The Akita (*Ins2*$^{+/C96Y}$) Mouse as a Platform for Diabetic Nephropathy Models

Duke/UNC/Stanford

Program Director

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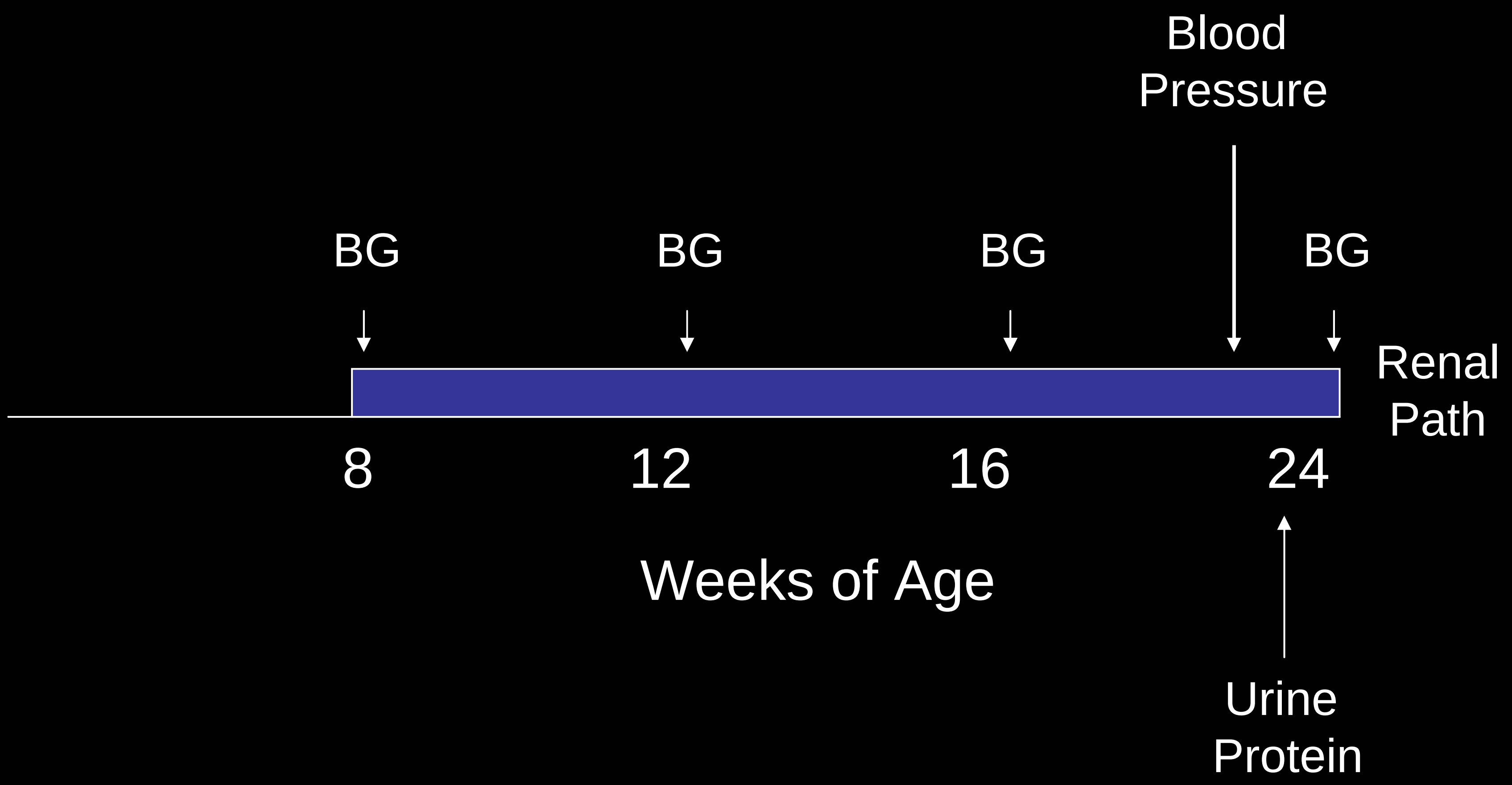
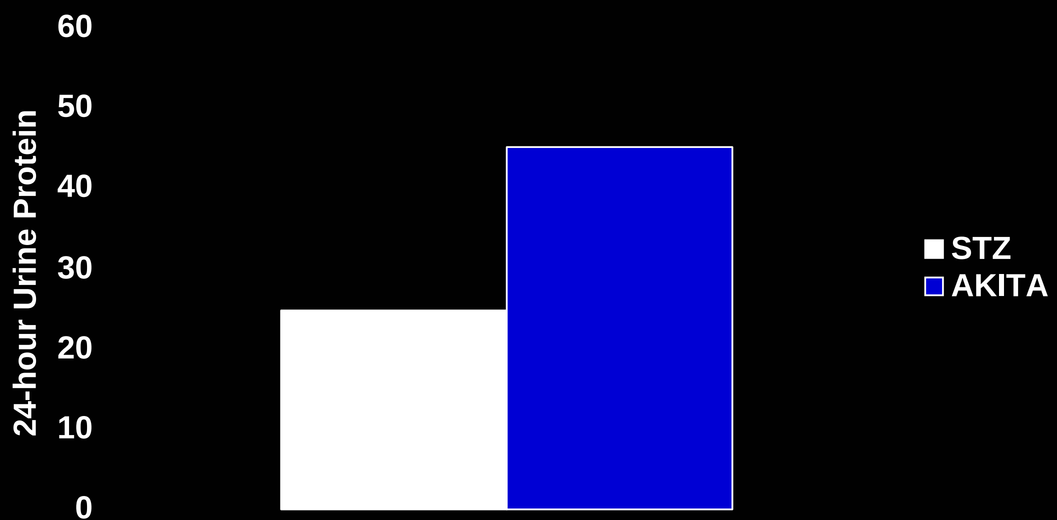
The Akita (*Ins2*$^{+/C96Y}$) Mouse

- C96Y mutation of the insulin 2 (*Ins2*) gene causes abnormal processing of insulin resulting in islet cell dysfunction and death.
- Heterozygous C57BL/6-*Ins2*$^{+/C96Y}$ mice spontaneously develop profound hyperglycemia.
- As with STZ-treatment, there is a significant gender difference in the severity of hyperglycemia (male>>female).

Study Protocol



Blood Glucose and Proteinuria in C57BL/6 Mice



Differential Blood Pressure Responses

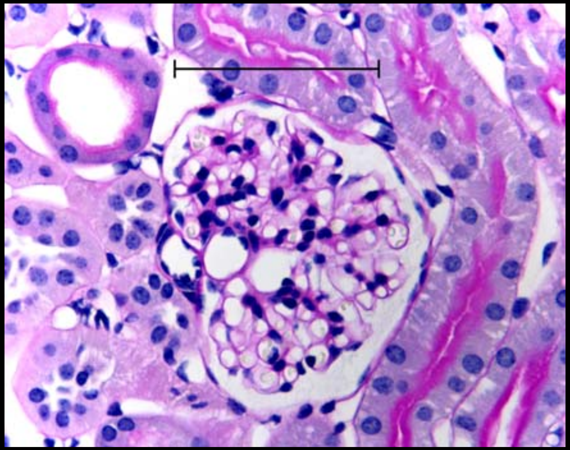
*

(*p=0.0018 vs Akita Control)

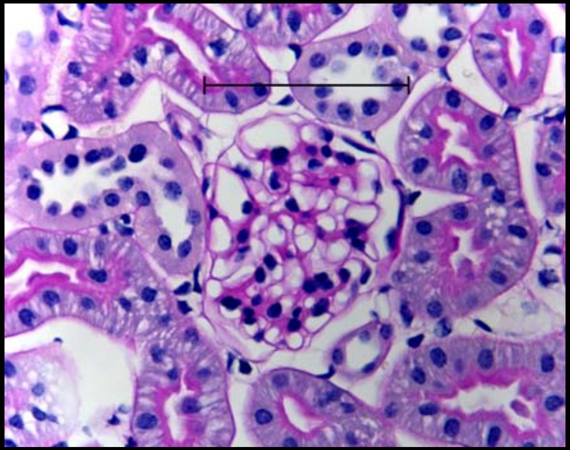
Renal Pathological Analysis

- Kidneys perfused *in situ* with 4% paraformaldehyde using a peristaltic pump at a rate of 7 mL/min.
- Perfusion-fixed tissue embedded in parafin and sections were stained with PAS for examination by light microscopy.
- Glomerular mesganial area was scored from zero to three on 25 to 40 glomerular profiles from a single section and the mean was entered as the score for the animal.
- Glomerular volume was calculated from the mean cross sectional area of 20 glomerular profiles on each animal using the method of Weibel .

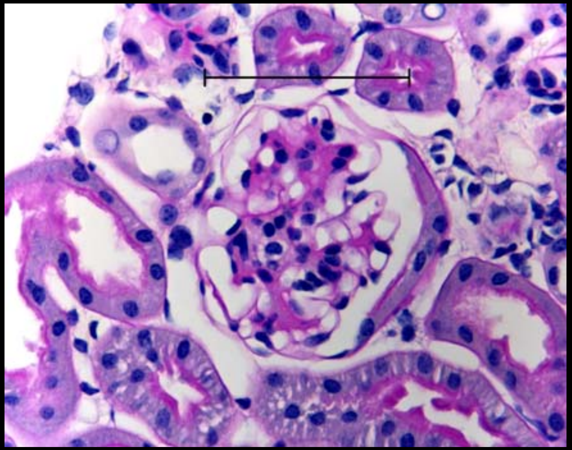
Grading of Mesangial Area



0

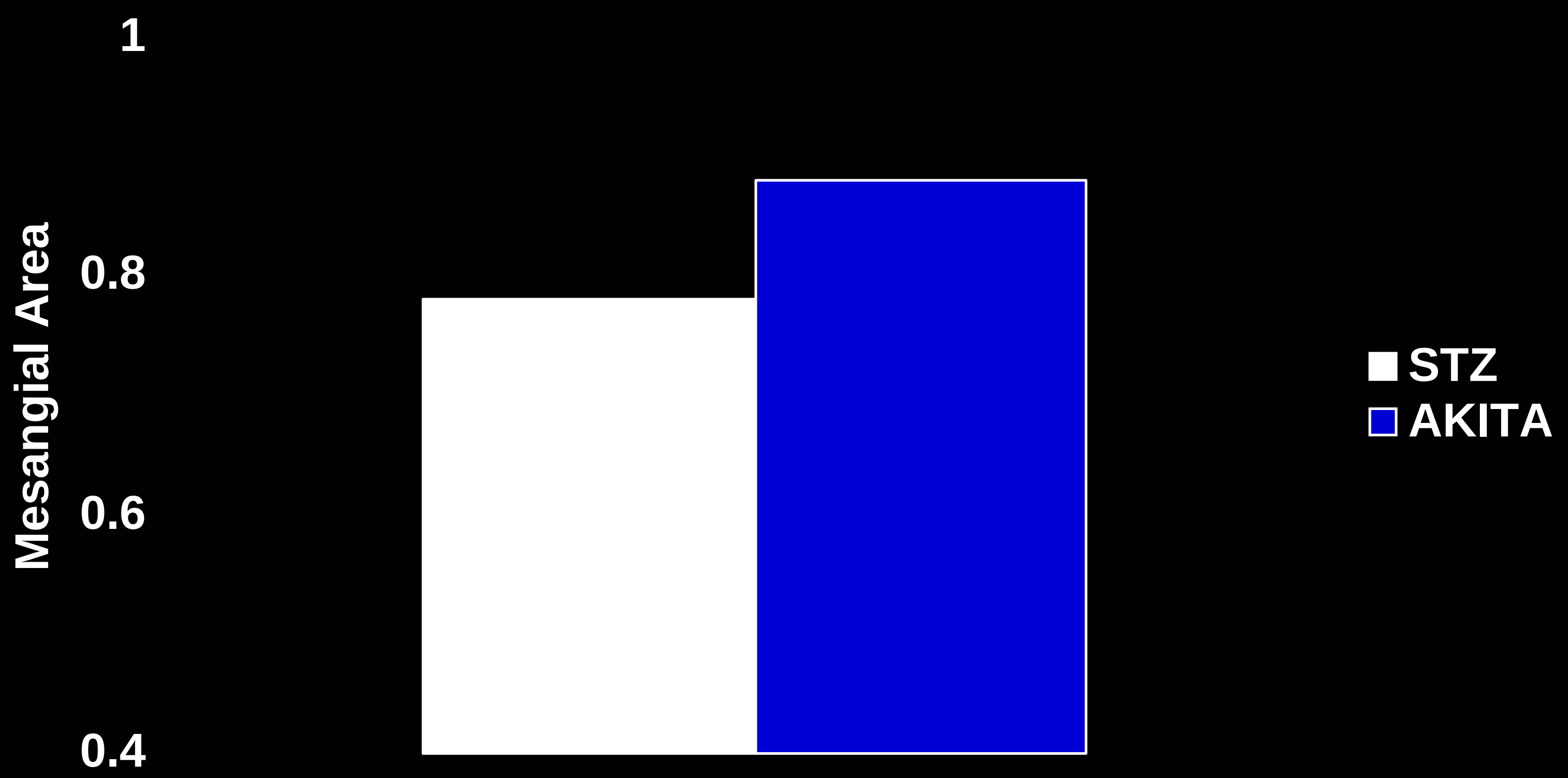


1

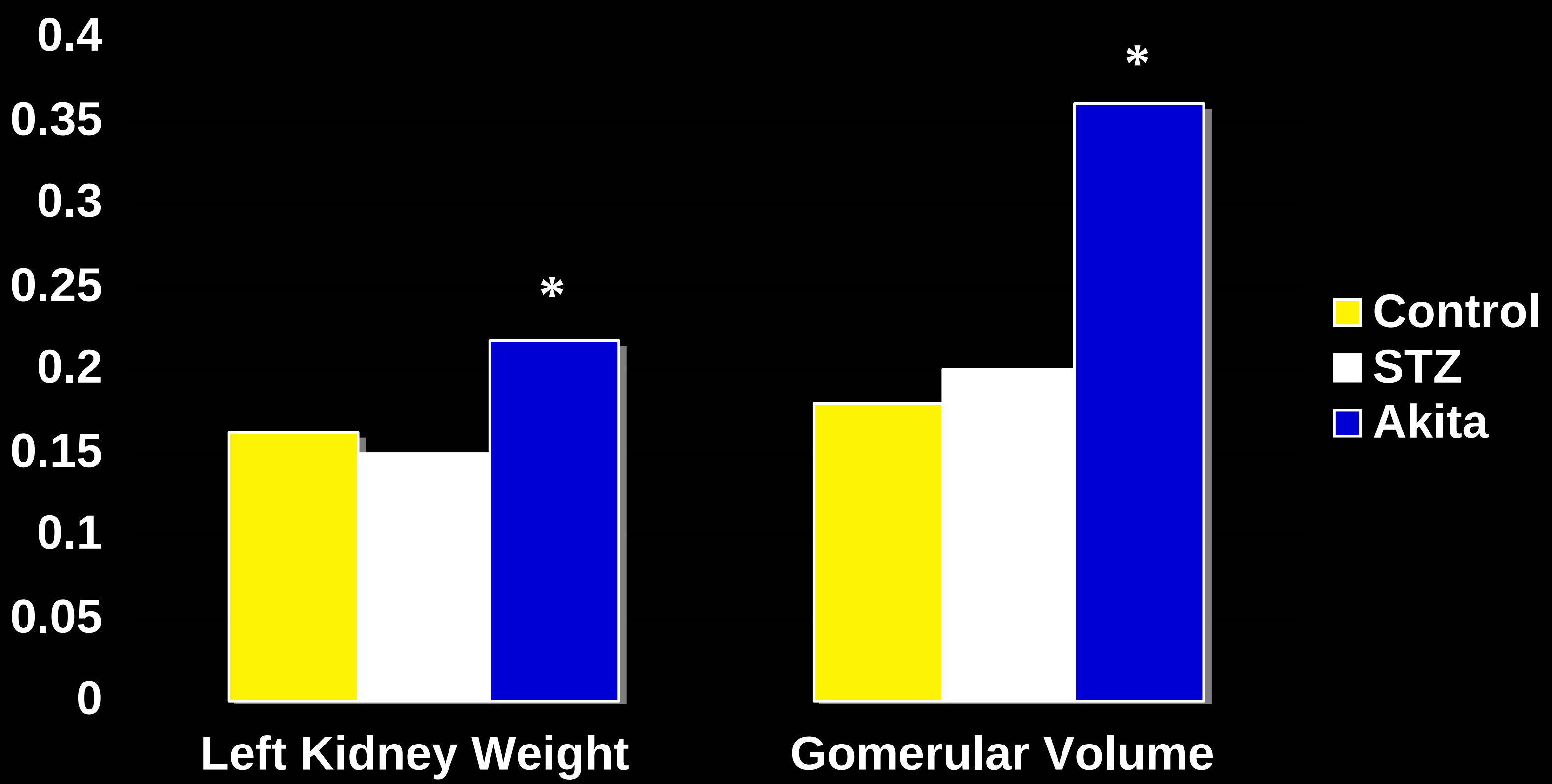


2

Mesangial Area in Diabetic C57BL/6 Mice



Increased Kidney Weights and Glomerular Volume in B6-Akita Mice



Strategies for Accelerating Kidney Pathology

- Longer duration (9-12 months)
- Uni-nephrectomy
- Superimpose additional mutations
- Back-cross onto susceptible backgrounds

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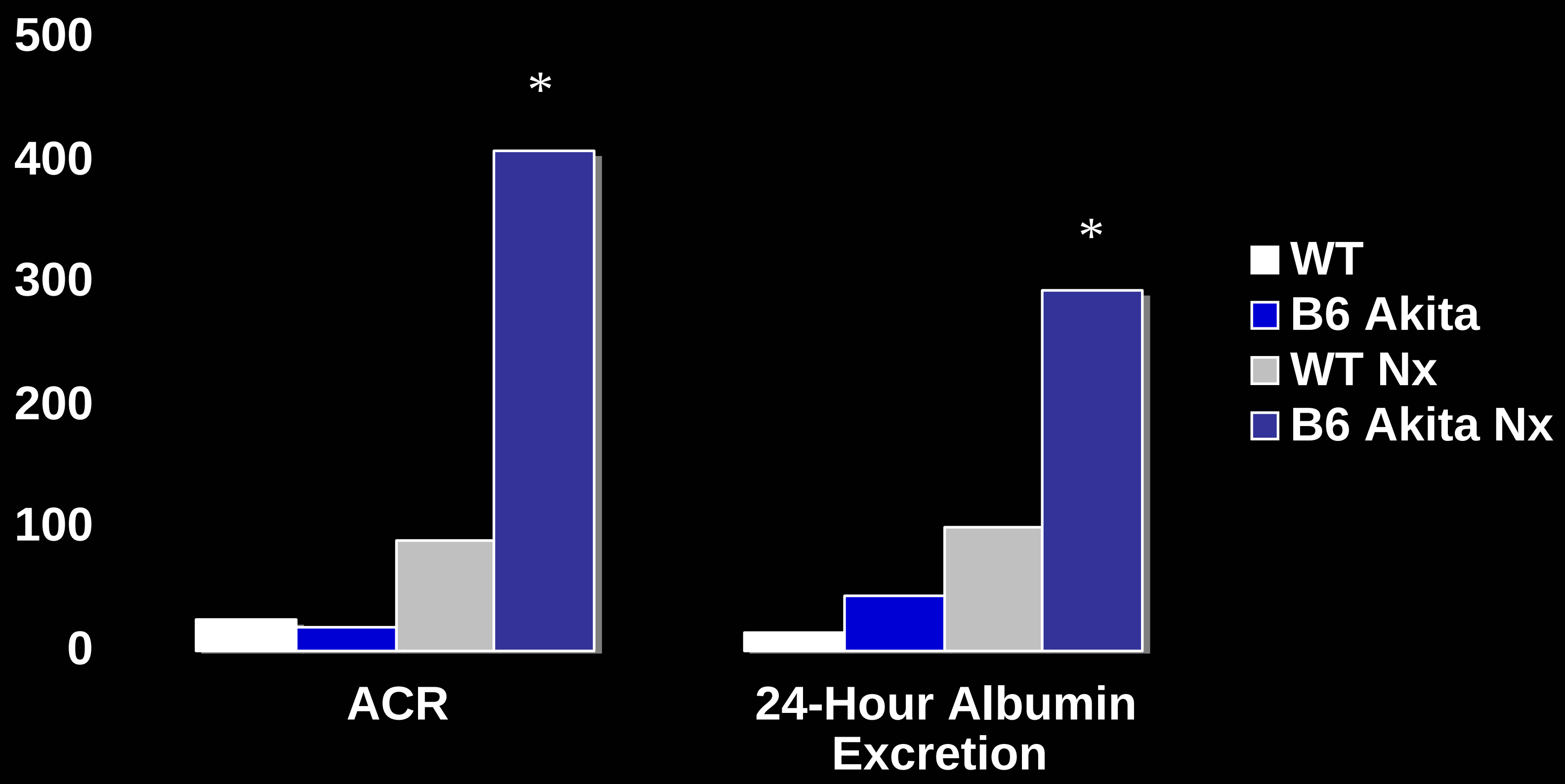
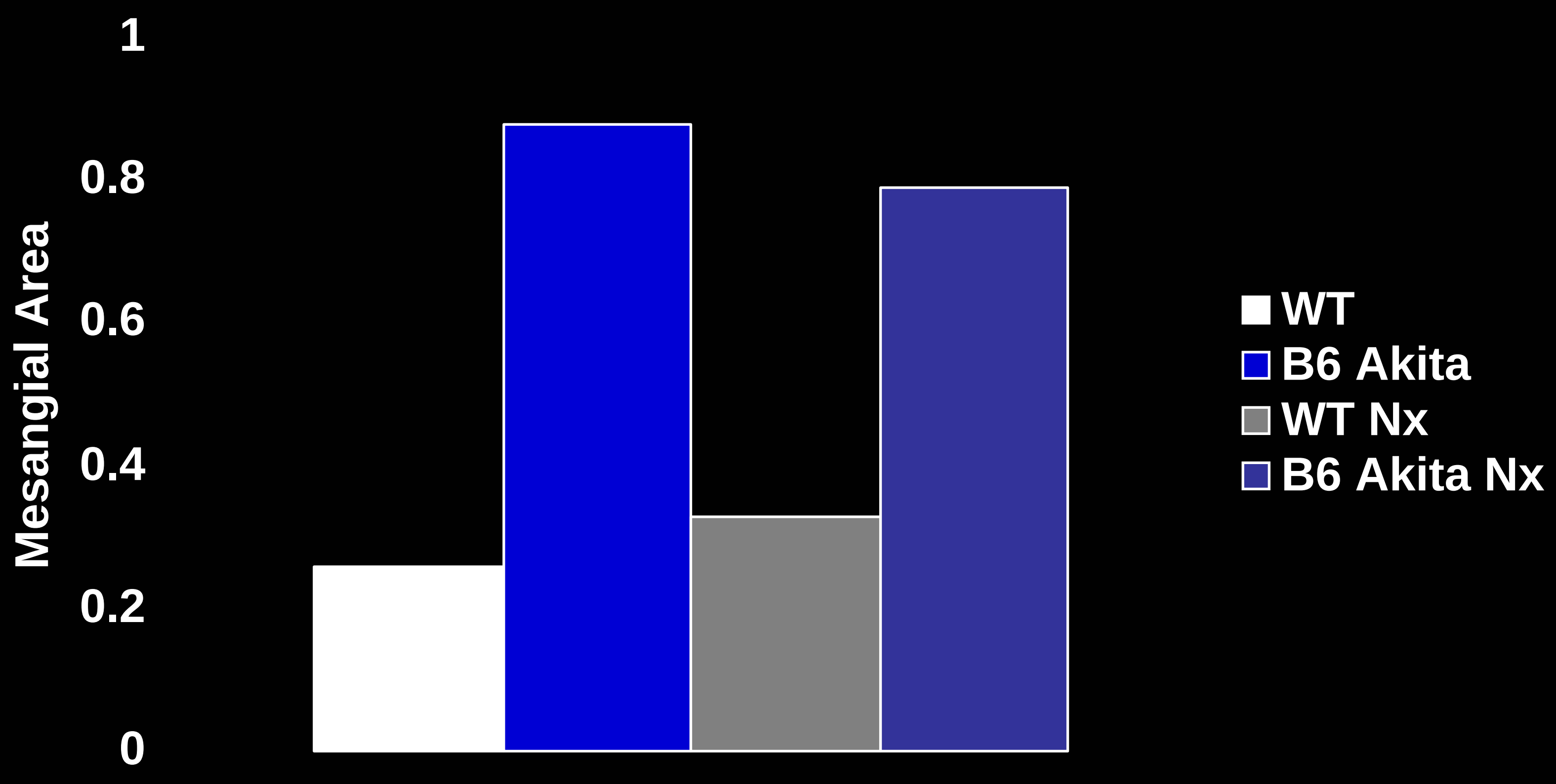
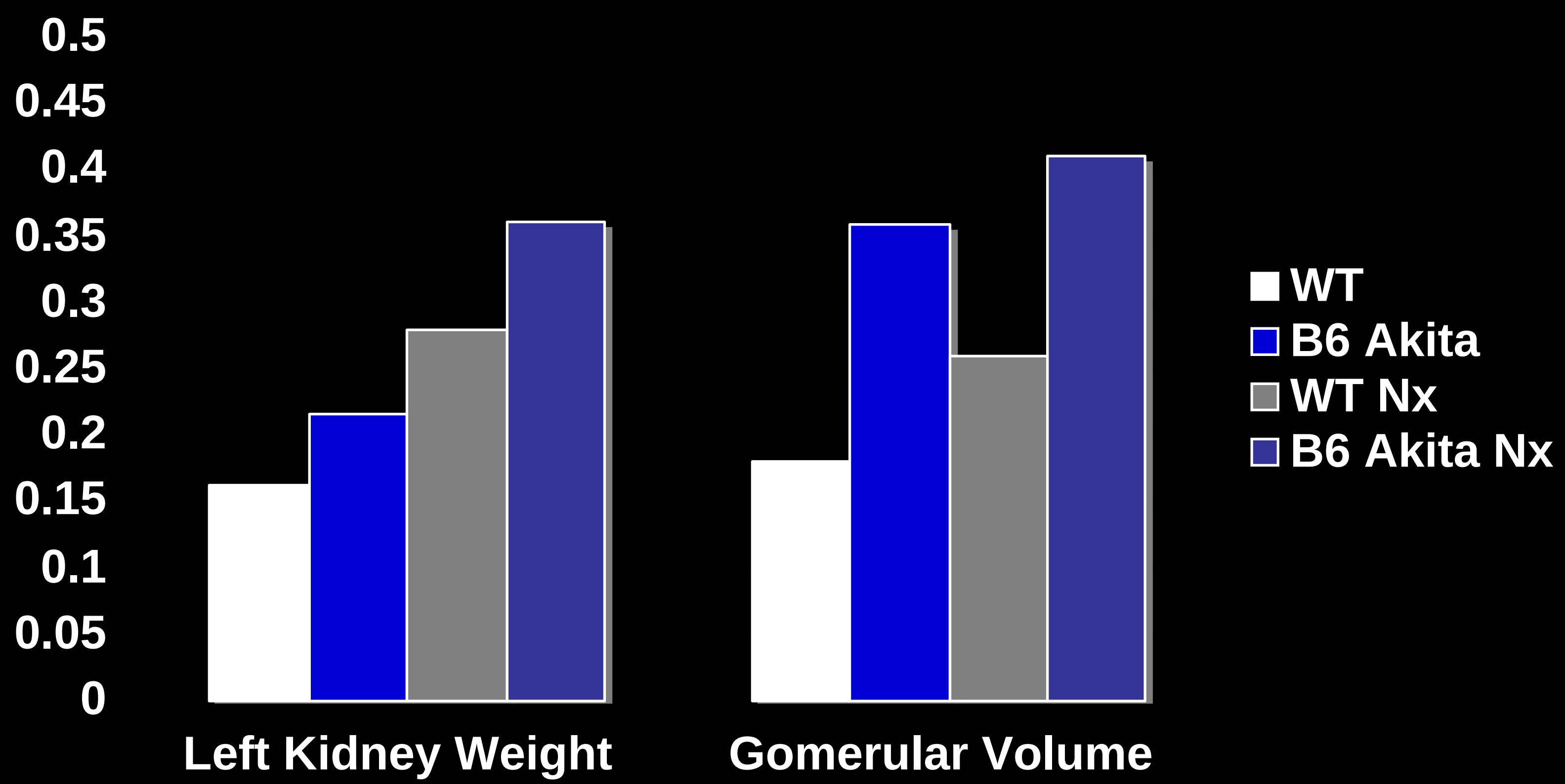
Effect of Uni-Nephrectomy on Albumin Excretion



Mesangial Pathology After Uni-Nephrectomy



Effect of Uni-Nephrectomy on Kidney Weights and Glomerular Volume



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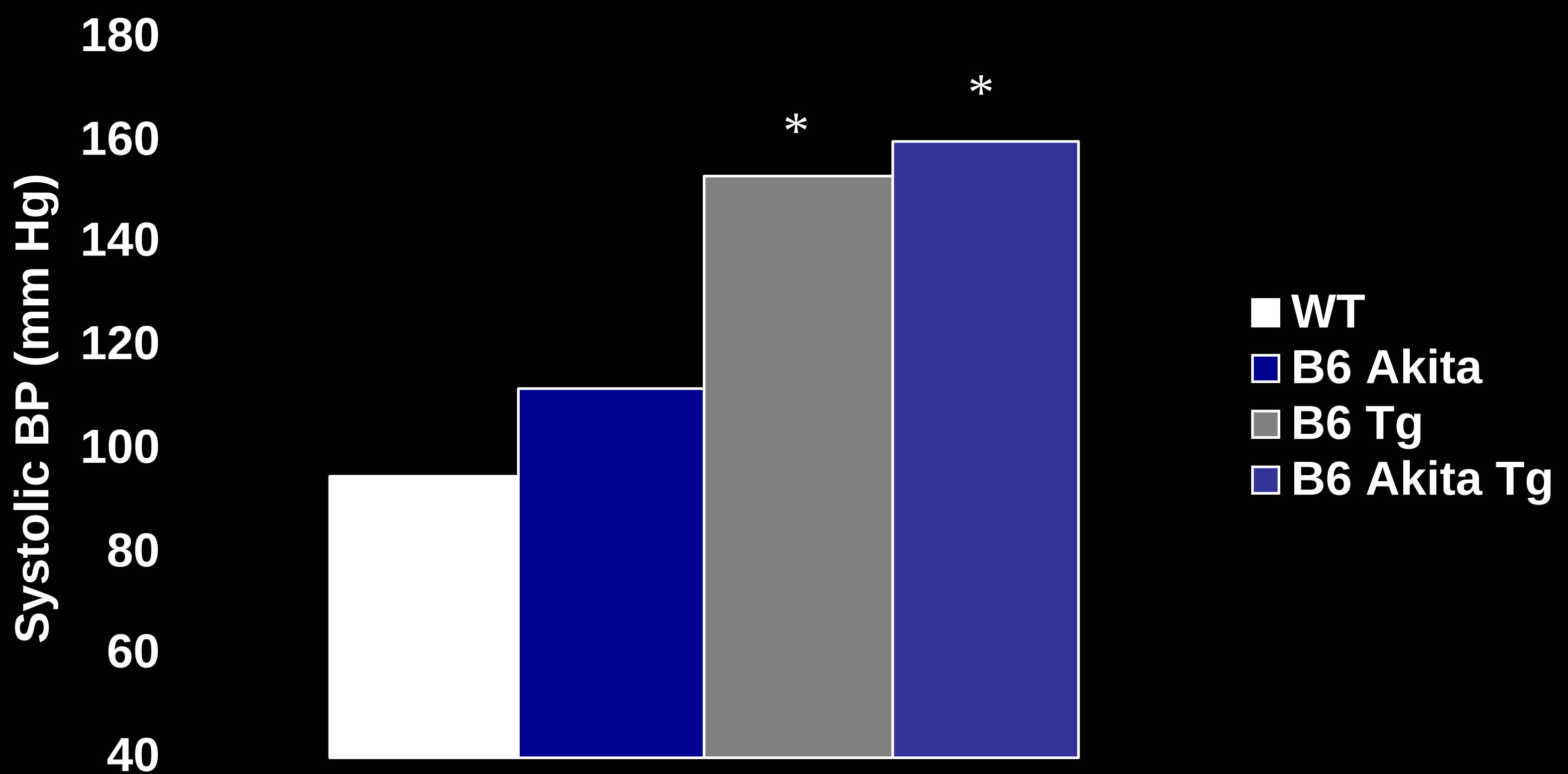
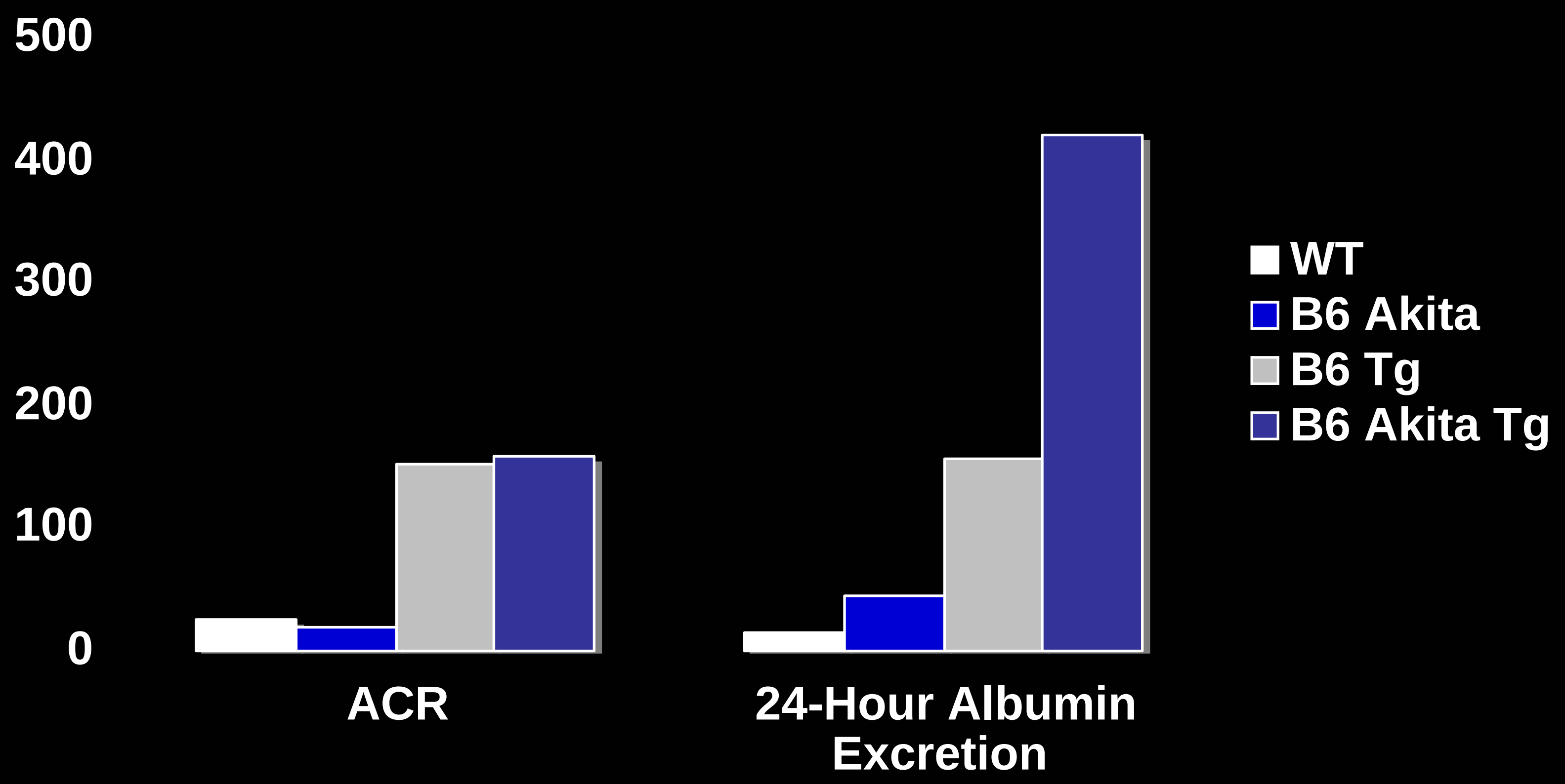
Renin Transgene

- Single-copy transgene targeted into Apo E locus
- Constitutive expression of renin under control of the albumin promoter

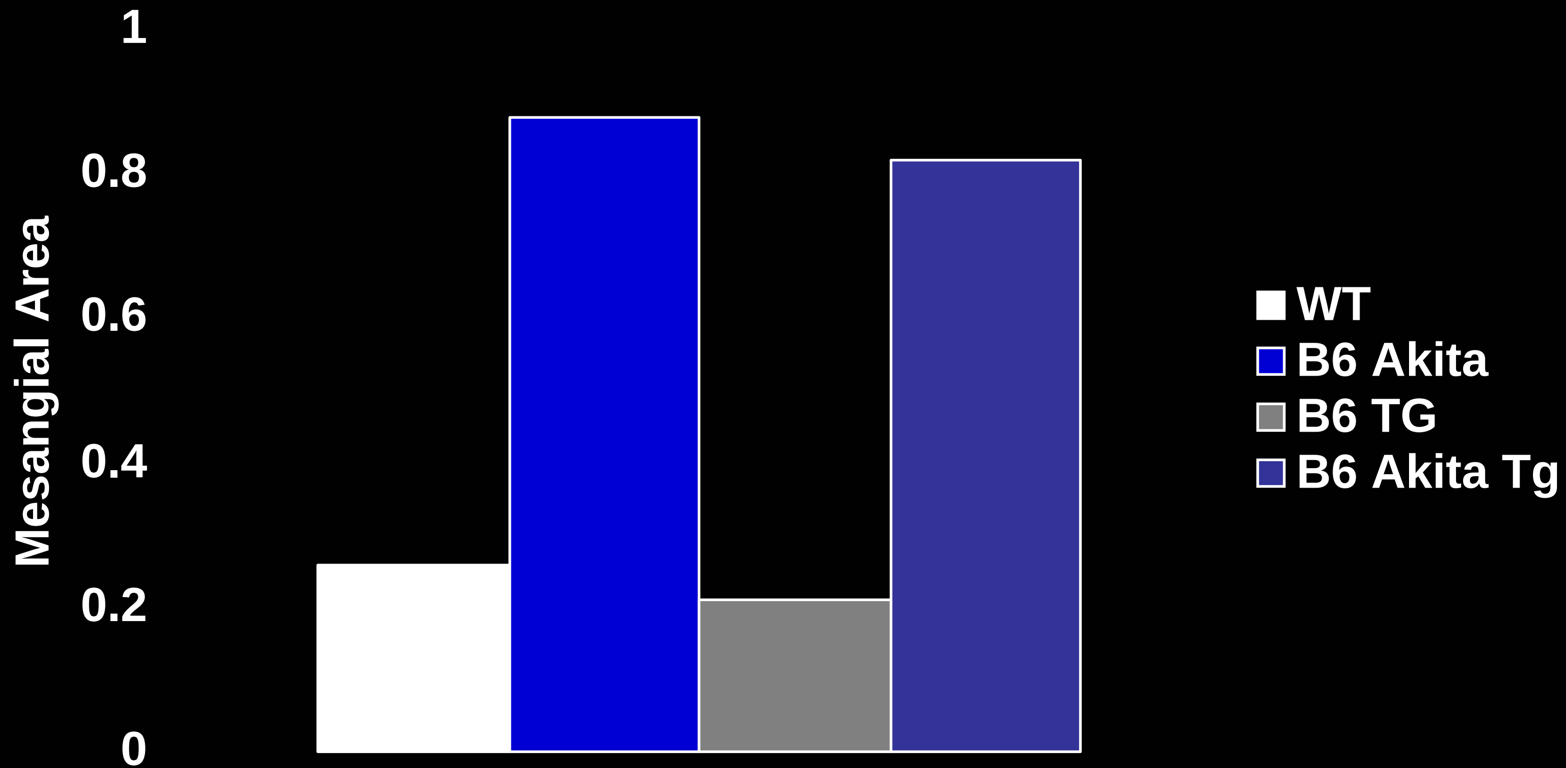
Blood Pressures in Renin Transgenic MIce



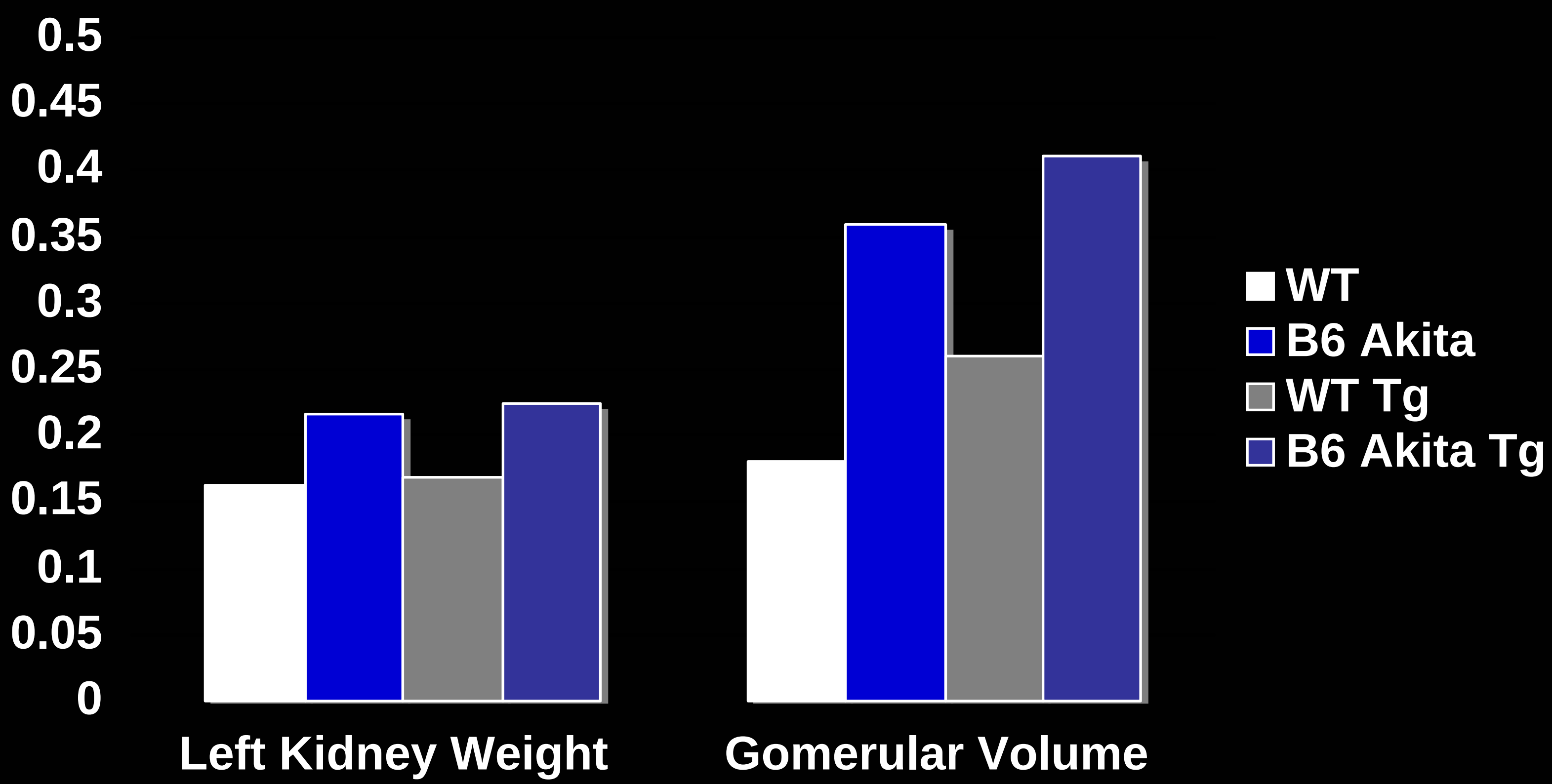
Effect of Renin Transgene on Albumin Excretion



Mesangial Pathology with Renin Tg



Effect of Renin Transgene on Kidney Weights and Glomerular Volume



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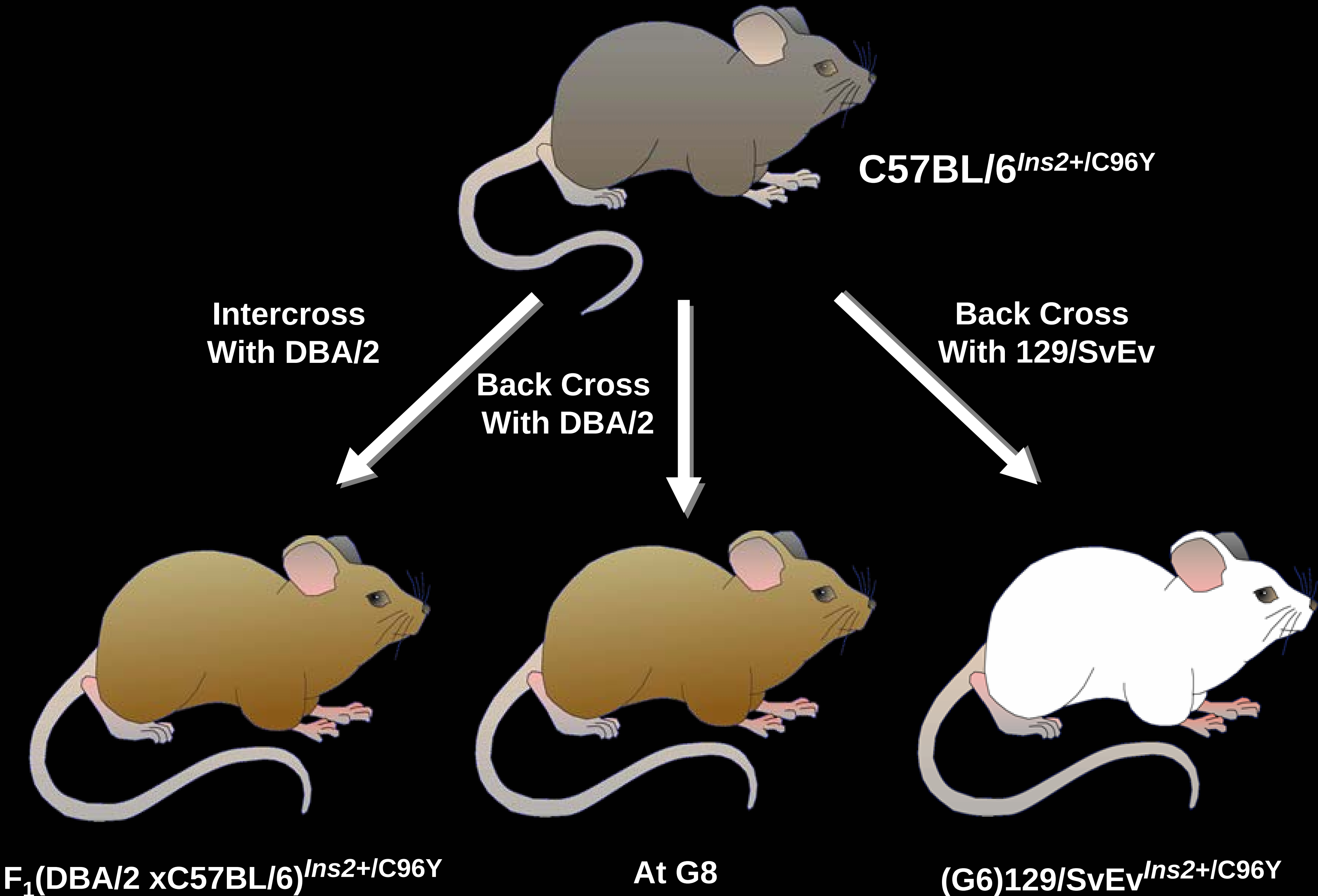
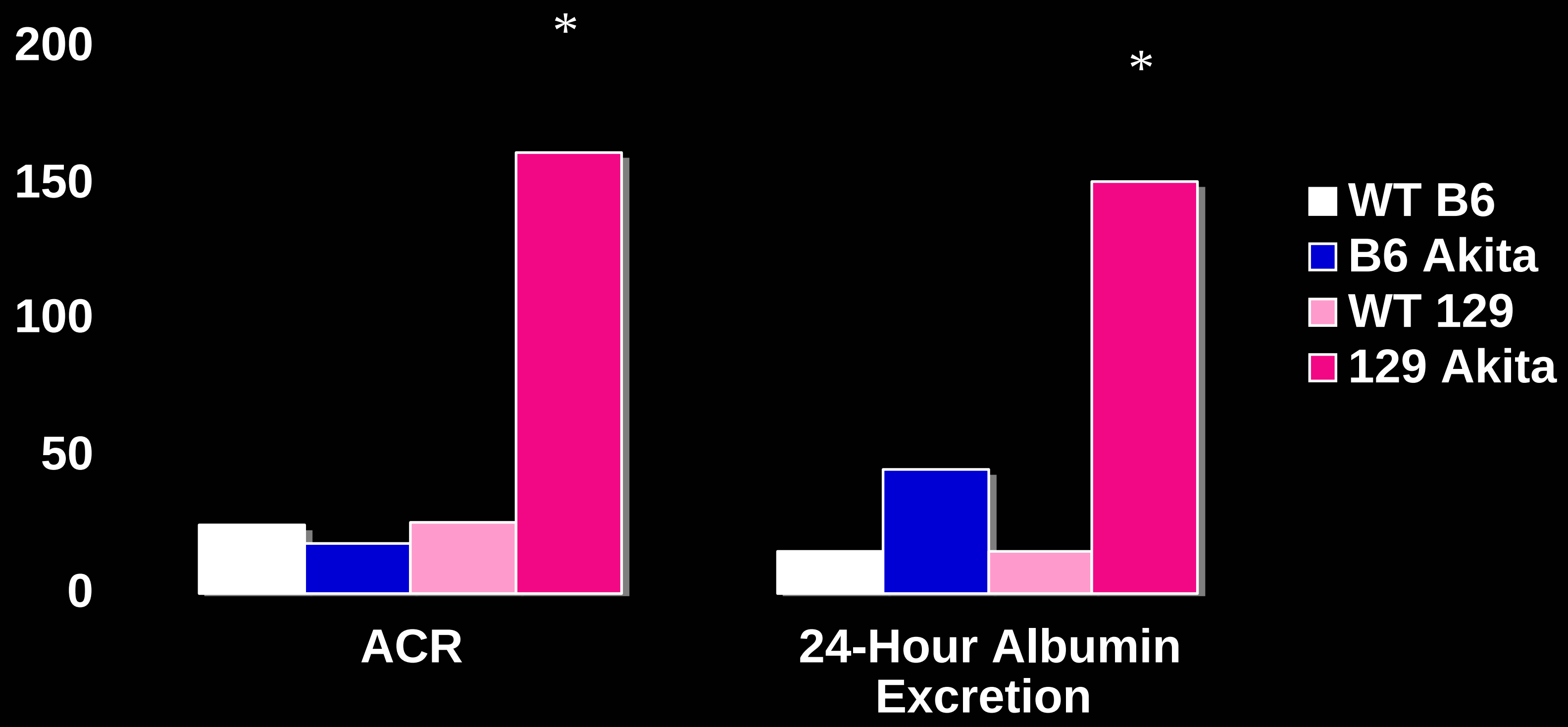
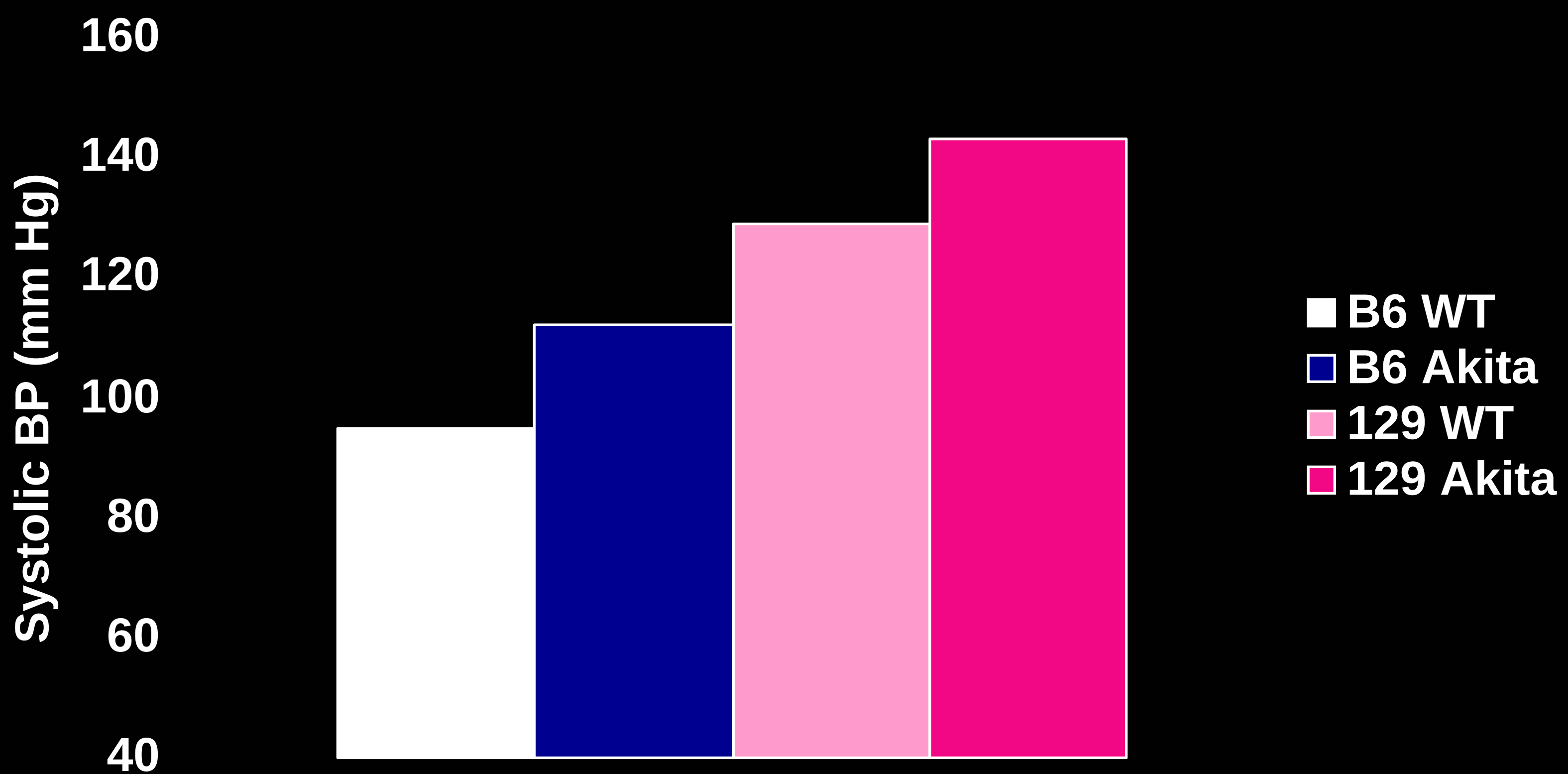
Generating Inbred *Ins2*$^{+/C96Y}$ Lines



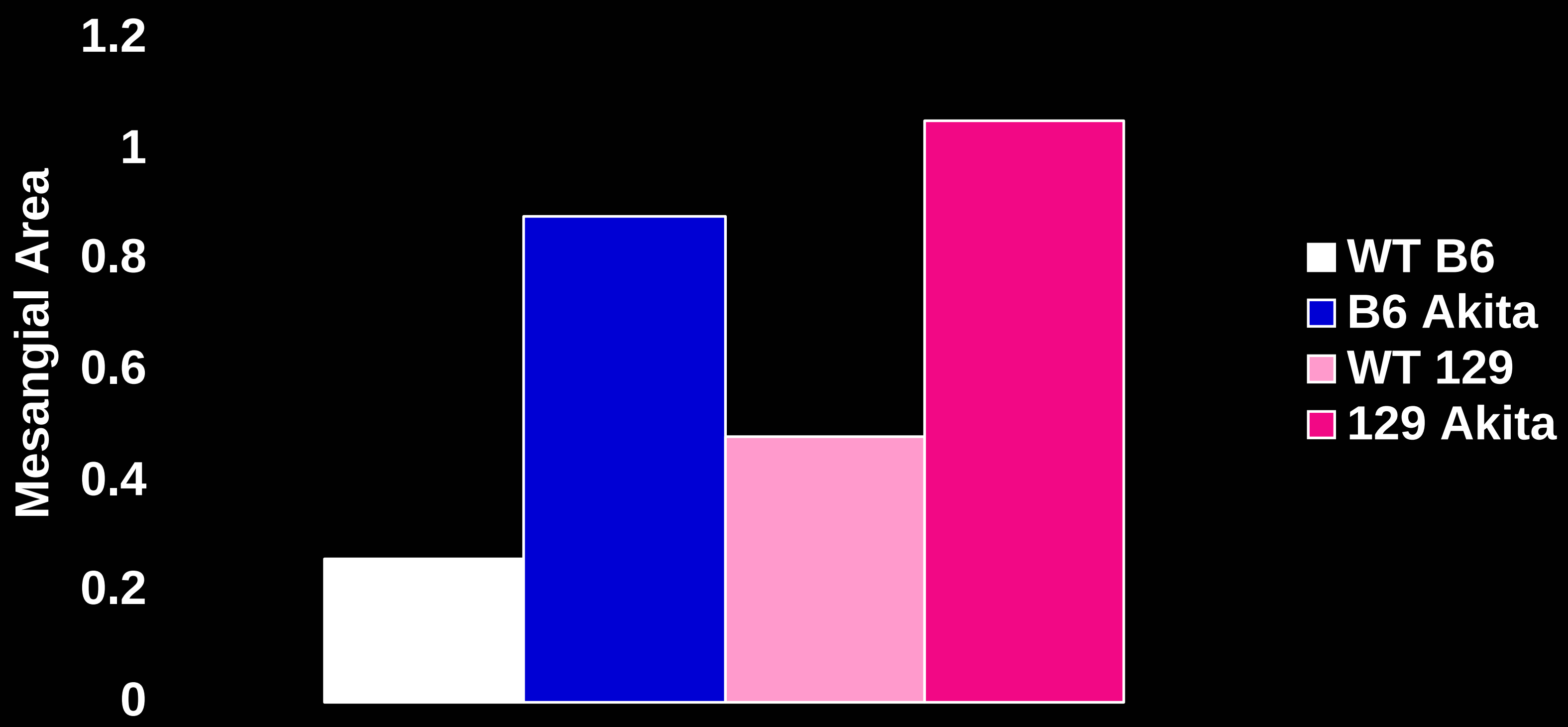
Albumin Excretion

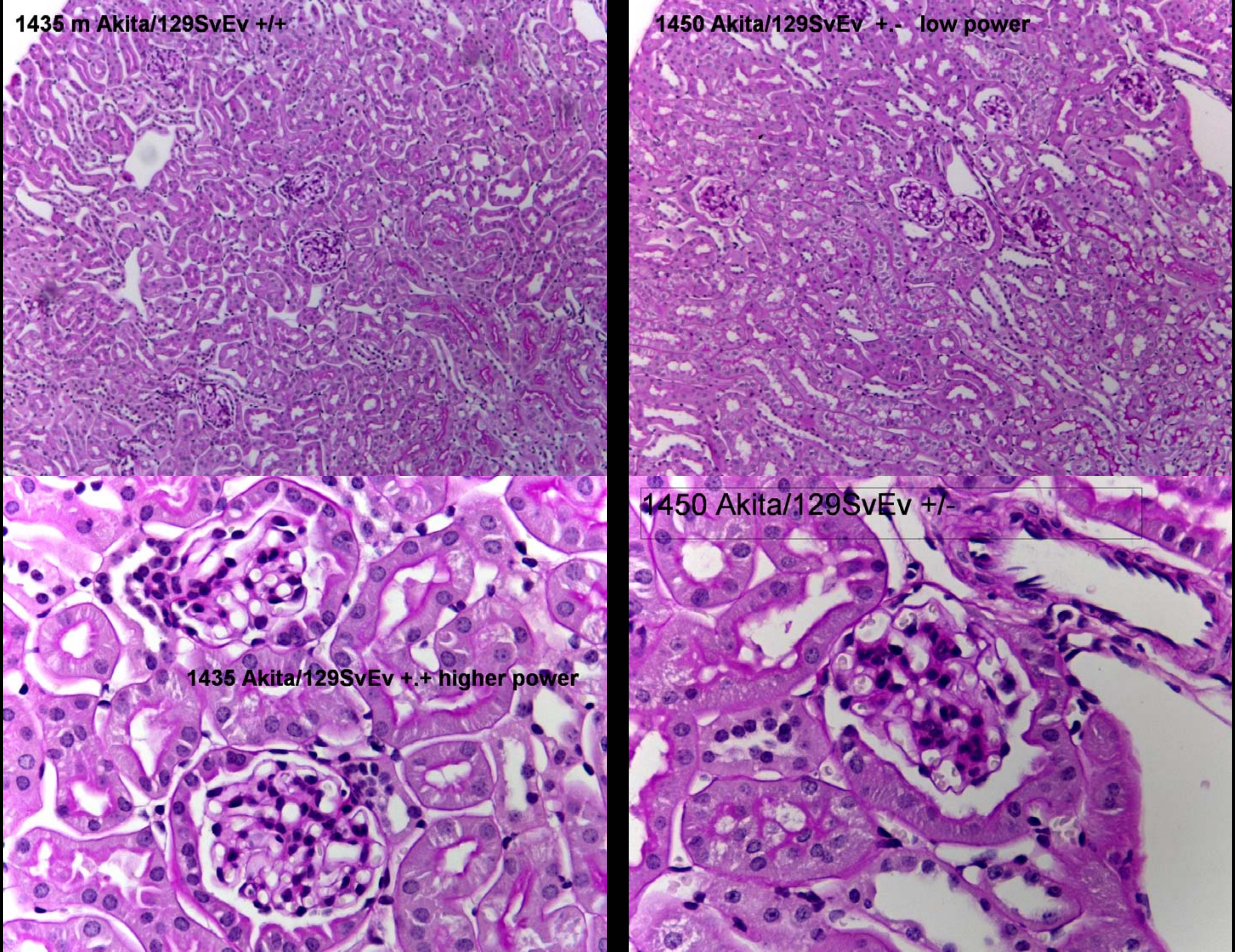


Blood Pressures in 129/SvEv MIce

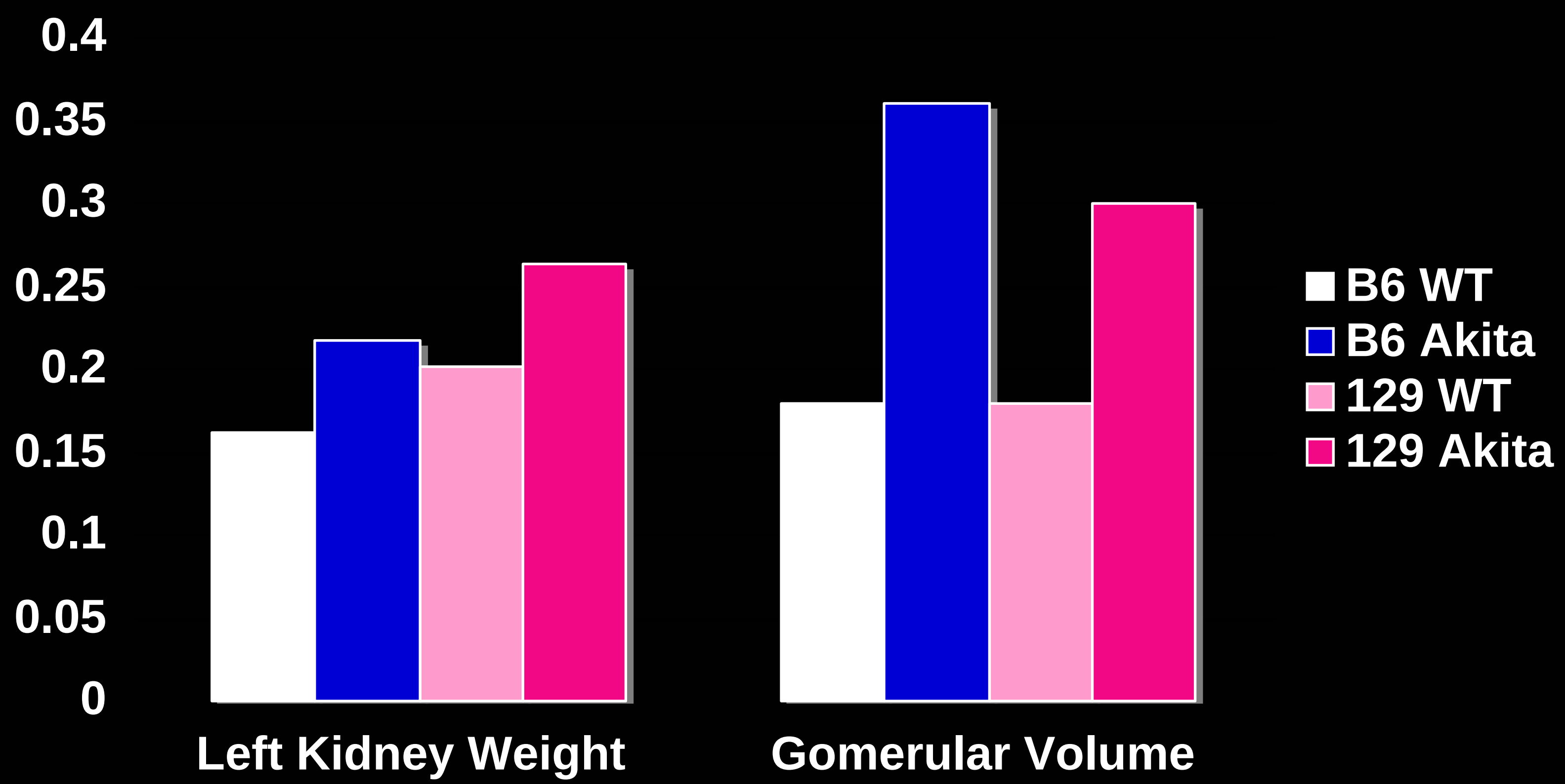


Mesangial Pathology in 129/SvEv Mice




1435 m Akita/129SvEv +/+
1450 Akita/129SvEv +.- low power
1435 Akita/129SvEv +.+ higher power
1450 Akita/129SvEv +/-

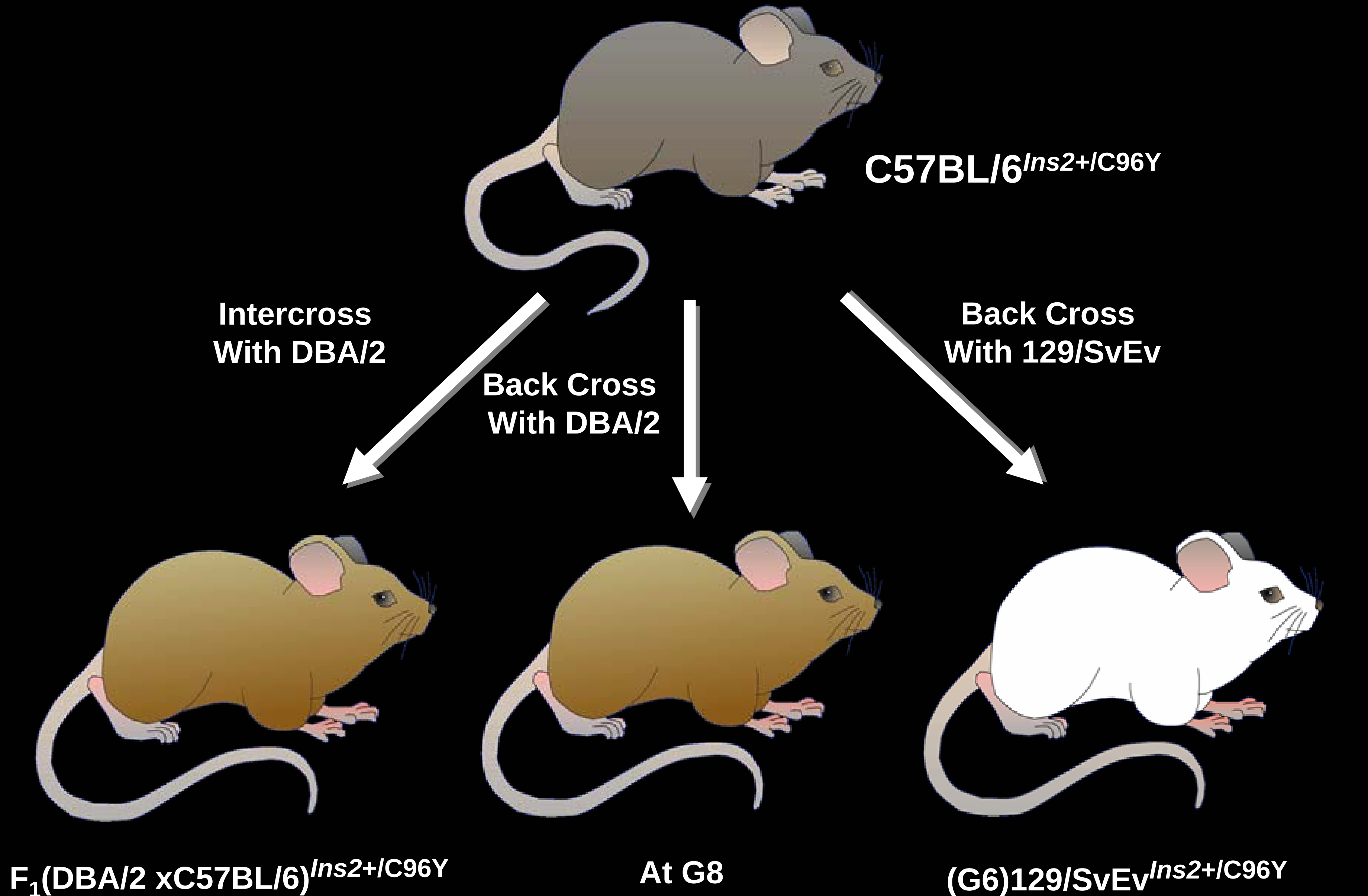
Kidney Weights and Glomerular Volumes



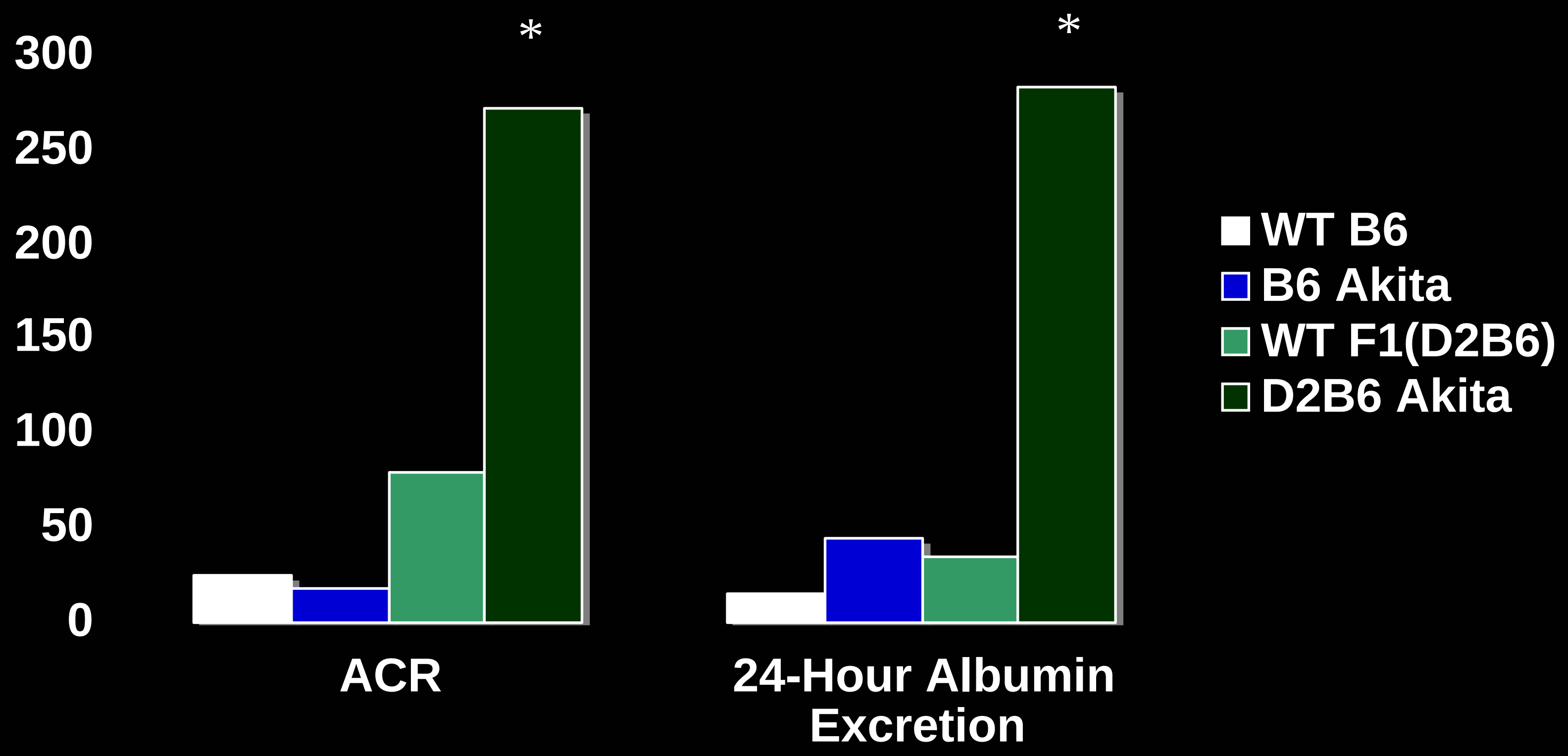
Studies in Progress: 129-Akita Mice

- Aging study to 9-12 months (at 23 weeks)
- Uni-nephrectomy study (in progress)
- Inter-cross with renin transgene (in progress)

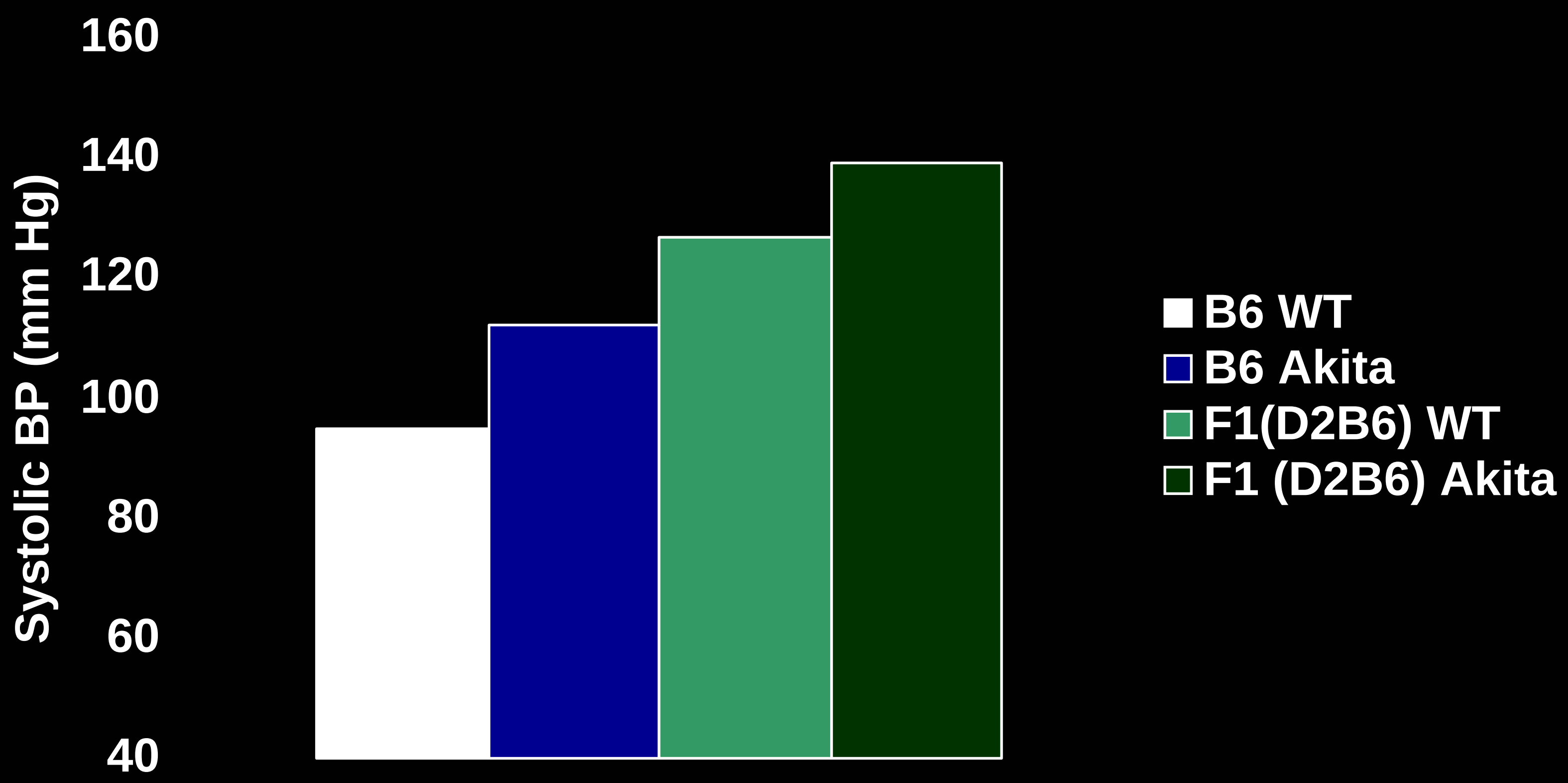
Generating Inbred *Ins2*$^{+/C96Y}$ Lines



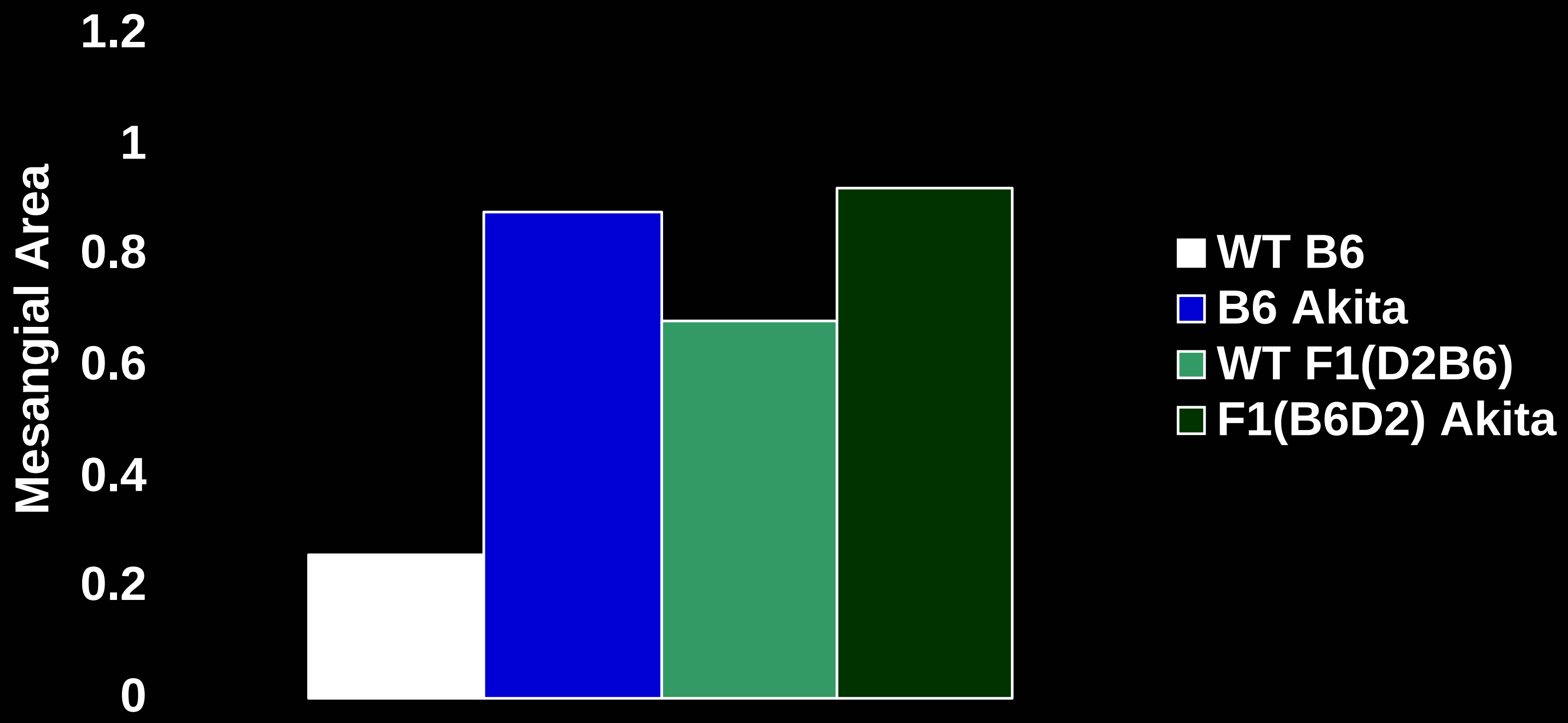
Albumin Excretion

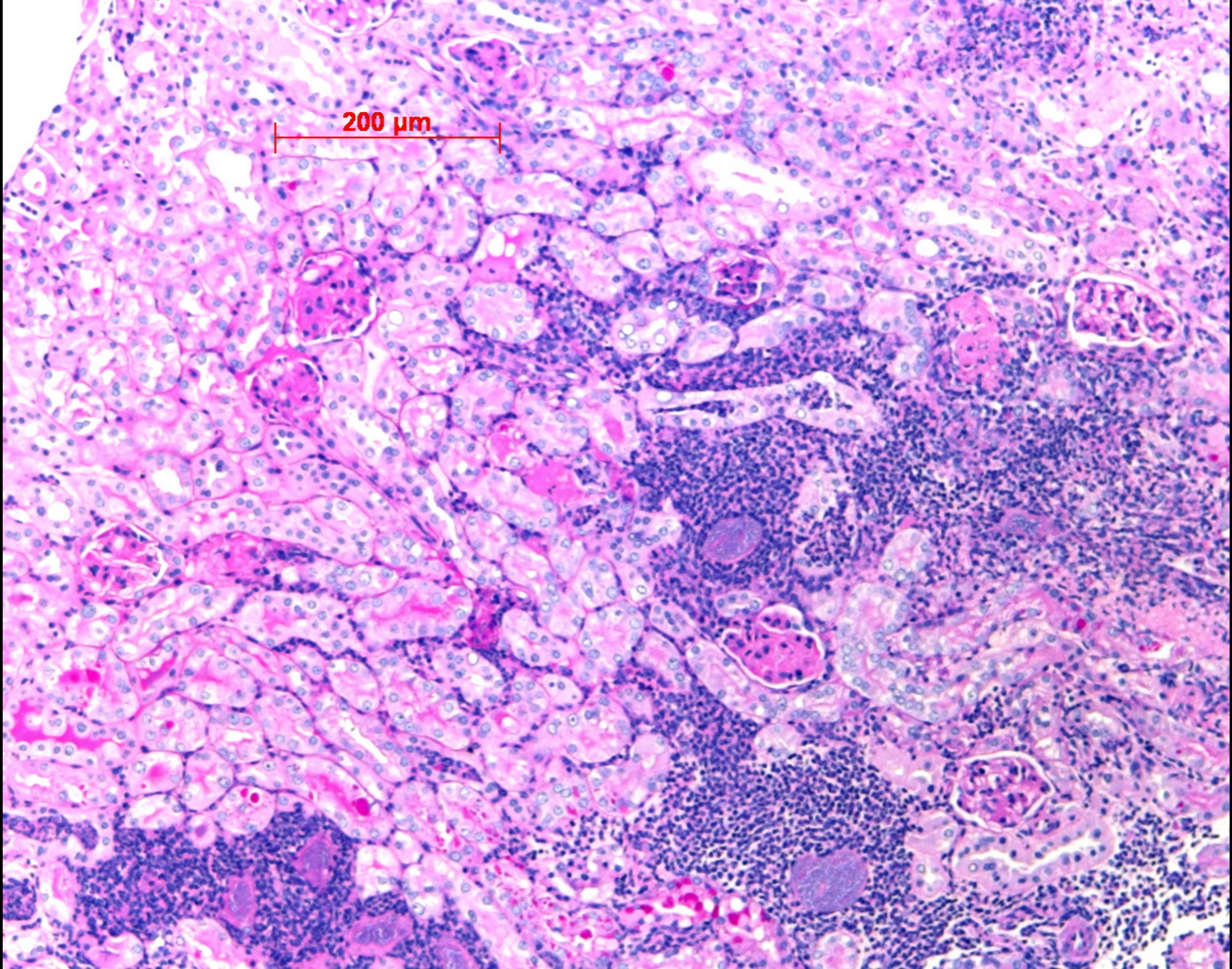


Blood Pressures in Renin Transgenic MIce

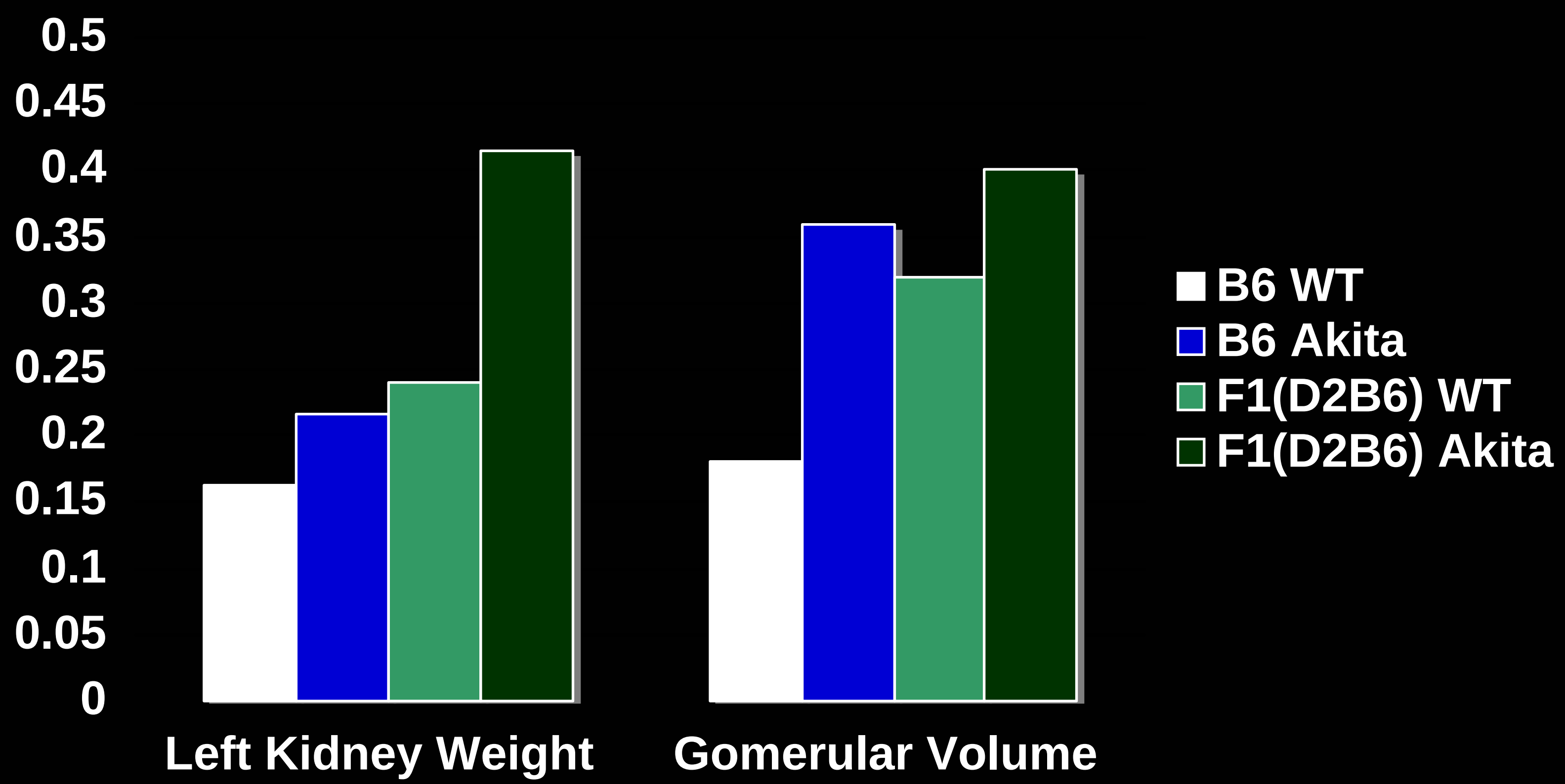


Mesangial Pathology After Uni-Nephrectomy



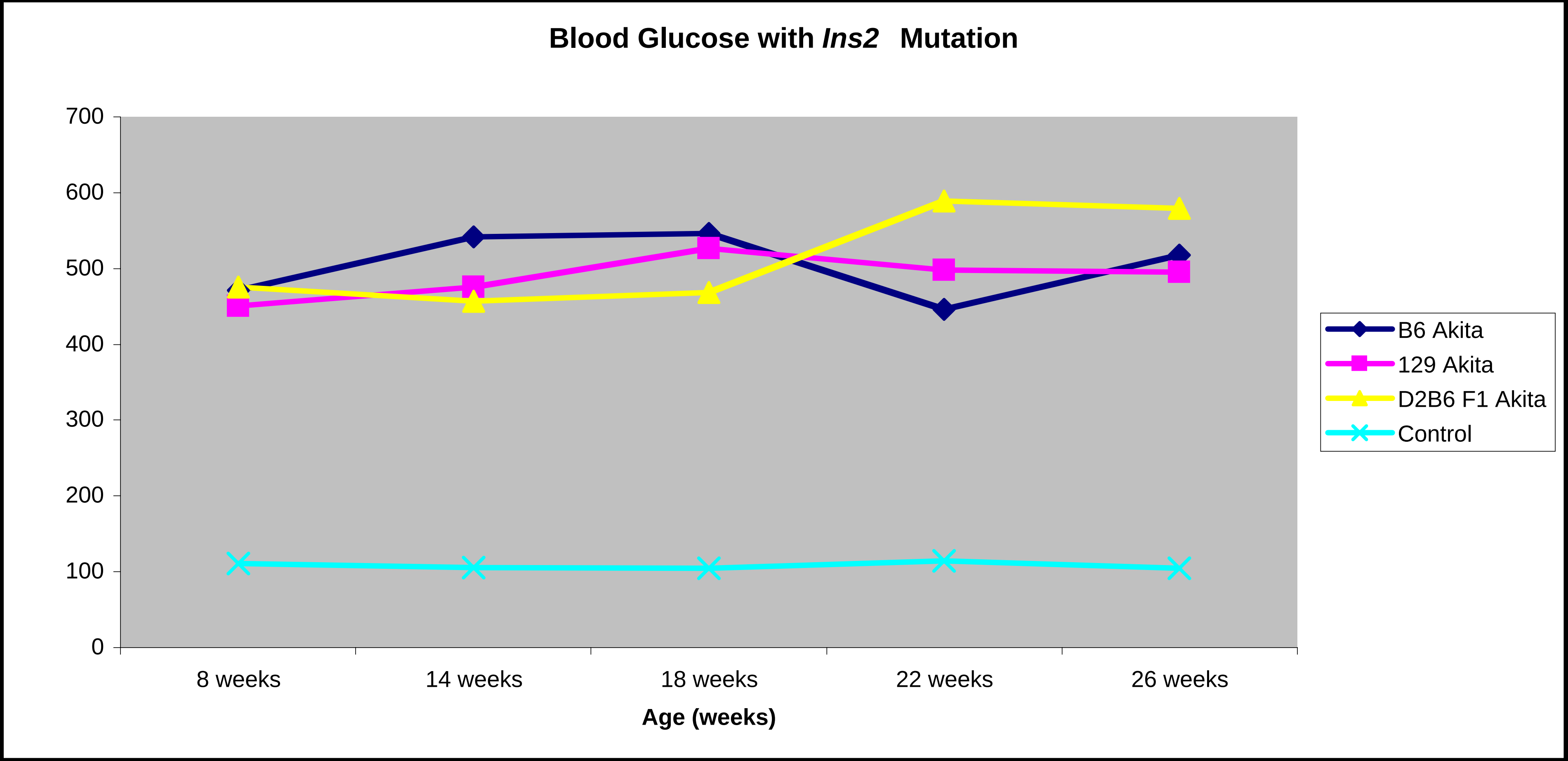

200 µm

Kidney Weights and Glomerular Volumes

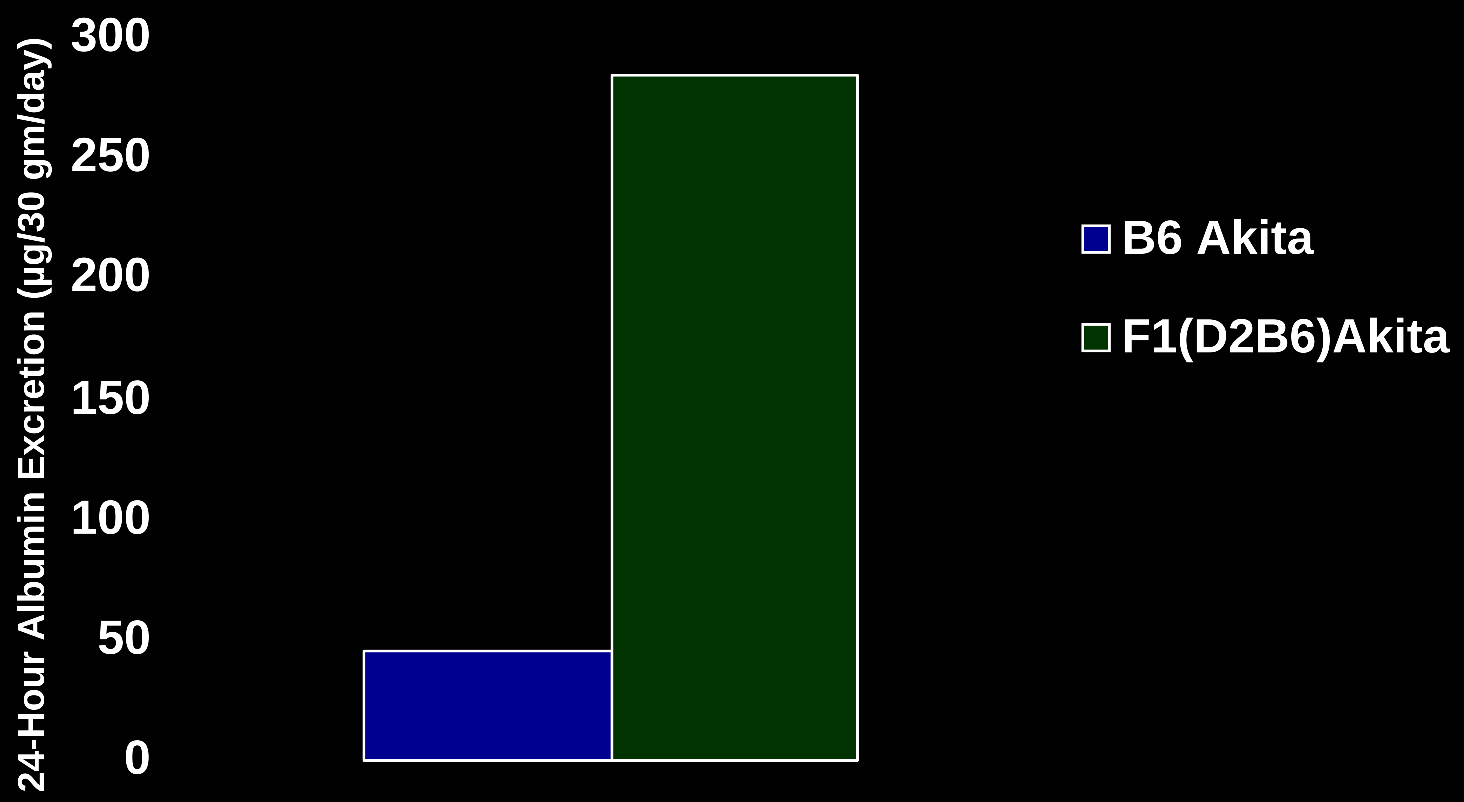


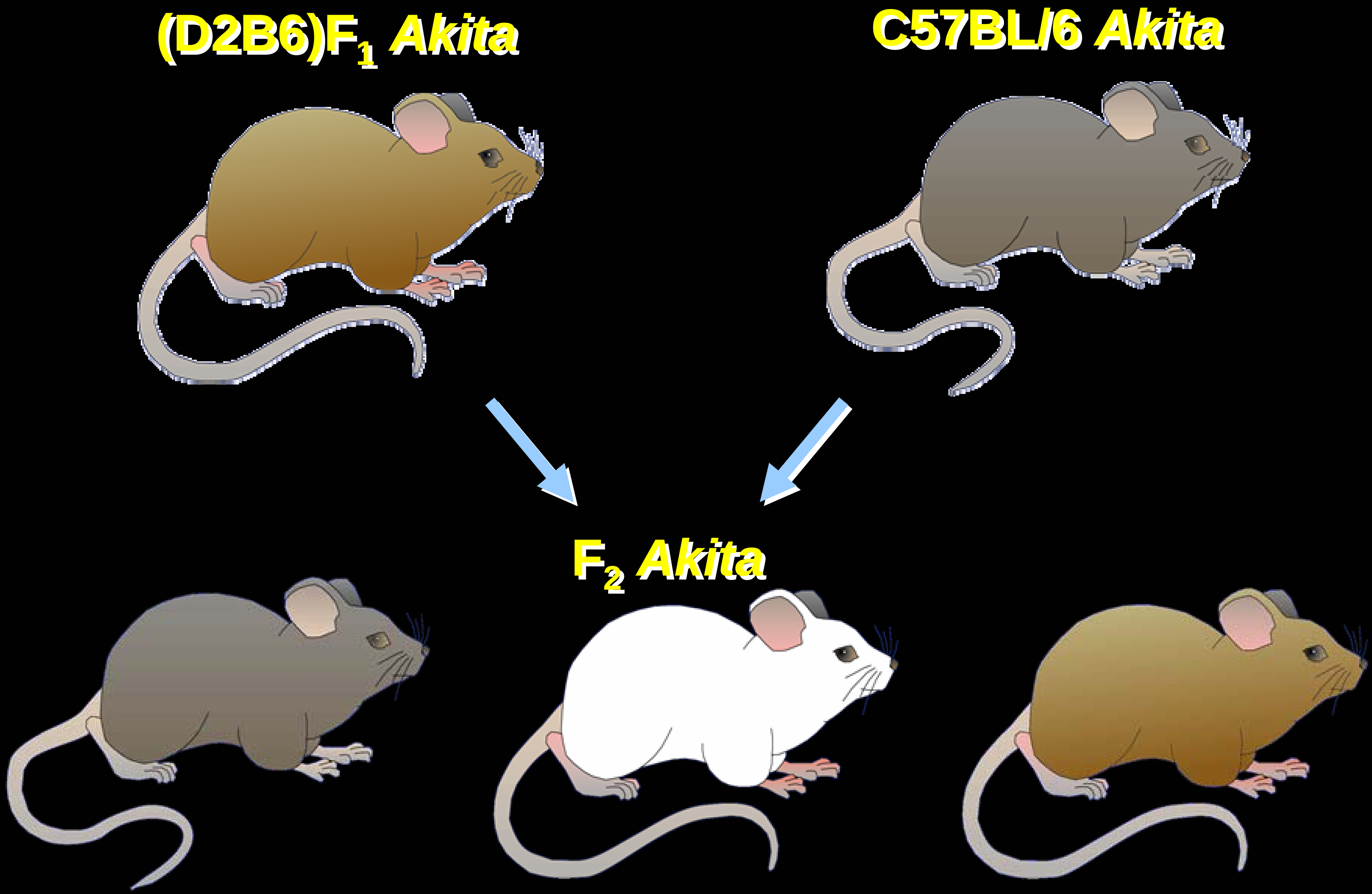
Other Studies with DBA/2-Akita Mice

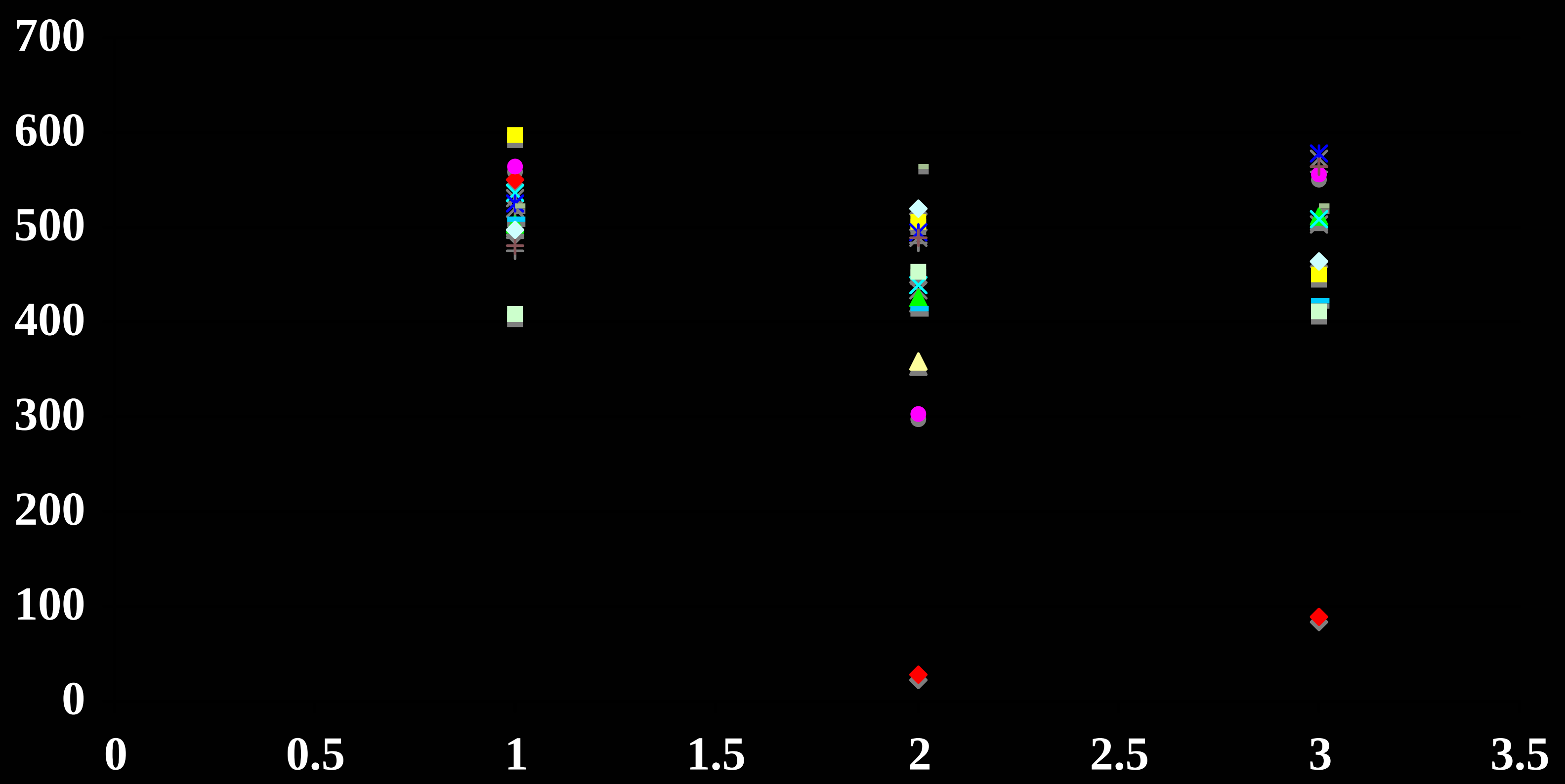
- Aging study to 9-12 months so far unsuccessful
- Studies in progress with N6 back-cross DBA/2 Akita mice
- Poor survival at N8


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*


700
600
500
400
300
200
100
0
0
0.5
1
1.5
2
2.5
3
3.5