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

Duke/UNC/Stanford

Program Director

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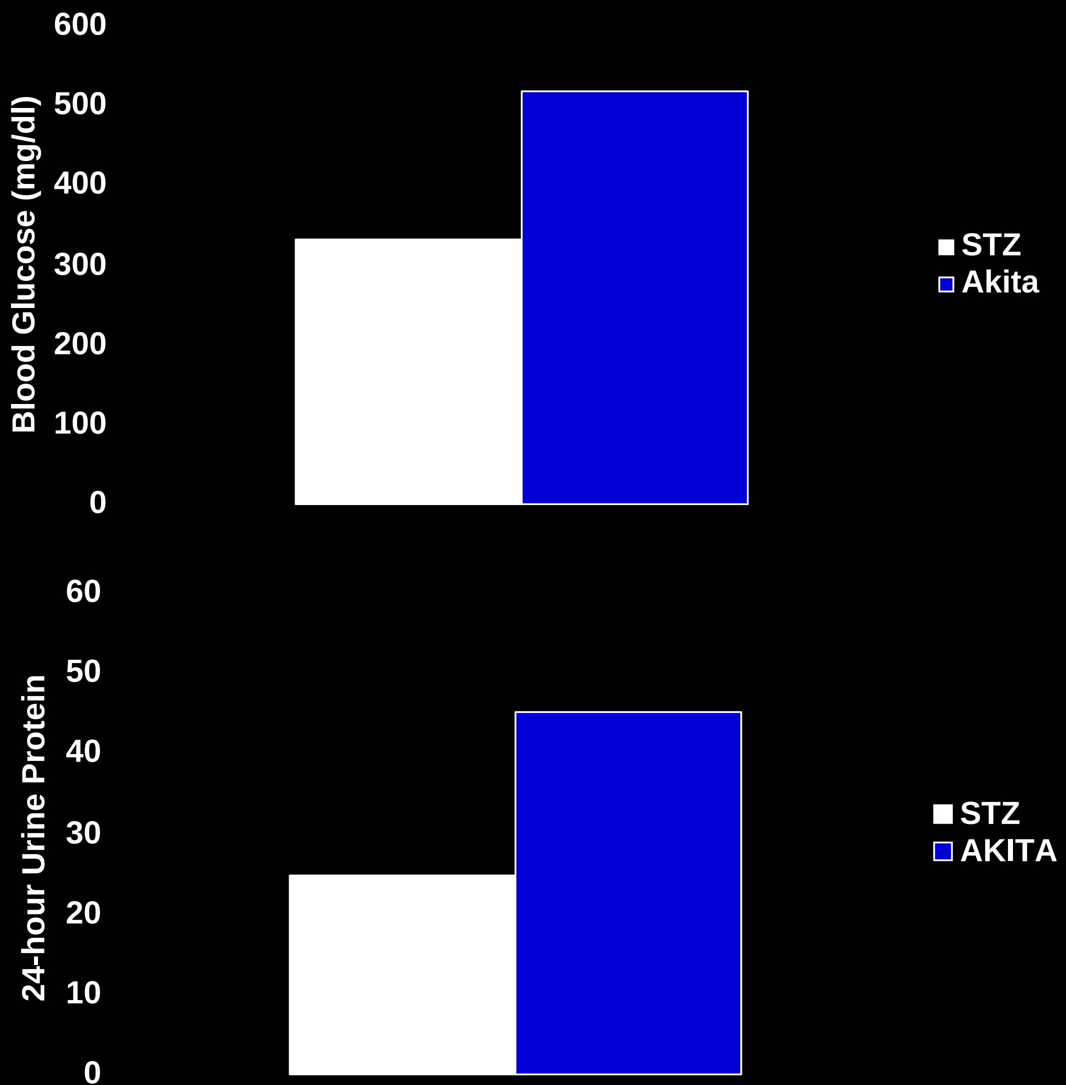
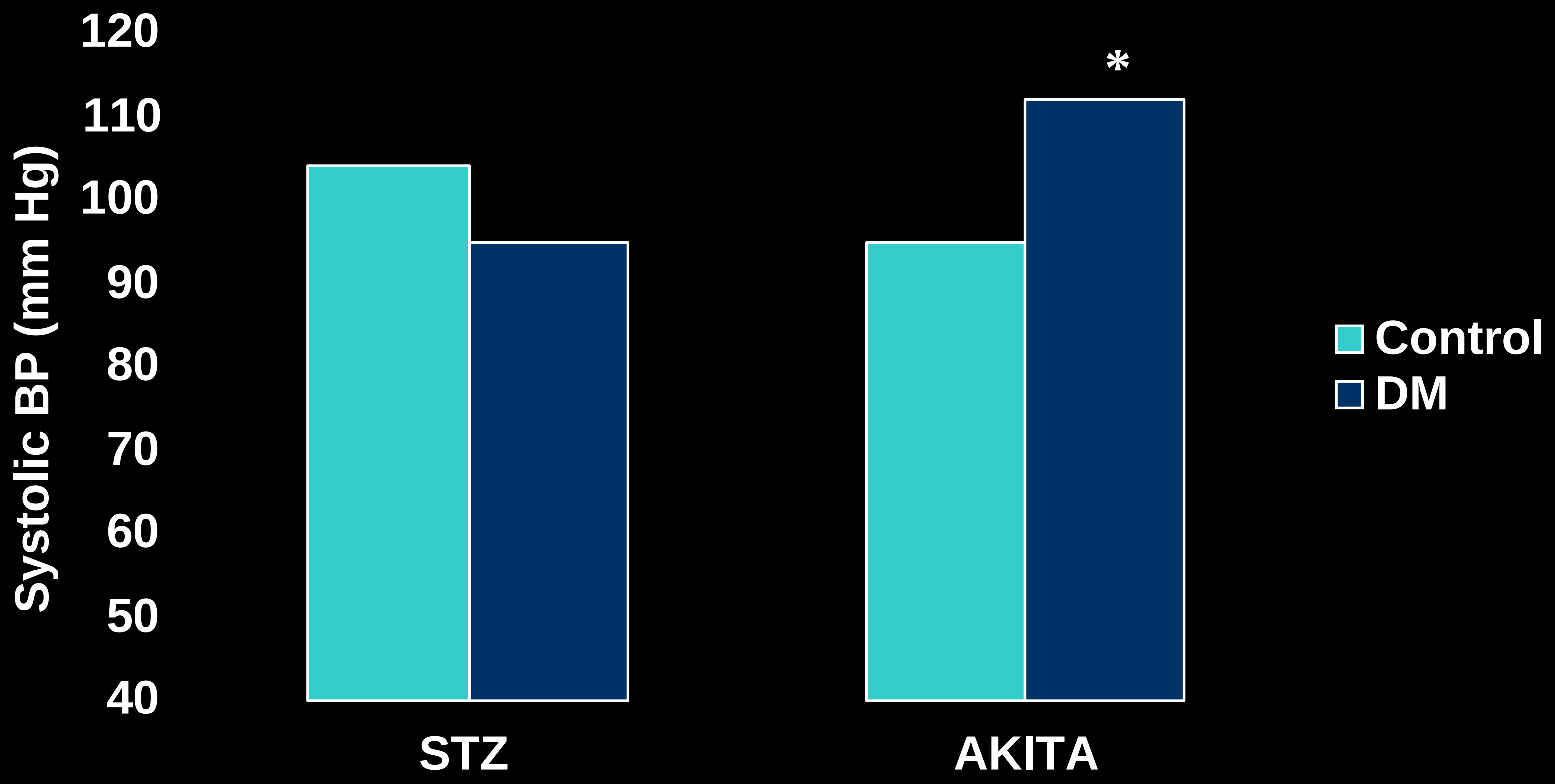
The Akita (*Ins2*$^{+/C96Y}$) Mouse

- 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).

Blood Glucose and Proteinuria in C57BL/6 Mice

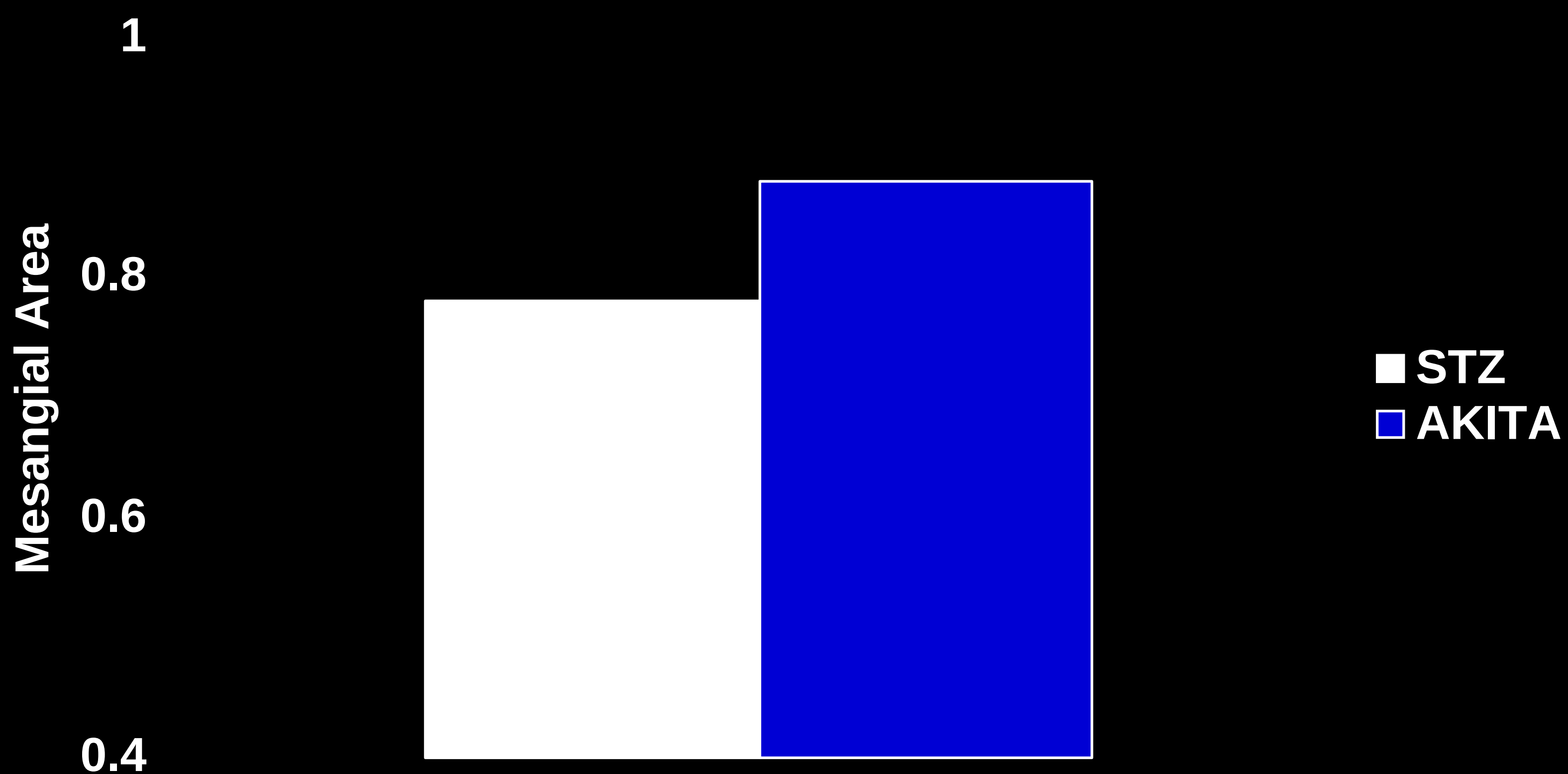


Differential Blood Pressure Responses

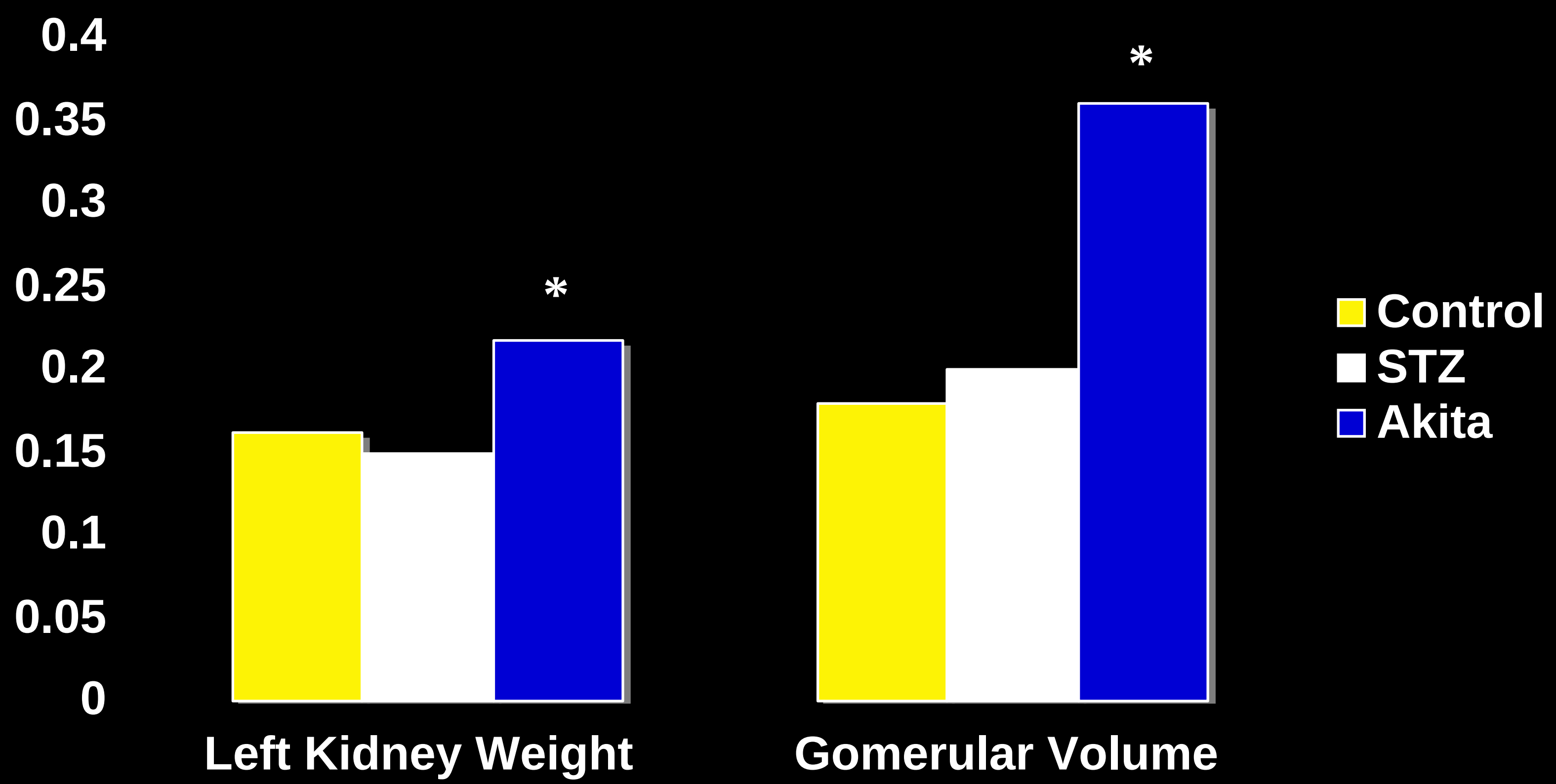


(*p=0.0018 vs Akita Control)

Mesangial Area in Diabetic C57BL/6 Mice



Increased Kidney Weights and Glomerular Volume in B6-Akita Mice



Strategies for Accelerating Kidney Pathology

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

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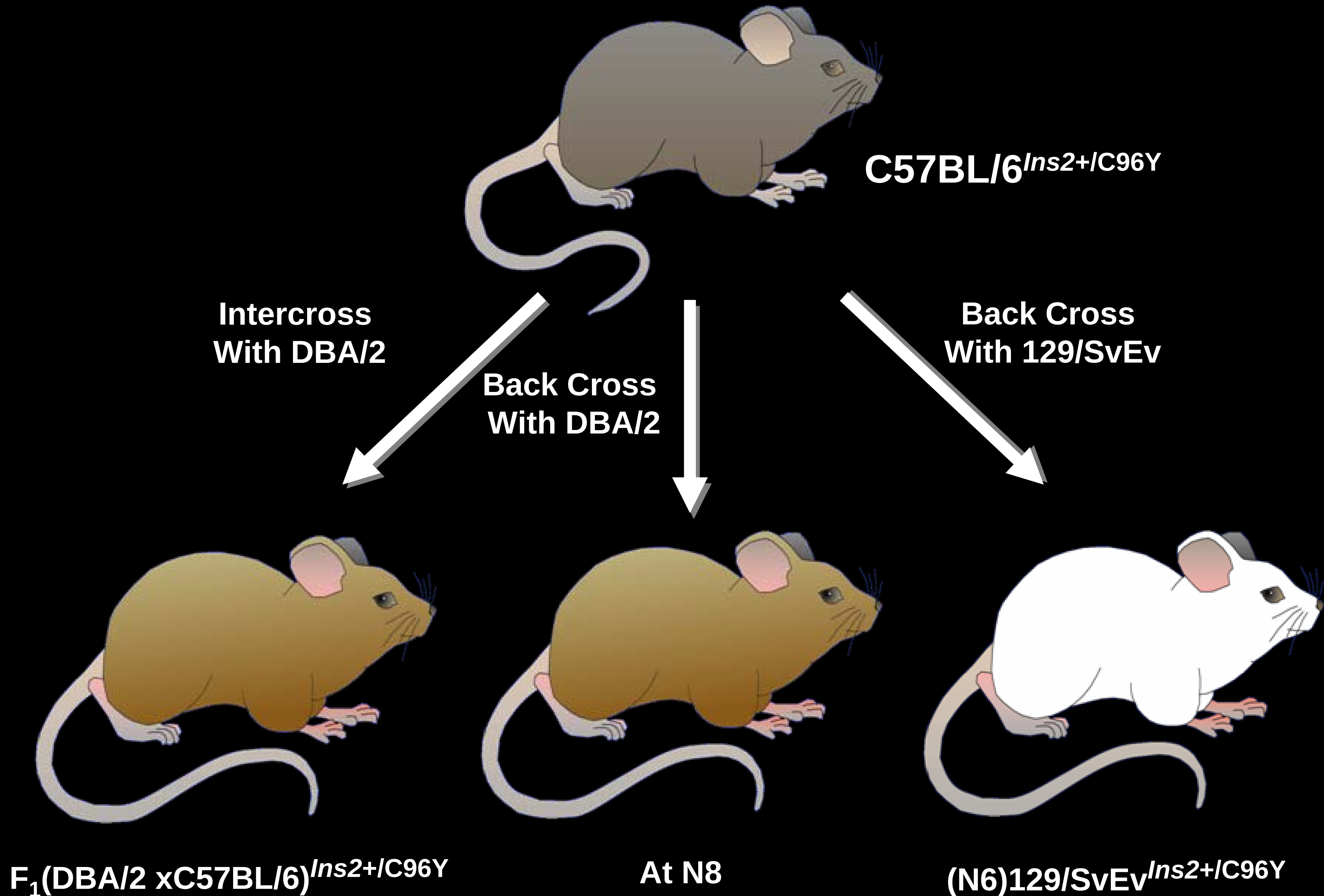
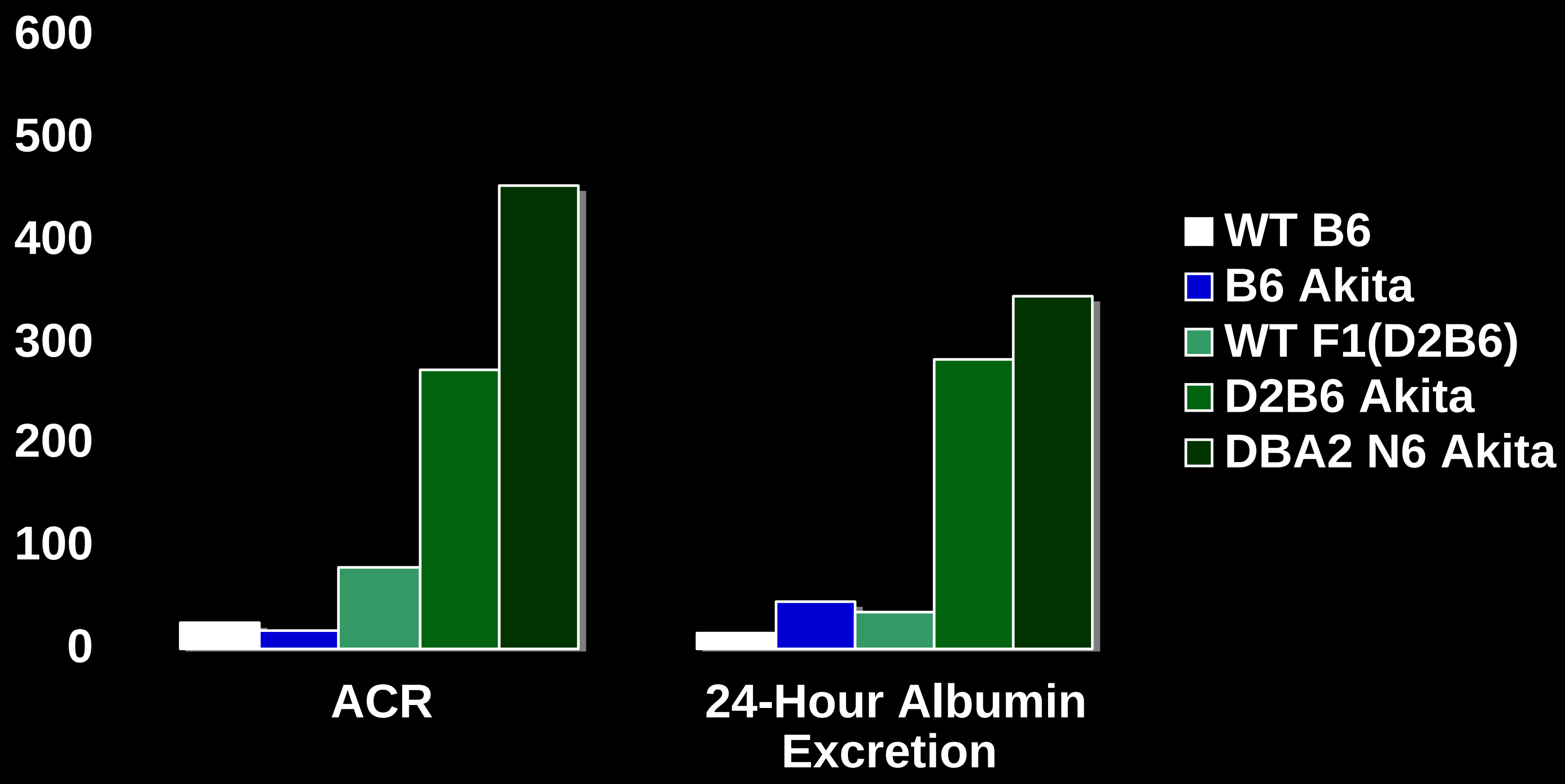
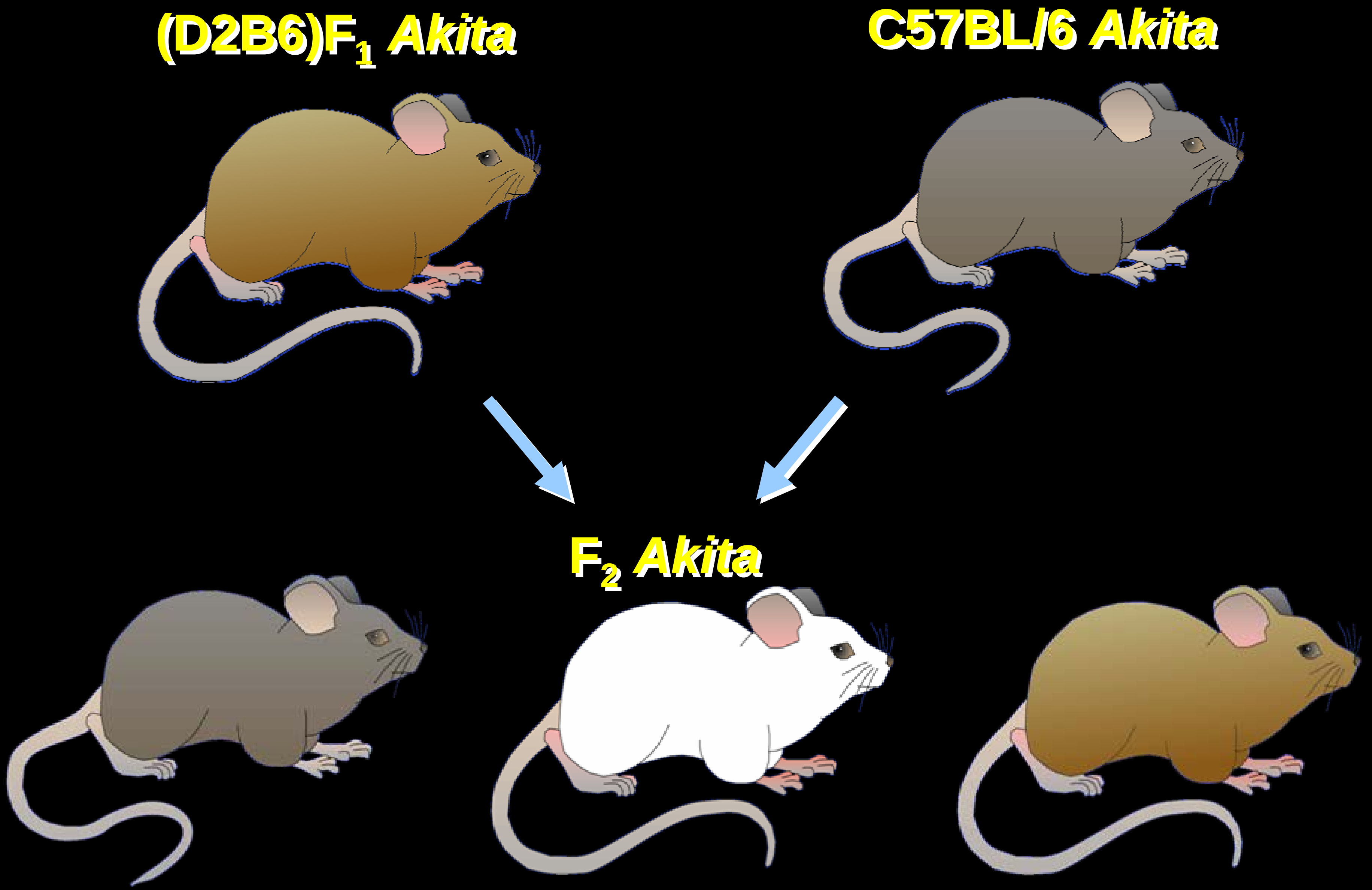
Generating Inbred *Ins2*$^{+/C96Y}$ Lines



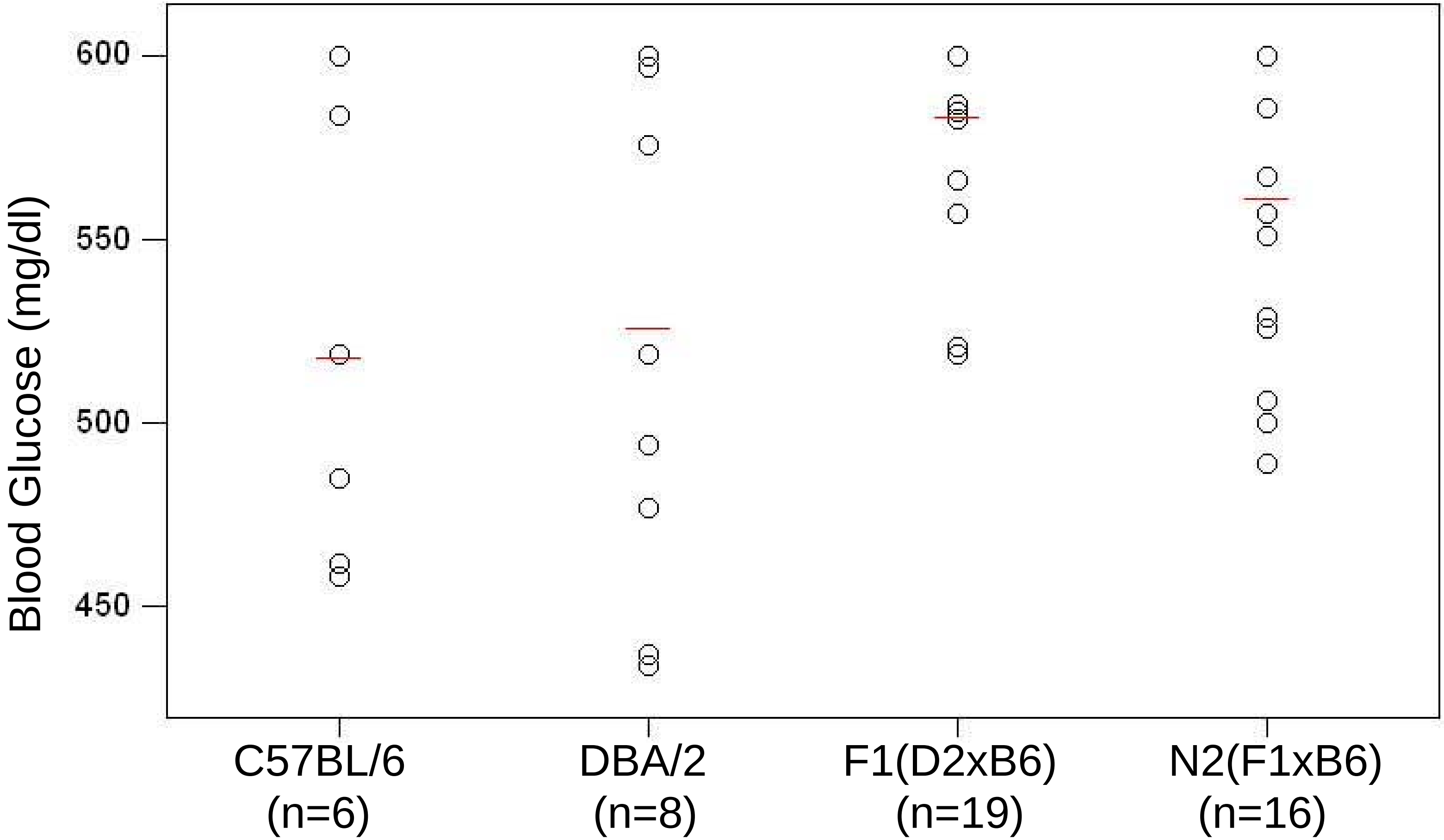
Albumin Excretion



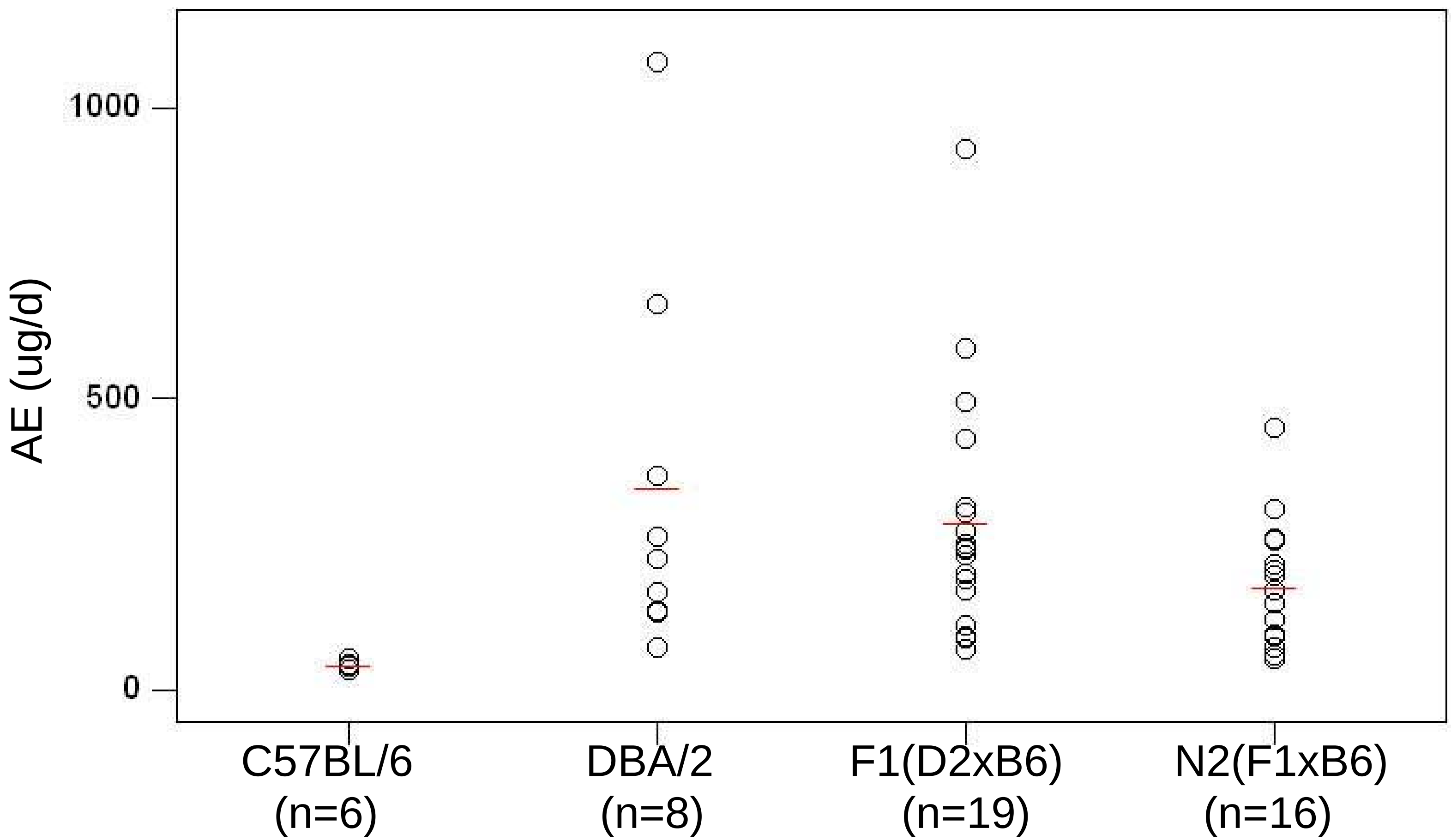


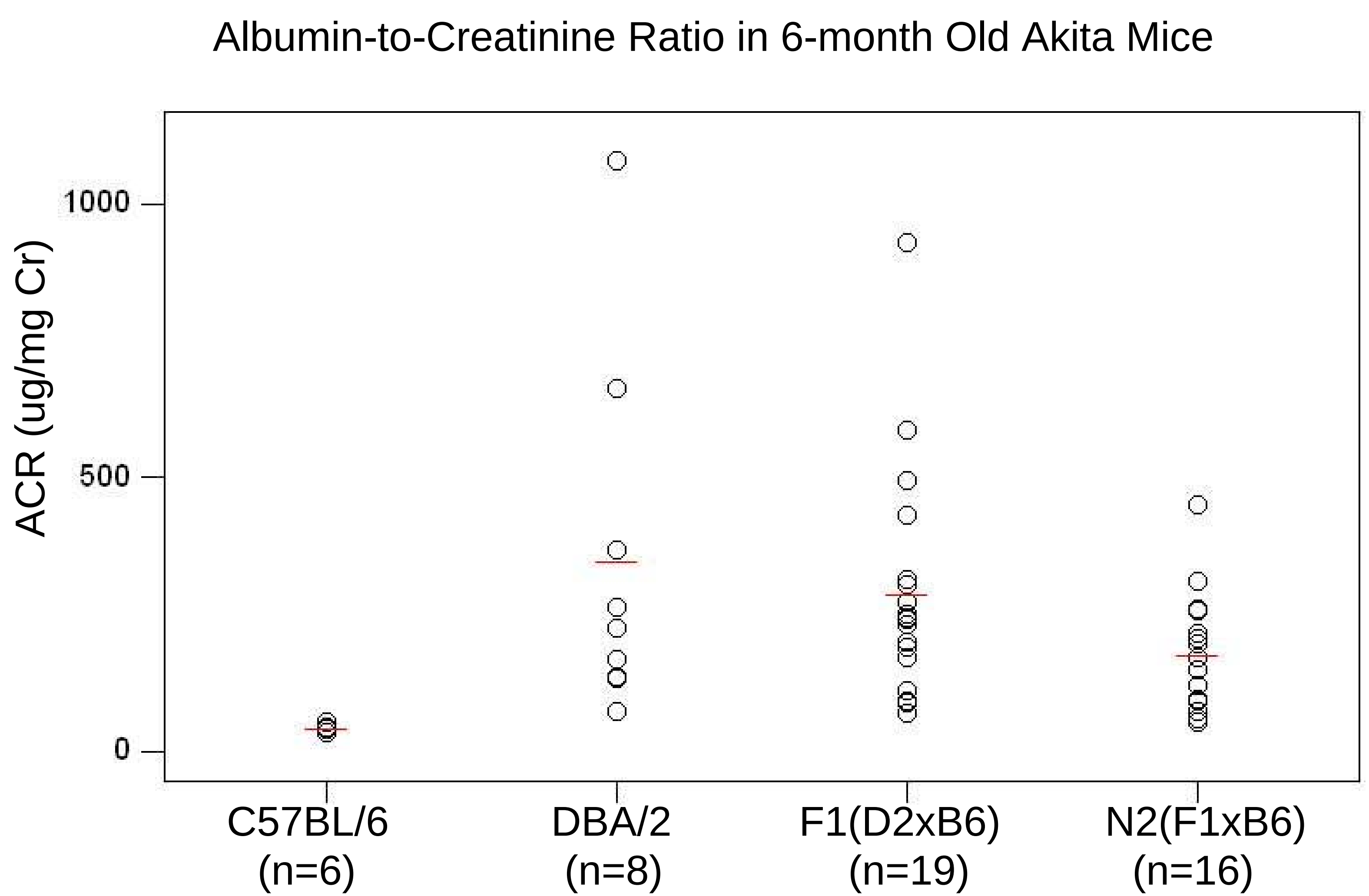
(D2B6)F_1 *Akita*
C57BL/6 *Akita*
F_2 *Akita*

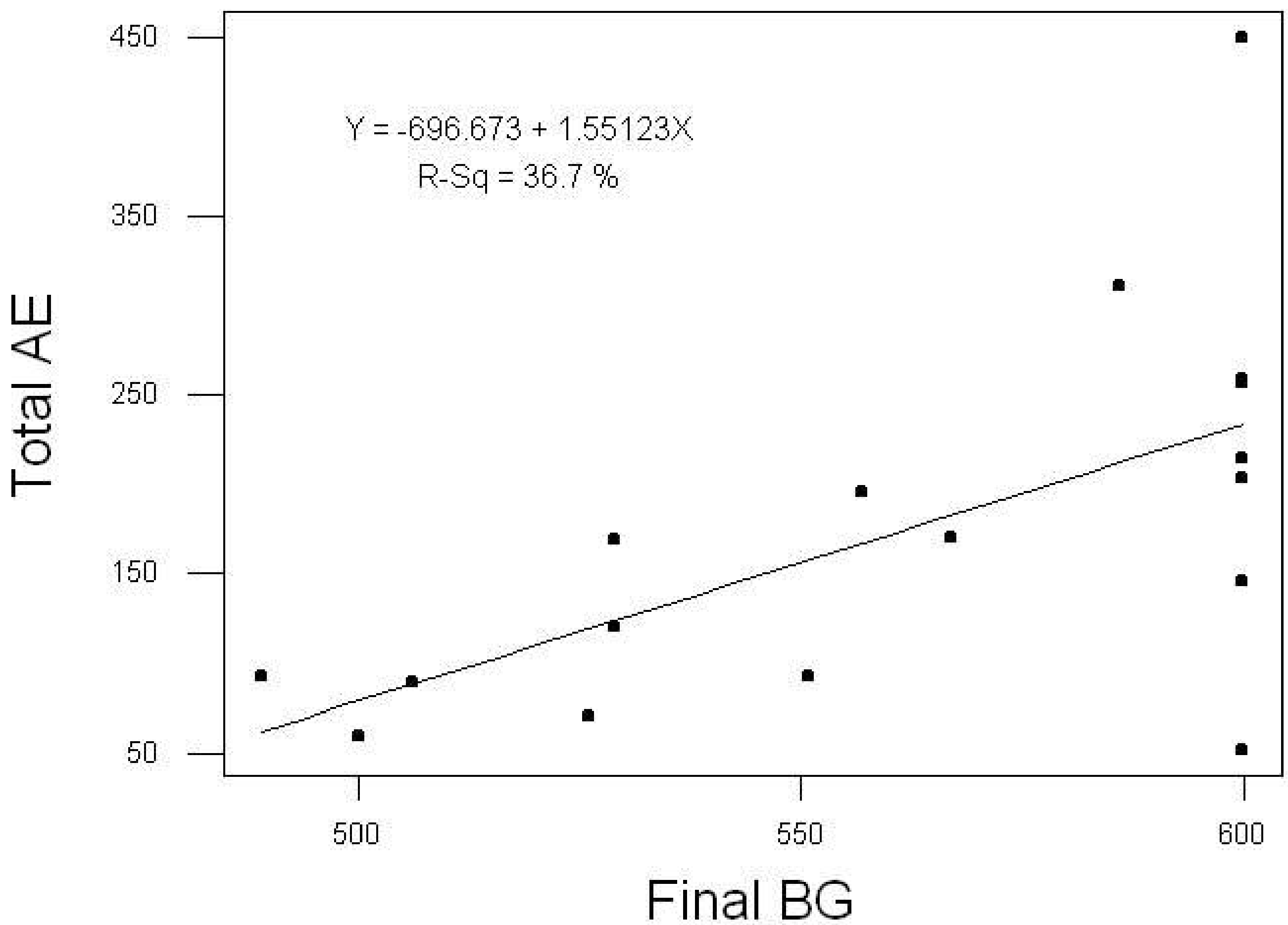
Blood Glucose in Akita Mice at 6 months of age



24 Hour Albumin Excretion in 6-month Old Akita Mice

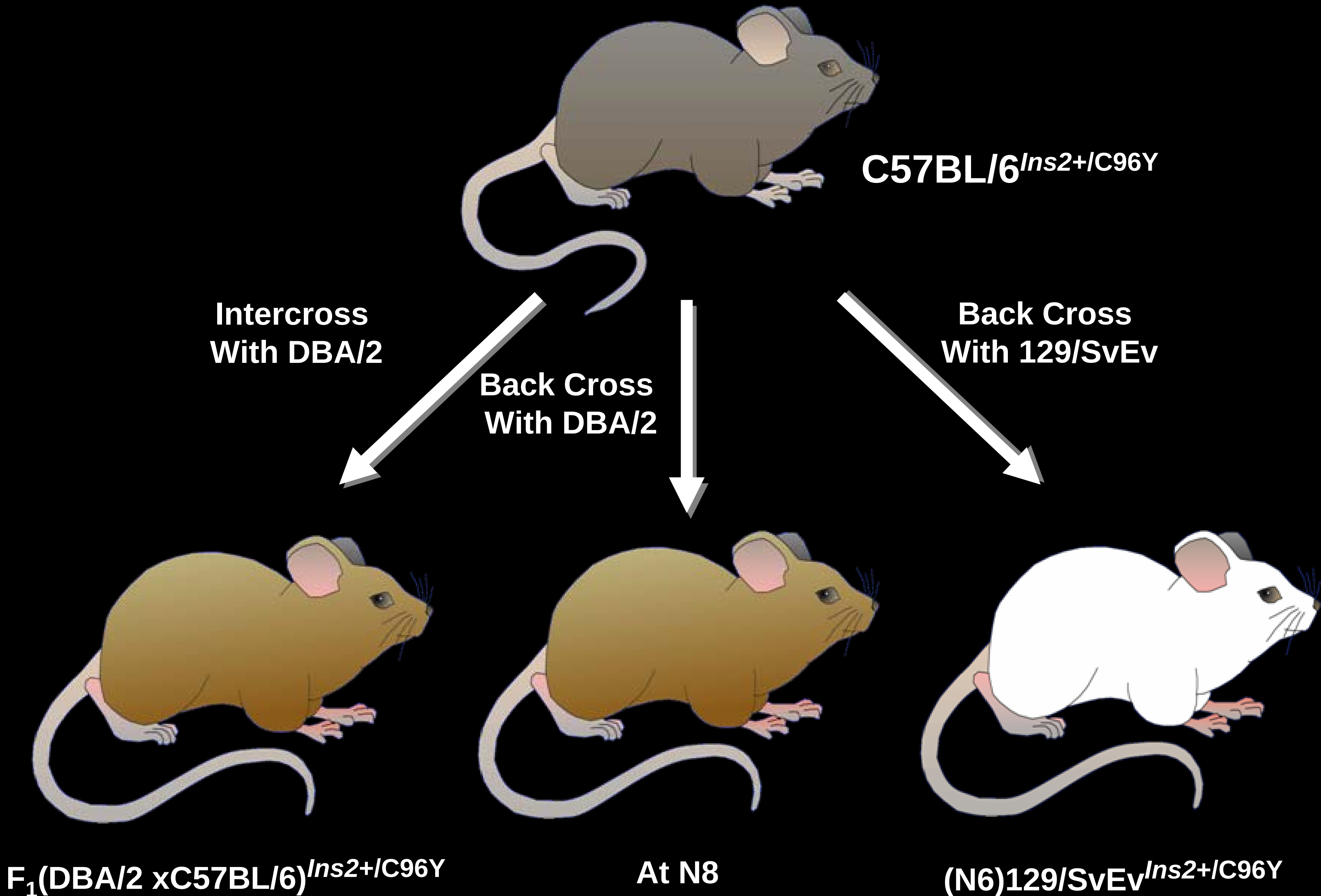



Albumin-to-Creatinine Ratio in 6-month Old Akita Mice
ACR (ug/mg Cr)
1000
500
0
C57BL/6
(n=6)
DBA/2
(n=8)
F1(D2xB6)
(n=19)
N2(F1xB6)
(n=16)

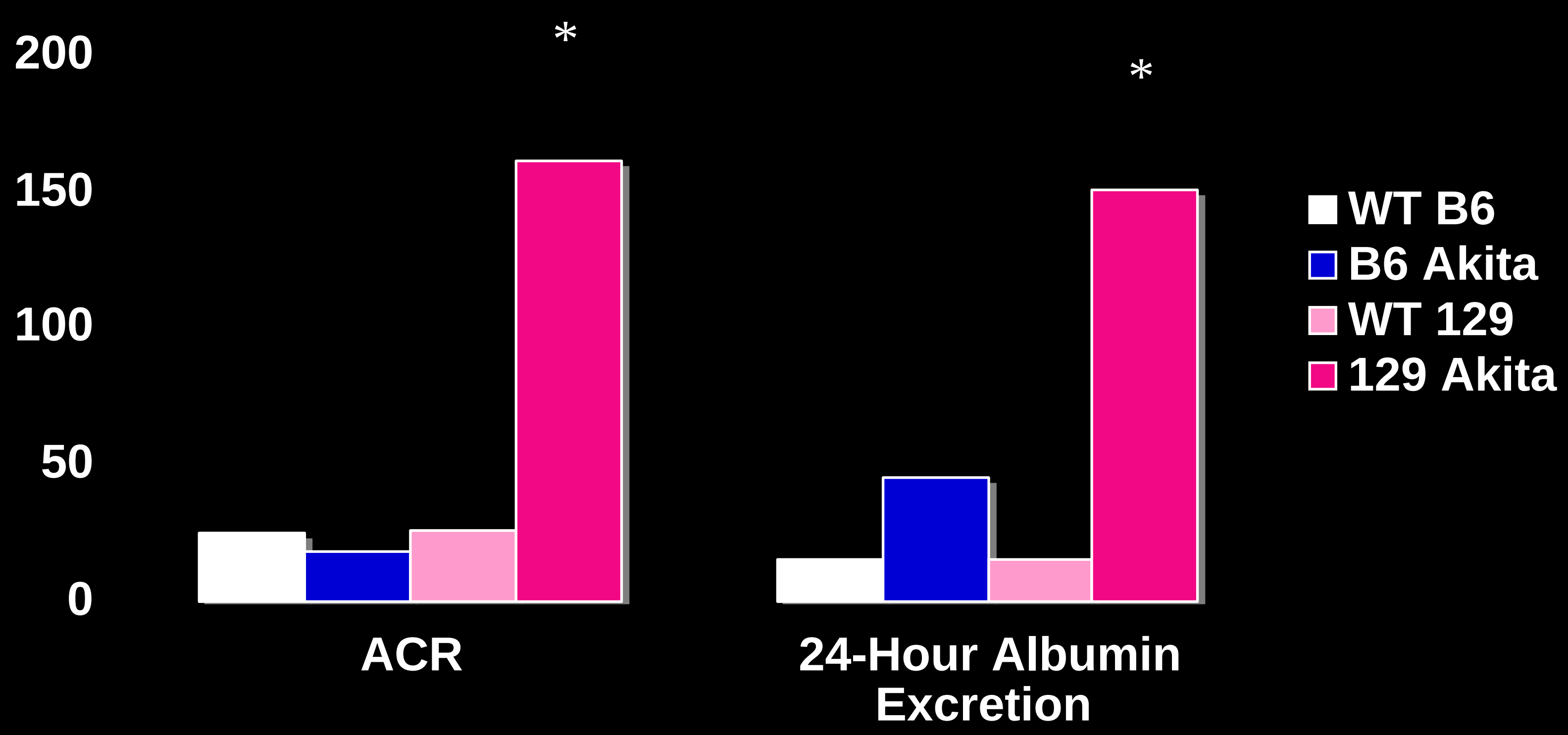


Y = -696.673 + 1.55123X
R-Sq = 36.7 %
450
350
250
150
50
500
550
600
Total AE
Final BG

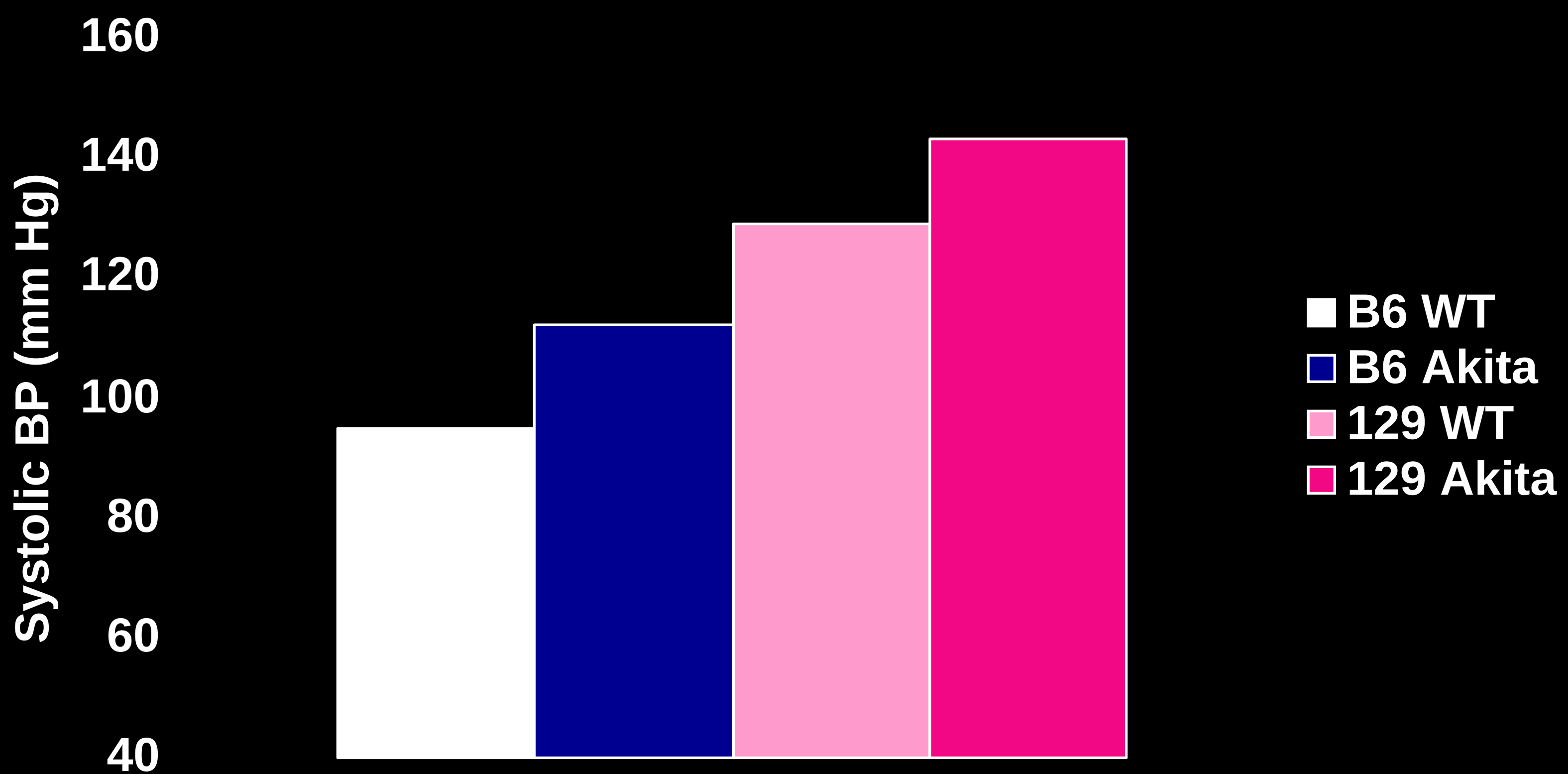
Generating Inbred *Ins2*$^{+/C96Y}$ Lines



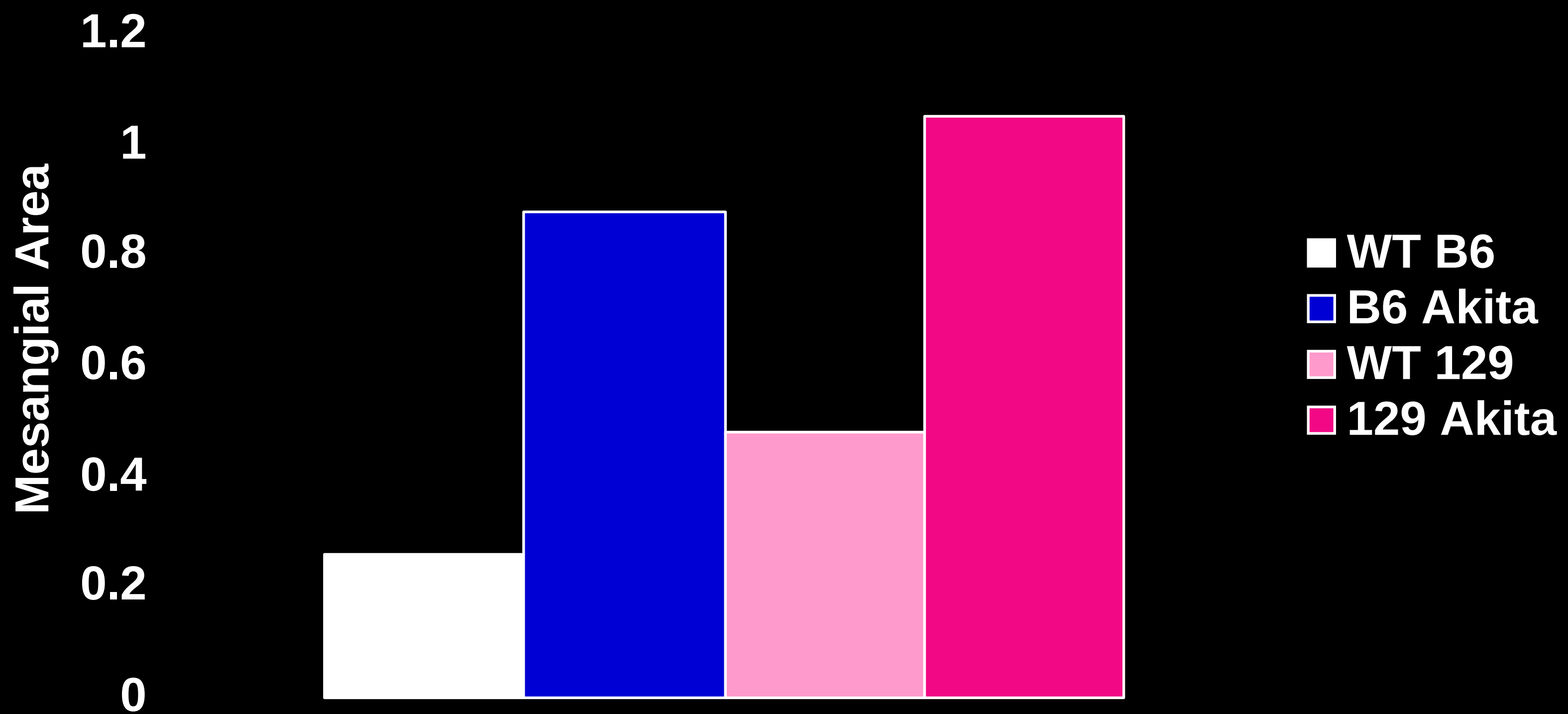
Albumin Excretion

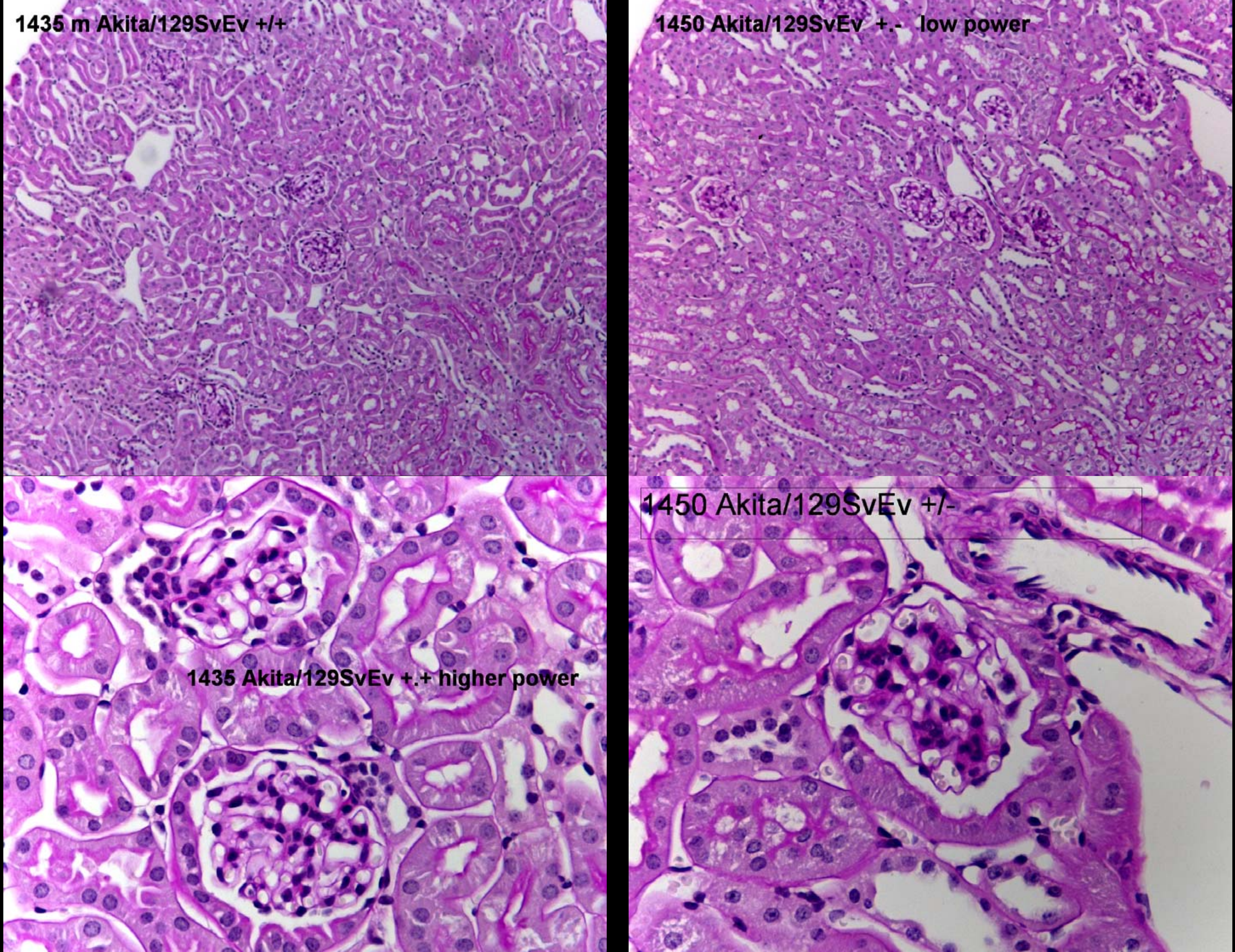


Blood Pressures in 129/SvEv MIce



Mesangial Pathology in 129/SvEv Mice




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

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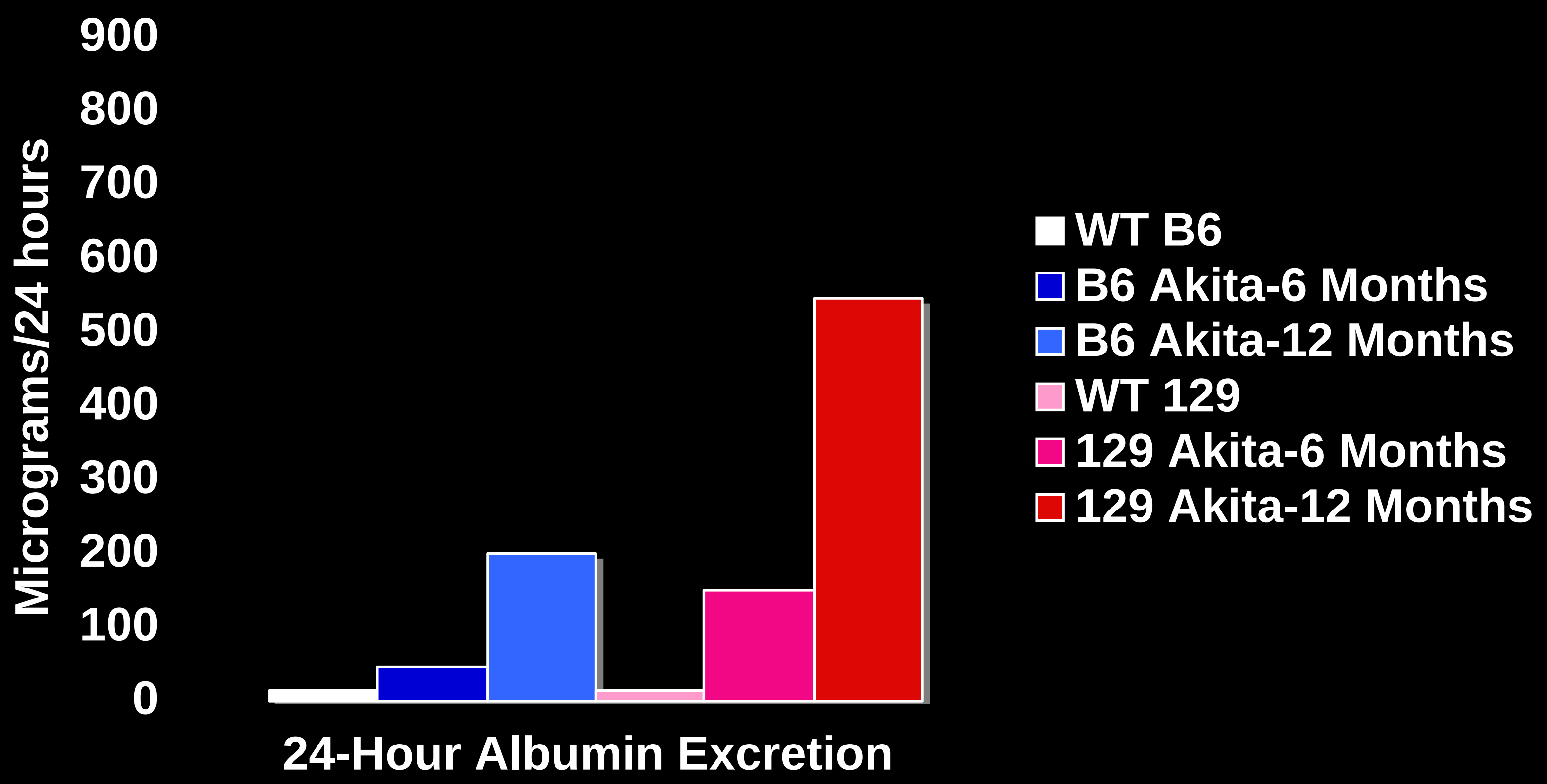
Albumin Excretion



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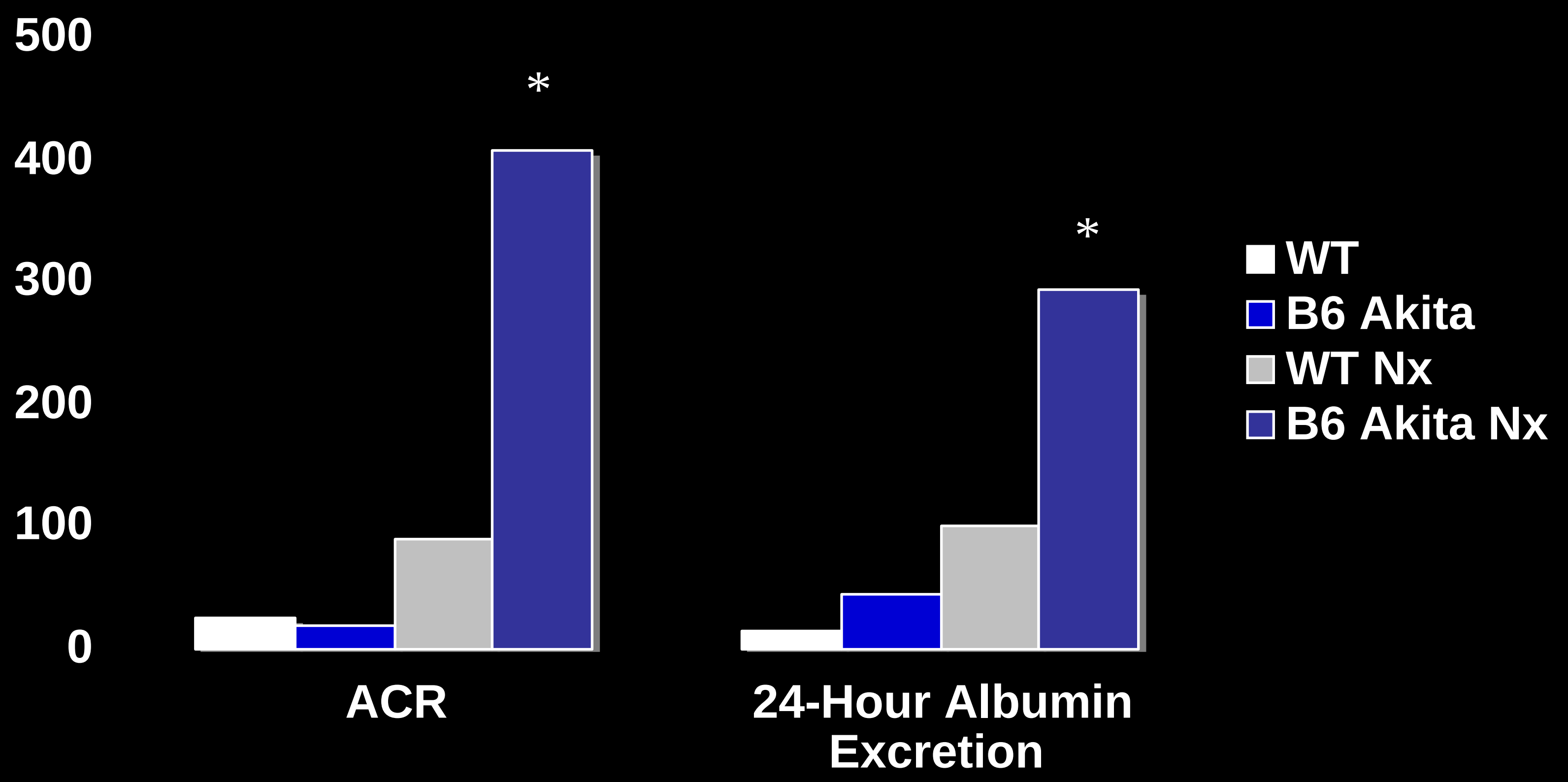
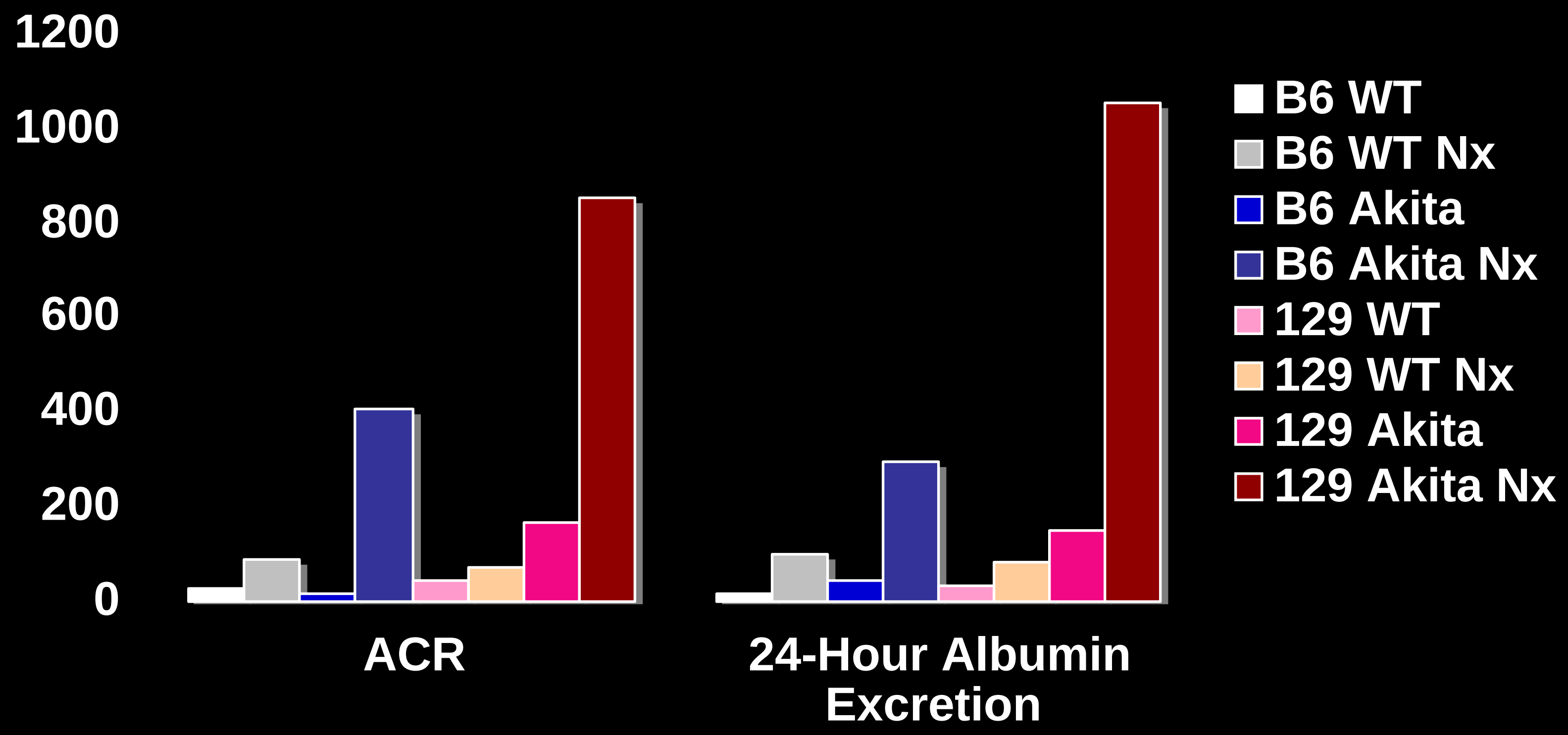
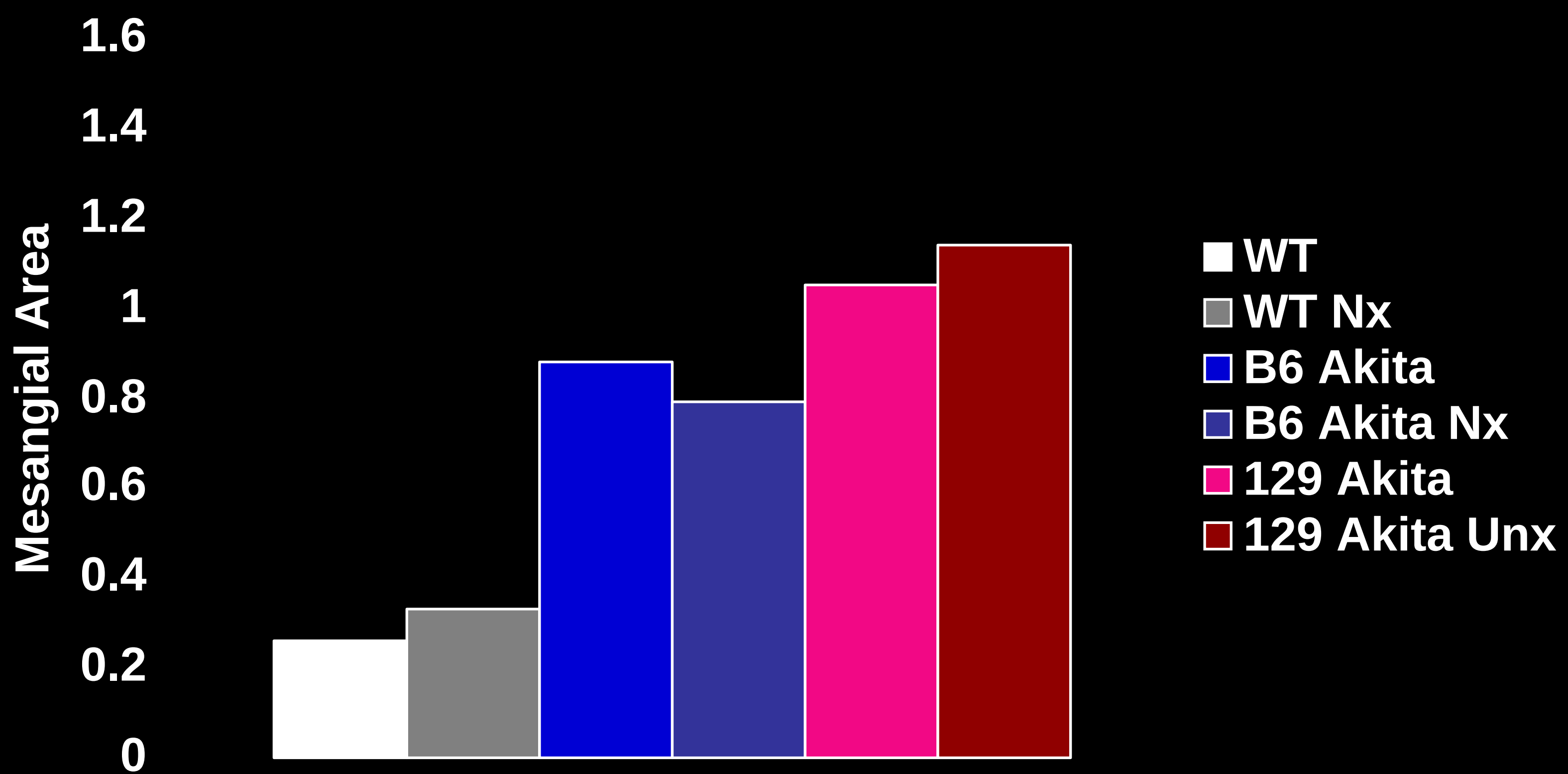
Effect of Uni-Nephrectomy on Albumin Excretion



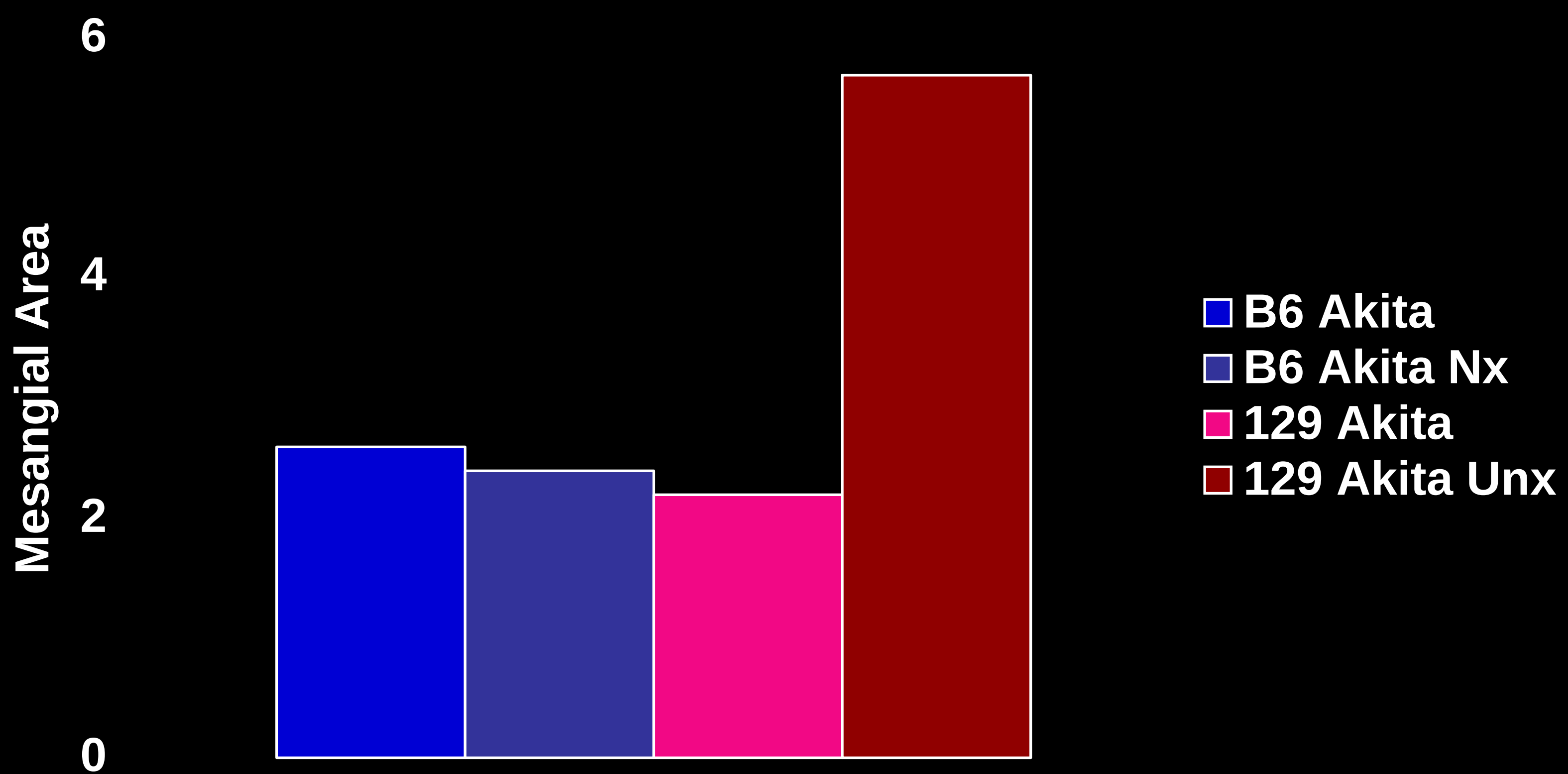
Effect of Uni-Nephrectomy on Albumin Excretion

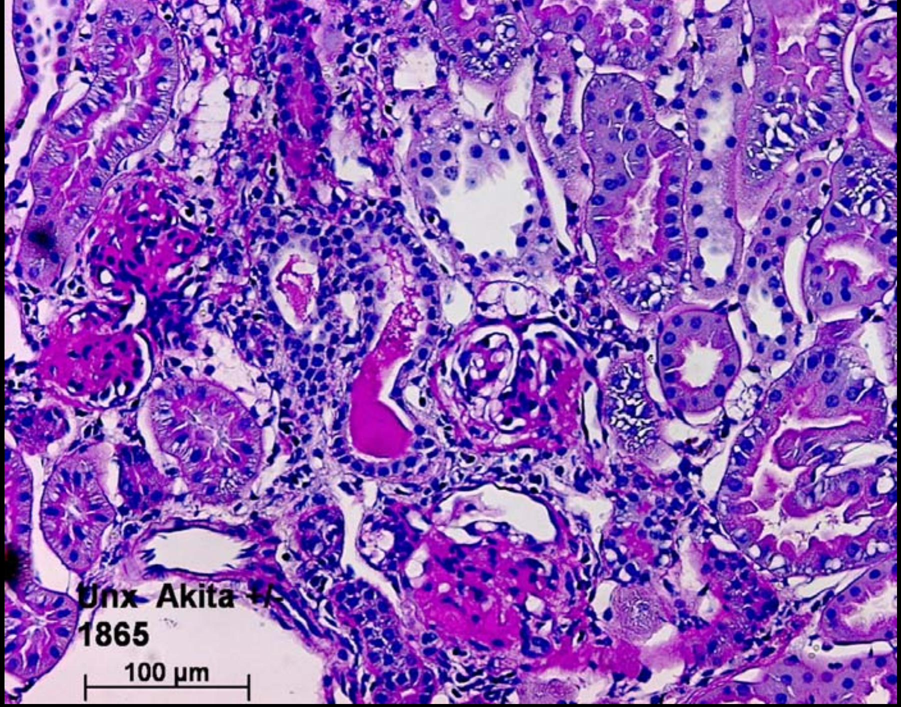


Mesangial Pathology Score After Uni-Nephrectomy

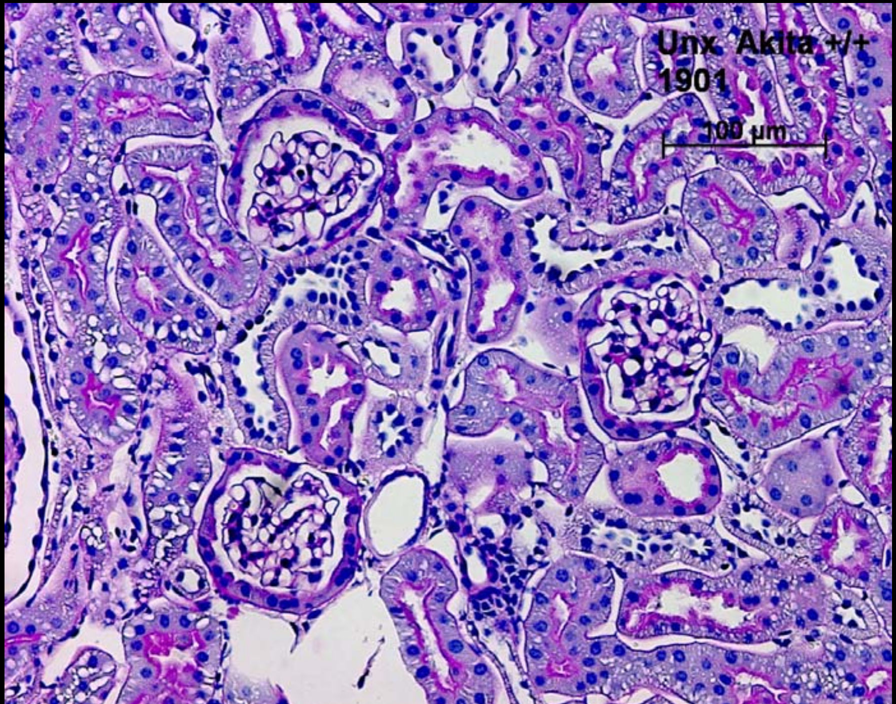


Mesangial Pathology Ratio
After Uni-Nephrectomy

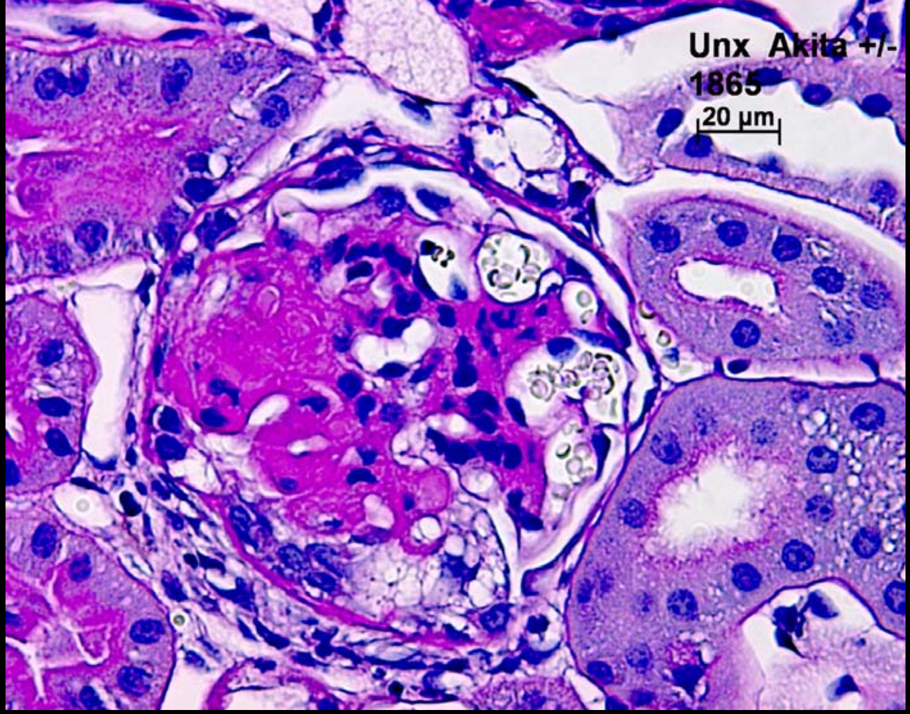




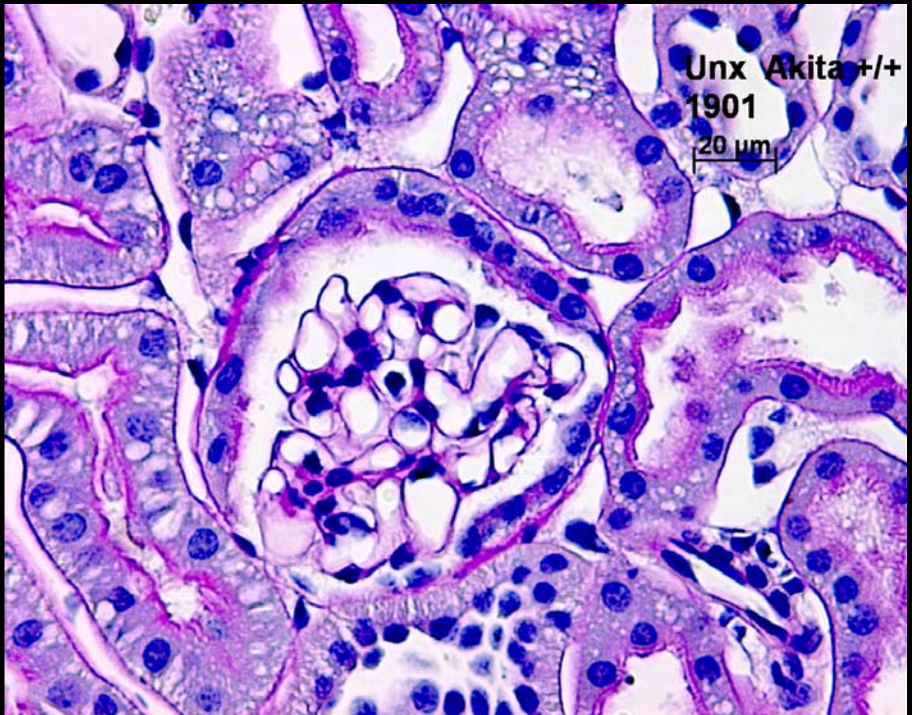
129 Akita Unx



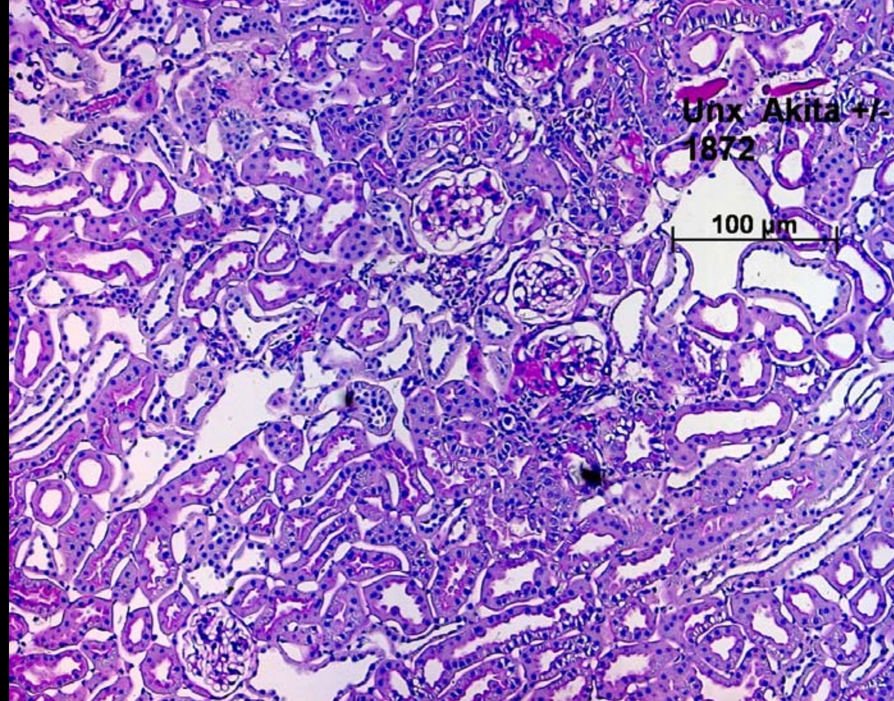
129 WT Unx

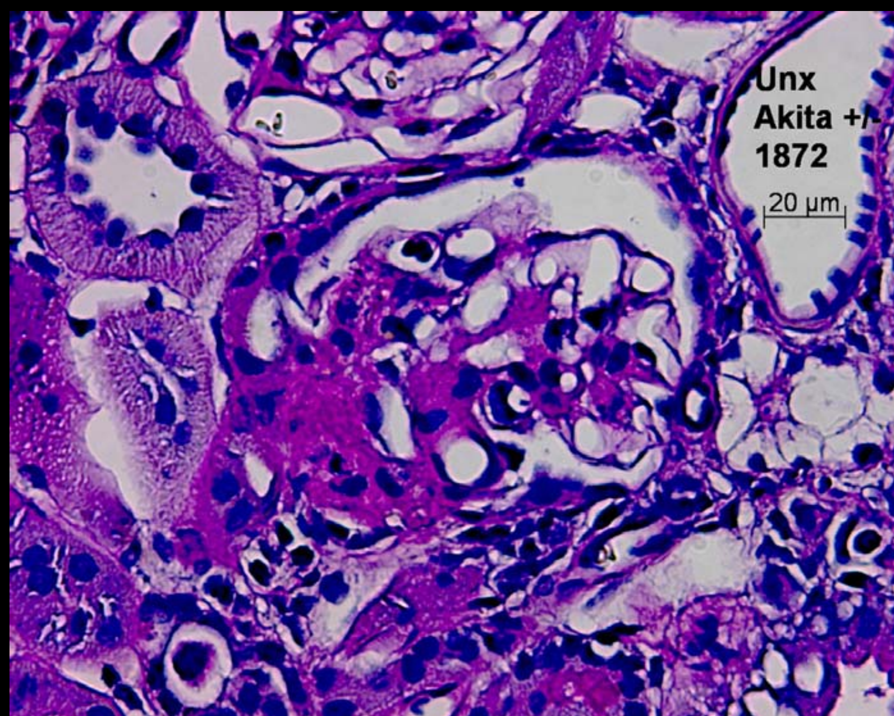


129 Akita Unx



129 WT Unx





129 Akita Unx

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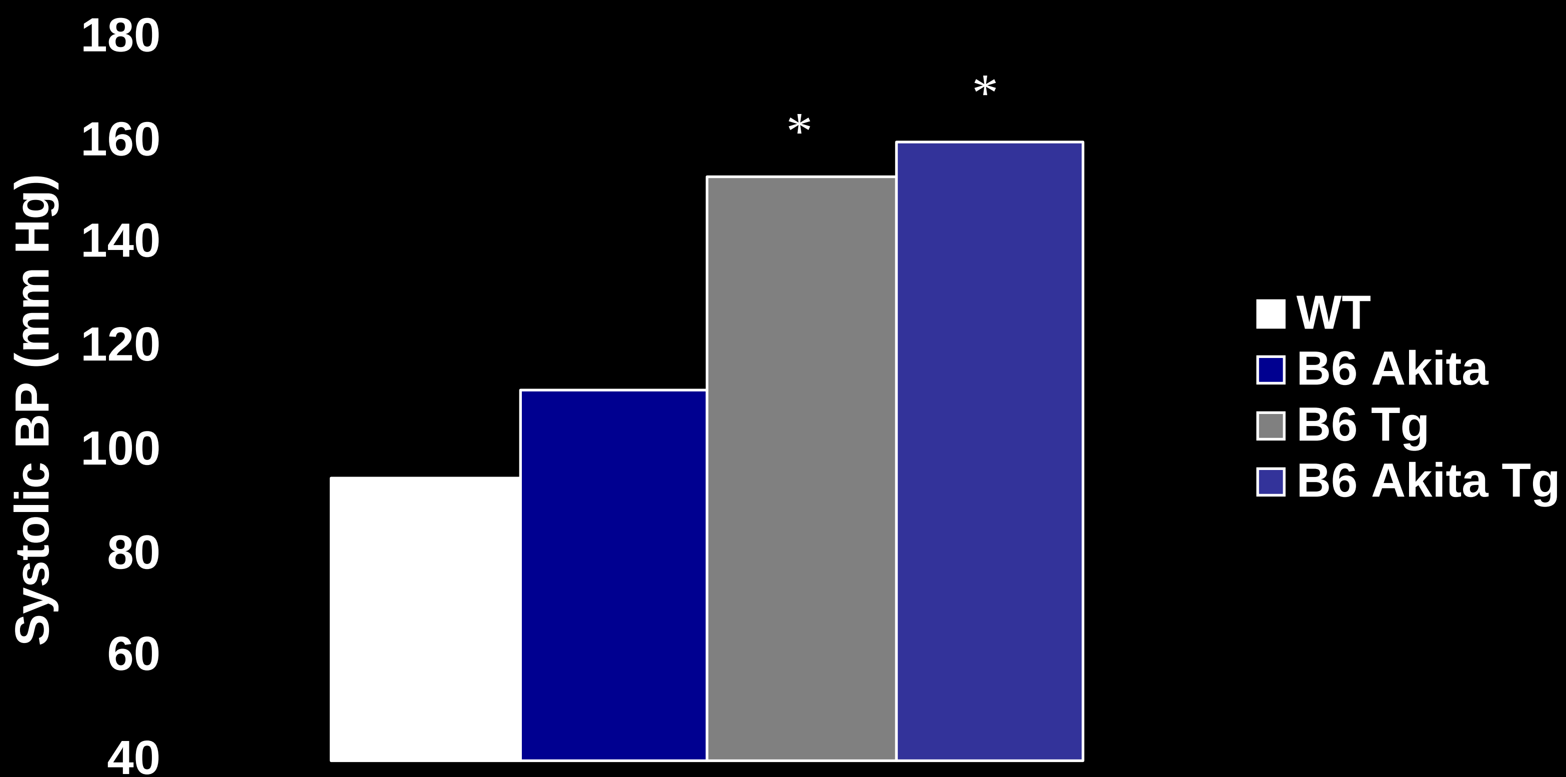
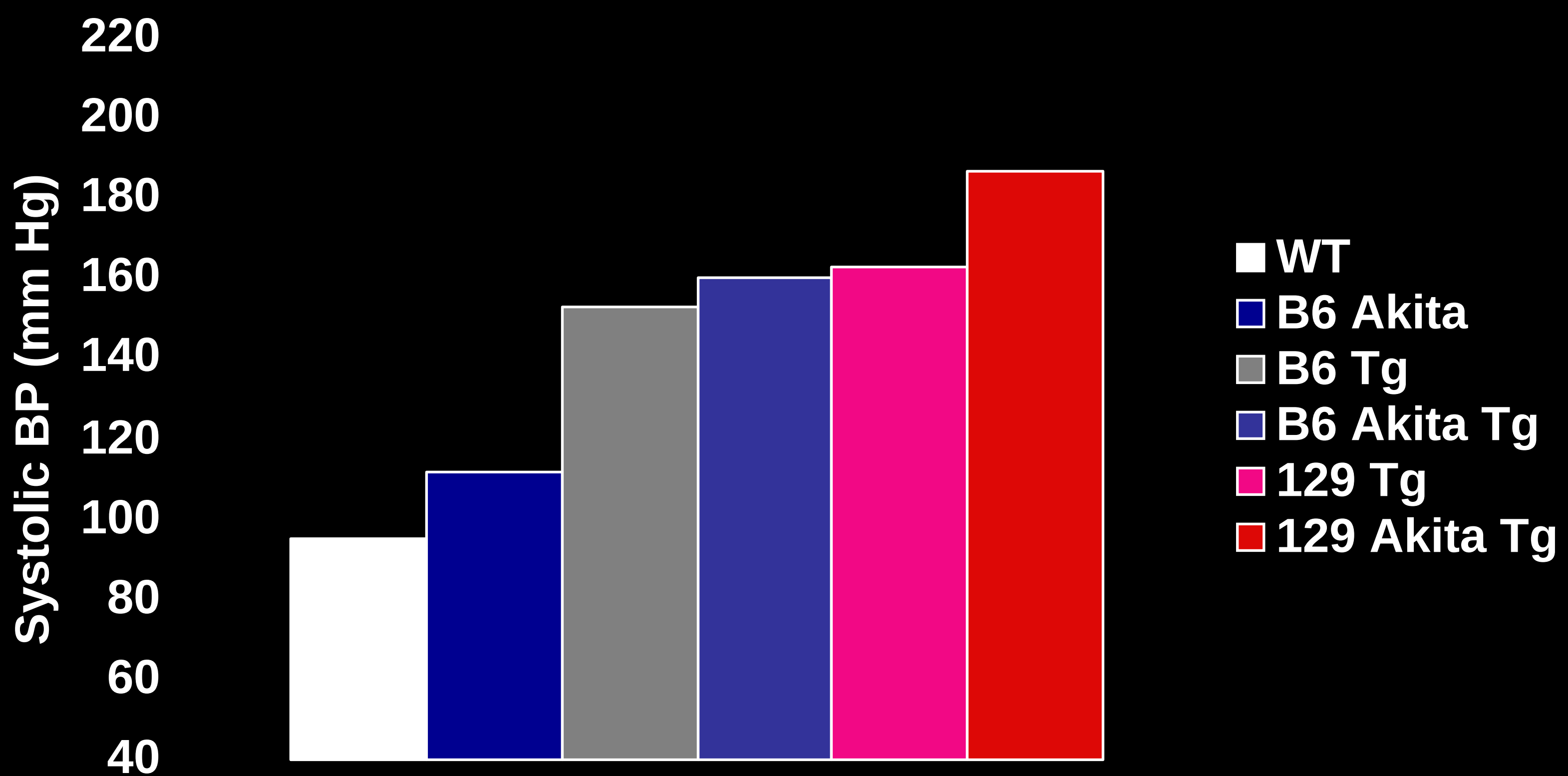
Renin Transgene

- Single-copy transgene
- Constitutive expression of renin under control of the albumin promoter

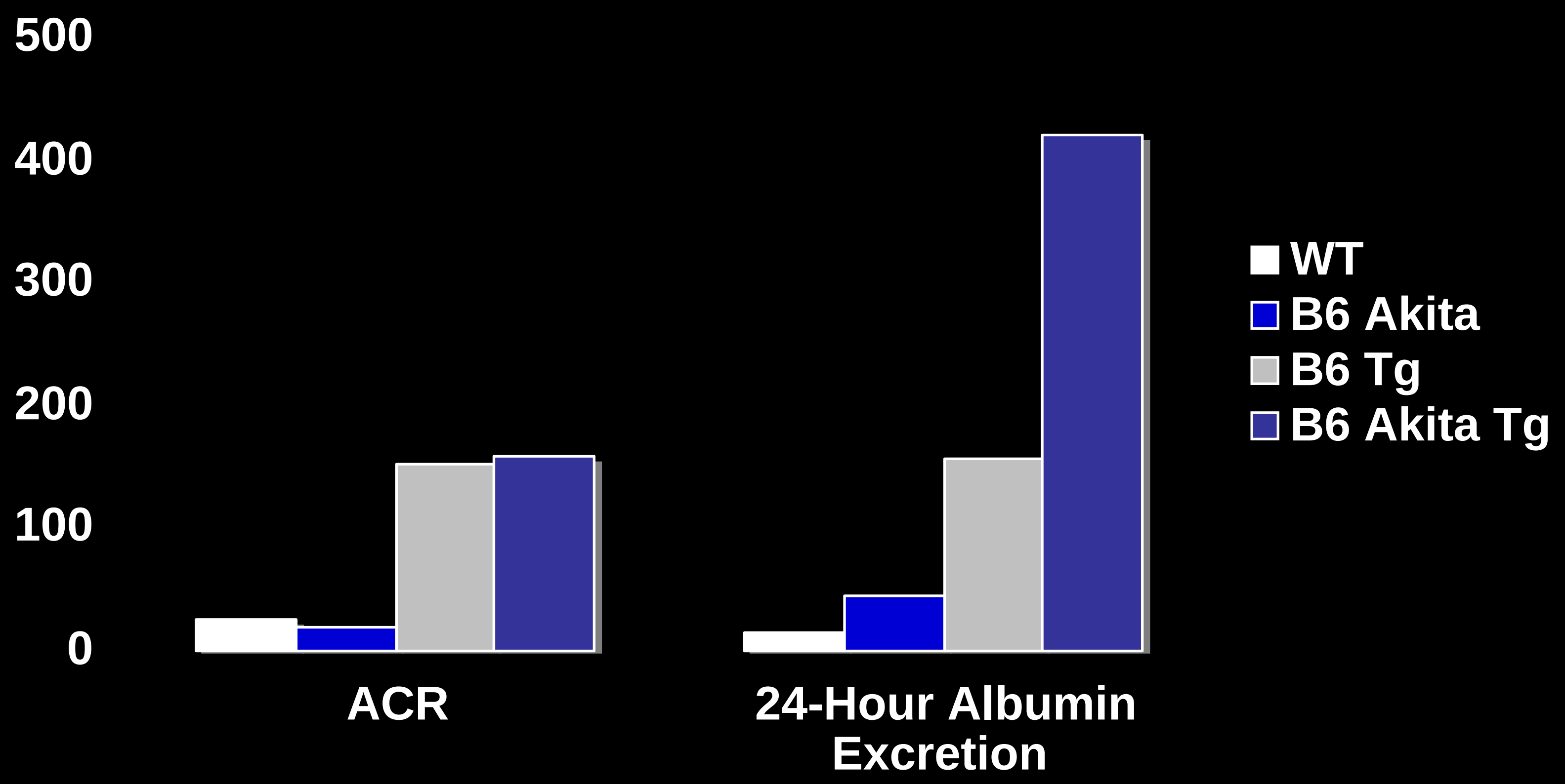
Blood Pressures in Renin Transgenic MIce



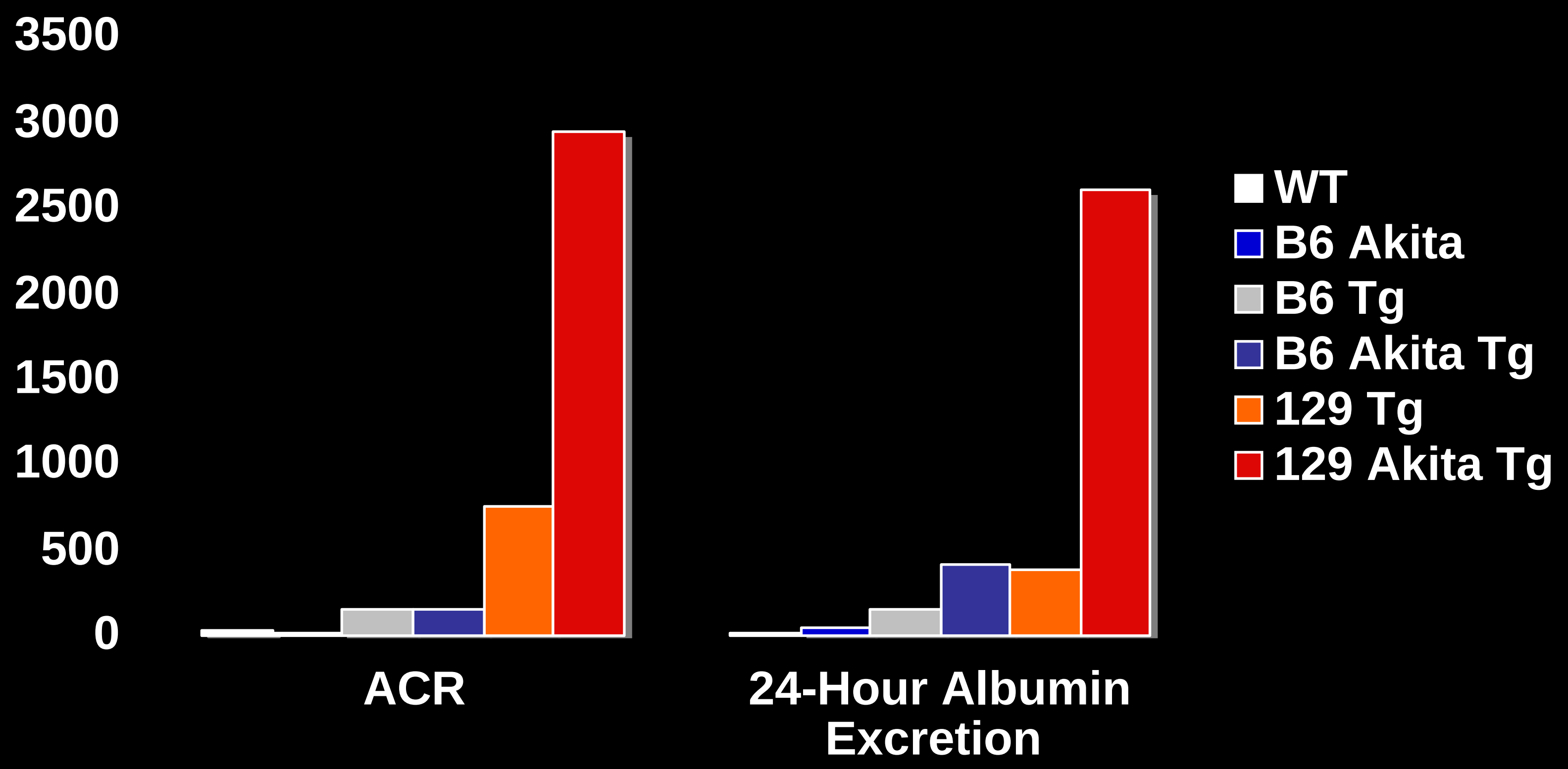
Blood Pressures in Renin Transgenic MIce



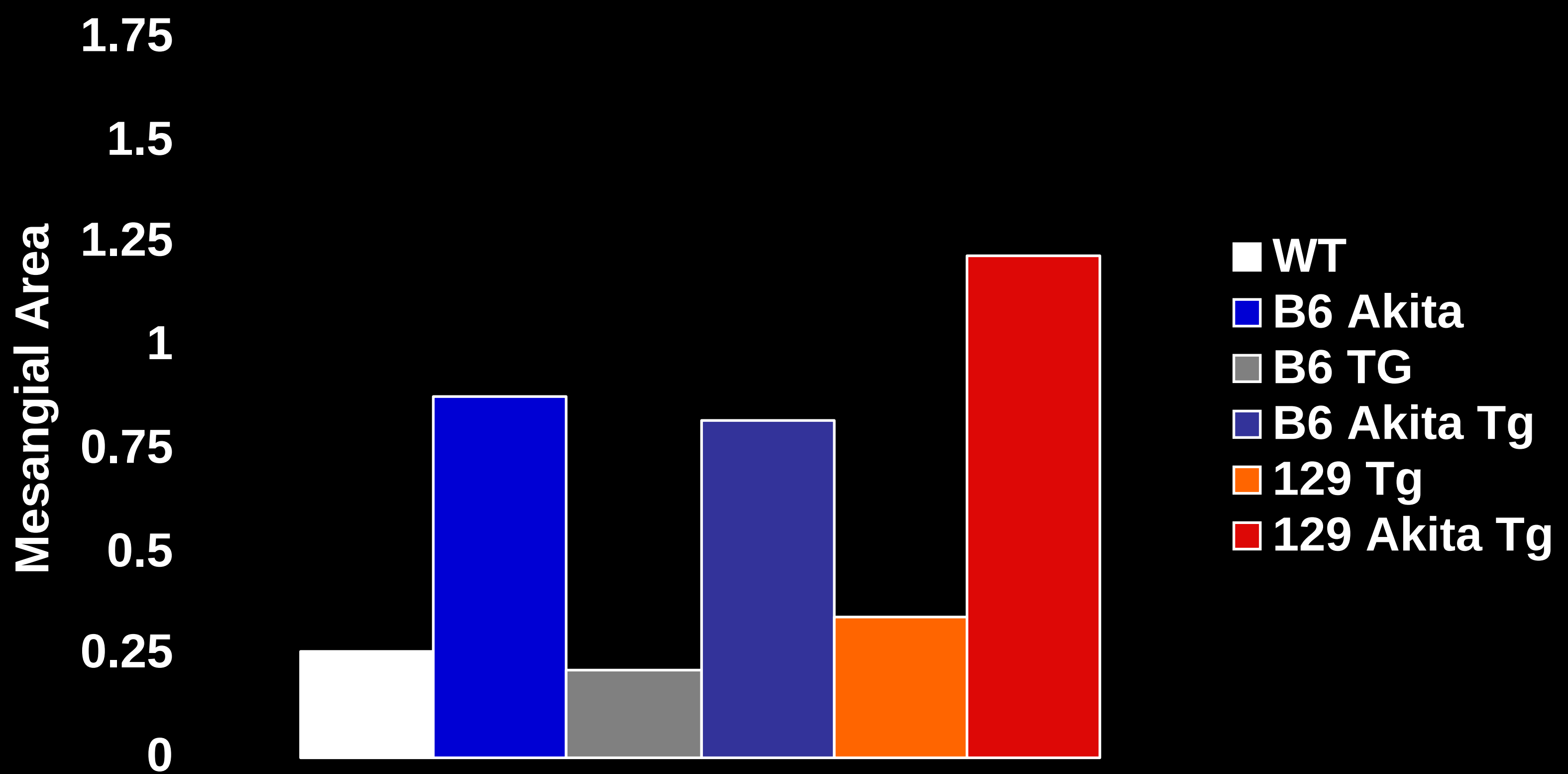
Effect of Renin Transgene on Albumin Excretion

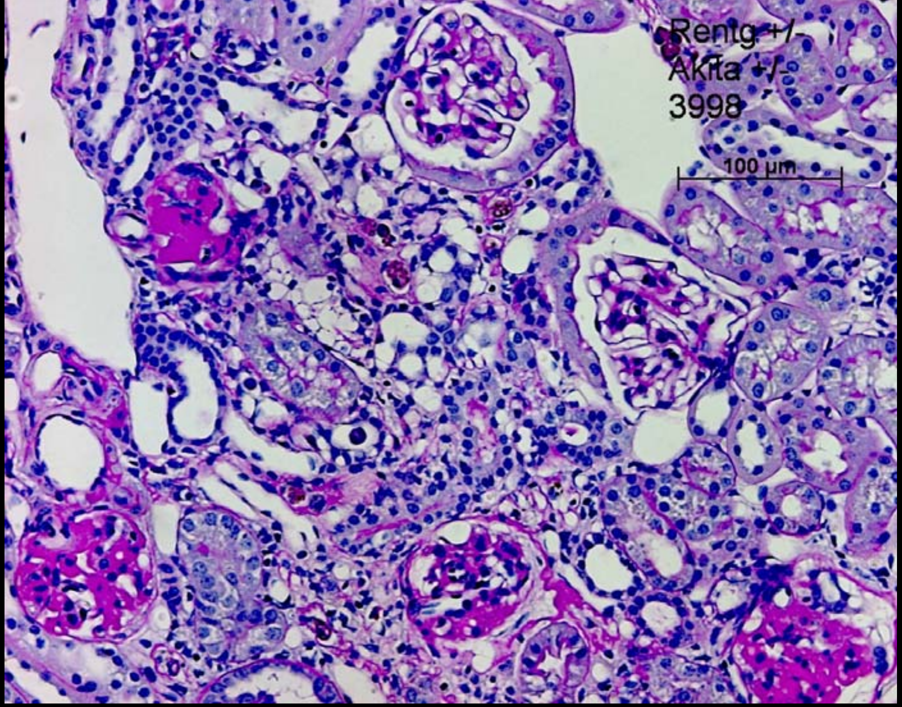


Effect of Renin Transgene on Albumin Excretion

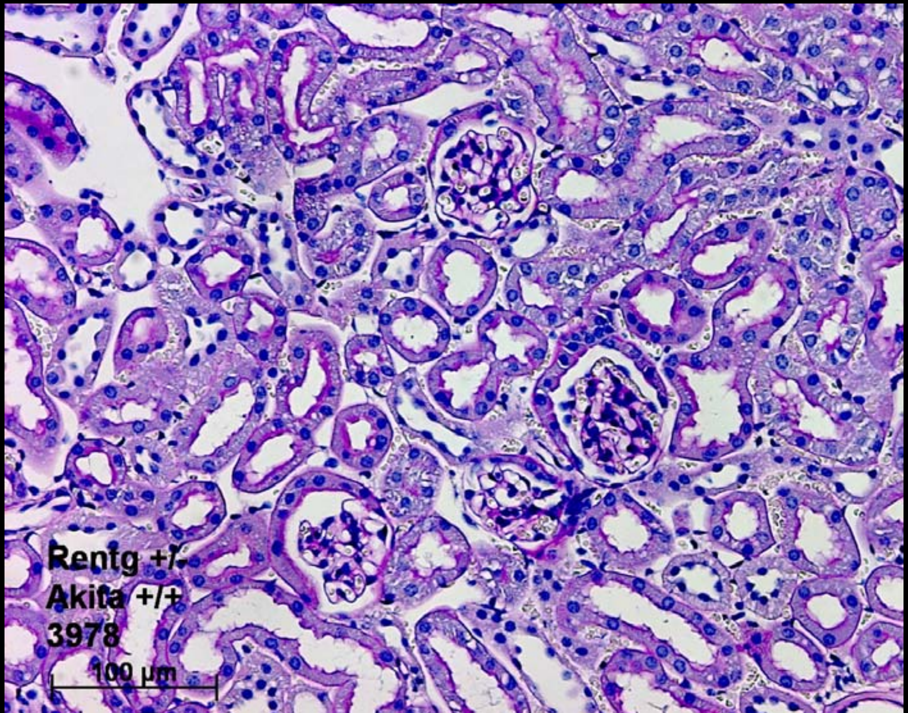


Mesangial Pathology with Renin Tg

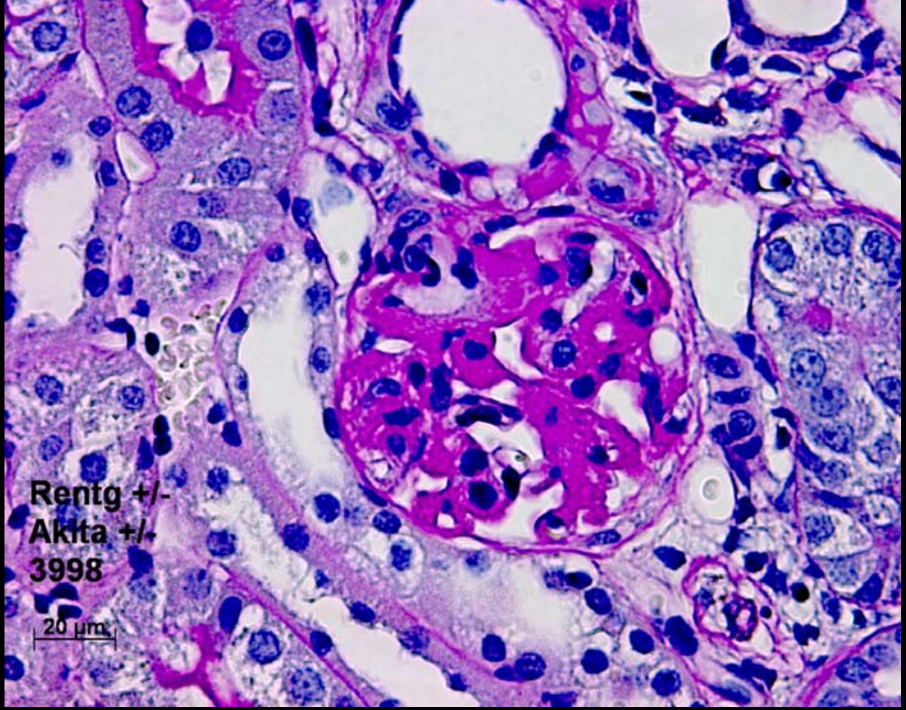




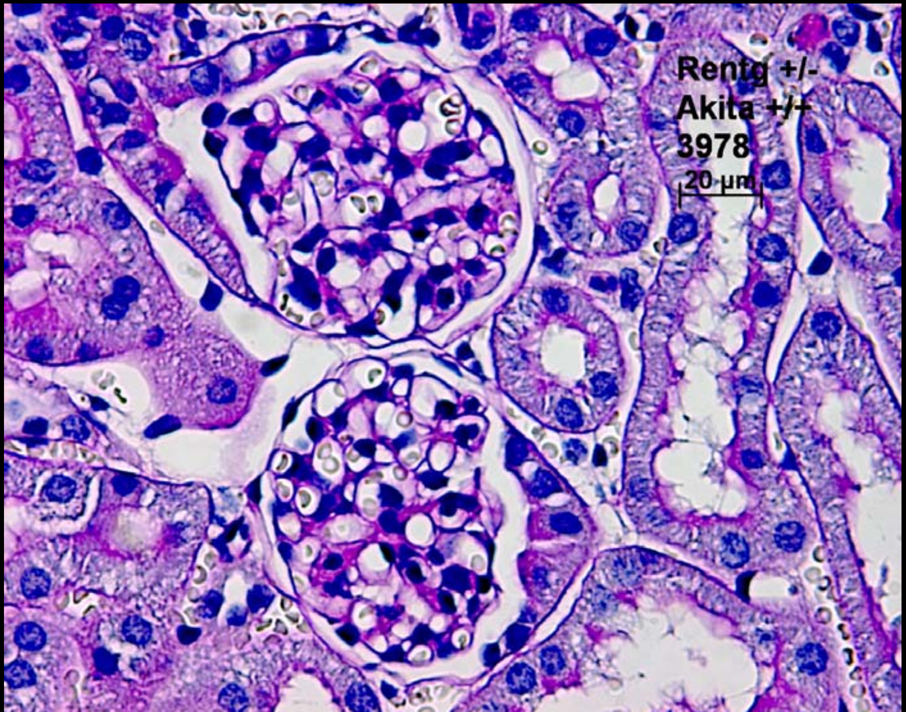
129 Akita Tg



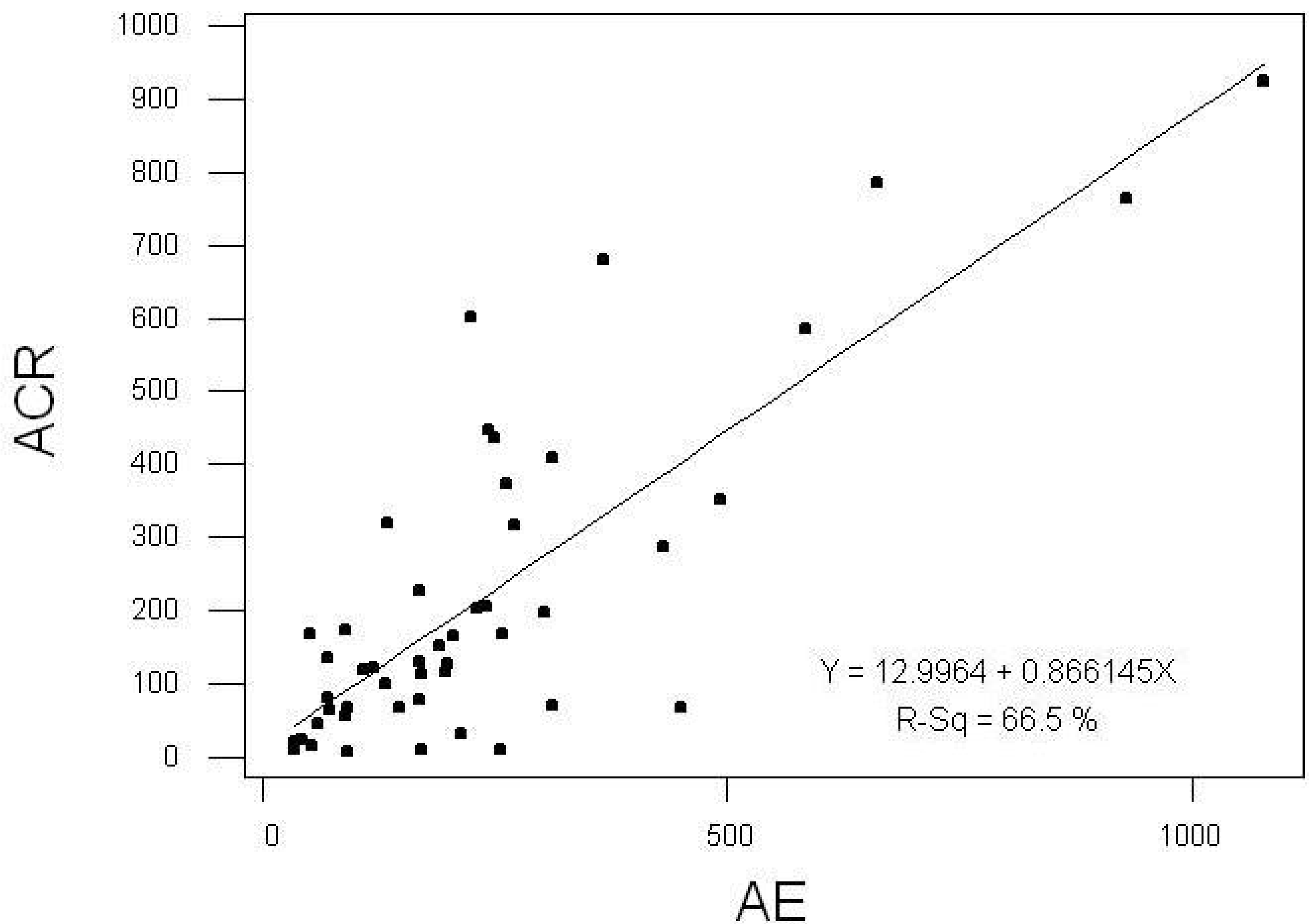
129 Tg



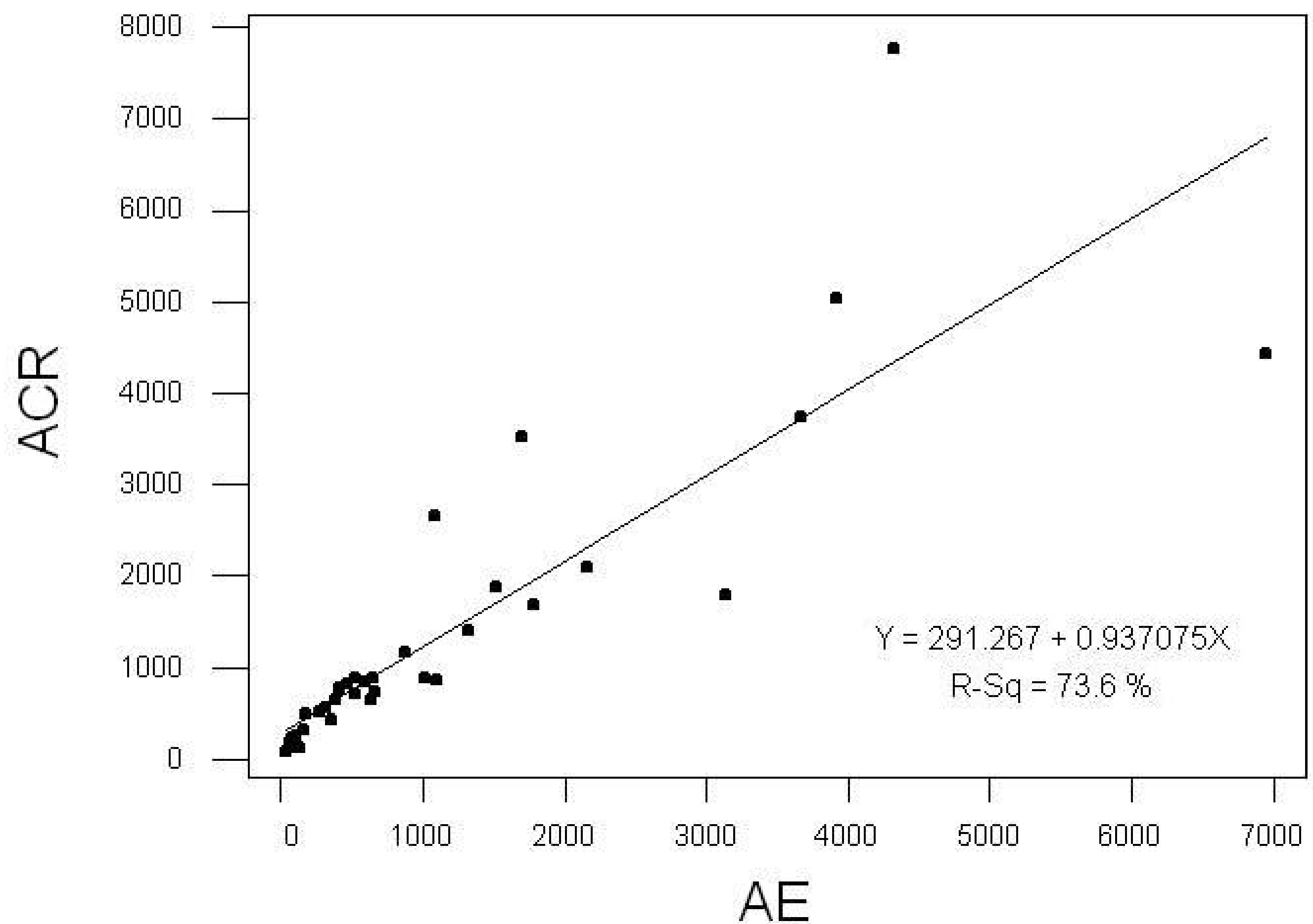
129 Akita Tg



129 Tg

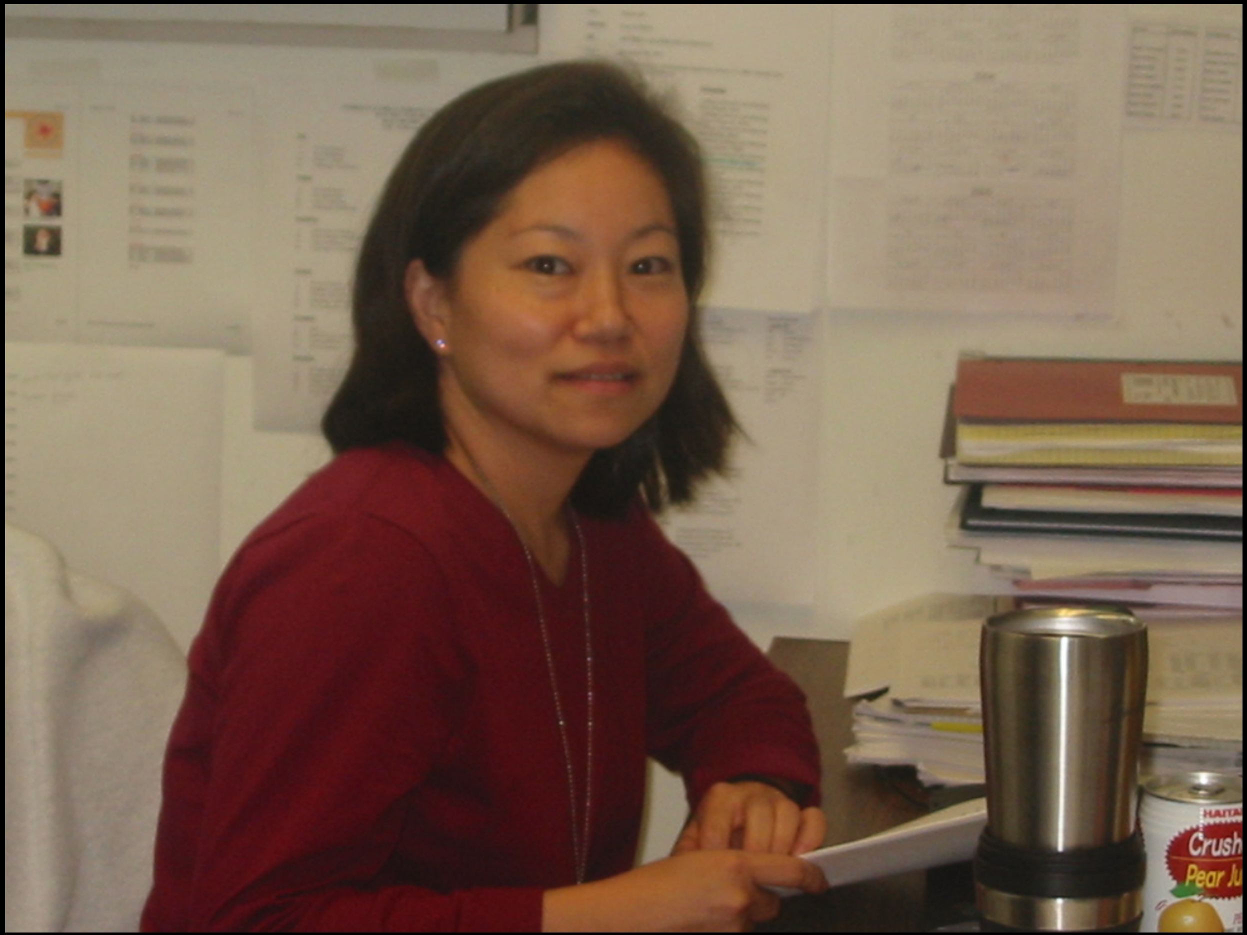


1000
900
800
700
600
500
400
300
200
100
0
ACR
Y = 12.9964 + 0.866145X
R-Sq = 66.5 %
0
500
1000
AE



ACR
AE
8000
7000
6000
5000
4000
3000
2000
1000
0
0
1000
2000
3000
4000
5000
6000
7000
Y = 291.267 + 0.937075X
R-Sq = 73.6 %

Kamie Snow
Research Associate
DUMC



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