Vanderbilt AMDCC

STRAIN BACKGROUND EFFECTS				
Breyer	Qi, Zhonghua	jianping jin	C57BL/6J	phenotype completed
Breyer	Qi, Zhonghua	jianping jin	DBA/2J	phenotype completed
Breyer	Qi, Zhonghua	jianping jin	FVB/NJ	phenotype completed
Breyer	Qi, Zhonghua	jianping jin	KK/HIJ	phenotype completed
			C57BL/6J x DBA/2J F2	actively phenotyping
Breyer	Qi, Zhonghua	jianping jin	backcross C57Ins2Akita toKK/HIJ	backcross (N2)
Breyer	Qi, Zhonghua	jianping jin	backcross C57Ins2AkitaDBA/2J	backcross (N6)
Breyer	tchekneva	polosukhina	backcross C57Ins2Akitato Balb/C*	backcross (N8)
Breyer	pending	pending	backcross C57Ins2Akitato FVB/NJ	ckcross (N10) transfer to our lab in prog
			* for ENU gene mapping studies	
eNOS null x diabetic				
Harris		suwan wang	C57BLKS/J-Nos3 tm1Unc	backcross(N10)finished
Harris		suwan wang	C57BLKS/J-Nos3 tm1Unc	backcross(N10)finished
Harris		suwan wang	C57BLKS/J-Lepr db Nos3 tm1Unc	backcross(N10x N10)
Harris		suwan wang	C57BLKS/J-Lepr db Nos3 tm1Unc	backcross(N10 x N10)
Harris		suwan wang	C57BLKS/J-Lepr db Nos3 tm1Unc	backcross(N10 x N10)
Harris		suwan wang	C57BLKS/J-m+/+Lepr db	
Harris		suwan wang	C57BLKS/J-m+/+Lepr db	
Harris		suwan wang	C57BLKS/J-m+/+Lepr db	
ENU mutants+akita				
Breyer	tchekneva	polosukhina	C57BL/6-Ins2 Akita ENU10	Phenotyping G3 +heretible
Breyer	tchekneva	polosukhina	C57BL/6-Ins2 Akita ENU18	Phenotyping G3 +heretible
Breyer	tchekneva	polosukhina	C57BL/6-Ins2 Akita ENU20	Phenotyping G3 +heretible
Breyer	tchekneva	polosukhina	C57BL/6-Ins2 Akita ENU57	Phenotyping G1/testing heretibility
Breyer	tchekneva	polosukhina	C57BL/6-Ins2 Akita ENU76	Phenotyping G3 +heretible
Breyer	tchekneva	polosukhina	C57BL/6-Ins2 Akita ENU#161	Phenotyping G2 +heretible
Breyer	tchekneva	polosukhina	C57BL/6-Ins2 Akita	actively phenotyping

Strain Variability

Diabetic nephropathy

DBA2 and KK vs. C57BL/6

Individual data for Ualb:Cre excretion in diabetic mice

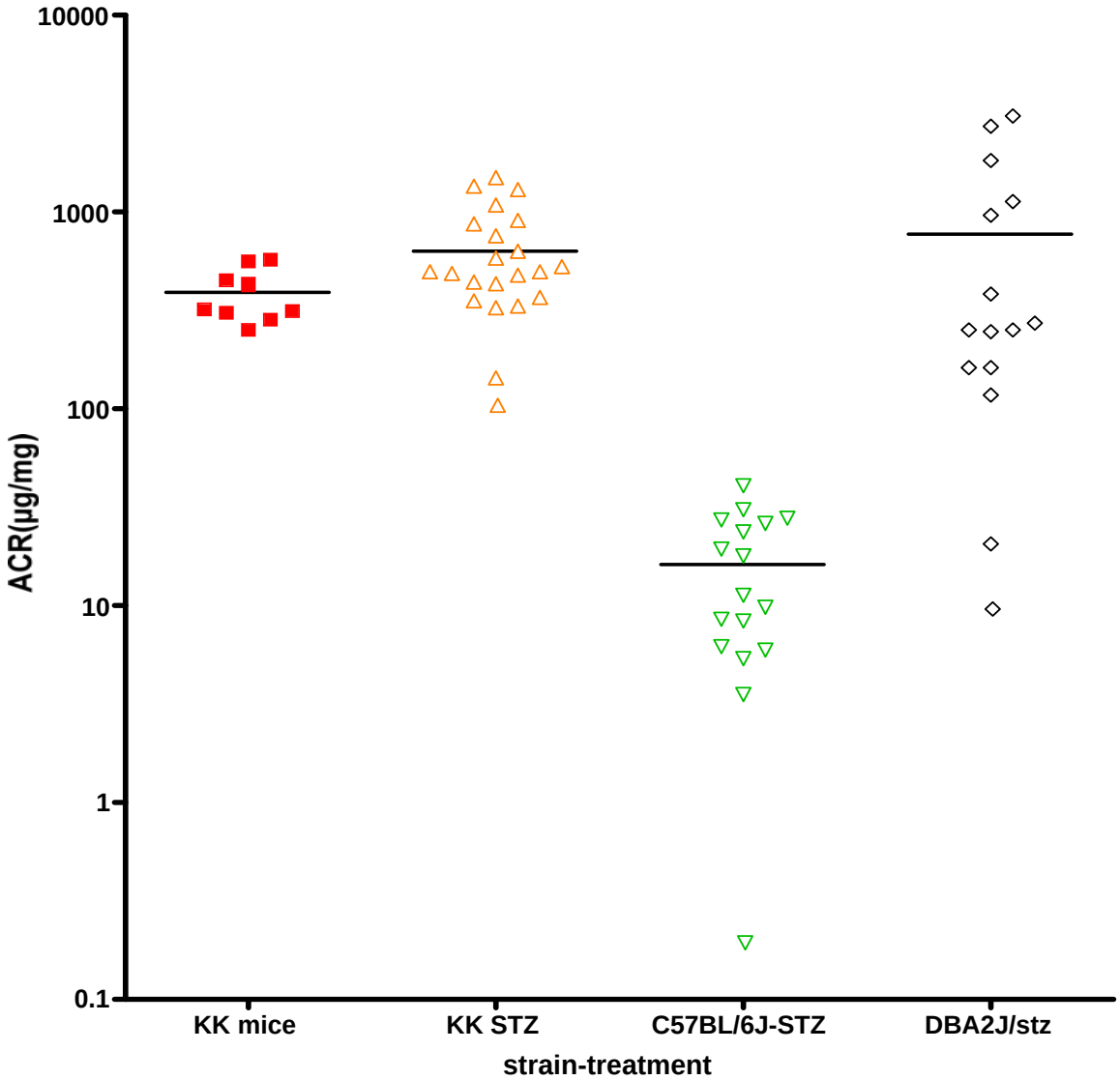
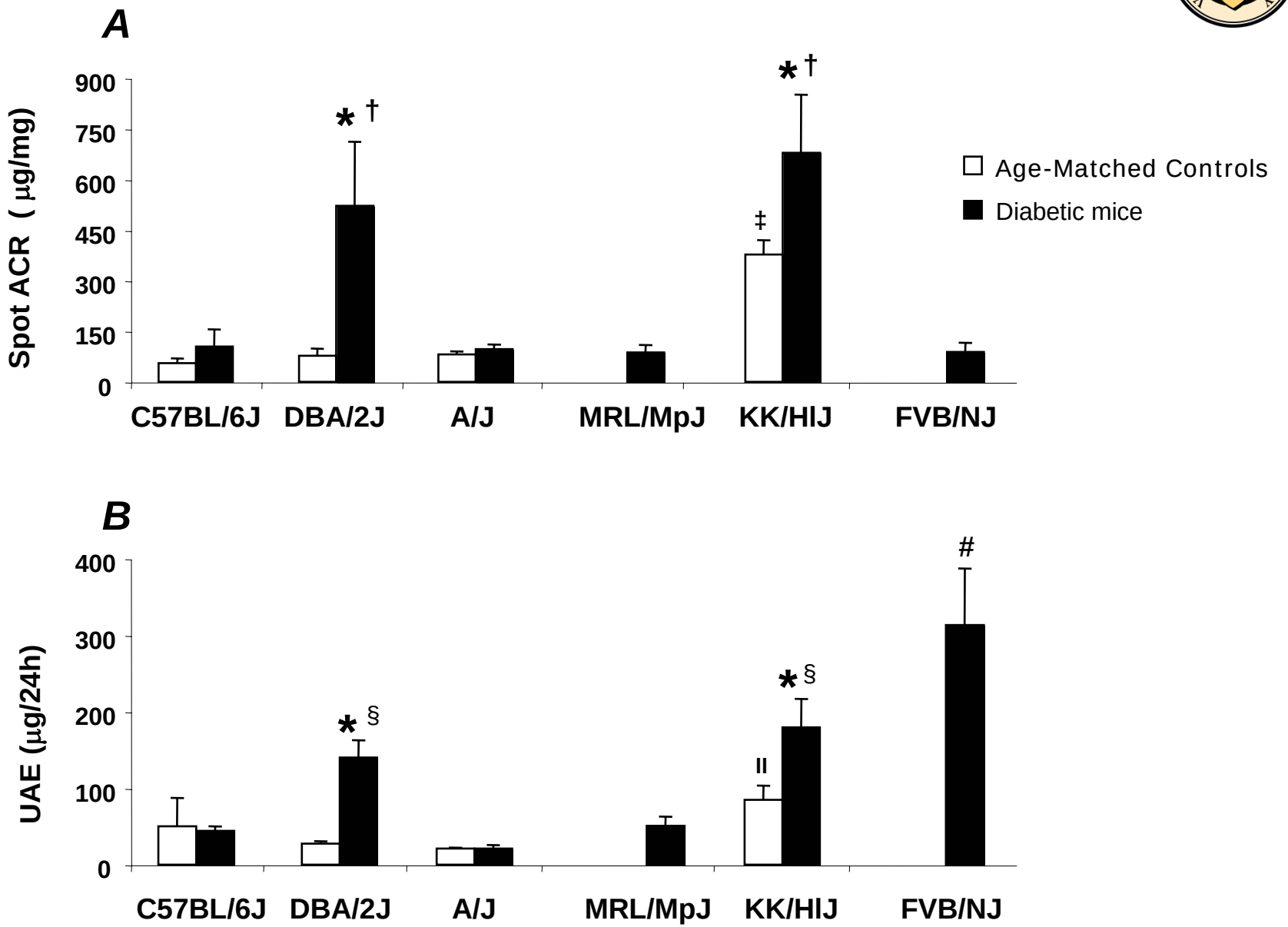
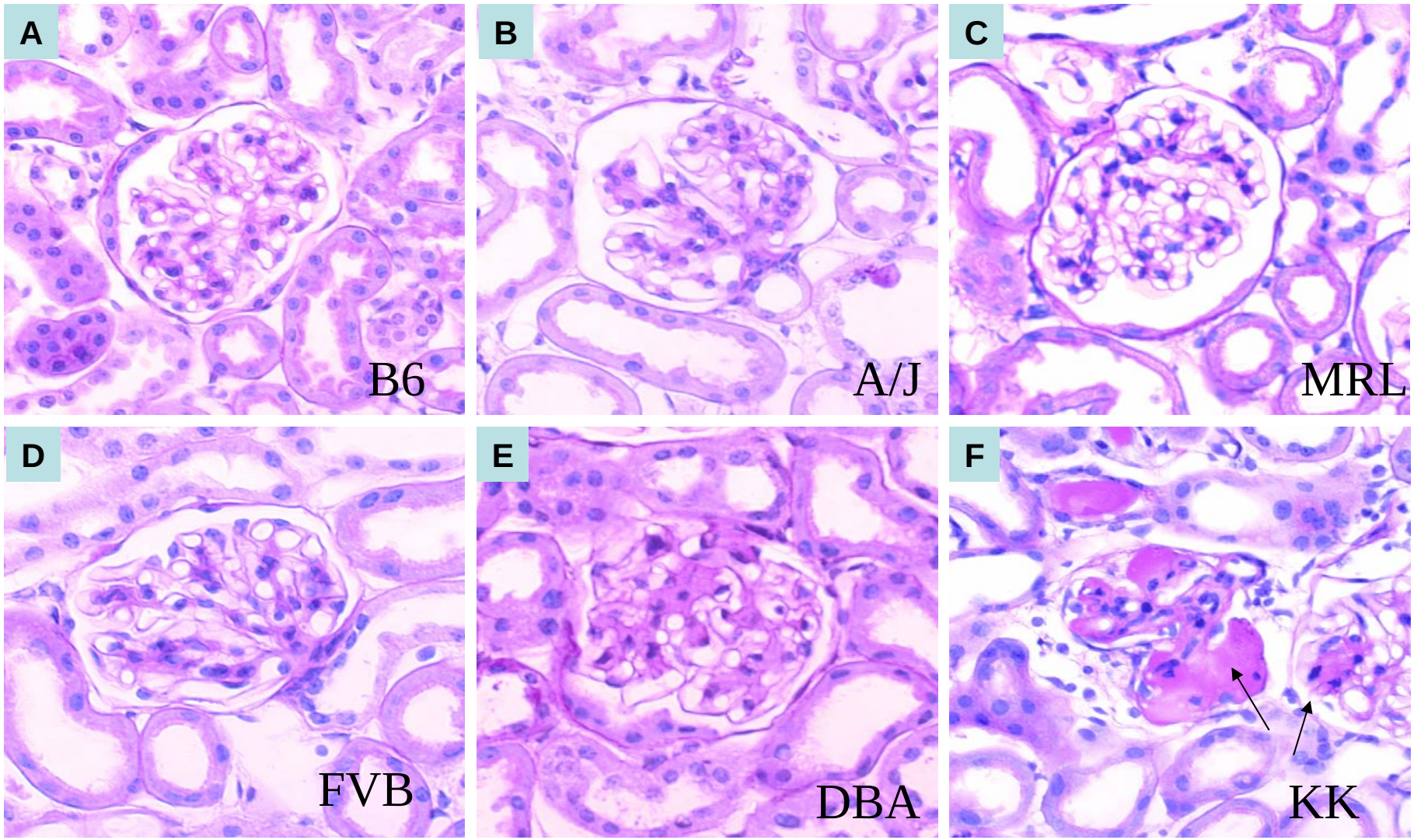


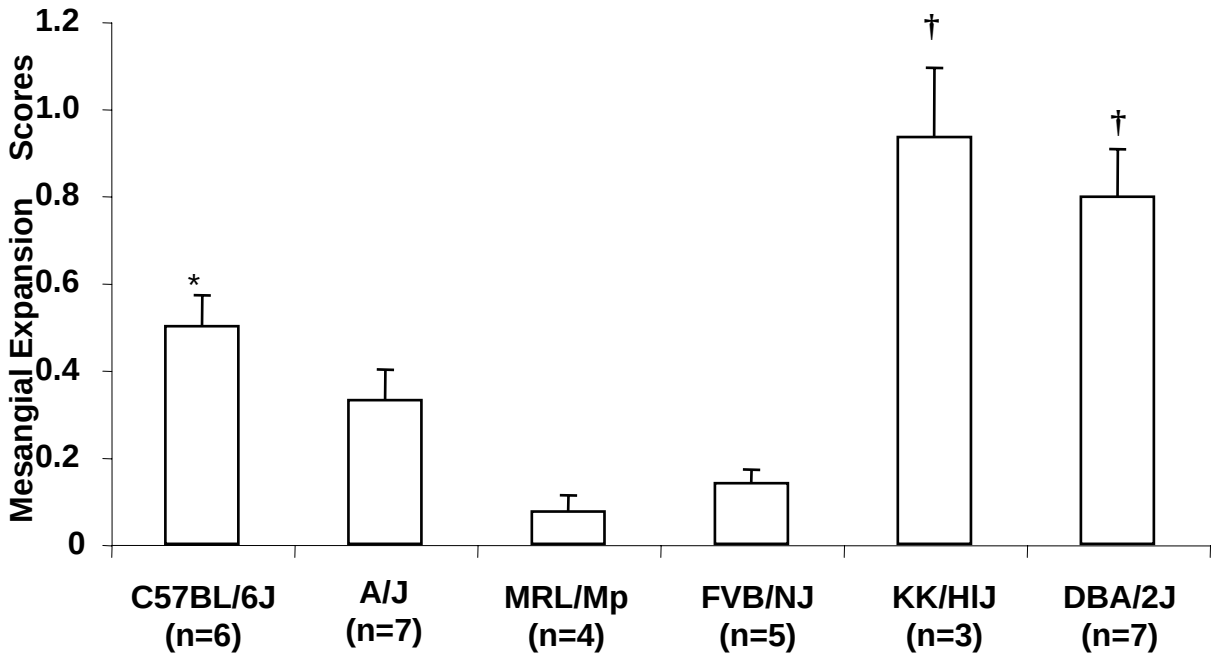
Figure 2. Urinary albumin excretion in diabetic inbred mice



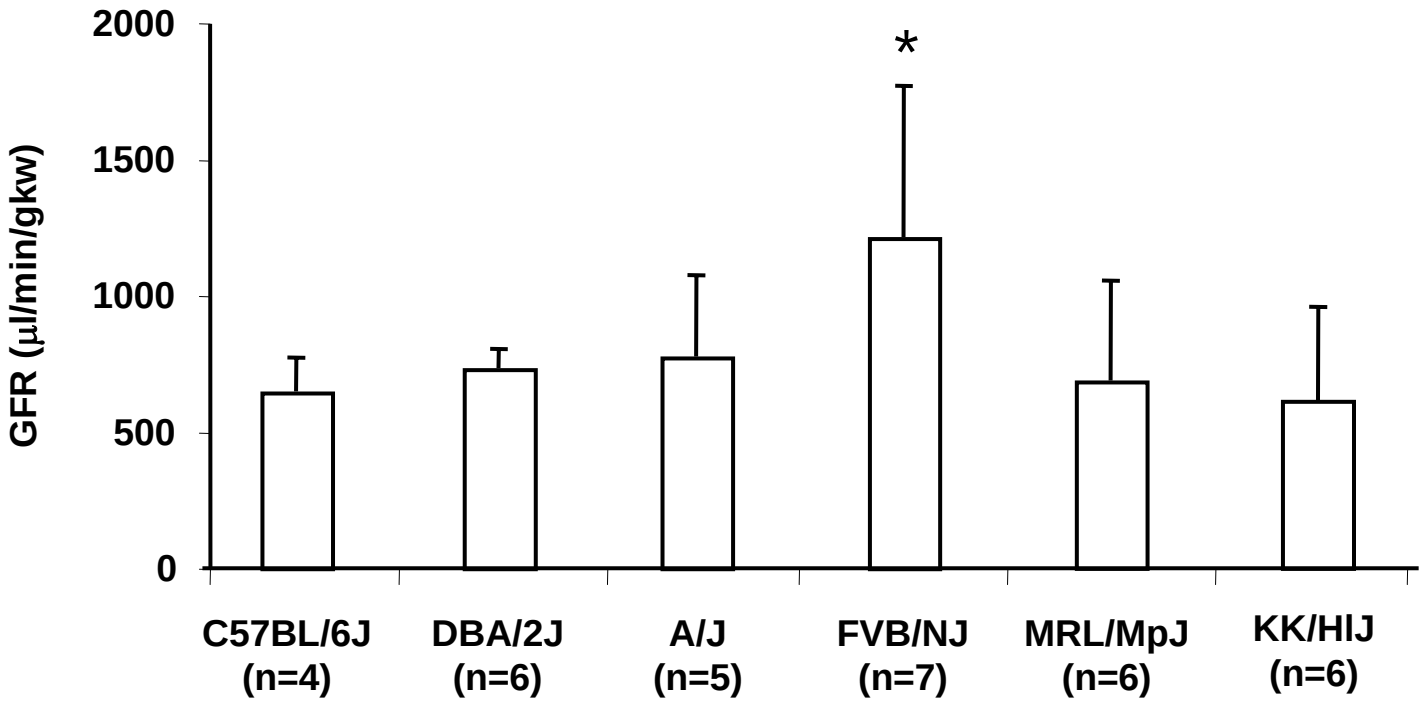
Representative glomerular histopathology of perfuse-fixed diabetic mouse kidneys



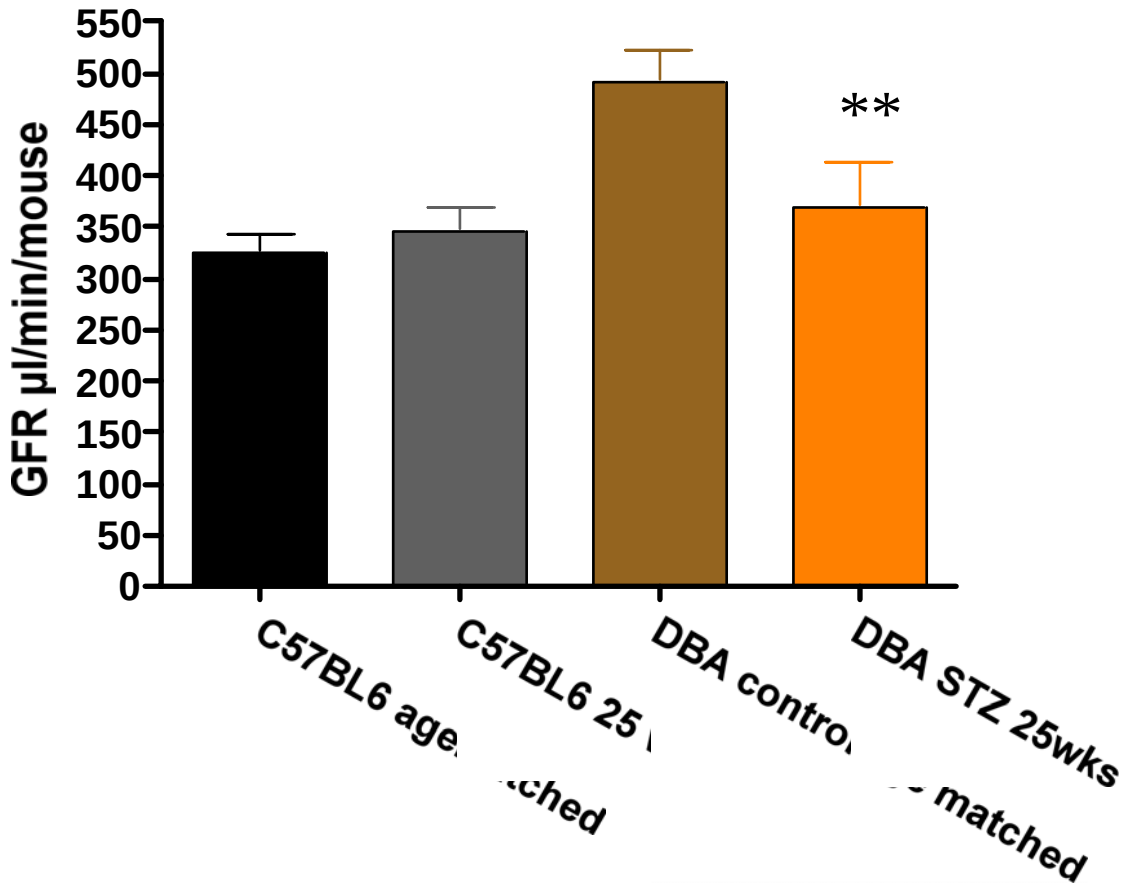
Glomerular mesangial expansion scores in diabetic inbred mice



GFR corrected for kidney weight in diabetic inbred mice



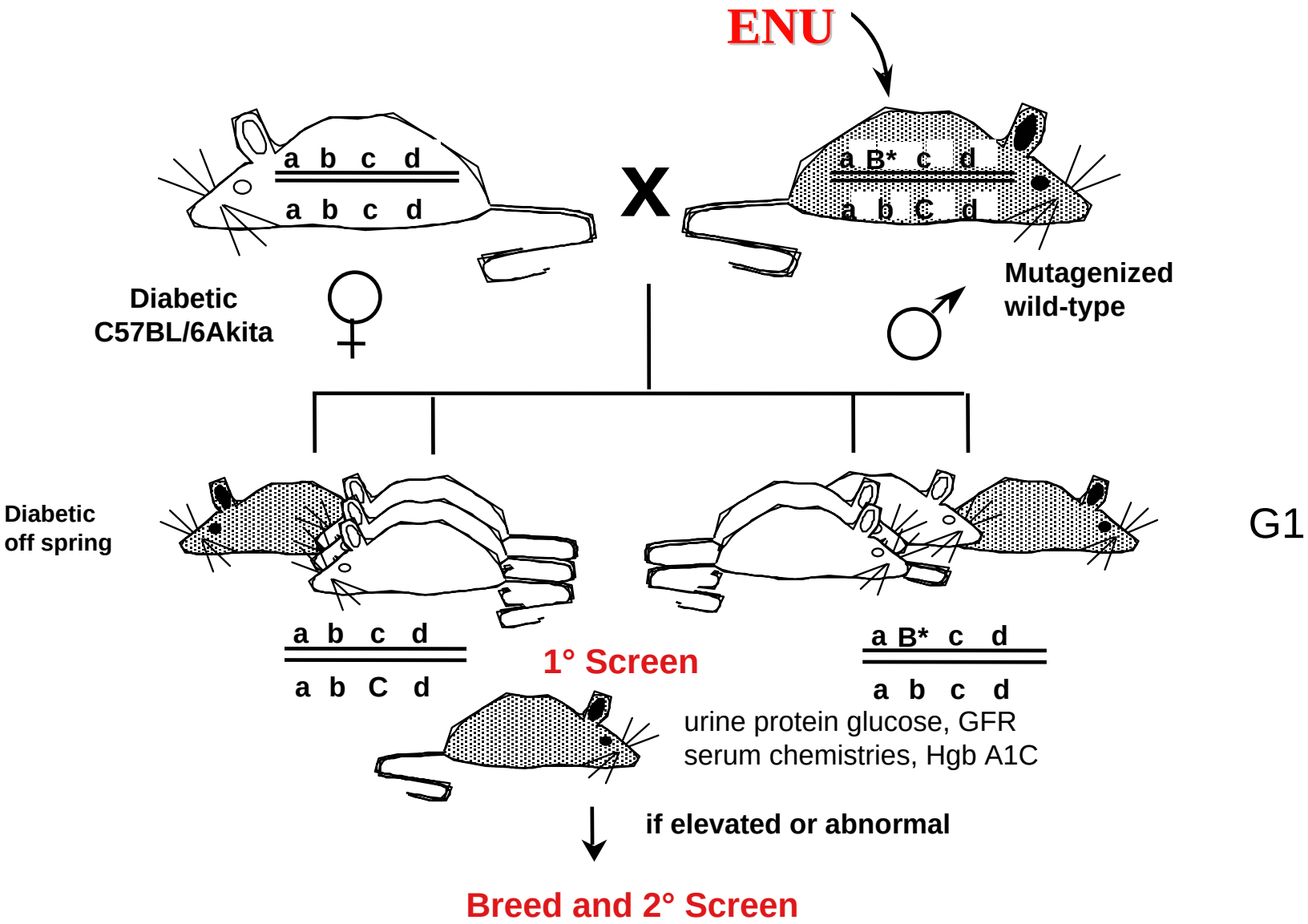
GFR in DM mice vs. Age matched controls



ENU mutagenesis

Diabetic nephropathy

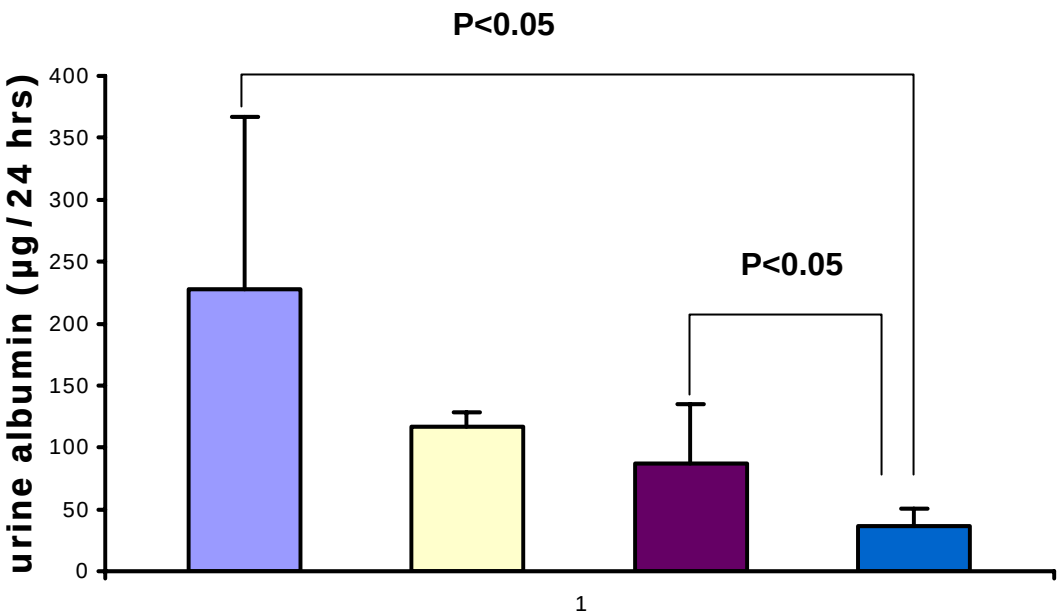
Mutagenesis: a sensitized screen



Albumin/creatinine ratio (ACR) mouse urine from G2 and G3 ENU progeny.

ENU founder lines (G1)	Total amount of G2 mice	Total amount of G3 mice	Amount of examined mice including founders	ACR (µg/mg)		
				Akita - mice	Akita+ mice	albuminuric Akita+ mice
ENU10	6	sperm cryopreservation	2 Akita-	41±22 n=11	39±15 n=7	190 ±93 n=19
			2 Akita+			
			3 Akita+ Alb			
ENU76	28	31	27 Akita-	28 ±32 n=189	* 42±47 n=100	* 167±113 n=42 *P<0.005
			20 Akita+			
			13 Akita+ Alb			
ENU20	22	36	26 Akita-	26 ±18 n=100	**41±37 n=75	**171±84 n=46 **P<0.005
			17 Akita+			
			16 Akita +Alb			
ENU161	6	breeding	2 Akita-	21 ±12 n=5	***34±43 n=3	***165 ±110 n=14 ***P<0.005
			1 Akita+			
			4 Akita +Alb			

24 hr urine albumin excretion



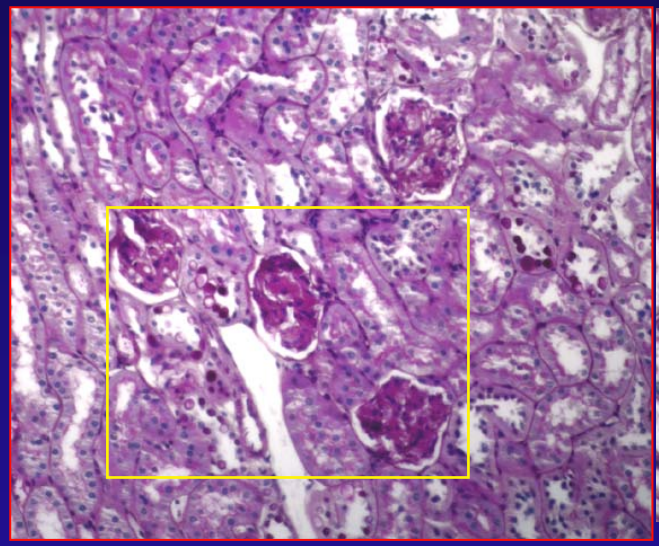
Blood chemistries for G2 progeny from ENU founders

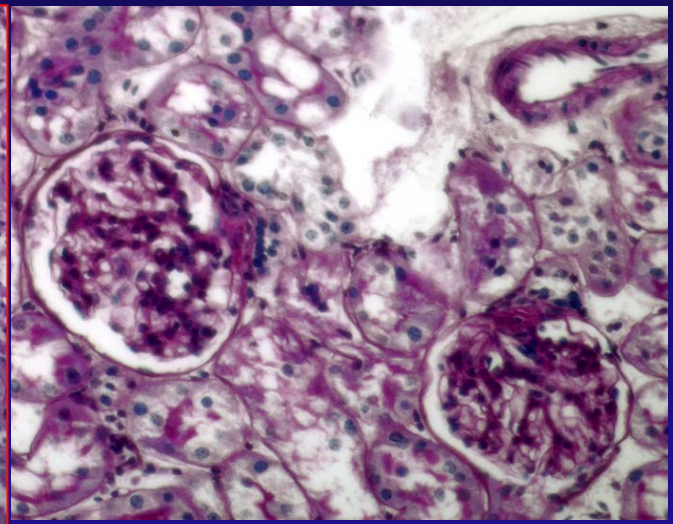
	Na mmol/l	K mmol/l	Cl mmol/l	BUN mg/dl	Creat mg/dl	Glu mg/dl	Hct% PCU	pH	pCO_2 mmHg	HCO_3 µmol/l	Hb g/dl
G2ENU10 n=3	147.0±9.3	5.1±0.2	110.3 ±8.4	44.3 ±24.4	0.128 ±0.02	574 ± 93	41±2	7.29 ±0.01 P<0.05	56.3±3.6 P<0.05	27.0 ± 2.0 P<0.05	14±0.7
G2ENU20 n=4	135.3 ±7.0	6.1 ±0.5	105 ±4.4	42.7 ±7.5 P<0.05	0.119 ±0.02	647 ±77	51.3 ±0.6 P<0.05	7.27 ±0.05 P<0.005	46.1 ±13.9 P<0.05	21 ±5.0	17.3 ±0.6
G2ENU76 n=3	142.3 ±1.1	5.2 ±0.3	110 ±1.3	40.3 ±1.8 P<0.005	0.180 ±0.01 P<0.005	663 ±80	49.0 ±1.3	7.25 ±0.06 P<0.05	44.4 ±4.7 P<0.05	20.3 ±5.1	16.3 ± 0.4
ENU161	145	5.9	113	32	0.07 ±0.001 n=4	790 ±125	50	7.28	47.3	23	17
Akita+ age matched mice n=4	144± 5.0	5.8 ±0.7	110.2 ±4.3	32 ±1.0	0.099 ±0.01	675 ±25	47.3 ±1.8	7.25 ±0.07	49.2 ±4.9	21.6 ± 2.4	18 ±1.5

Values obtained with iSTAT (Vandy MMPC) and HPLC for creatinine (Dr. S. Dunn, Thos. Jefferson Univ.)

Renal Histopathology in ENU mutants

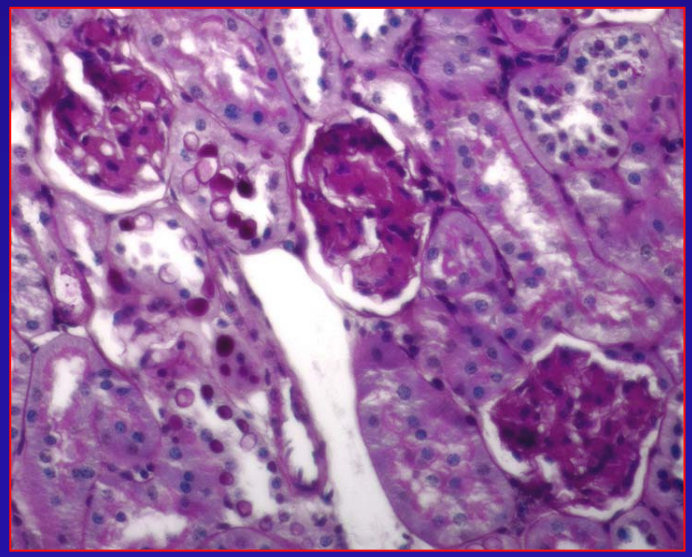
ENU 76

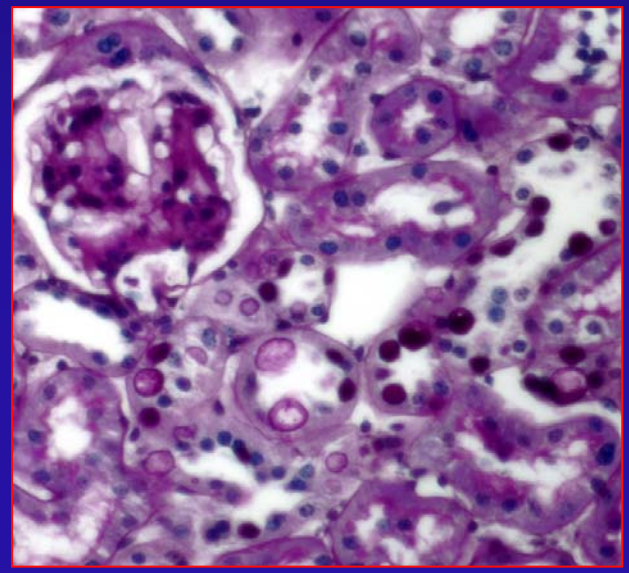




ENU 129 PAS
Non-albuminuric

ENU 76





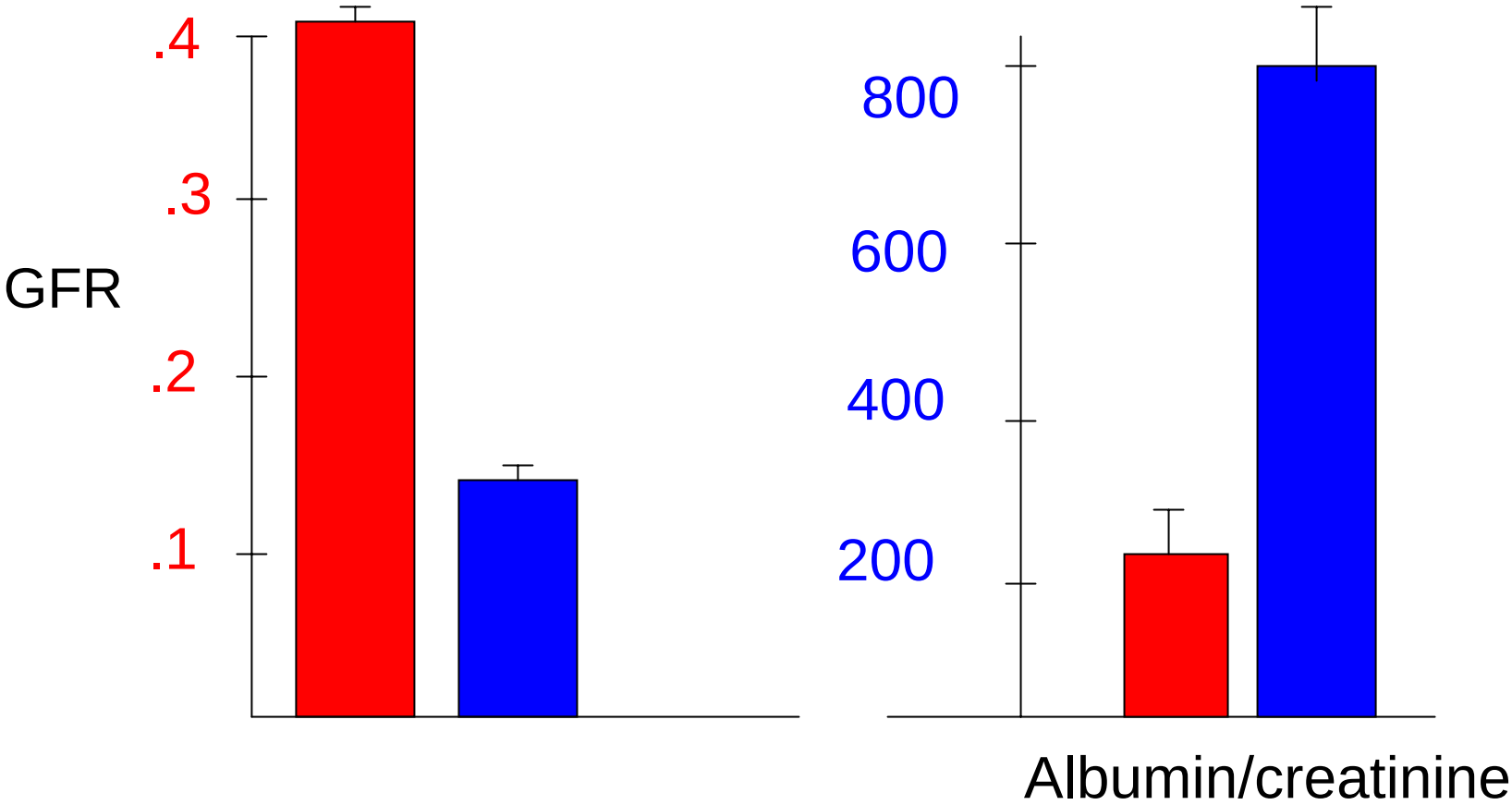
ENU 10

Modifier Genes

eNOS -/-

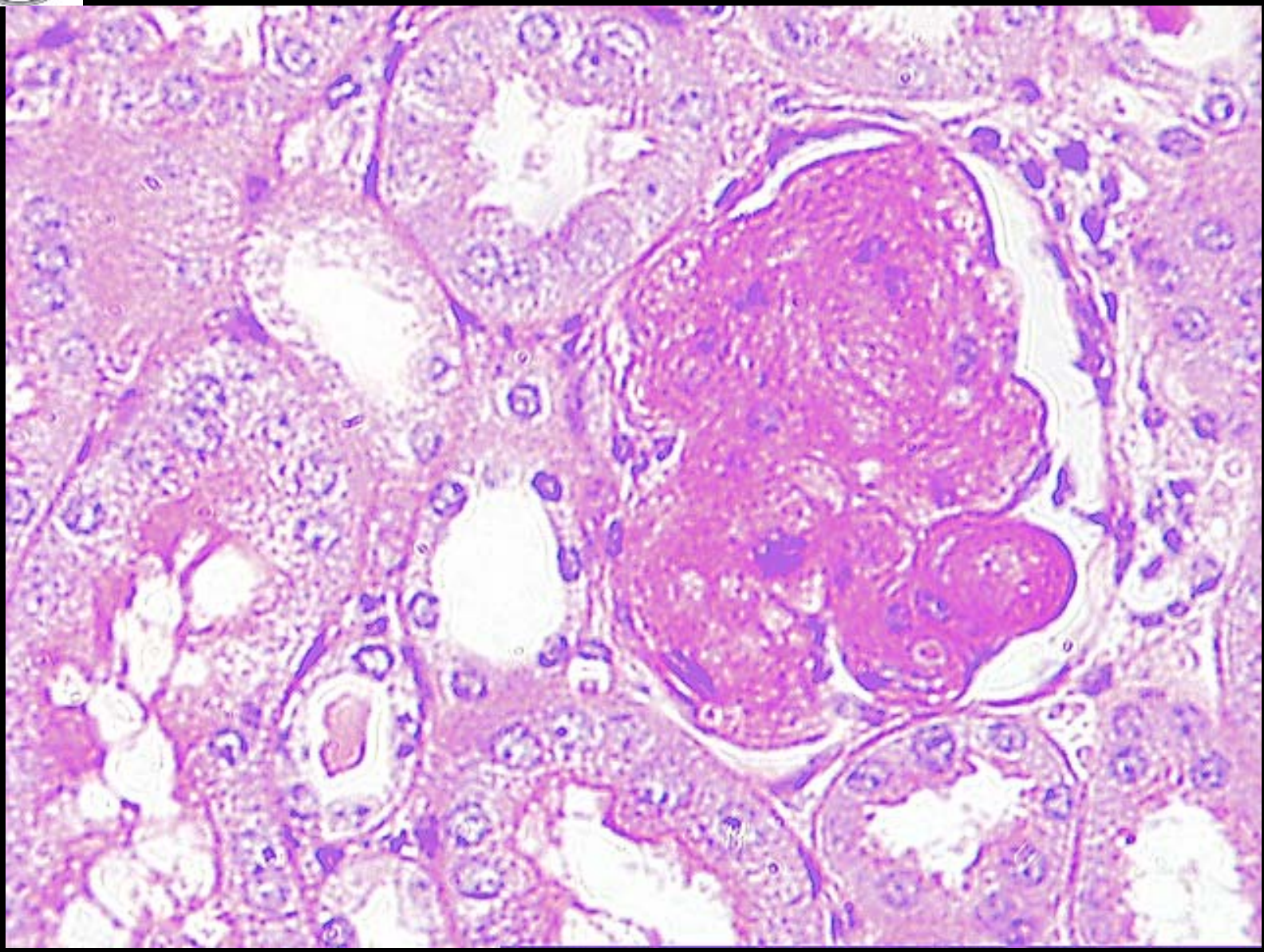
2) apoE -/-
3) ldlr -/-

db/db(26-40 wk) vs *dbdb*$^{eNOS-/-}$ (18-22 wk)

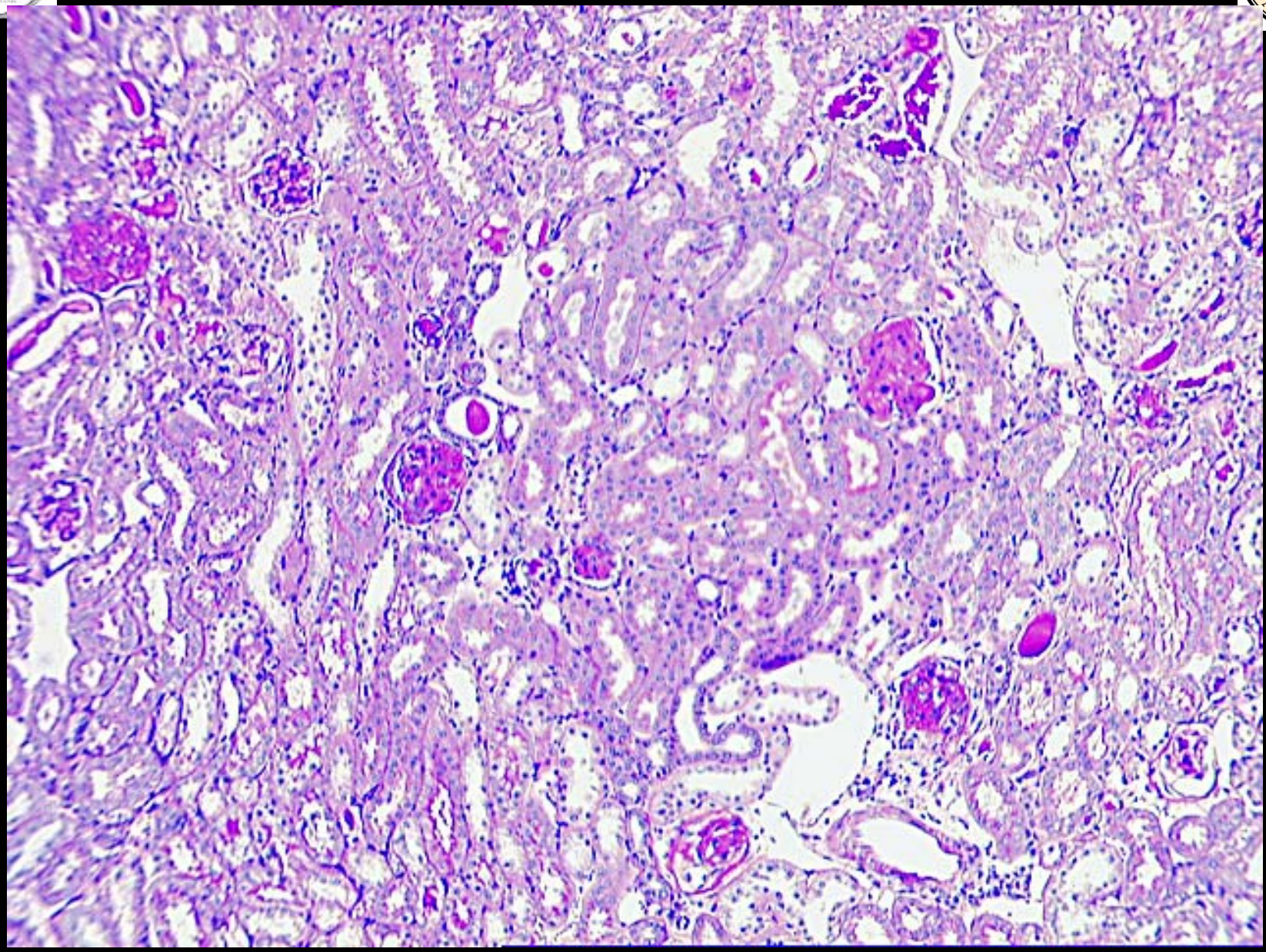


BKS background (n=6)

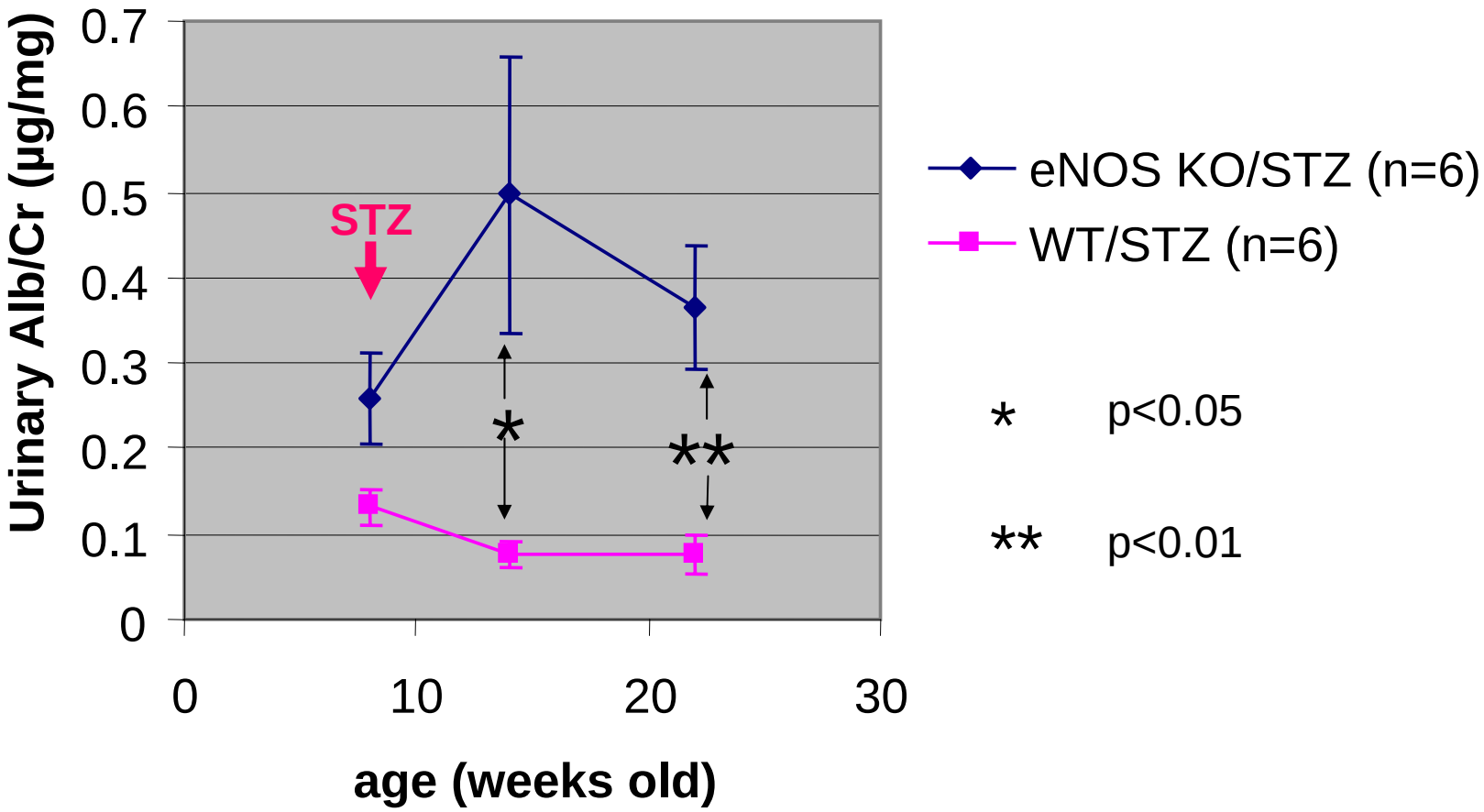
eNOS-/- /db/db BKS background PAS



eNOS-/- /db/db BKS background PAS

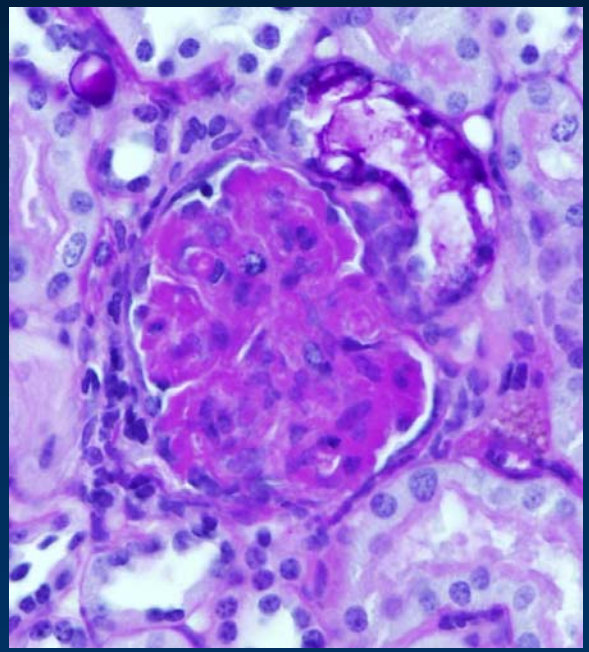


STZ diabetes eNOS (-/-) mice

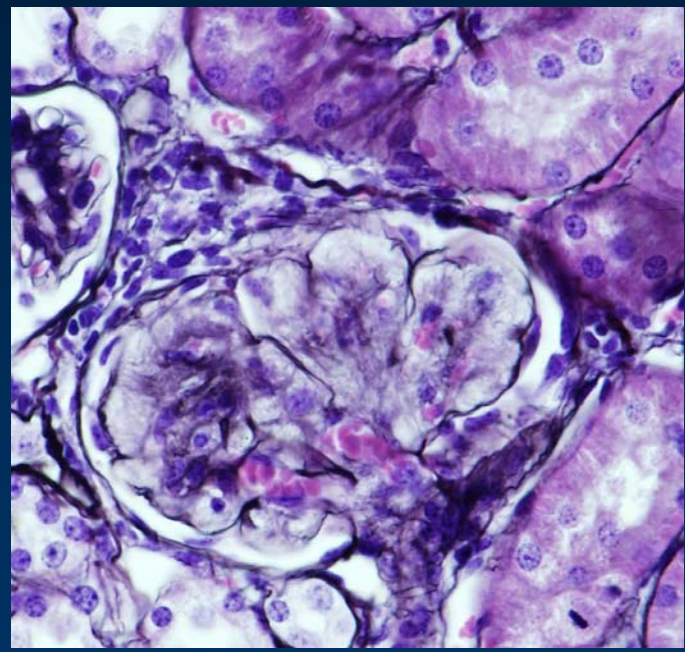


Note: There was no significant difference in blood glucose level, systolic blood pressure, body weight, kidney/body weight ratio, and urine volume between the two groups.

STZ diabetes eNOS (-/-) mice: Glomerular pathology at 20 weeks after the onset of diabetes



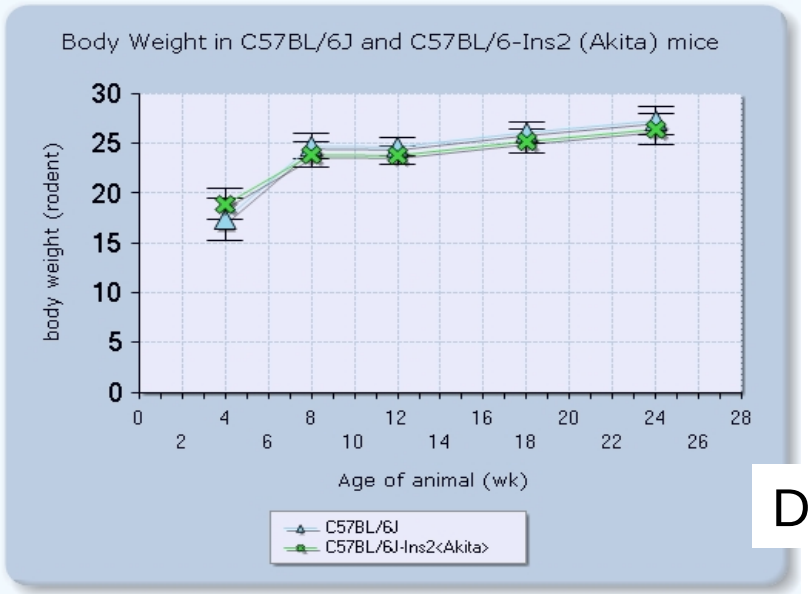
Thrombosis
(1-5% of the glomeruli)



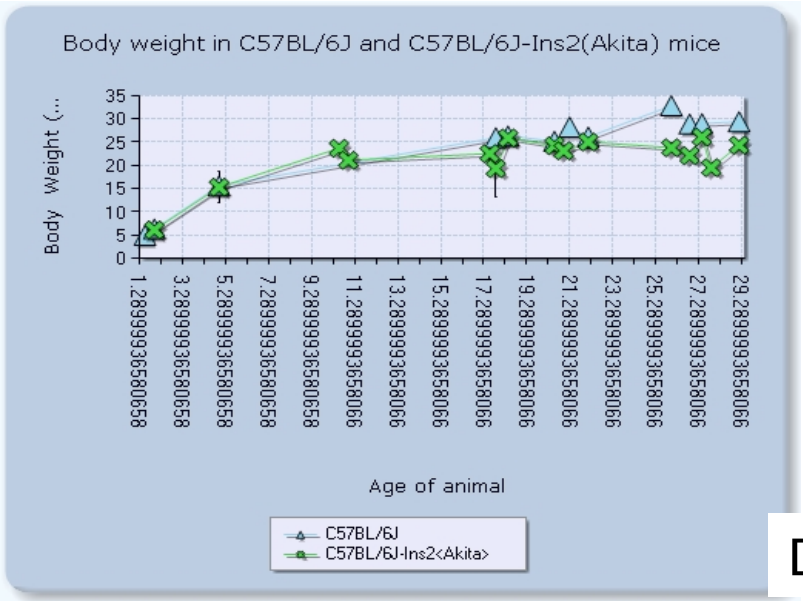
Mesangiolysis
(5-10 % of the glomeruli)

PAN-AMDCC
NEPHROPATHY DATA

Data comparison across consortium (Body weight in Akita mice)

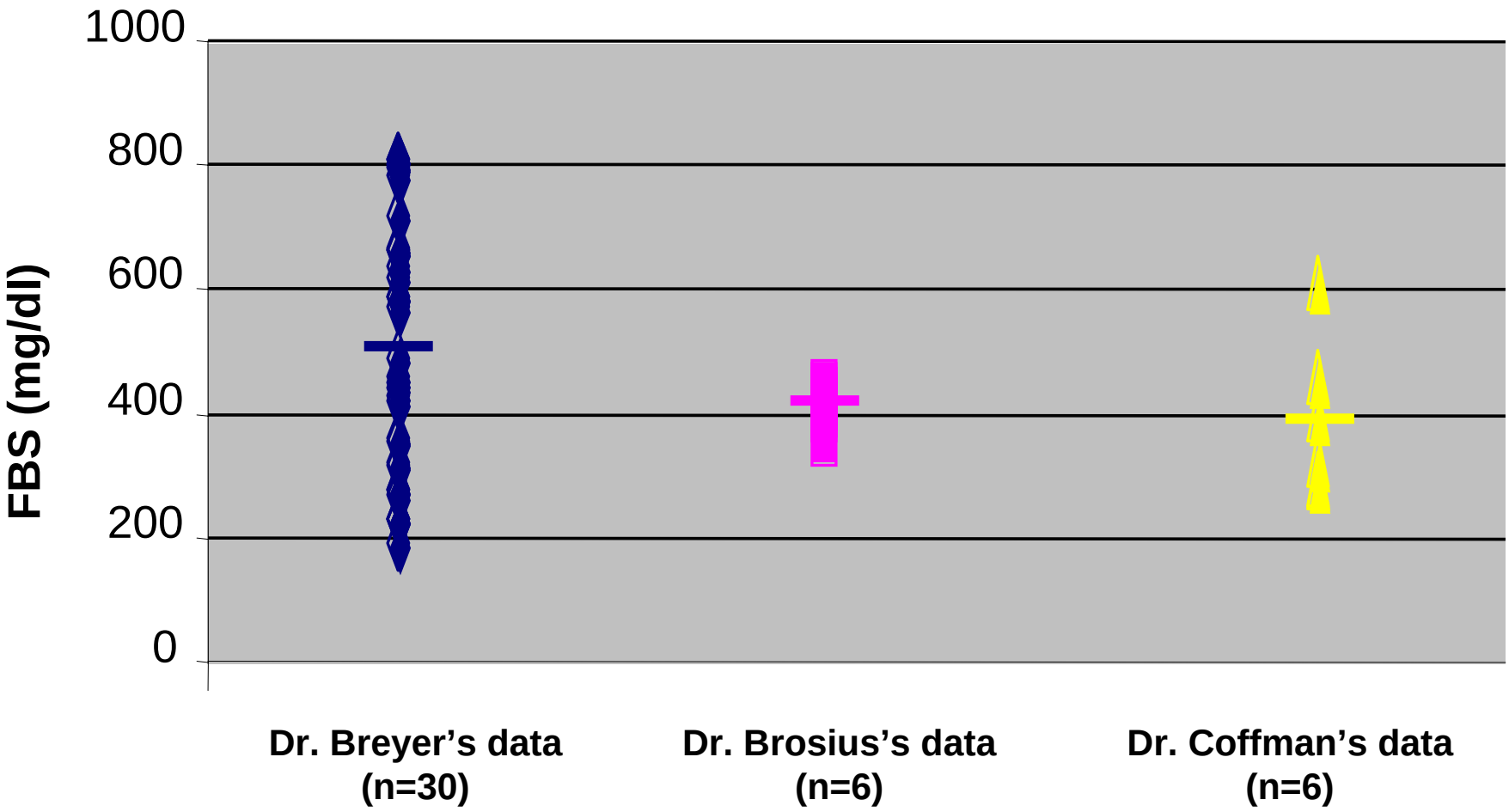


Dr. Coffman's data

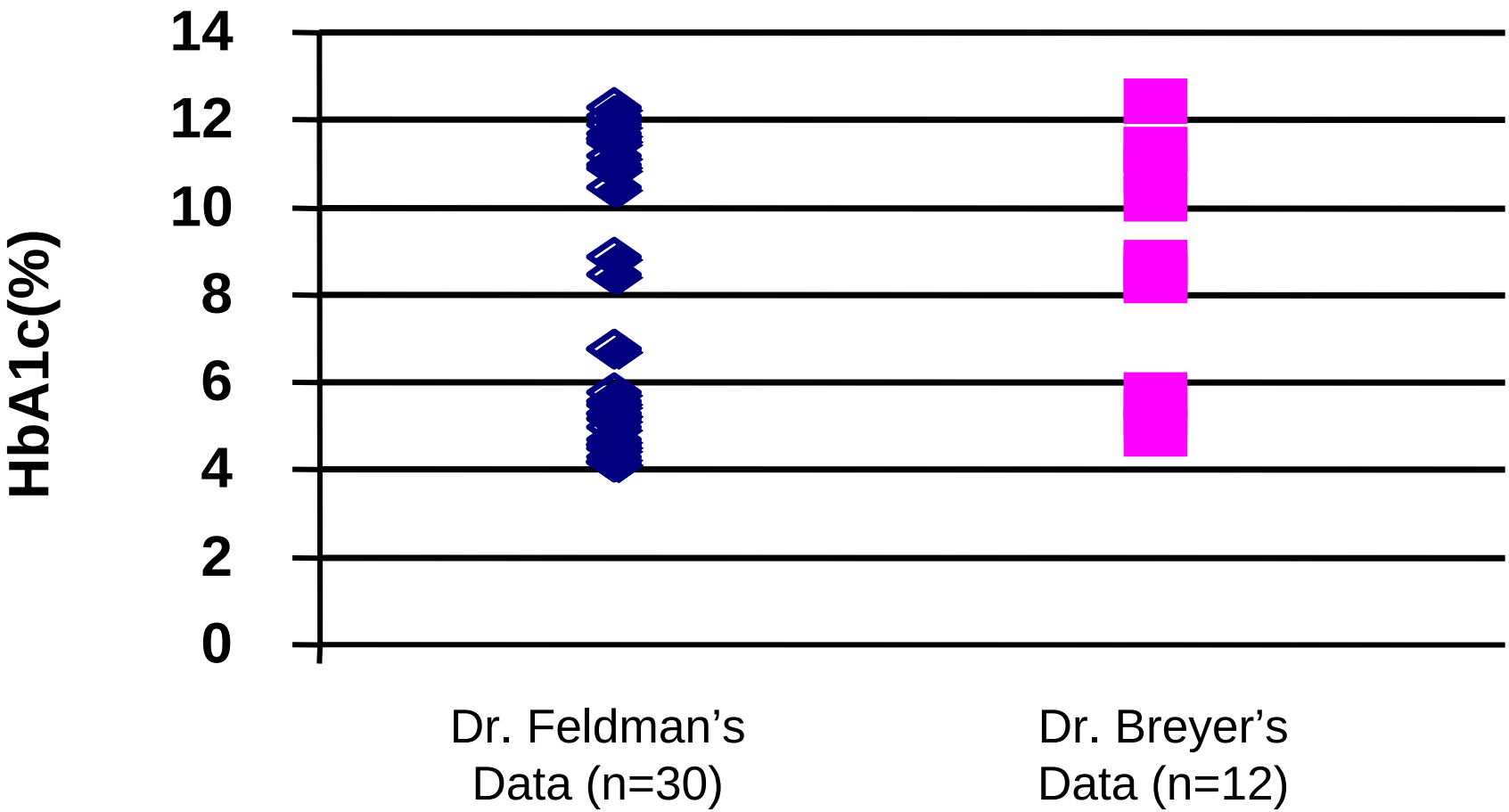


Dr. Bottinger's data

Fasting blood glucose in STZ induced diabetic C57BL/6J mice following approximately 15 weeks of hyperglycemia

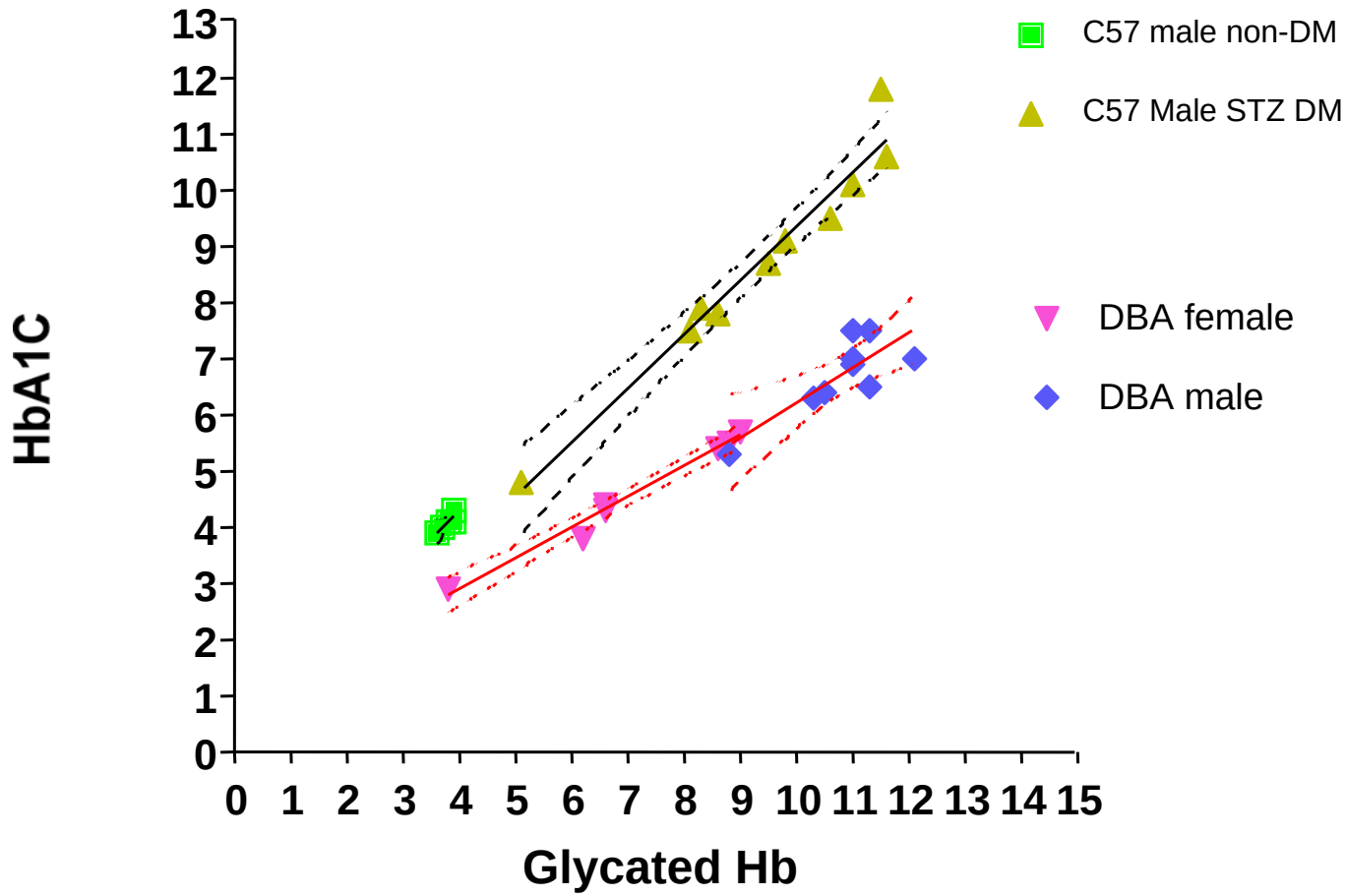


HbA1c in STZ induced diabetic C57BL/6J mice following approximately 25 weeks of hyperglycemia from two AMDCC groups

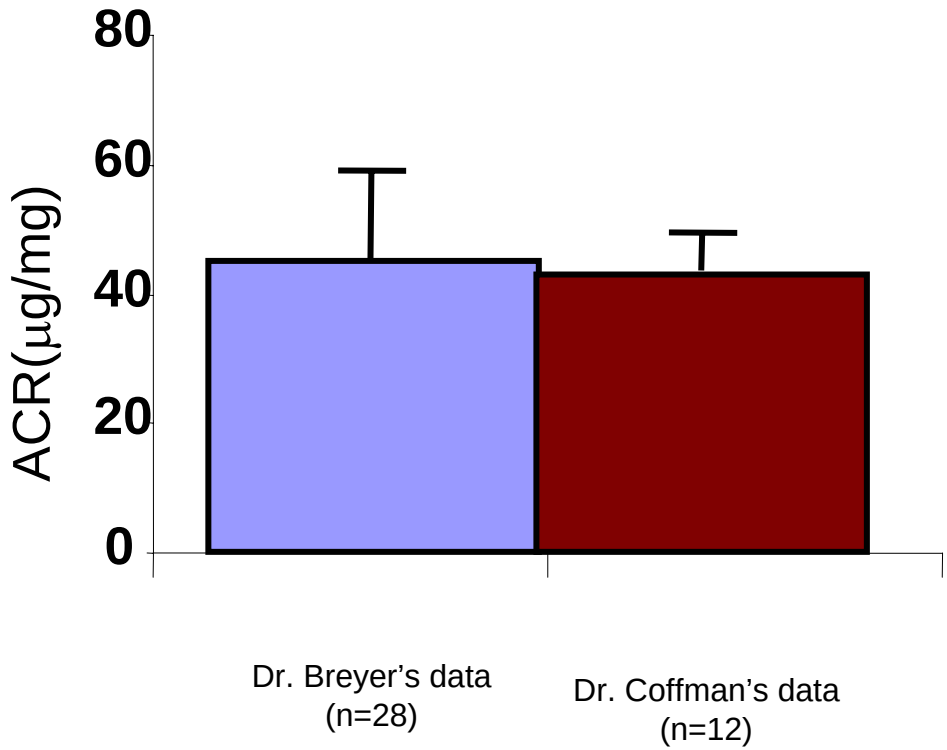


Biorad Variant HPLC Glycated Hb vs DCA2000

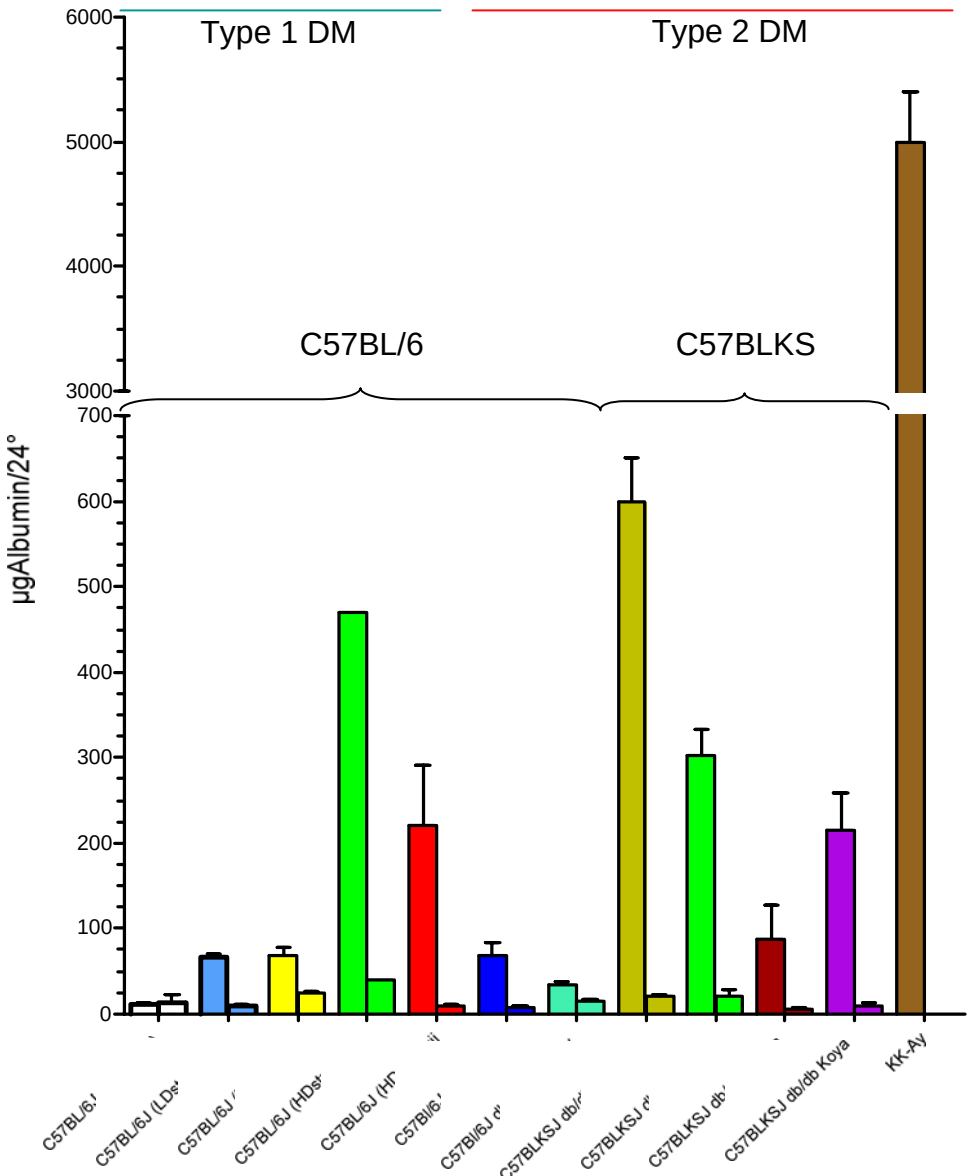
Correlation between Glycated Hb and HbA1C by strain



Spot urine ACR in STZ induced diabetic C57BL/6J mice following approximately 15 weeks of hyperglycemia



Albuminuria in MOUSE MODELS OF DIABETIC NEPHROPATHY



24hour Urine Albumin excretion reported in the literature for mouse models of Diabetes