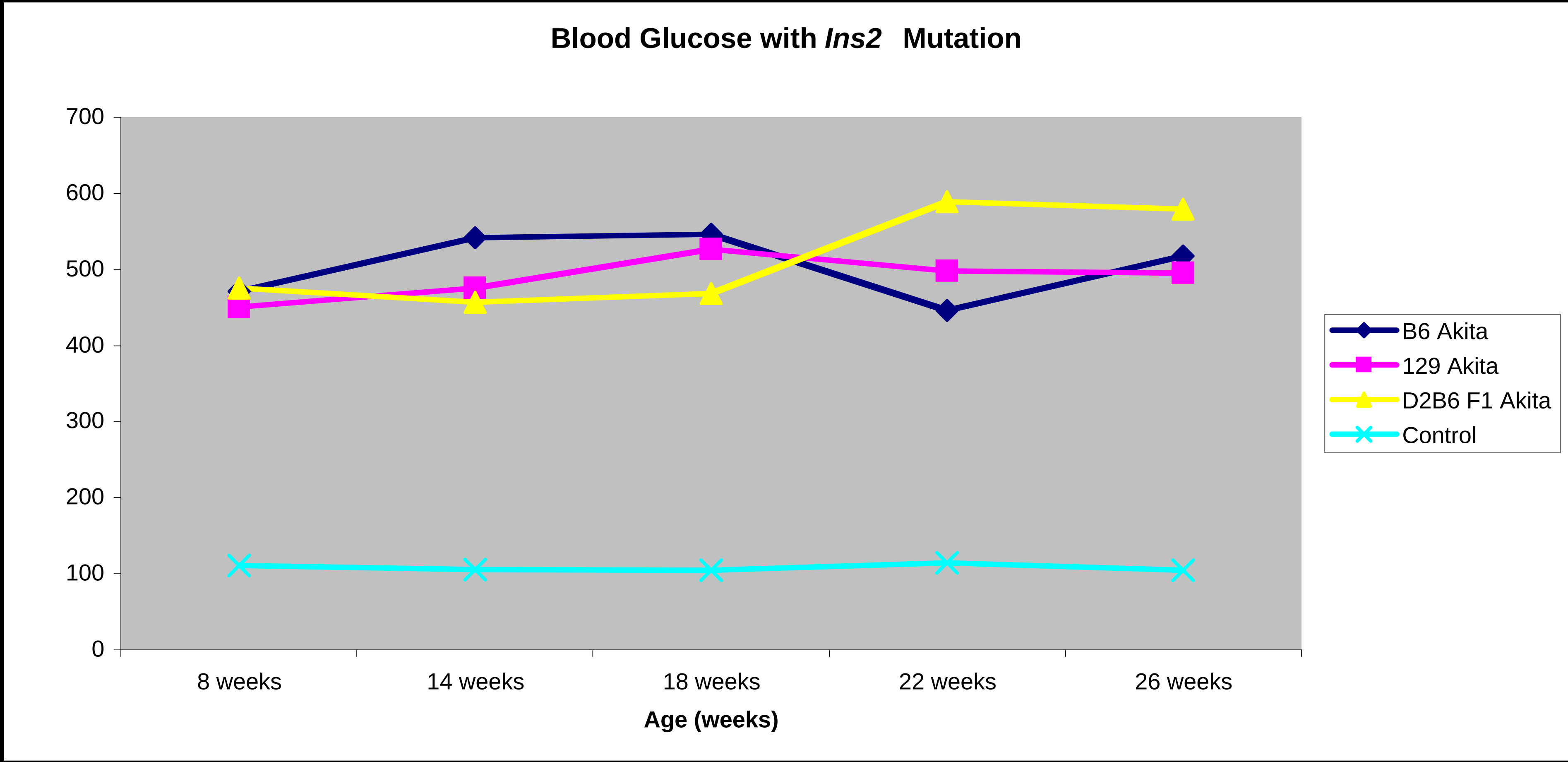

*There was a 52% increase in glomerular volume (Vg) in the F1(D2B6)Akita mice.*

# Mesangial Expansion in Diabetic Mice



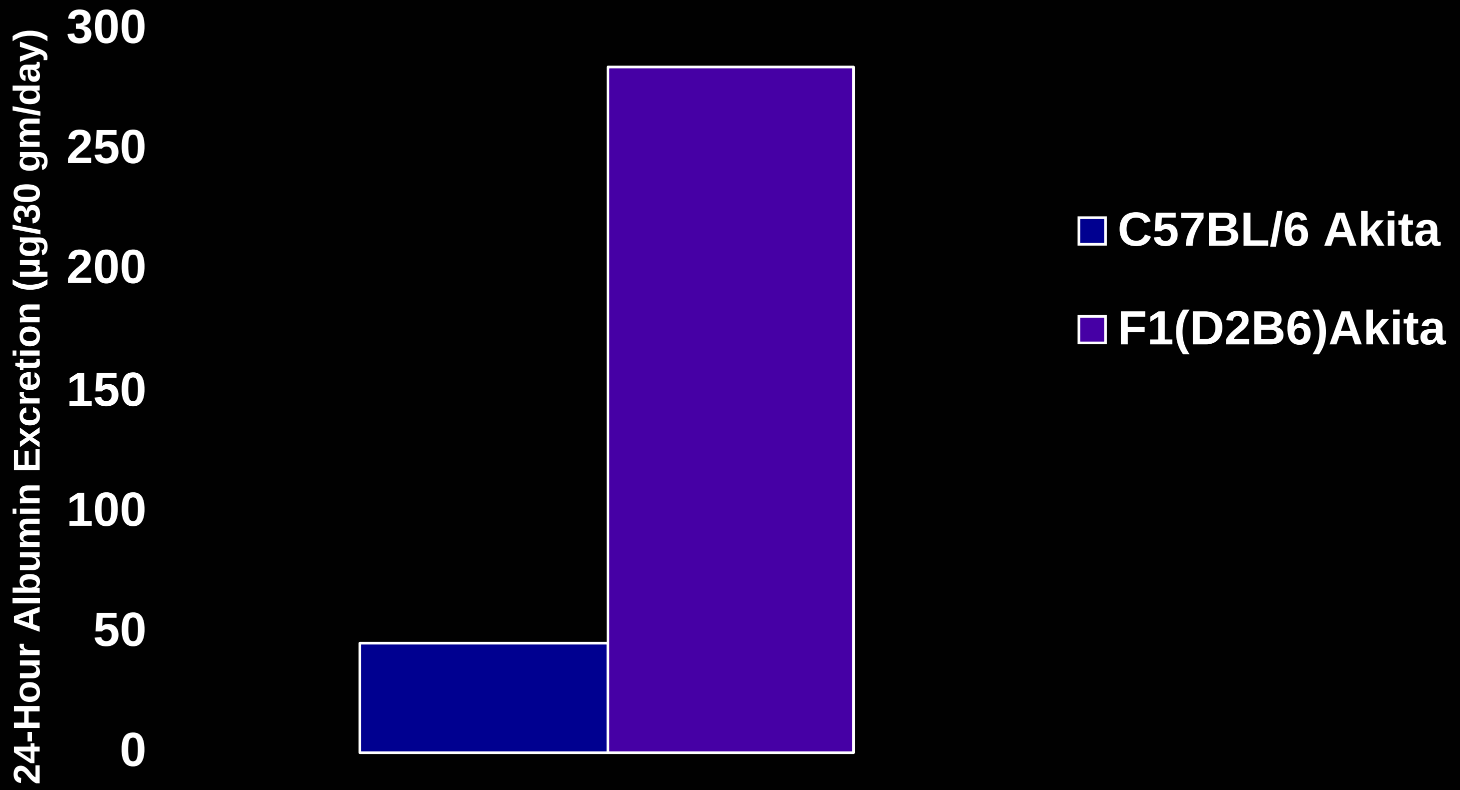
# Glomerular Volumes (Vg) are Increased in Akita Mice

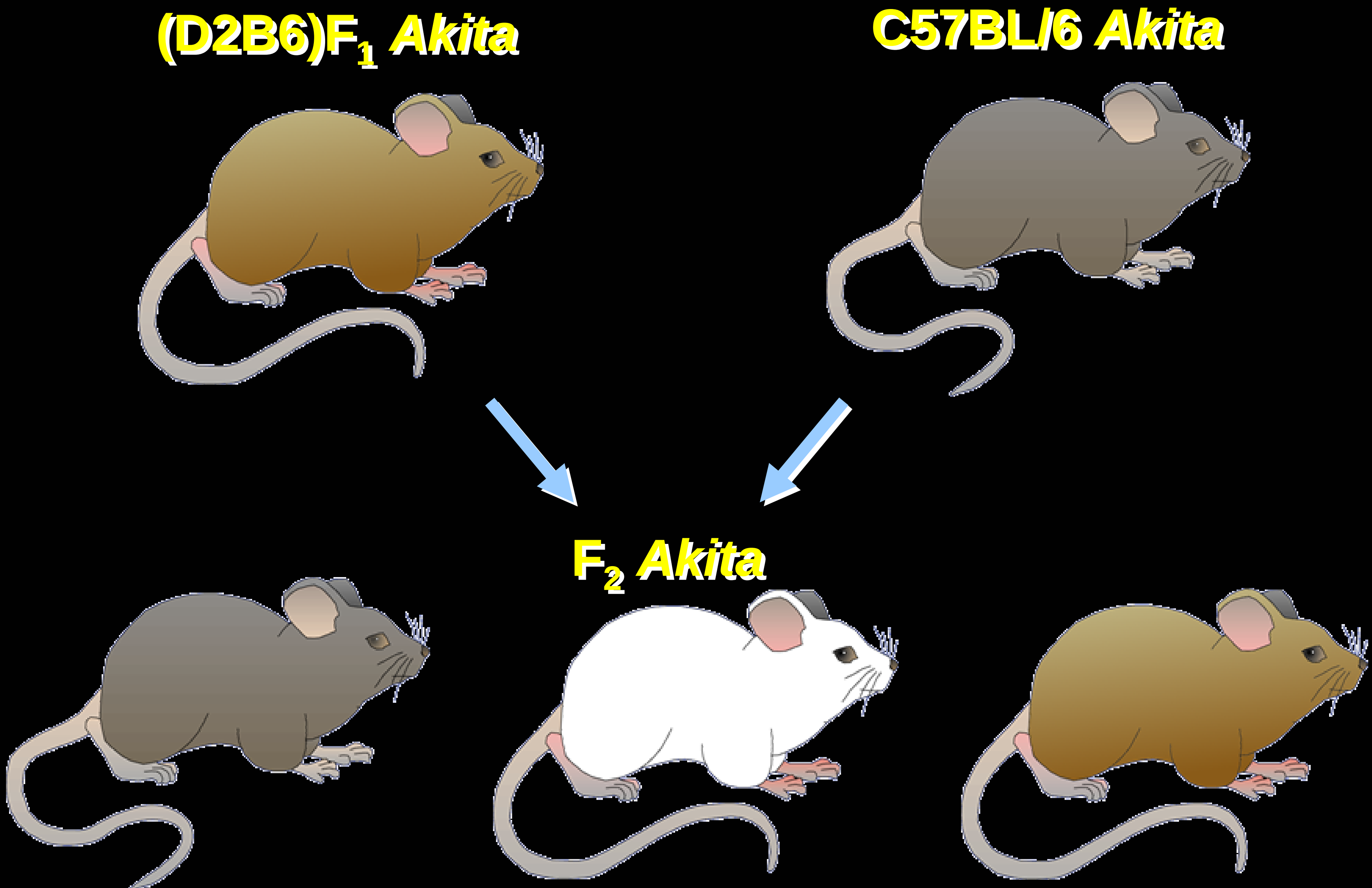




Blood Glucose with *Ins2* Mutation
700
600
500
400
300
200
100
0
8 weeks
14 weeks
18 weeks
22 weeks
26 weeks
Age (weeks)
B6 Akita
129 Akita
D2B6 F1 Akita
Control

## 24-Hour Albumin Excretion in Akita Mice





(D2B6)$F_1$ *Akita*
C57BL/6 *Akita*
$F_2$ *Akita*

# Studies in Progress

- Large group of animals for long-term studies
- Uni-nephrectomy in Akita lines
- Back-crossing of *Ins2*$^{+/C96Y}$ onto DBA/2 and other backgrounds
- Back-cross of (D2B6)F1- *Ins2*$^{+/C96Y}$ with C57BL/6

Susceptibility Mutation

*Model Development*

+ ApoE-/-

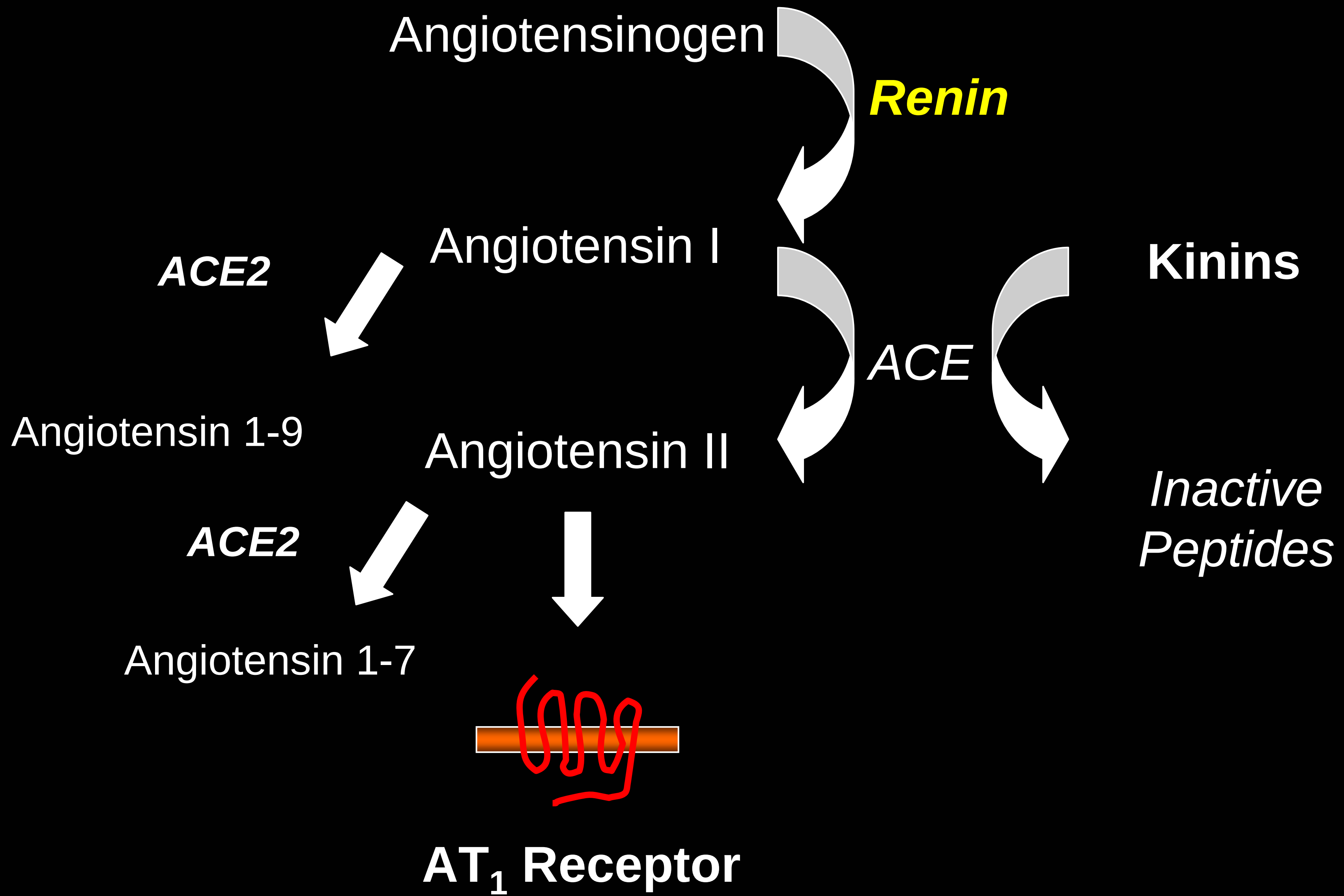
+STZ

**Kidney Phenotype Screen**

**Vascular & Kidney Phenotype Screen**

**Transfer mutations to diabetic backgrounds**

*Generate ES Cell Lines From Diabetic Mice*

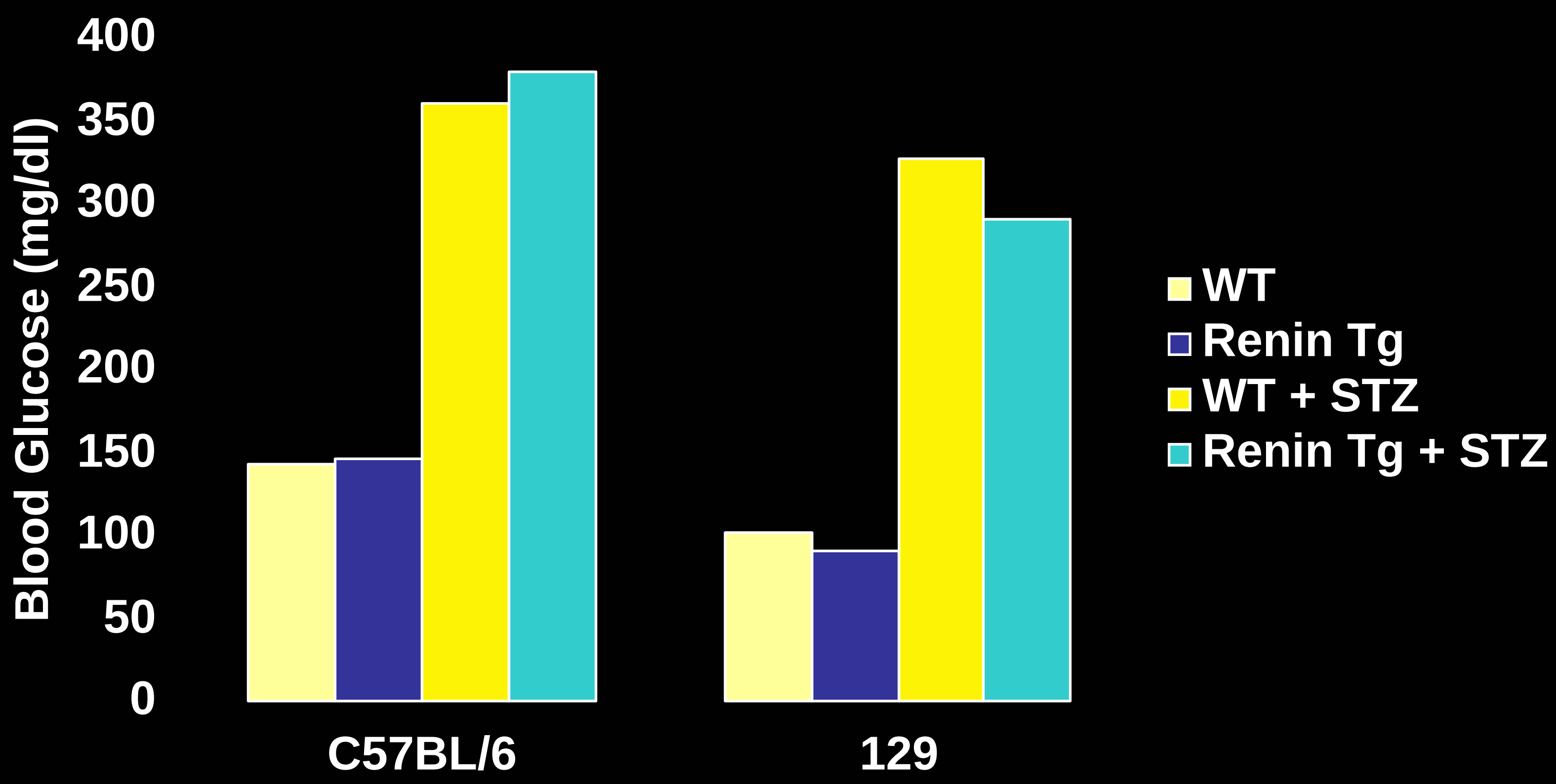


Angiotensinogen
Renin
Angiotensin I
ACE2
Kinins
ACE
Angiotensin 1-9
Angiotensin II
Inactive Peptides
ACE2
Angiotensin 1-7
AT1 Receptor

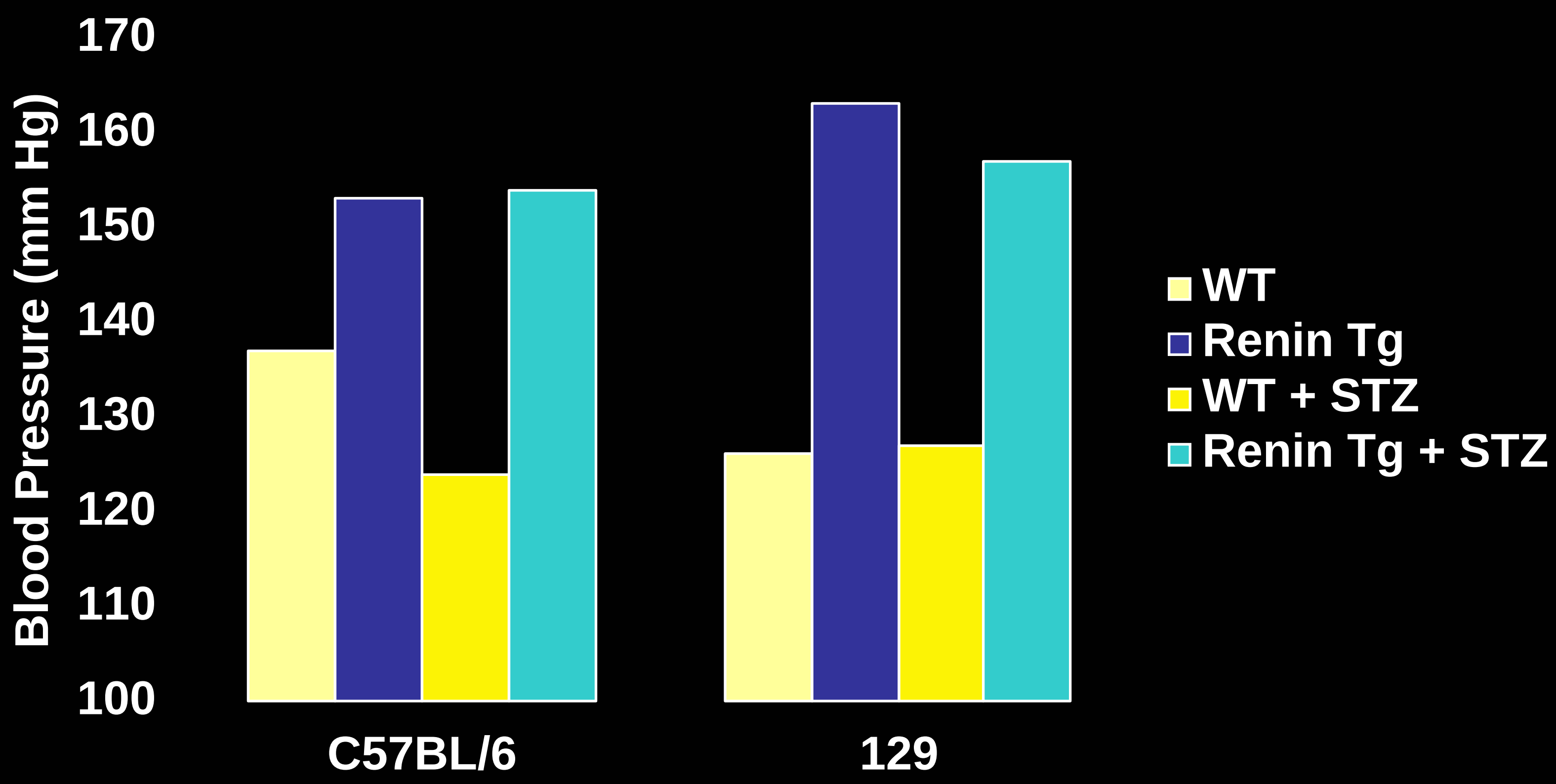
# Renin Transgenic Mice

- Single-copy transgene on C57BL/6 and 129/SvEv backgrounds
- Renin expression driven by albumin promoter

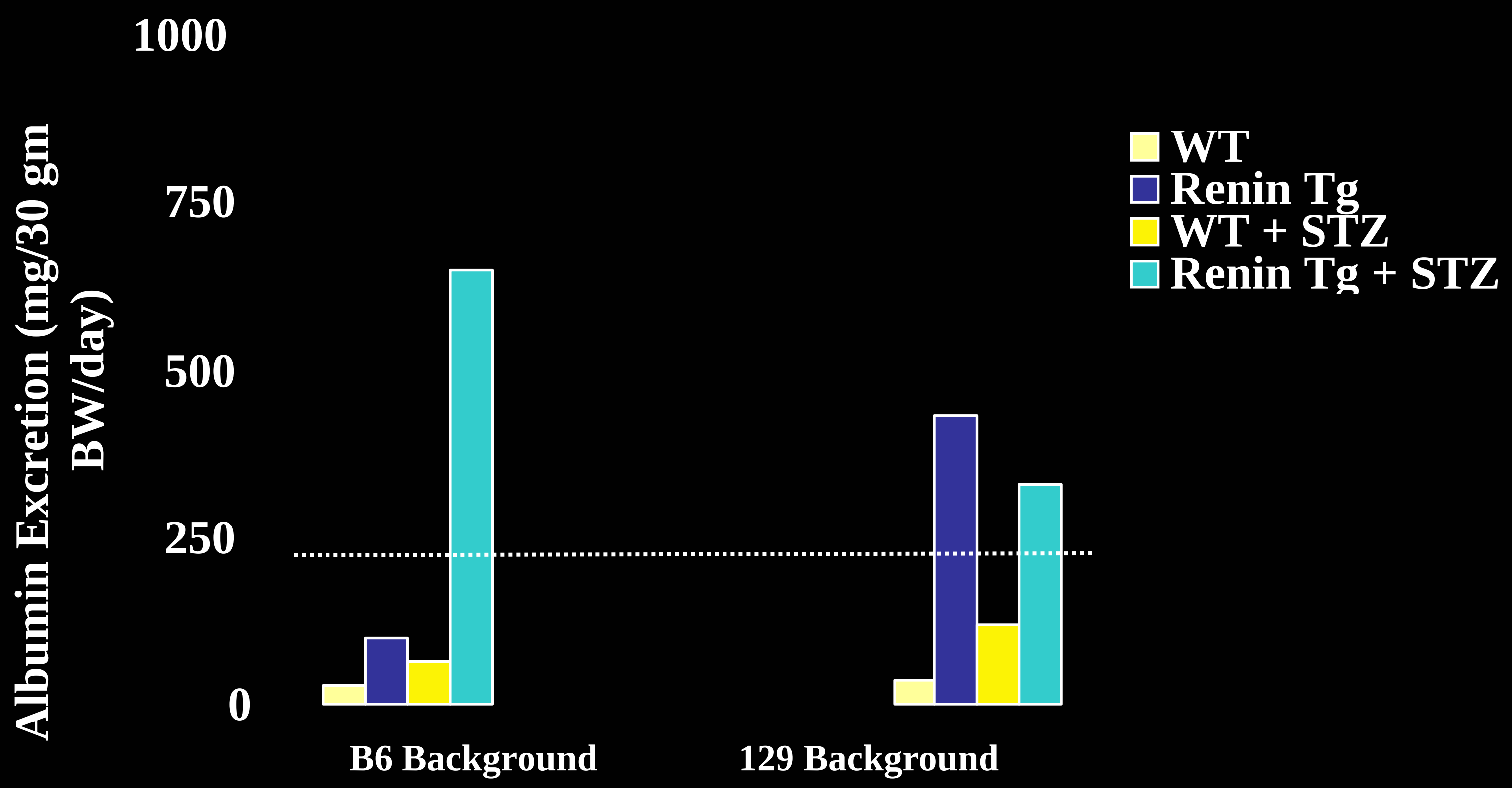
# Blood Glucose in Renin Tg Mice



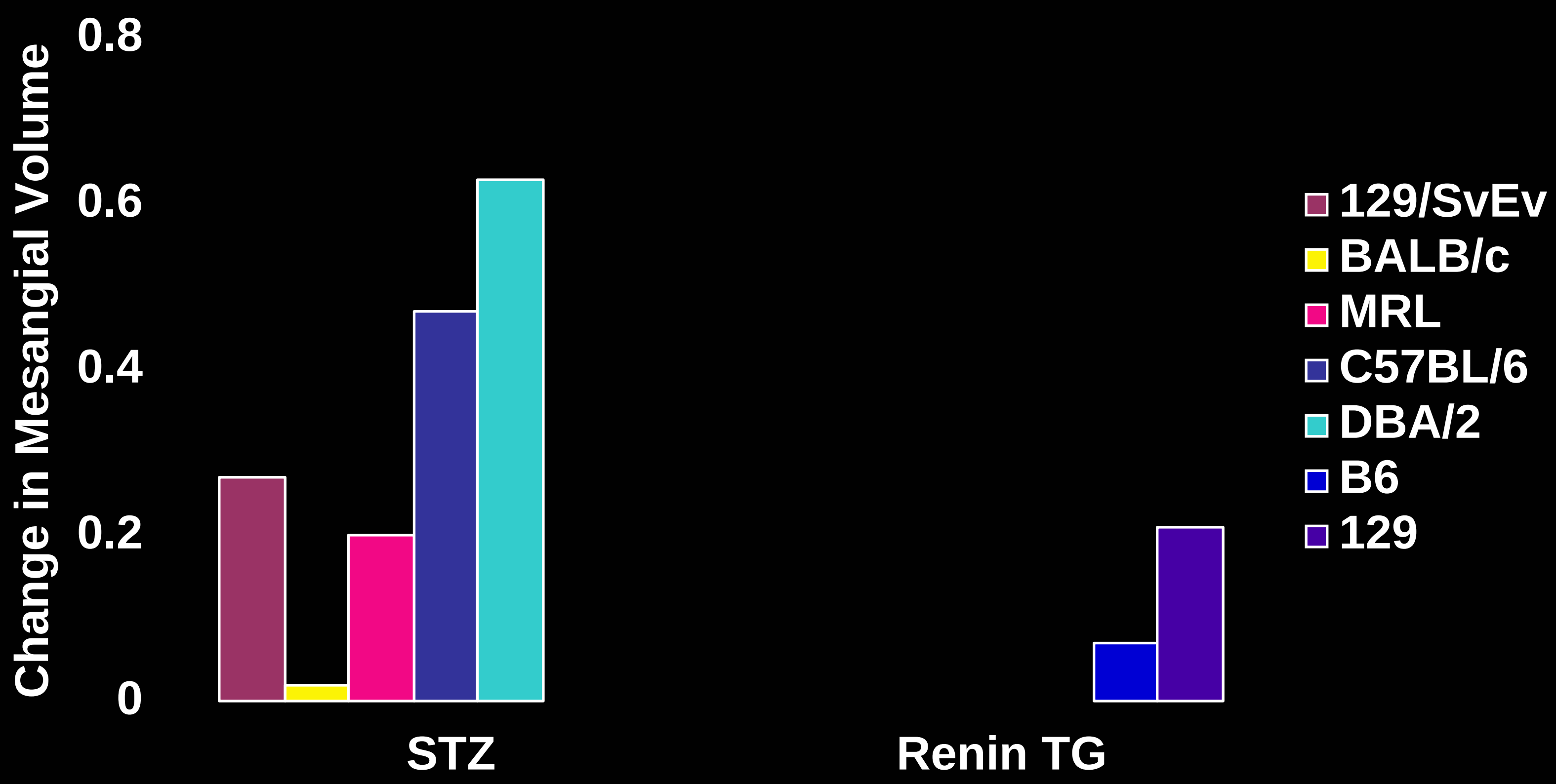
# Blood Pressures in Renin Tg Mice



# Albuminuria in Renin Tg Mice



# Mesangial Expansion in Diabetic Mice



# Other Studies in Progress

- Inter-crossing of ***Ins2***$^{+/C96Y}$ with Renin-Tg on C57BL/6 and 129/SvEv backgrounds
- Generating and characterizing ApoE-deficient *Akita* lines
- Generating and characterizing mouse lines with enhanced CTGF expression
- Phenotyping for other complications in promising lines (B2R ko-*Akita*, (D2B6)F1-*Akita*, 129-*Akita*)