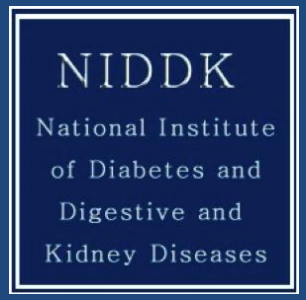
AMDCC Mouse Generation and Husbandry Core at The Jackson Laboratory



T1D-MGHC Project Highlights

Ed Leiter, T1DR Principal Investigator
Cathleen Lutz, T1DR Co-Principal Investigator
Karen Svenson, T1DR Co-Principal Investigator
Racheal Wallace, T1DR Operations Manager
Peter Reifsnyder, Research Assistant II
Ralph Colson, Research Assistant II
Pam Stanley, Research Assistant

Projects Summary

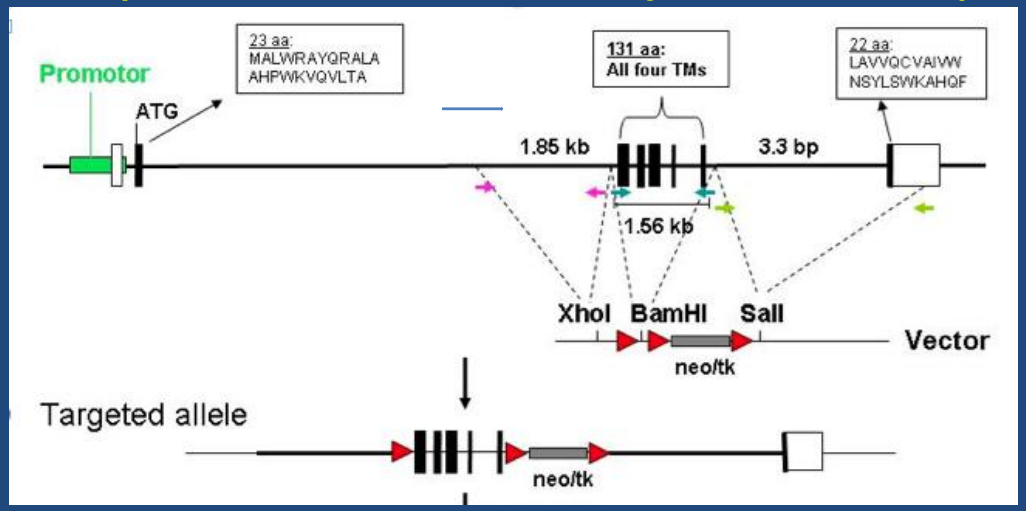
Mouse Generation Husbandry Core Projects
- completed: 9
- In-progress: 6
- New: 3

Phenotyping Projects
- completed: 10
- In-progress: 8
- Matings in-progress: 6

Cryopreservation
- completed: 20
- In-progress: 5
- To be started:
  - Soon: 7
  - Post development: 16

Dr. Erwin Bottinger

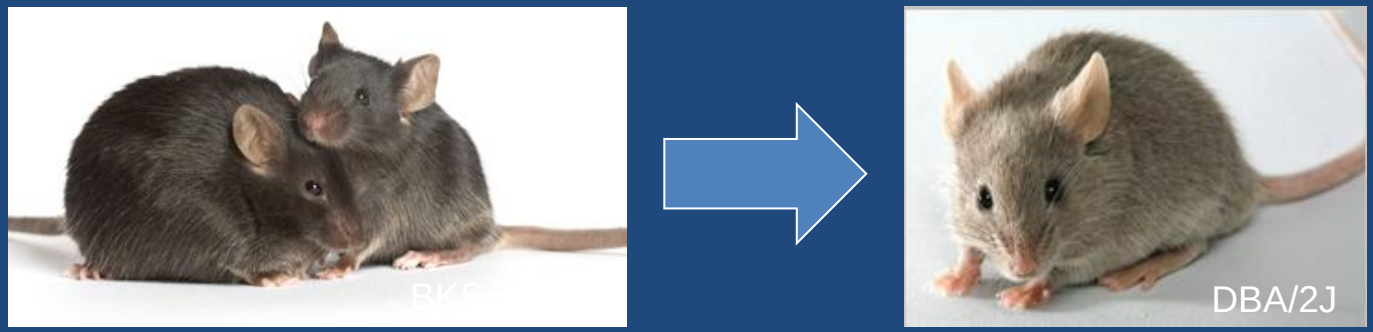
Project: Produce 129/B6 chimeric mice containing a conditional *MpV17* mitochondrial inner membrane protein (*Mpv17*^{loxP}) to explore tissue specific mitochondrial dysfunction in podocytes.



Chimeric males

1. Quality control and prep plasmid for electroporation
2. Electroporation of 129 ES cells
3. Southern blot to identify correctly oriented ES cell clones
4. Expand 2-4 correctly oriented ES cell clones
5. ES cell preparation for microinjection.
6. ES cell/blastocyst injections
7. Identify highly chimeric males for shipment to Mt. Sinai.

Transfer *Lepr*^{db} mutation to DBA/2J background



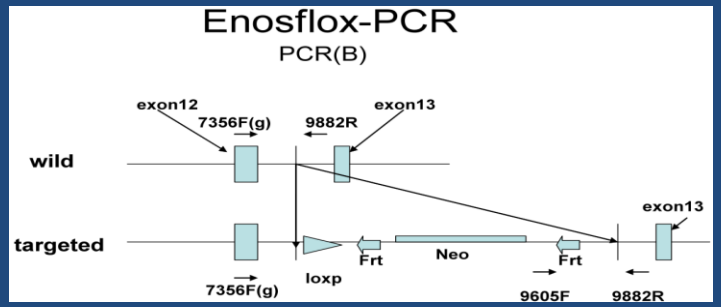
1. Cross BKS-*Lepr*^{db} to DBA/2J to develop D2-*Lepr*^{db} congenic.
   - Currently waiting for N2 progeny to test
2. Developed a BKS/DBA/2 SNP marker panel
3. Intercross to identify homozygous *Lepr*^{db} mice for phenotyping
4. Transfer D2-*Lepr*^{db} stock to public distribution

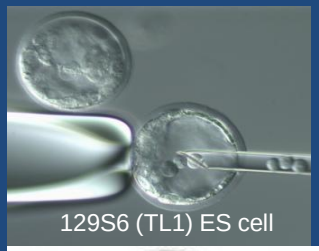
Import and phenotype B6.hApoE4, hLdlr, Akita

1. Import and rederive B6-*hApoE4, hLdlr* and B6-*hApoE4, Akita* mice
2. Genotype for mutant alleles
3. Intercross to establish B6-*hApoE4, hLdlr, Akita* mice to phenotype
4. Distribute to AMDCC members as collaborative effort with Dr. Nobuyo Maeda (UNC).

Dr. Ray Harris

Project: Produce 129 targeted lines for a conditional nitric oxide synthetase (Enos=*Nos3*) to explore tissue specific pathogenic endothelial changes.



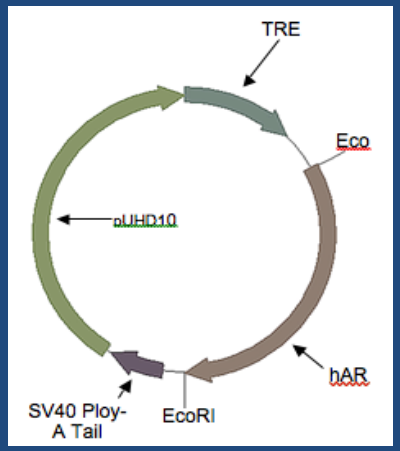


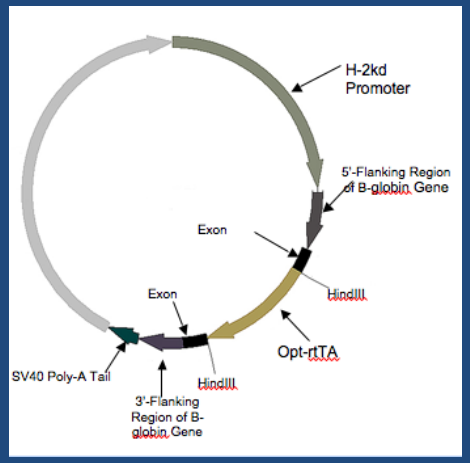
Chimeric male

1. Tested 12 chimeric males for germline transmission containing correct construct
2. Mated chimeric founders to 129S4-Flpe
3. Shipped mice *Nos3*^{floxed}, *Flpe* heterozygous mice to PI for further breeding and to test *Nos3* expression
4. Two lines, one from each clone, selected to transfer conditional *Nos3* mutation onto the DBA/2J background.
   - N2 offspring with 22-40 segregating SNPS selected for breeding
5. Cryopreserve selected neo-less 129-*Nos3*^{floxed} lines.

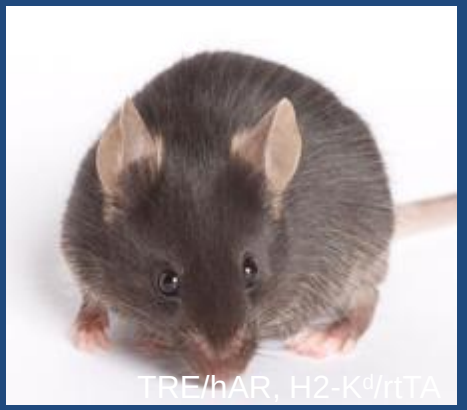
Dr Ed Fisher

Project: Produce a tetracycline inducible (tet-On), bi-transgenic tetO-human aldose reductase and H2-K^d -rtTA in the B6/J background.





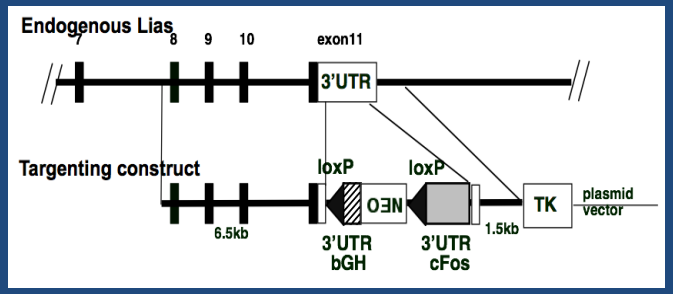

TRE/hAR, H2-K^d/rtTA founder

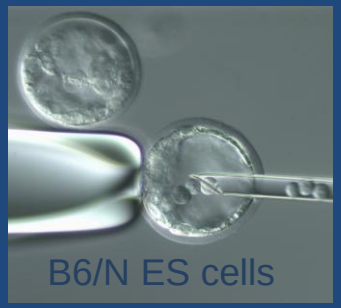

TRE/hAR, H2-K^d/rtTA

1. Established germline transmission of 14 founders.
2. Shipped double transgenic mice from each founder line for PI to complete expression studies.
3. PI identified 3 lines to breed to B6-*Ldlr KO*
   - Shipped transgenic, *Ldlr* KO mice from 1 line
4. Cryopreserve three B6-TRE/hAR, H2-K^d/rtTA transgenic lines and in combination with the *Ldlr* KO
5. Establish qPCR to identify homozygous transgenic mice

Dr. Nobuyo Maeda

Project: Produce a high/low set of B6 lines for Lipoic Acid Synthetase (*Lias*) expression





1. Identified germline transmission from 1 chimeric founder.
2. Mated founder's progeny to C57BL/6J (*Tyr*+ and *Nnt*-) and replaced Tyr^{c} and Nnt^{+} with the B6/J alleles.
3. Shipped heterozygous and homozygous mice to PI for $Lias^{high}$ activity determination
4. Mated to Tg(EIIA-cre) to create $Lias^{low}$
5. Ship heterozygous and homozygous mice to PI for $Lias^{low}$ activity determination
6. Cryopreserved *Lias-H* and *Lias-L*
7. Established and shipped first shipment of B6-$Lias^{low}$ $Ins2^{Akita}$

Dr. Dale Abel

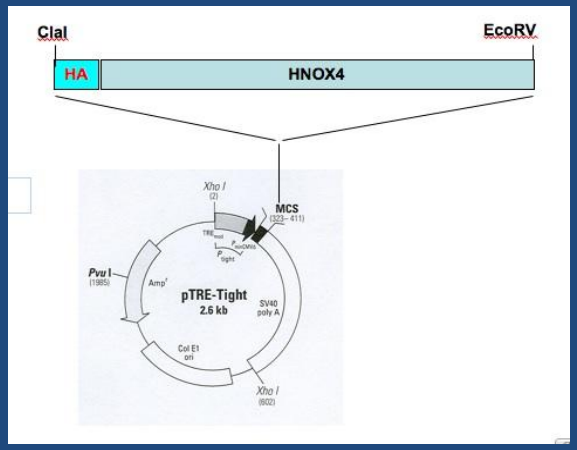
Project: Produce congenic C57BL/6-Ins2^{Akita} Netrin^{floxed} (*Ntn1^{floxed}*) *T*g(CAG-cre/Esr1) for evaluation of selective over-expression of Netrin

generation = N5	B6-Ntn1<floxed>						
SNP Marker	Mouse#						
	BS183	BS301	BS309	BS313	C57BL/6J	129S1	B6+129
05-149044358-M	C	C	C		C	A	het
06-003167392-M	C	C	C	C	C	T	het
06-030516093-G	A	A	A	A	A	C	het
06-060887613-G	A	A	A	A	A	G	het
06-090142535-M	C	C	C	C	C	A	het
06-095139289-M	het	het	het	het	T	A	het
Gt(Rosa)26 - Ntn1	heterozygous by PCR						
06-112199886-M	het	het	het	het	G	T	het
06-119728826-G	het	het	het	het	T	A	het
06-122941044-M	het	het	het	het	T	A	het
06-128926170-M	C	C	C	C	C	T	het
06-135955068-M	C	C	C	C	C	A	het
06-140532504-G	C	C	C	C	C	G	het
06-146079591-M	A	A	A	A	A	C	het
06-149052281-M	C	C	C	C	C	G	het
07-022997618-M	C	C	C	C	C	T	het
08-123340602-N	C	C	C	C	C	T	het
09-102158958-M	C	C	C	C	C	T	het

1. Imported and rederived *Ntn1^{floxed}* mutation on a mixed background
2. Developed a B6/129 SNP marker panel
3. Transferred the Ntn1 mutation onto a congenic C57BL/6J background.
4. Distributed small batch of B6.*Ntn1^{floxed,} Ins2^{Akita}* and B6.Tg(CAG-cre/Esr1) – more mice are needed.
5. Cryopreserve *B6.Ntn1^{floxed}*

Dr. Kumar Sharma

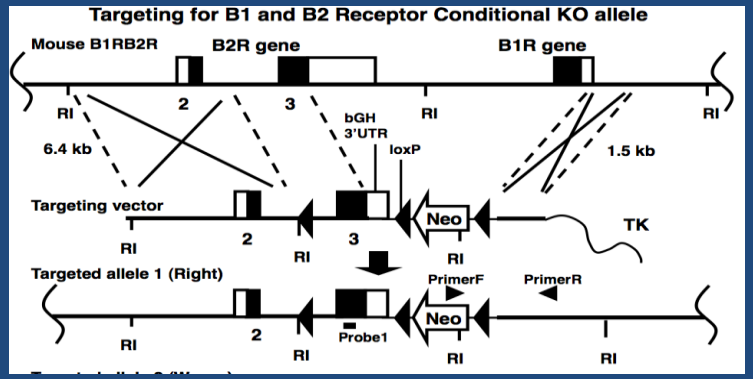
Project: Produce a tetracycline inducible (tet-On), Nox4 transgenic stock on FVB/N and DBA/2 backgrounds. The objective is to assess the effects of hyperglycemia on nephropathy after tissue specific over-expression of human NOX4.

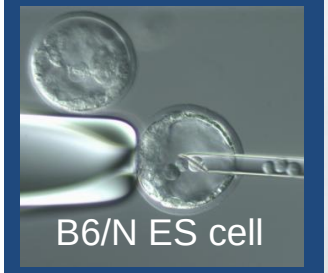


1. Established and shipped FVB transgenic offspring from 10 founders to complete expression studies.
2. Transfer FVB-Tg(NPHS2-rtTA) transgene onto DBA/2J and C57BL/6J
   - Waiting for N3 pups on the DBA background to screen.
3. Transfer the Tet0-Nox4 transgene from 2 lines onto C57BL/6J
4. Cross B6-Ins2^{Akita} with the B6-Tg(Tet0-Nox4) lines
5. Cryopreserve 4 FVB-Tg(Tet0-Nox4) lines, 2 B6-Tg(Tet0-Nox4) lines, B6 -Tg(NPHS2-rtTA) and DBA-Tg(NPHS2-rtTA) stocks

Drs Oliver Smithies / Masao Kakoki

Project: Produce a bradykinin 1 receptor knockout with a conditional bradykinin 2 receptor knockout in a C57BL/6 background to explore tissue specific impact of impaired bradykinin signaling.





1. 8 medium – low chimeric males
2. Re-injected clone with laser assisted technology, no chimeric pups
3. Set up second targeting experiment using B6/J-albino ES cells.
4. Germline transmission from one of the original chimeric males
5. Sequenced all 3 lox sites
6. Established and shipped small quantity of *B1R/B2R* conditional mice
7. Breeding away from the *Tyr*^{c} and wt *Nnt* and ship mice
8. Cryopreservation.

Dr. Firouz Daneshgari

Project: To combine the floxed *Sod2* allele with the transgene transgelin-Cre/Esr (Tagln-creER) on a C57BL/6 background to explore the impact of increased ROS production in smooth muscle, specifically on diabetic bladder dysfunction

1. Imported/rederived B6. *SOD2^{floxed}* and B6-Tagln-cre/Esr stocks
2. Bred the 2 alleles together.
3. Distributed heterozygous and homozygous neo-less B6. *SOD2^{floxed}* mice also heterozygous for Tagln-cre/Esr
4. Cryopreserved of B6. *SOD2^{floxed}* and B6-Tagln-cre/Esr stocks

Dr. Eva Feldman

Project: Transfer the B6.*SOD2*^{floxed} and B6.Tg(Nestin-cre) alleles onto the BKS.*Lepr*^{db} background to evaluate the role of ROS production in diabetic neuropathy.

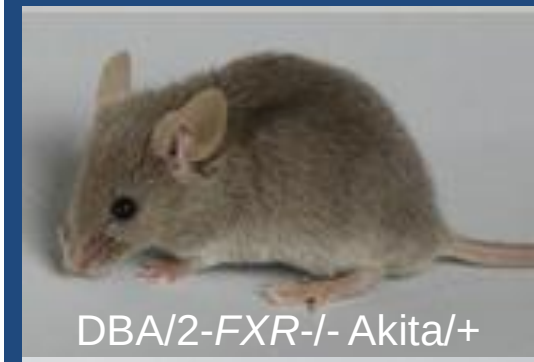
SNP Marker	Animal ID						
sample	BH377	BH381	BH382	C57BL/6J	C57BLKS/J	DBA/2J	SJL
04-006370062-M	G	G	G	A	G	G	A
04-032923355-M	T	T	T	C	T	T	T
04-085096243-M	T	T	T	C	T	T	C
04-097015585-M	G	G	G	A	G	G	G
04-122948823-M	G	G	G	A	G	G	G
12-017285410-N	G	G	G	A	G	G	A
12-031510473-N	A	A	A	G	A	A	G
12-048364436-M	C	C	C	C	C	C	T
12-049281625-M	T	T	T	C	T	T	T
12-059204373-M	T	T	T	T	T	T	G
12-063406537-M	A	A	A	A	A	A	G
12-064212930-N	G	G	G	A		G	G
12-067428336-M	A	A	A	A	A	A	C
12-083253104-M	het	het	het	A	A	A	G
12-092440423-M	G	G	G	G	G	G	C
12-099526845-G	G	G	G	G	G	T	T
12-104882822-M	T	T	T	T	T	T	C
12-113315003-M	C	C	C	C	C	G	G

1. Imported/rederived B6.*SOD2*^{floxed}
2. Transferred *SOD2*^{floxed} and Tg(Nes-cre) alleles to BKS.*Lepr*^{db} utilizing speed congenic technology .
3. Bred *SOD2*^{floxed} in the BKS.*Lepr*^{db} background to homozygosity
4. Distributed BKS. *Lepr*^{db} *SOD2*^{floxed} and heterozygous BKS-*Lepr*^{db} Tg(Nes-cre) breeders to produce experimental animals.
5. Cryopreservation of BKS-*Lepr*^{db} *SOD2*^{floxed} and BKS-*Lepr*^{db} Tg(Nes-cre)

Dr. Moshe Levi

Project: Transfer the Farnesoid X receptor (*FXR=Nr1h4*) knockout allele onto DBA/2J and FVB/NJ with *Ins2*^{Akita} to evaluate the consequences of *FXR* deficiency in diabetic renal and cardiovascular complications.

SNP	FVB-FXR, Akita Mouse ID					
	FX351	**FX352**	**FX353**	**129**	**FVB**	**C57BL/6**
10-077371167-G	A	A	A	G	A	G
10-086567143-M	T	T	T	T	C	T
10-086817590-G	T	T	T	T	A	A
M-05799_1	G	G	G	G	C	G
FXR (Nr1h4 by PCR)	**-/-**	**-/-**	**-/-**			
10-099683776-N	C	C	C	C	G	C
10-100345477-M	T	T	T	T	C	T
10-107333522-M	T	T	T	T	C	C
10-107789430-G	G	G	G	A	A	G
10-120289167-M	G	G	G	A	G	A



1. Used speed congenic technology to transfer FXR KO from B6 to FVB/NJ and DBA/2J.
2. Developed SNP panel to distinguish donor strain from target background strain.
3. Bred to *Ins2*^{Akita} mutation of same background strain.
4. Distributed *FXR*-/-, with and without *Akita* on the DBA and FVB backgrounds
5. Cryopreserved DBA and FVB *FXR, Akita* stocks

Drs Oliver Smithies/Masao Kakoki

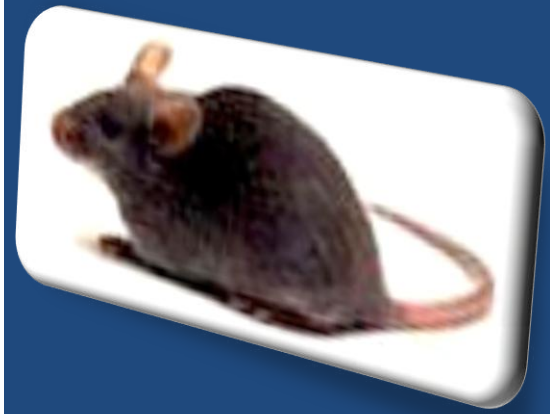
Project: Produce Bradykinin B1 and B2 receptor double knockout (*Bdkrb2/Bdkrb1*^{tm1Mki}) with the *Ins2*^{Akita} mutation on a C57BL/6 background to explore the impact of defective bradykinin signaling.

1. Imported and rederived B6 Bradykinin B1 and B2 receptor double knockout mice and mated with B6/J-*Akita.*
2. Bred B6 Bradykinin B1 and B2 receptor mutation to homozygosity with *Akita* segregating.
3. Distributed B6 Bradykinin B1 and B2 receptor knockout, *Akita*/+ and breeders
4. Fix segregating population for B6/J mutant *Nnt* allele
5. Cryopreserved B6-BR1BR2, *Akita*
6. Transferring to public distribution

Dr. Frank Brosius

Project: Produce congenic 129S6-*Ins2*^{Akita}, *Jak2*^{loxp} Tg(Nphs2-cre) for evaluation of selective over-expression of Janus Kinase

SNP Marker	129S6.B6-Akita	129S6.B6-Akita	129S6.Cg-NPHS2-cre	129S6.Cg-NPHS2-cre	129S6-Gt(ROSA)-Jak2	129S6	129S1	C57BL/6J	129S1 XB6	SJL
01-184035421-M	C	C	C	C	C	C	T	C	het	
03-096257069-G	C	C	C	C	C	C	T	C	het	
04-003163167-M	T	T	het	het	T	T	T	G	het	
04-009404597-G	NA	NA	het	het	NA	NA	G	A	het	
04-010285677-G	NA	NA	het	het	NA	NA	G	A	het	A
04-013376218-G	NA	NA	het	het	NA	NA	T	C	het	
04-020201305-G	NA	NA	het	het	NA	NA	A	T	het	
04-030080285-M	NA	NA	het	het	NA	NA	G	A	het	
04-032923355-M	T	T	het	het	T	T	T	C	het	
04-039199957-M	NA	NA	het	het	NA	NA	NA	NA	NA	
04-058850394-M	T	T	T	T	T	T	T	C	het	
04-092052171-M	G	G	G	G	G	G	G	A	het	
06-003167392-M	T	T	T	T	T	T	T	C	het	
06-029636236-G	T	T	T	T	T	T	T	G	het	
06-060887613-G	G	G	G	G	G	G	G	A	het	
06-090142535-M	A	A	A	A	A	A	A	C	het	
Gt(ROSA)26										
06-122941044-M	A	A	A	A	A	A	A	T	het	
06-149052281-M	G	G	G	G	G	G	G	C	het	
11-094206790-M	C	C	C	C	C	C	T	C	het	
11-118804416-N	A	A	A		A	A	A	G	het	



1. Imported/rederived stop-floxed-*Jak2*, Tg(NPHS2-cre), 129-*Ins2* ^{Akita} and 129S6-Tac
2. Developed 129S6 / B6 / FVB SNP panel
3. Completed 129S6 congenic backcross of the Tg(NPHS2-cre)
4. Shipped 129S6-*Jak2*^{loxp}, *Akita* and 129S6-TG(NPHS2-cre) breeders
5. Cryopreserved of 129S6-*Jak2*^{loxp}, *Akita*, 129S6-Tg(NPHS2-cre) and 129S6-*Ins2* ^{Akita}
6. Transferred 129S6-*Ins2* ^{Akita} and 129S6-Tg(NPHS2-cre) to public distribution

MGHC stocks transferred to the public repository

Stock# 006867 – FVB.B6-*Ins2*^{Akita}/MlnJ

Stock# 007562 – D2.B6-*Ins2*^{Akita}/MatbJ

Stock# 007688 - 129S6.B6-*Ins2*^{Akita}/Cof

Stock# 008286 - 129S6.129P2(B6)-*Nos3*^{tm1Unc}/J

Stock# 006860 – B6.129-*Ins2*^{Akita}*Bdkrb2*^{tm1Jfh}/SmiJ

Stock# 008523 - 129S6.Cg-Tg(NPHS2-cre)295Lbh/BroJ

Stock# 012371 – C57BL/6-*Bdkrb1/Bdkrb2*^{tm1Mki}/J

Next 6-8 Months

1. We will complete 15 of 17 approved projects maintaining small quantities for AMDCC distribution or transferring to public distribution.
   - We have used or created 57 inbred or mutant stocks to accomplish these goals.
     - This does not account for multiple founder lines that are not to be continued.

2. Continue
   - cryopreservation of stocks with multiple or single mutations.
   - Phenotyping studies of multigenic stocks.
   - Speed congenic projects.
   - Distribute multigenic stocks to project investigators/collaborators.

TJL Scientific Resources Utilized

Assisted Reproductive Services

- Importation
- Re-derivation
- Cryopreservation
- Cell Biology
- Microinjection

Phenotyping Services

- Necropsy Service
- Histotechnical Service
- Physiology Service
- Pathology/Veterinary Science

Genome Services

- Molecular Biology Service
- Transgenic Genotyping Service
- SNP Genotyping Service
- Fine Mapping Service

Vivarium Management

- Research Animal Facility
  - Basic Animal Husbandry
- Laboratory Animal Health
  - Microbiologic screening of barrier colonies

Operations

- TJL Customer Service
  - Mouse orders/shipping
- TJL Marketing
  - information/catalog
- Nomenclature
- Information Technology
- Multimedia Services

Lessons Learned

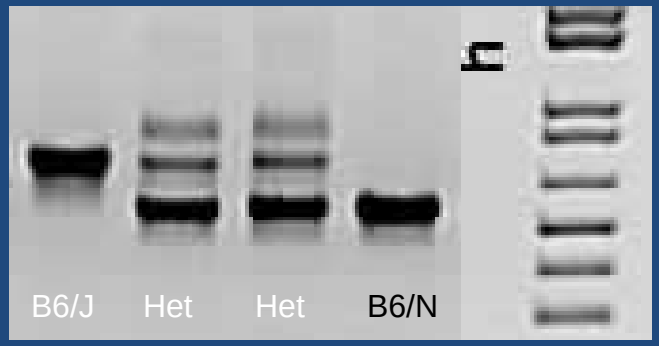
To determine substrain of all C57BL/6 congenic stocks imported by genotyping for the B6/J-specific *Nnt* mutation

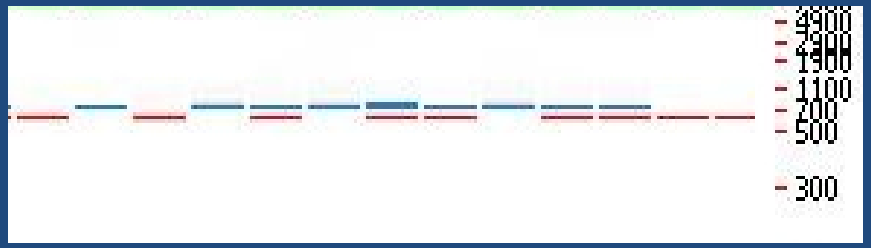
To implement quality control steps on all constructs or ES cell clones shipped to us for microinjection/electroporation. Although this step may delay the project, time is saved by verifying the integrity of the targeting construct.

To obtain all necessary information from project investigators regarding the genotyping of their constructs.

In making a congenic stock, take care to fix the Y chromosome.

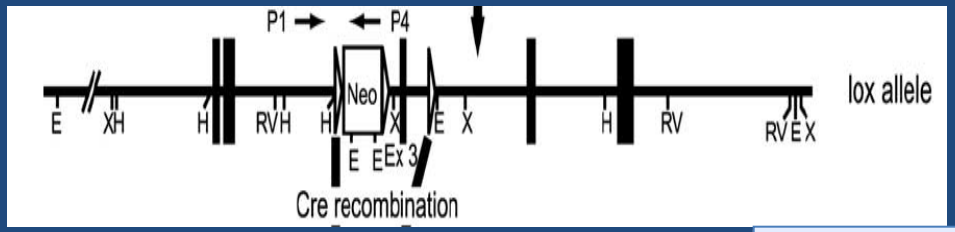
Nnt mutation in B6/J

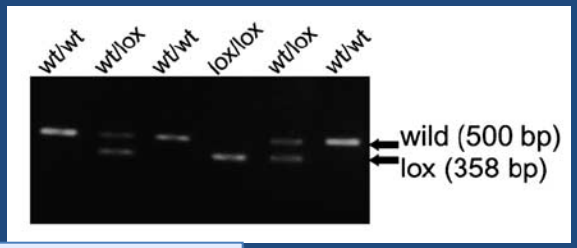




Segregating *Nnt* in Phenotyped *B6.Bdkrb1/2-/-, Akita*

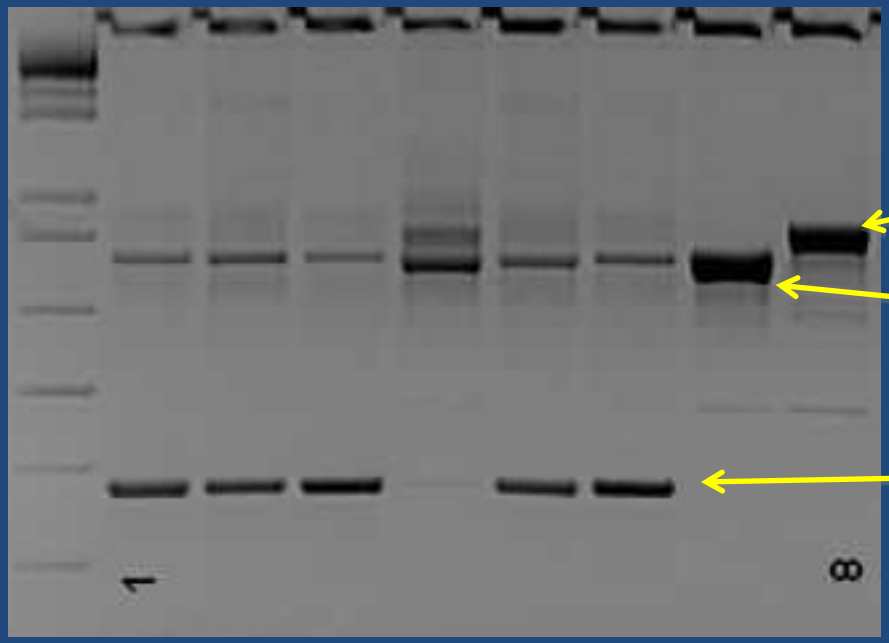
Sod2^{flox} allele





Ikegama, BBRC 296, 729-736

Sod2^{flox} cut by Tg(CMV-Cre)



Sod2^{Flox}/*Sod2*^{Flox}, uncut by Cre

WT allele (CMV-cre)

Sod2^{Flox} allele cut by CMV-Cre

Phenotyping Data

JAX Phenotyping

Diabetes-associated parameters: body weight, plasma glucose, plasma and pancreatic insulin

Histology: pancreas, liver, spleen, kidneys (to C. Alpers), heart (to K. O'Brien), sciatic nerve and plantar skin (to N. Calcutt), eyes (to R. LeBoeuf)

Kidney physiology: spot ACR at 17, 21`, 25 wk; ACR and total albumin in 24 hr-collected urine@21 and 25 wk; kidney weight at necropsy.

Heart physiology: systolic blood pressure and pulse rate at 19 wk; EKG@13 and 21 wk.

DEXA for lean and fat body mass, bone mineral density and content @ 26 wk

Plasma chemistry at necropsy: glucose, total cholesterol, HDL-cholesterol,triglycerides, free fatty acids, BUN, glutamate dehydrogenase

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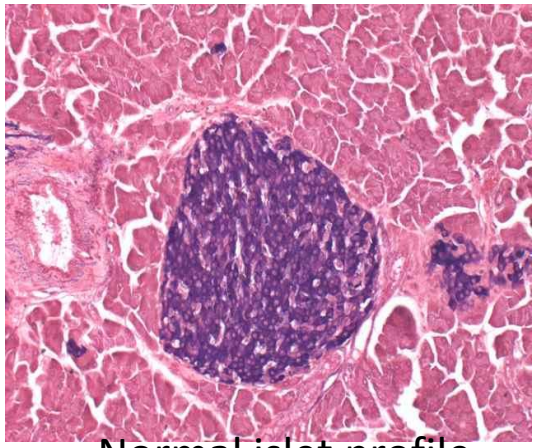
The Jackson Laboratory

Models Phenotyped or in Progress

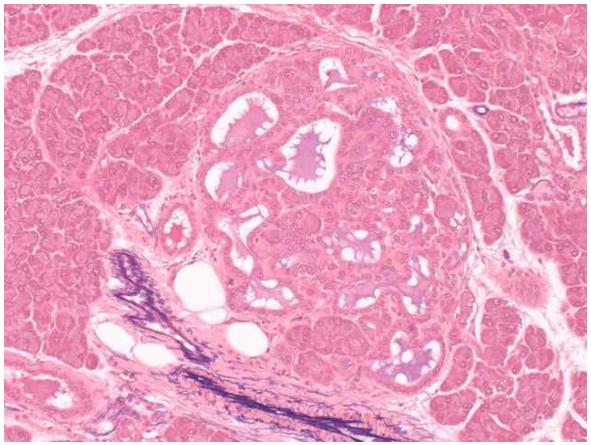
Stock	Completed	In Progress
FVB-Lepr^{db}	√	
BTBR-Lep^{ob}		√
FVB-Ins2^{Akita}	√	
DBA/2-Ins2^{Akita}	√	
B6-Ins2^{Akita}	√	
129/SvEvTac Ins2^{Akita}	√	
B6-Bdkr1/2 KO Ins2^{Akita}	√	
DBA/2-FXR KO Ins2^{Akita}	√	
FVB-FXR KO Ins2^{Akita}	√	
B6-Ldlr KO Ins2^{Akita}		√
129B6F1-eNos KO Ins2^{Akita}	√	
B6-eNos KO Ins2^{Akita}		√
129/SvEvTac-eNos KO Ins2^{Akita}		√
FVB-OVE26 (Rip-Calmodulin)		√
(PWBxFVB-OVE26)F1		√
(NONxFVB-OVE26)F1		√
ALRxFVB-OVE26)F1		√

Comparison Under the Same Vivarium Conditions of Two Different Ins2^{Akita} Stocks Nullizygous for a Farnesyl X Receptor

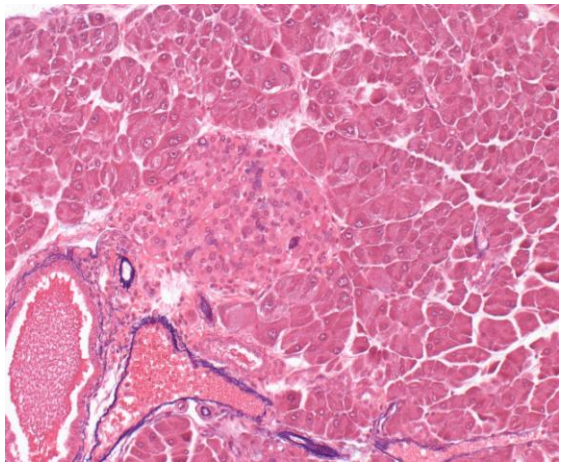
Project for Dr. Moshe Levi: Speed congenic transfer of a targeted FXR allele from the B6 background onto both the FVB/NJ and DBA/2J inbred strain backgrounds



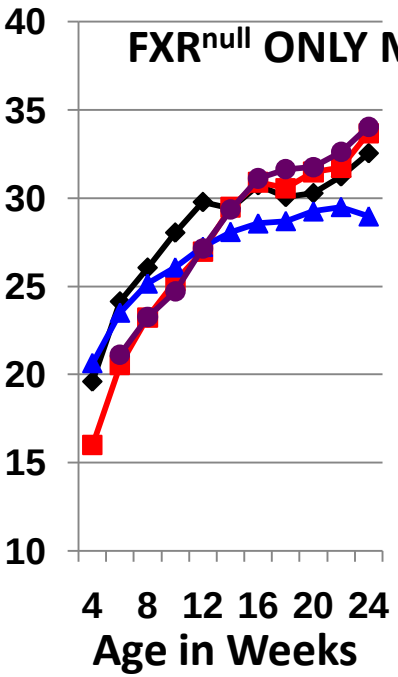
Normal islet profile
(both backgrounds)

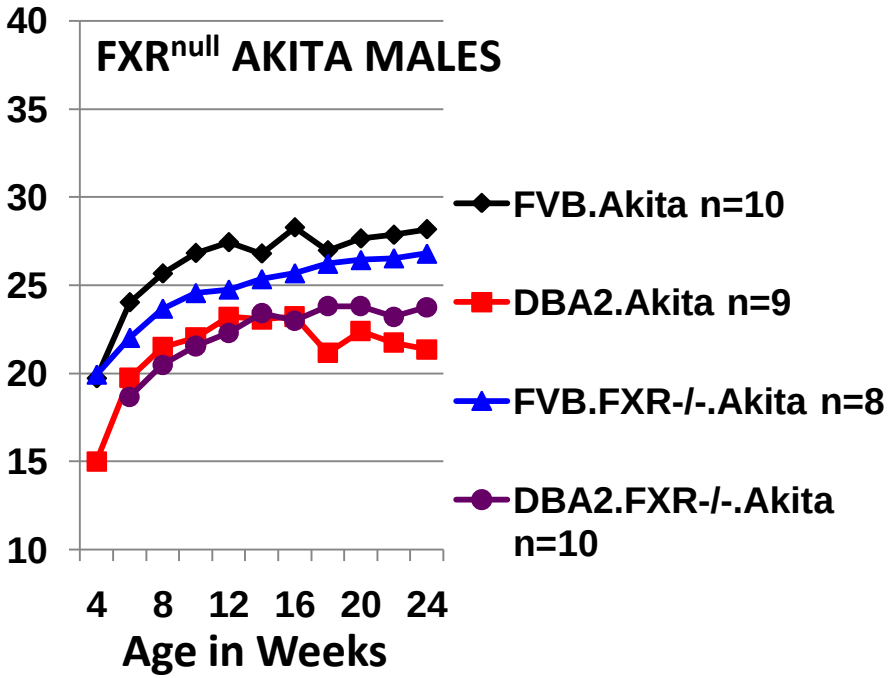


D2-FXRnull Akita
Atrophic, sparse islets,
unusual ductal proliferation



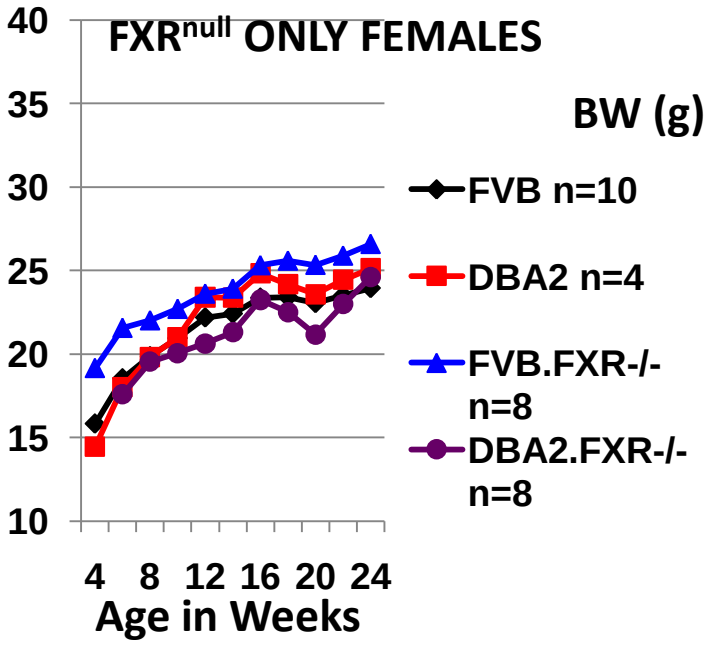
FVB-FXRnull Akita-heavily insulin degranulated and sparse islets



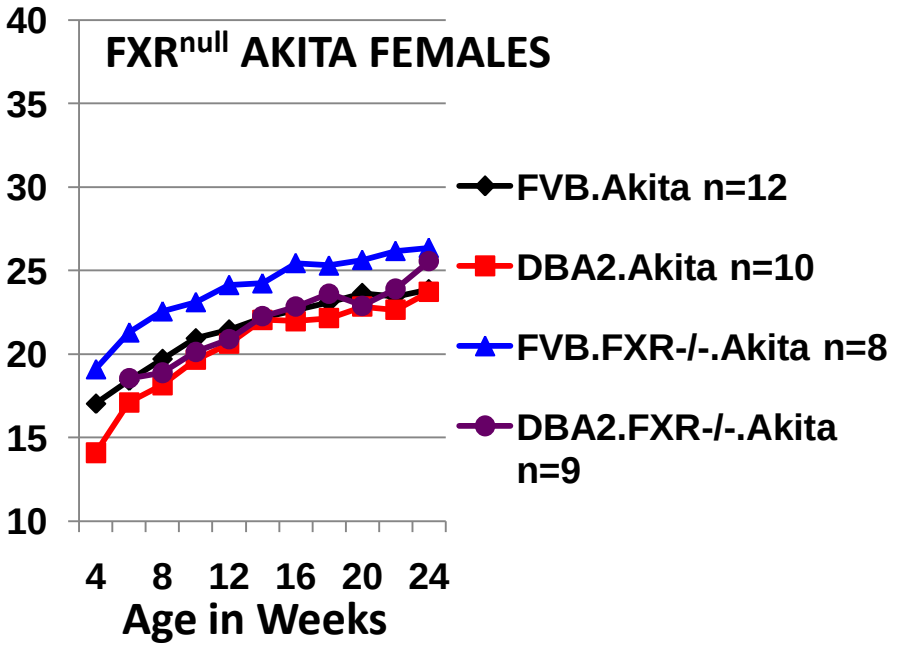


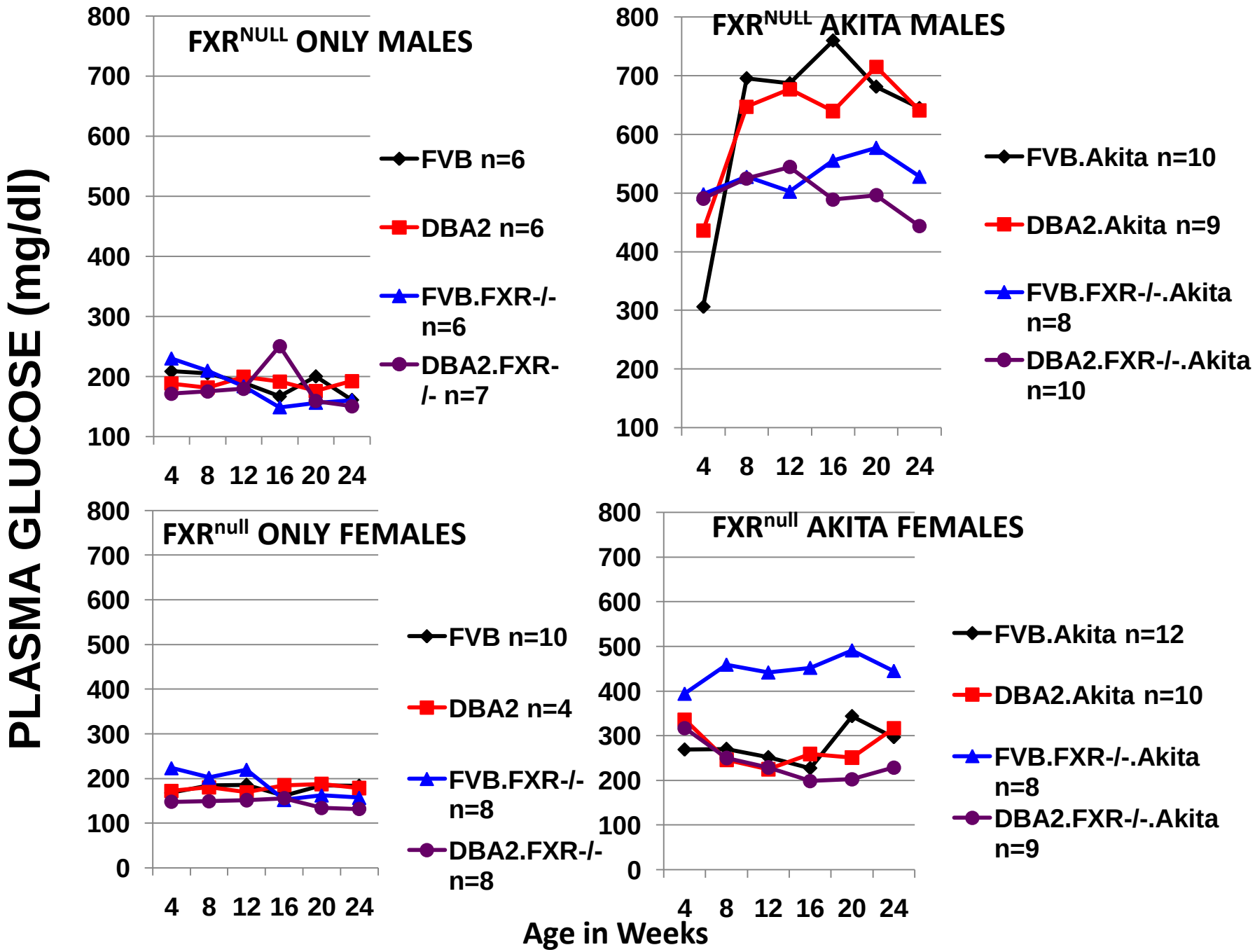
Males

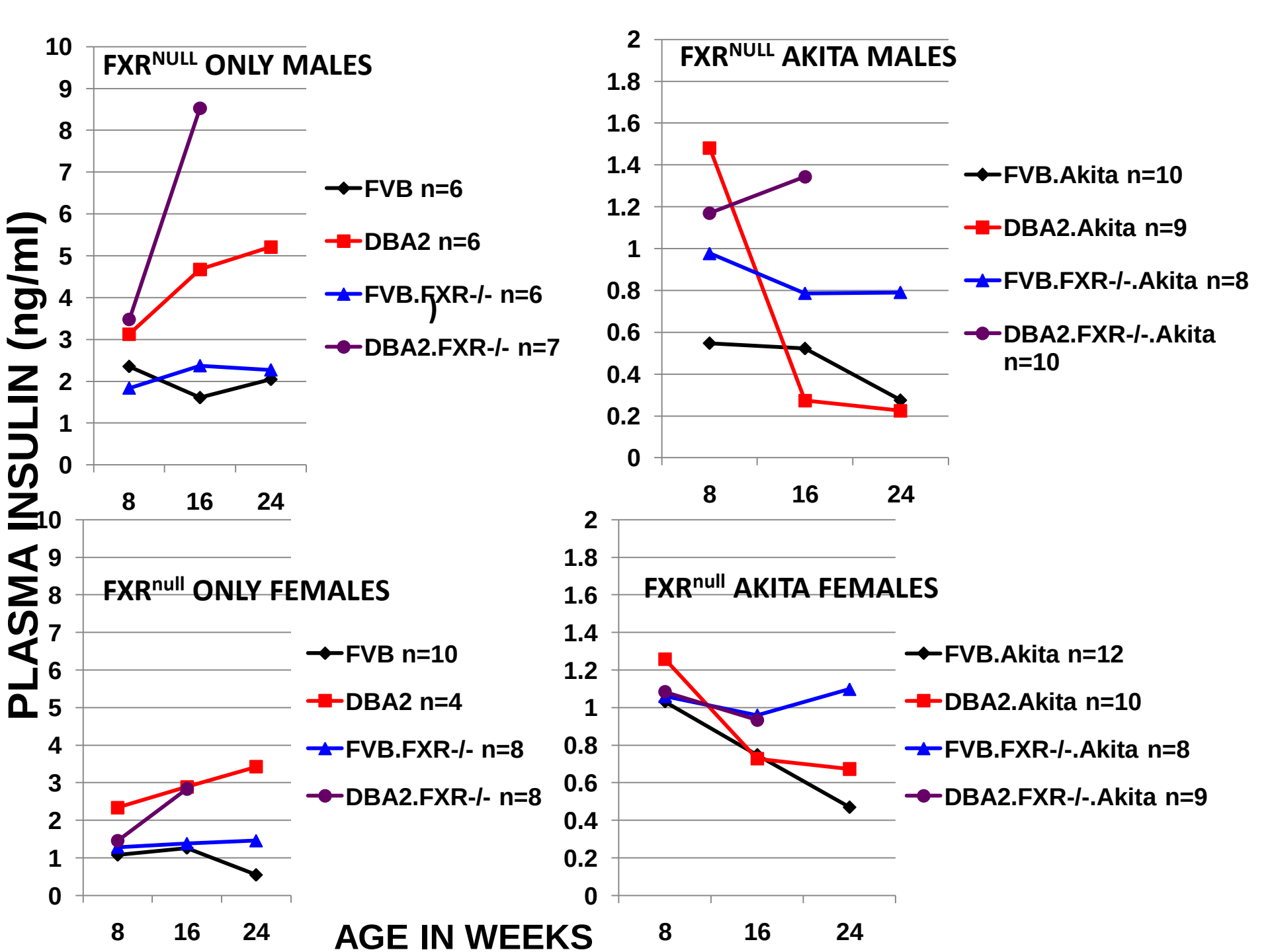
BODY WEIGHTS (g)



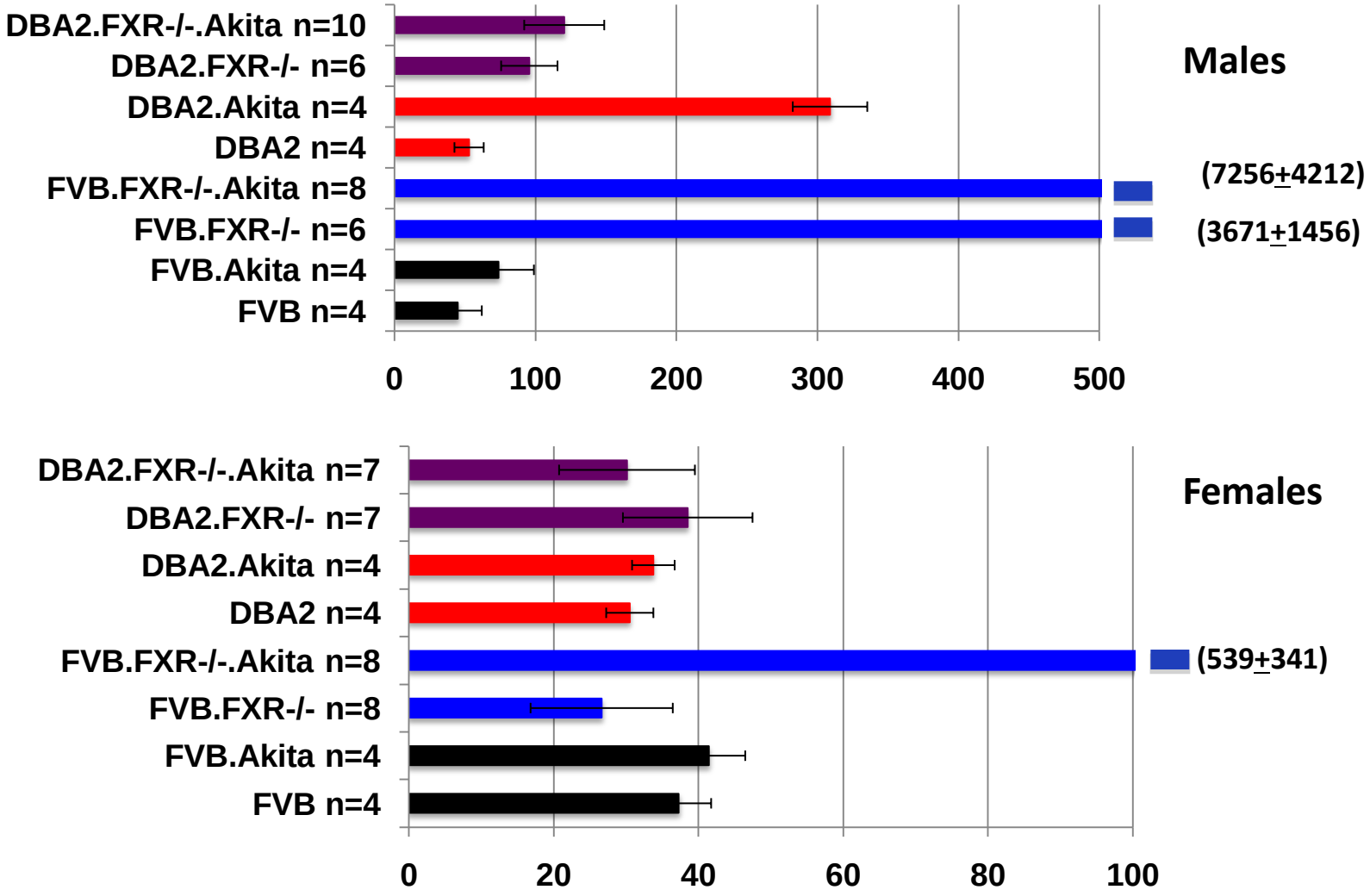
Females



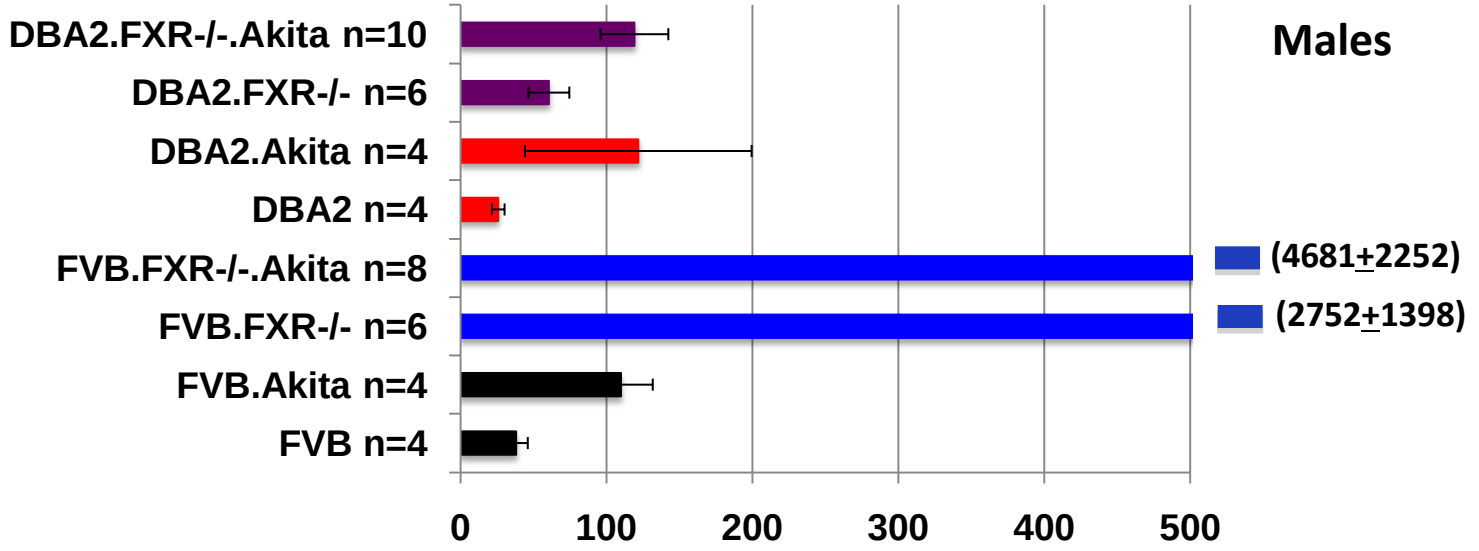

PLASMA GLUCOSE (mg/dl)
FXRNULL ONLY MALES
FVB n=6
DBA2 n=6
FVB.FXR-/- n=6
DBA2.FXR-/- n=7
FXRNULL AKITA MALES
FVB.Akita n=10
DBA2.Akita n=9
FVB.FXR-/-.Akita n=8
DBA2.FXR-/-.Akita n=10
FXRnull ONLY FEMALES
FVB n=10
DBA2 n=4
FVB.FXR-/- n=8
DBA2.FXR-/- n=8
FXRnull AKITA FEMALES
FVB.Akita n=12
DBA2.Akita n=10
FVB.FXR-/-.Akita n=8
DBA2.FXR-/-.Akita n=9
Age in Weeks

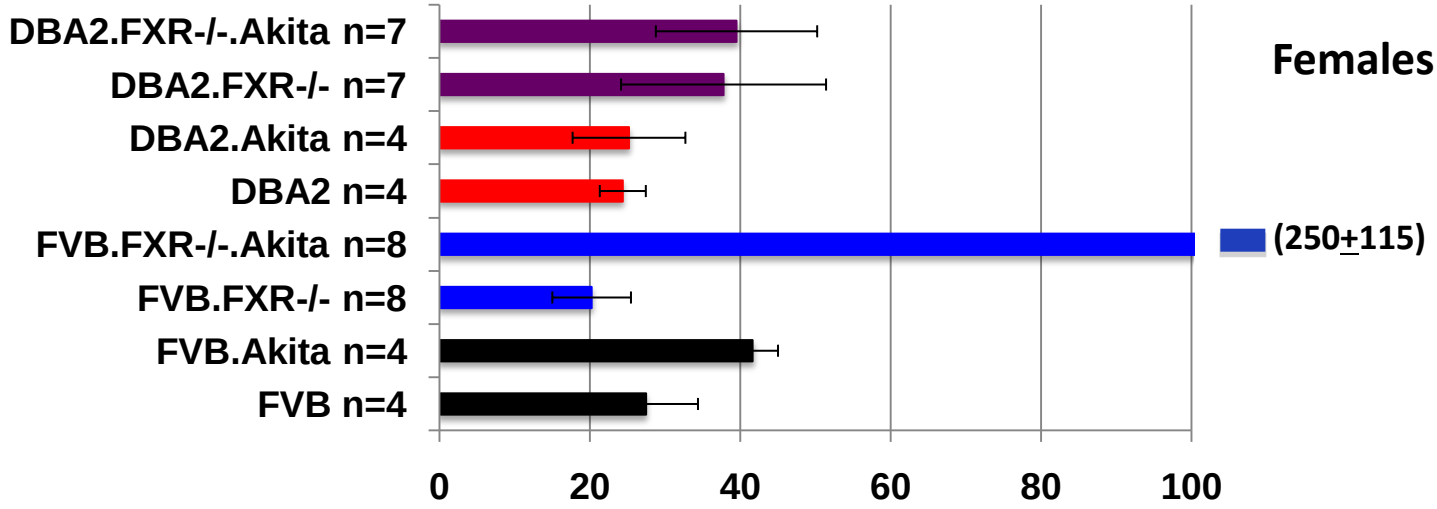

PLASMA INSULIN (ng/ml)
FXR^NULL ONLY MALES
FVB n=6
DBA2 n=6
FVB.FXR-/- n=6
DBA2.FXR-/- n=7
FXR^NULL AKITA MALES
FVB.Akita n=10
DBA2.Akita n=9
FVB.FXR-/-.Akita n=8
DBA2.FXR-/-.Akita n=10
FXR^null ONLY FEMALES
FVB n=10
DBA2 n=4
FVB.FXR-/- n=8
DBA2.FXR-/- n=8
FXR^null AKITA FEMALES
FVB.Akita n=12
DBA2.Akita n=10
FVB.FXR-/-.Akita n=8
DBA2.FXR-/-.Akita n=9
AGE IN WEEKS

24-hr Albumin/Creatinine Ratio, 25 wks (µg/mg)

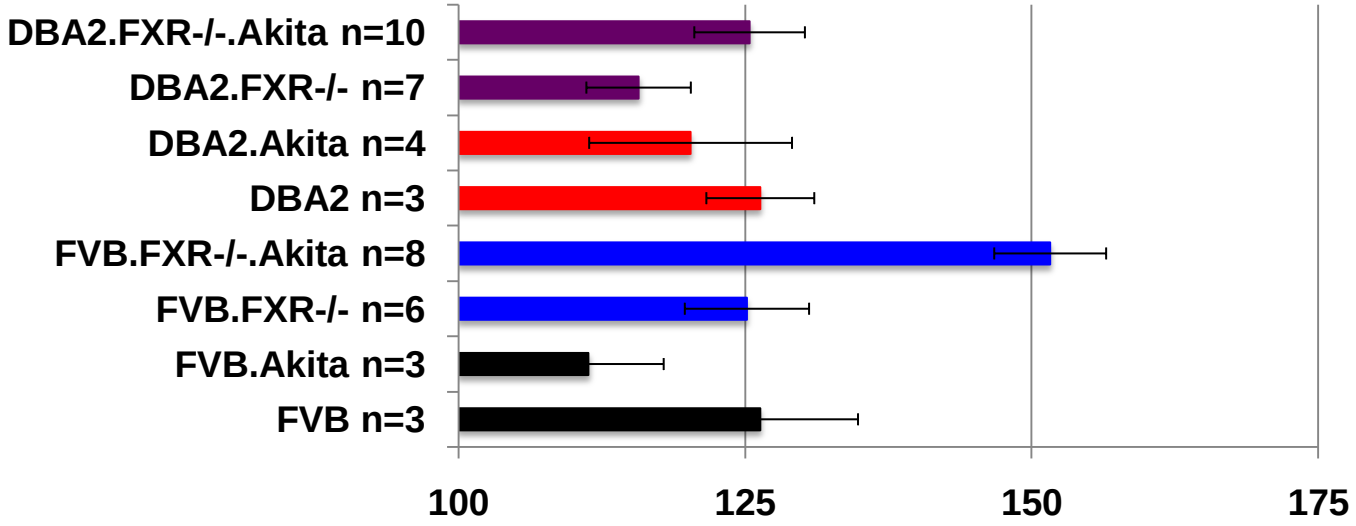


24-hr Total Albumin Secretion, 25 wks, (µg)

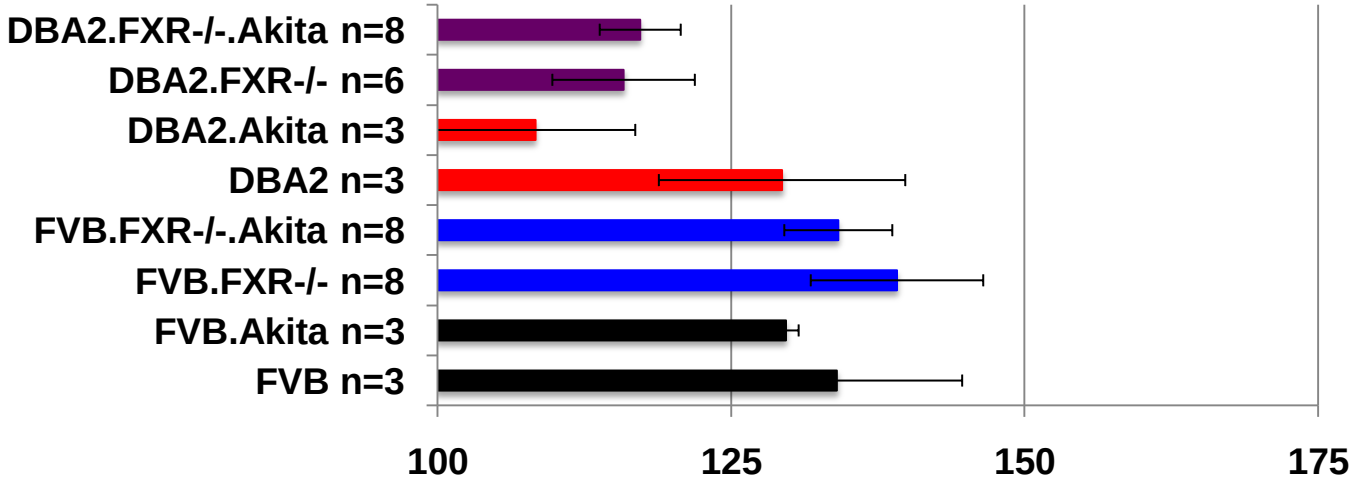




Systolic Blood Pressure, 19 wks (mm/Hg)



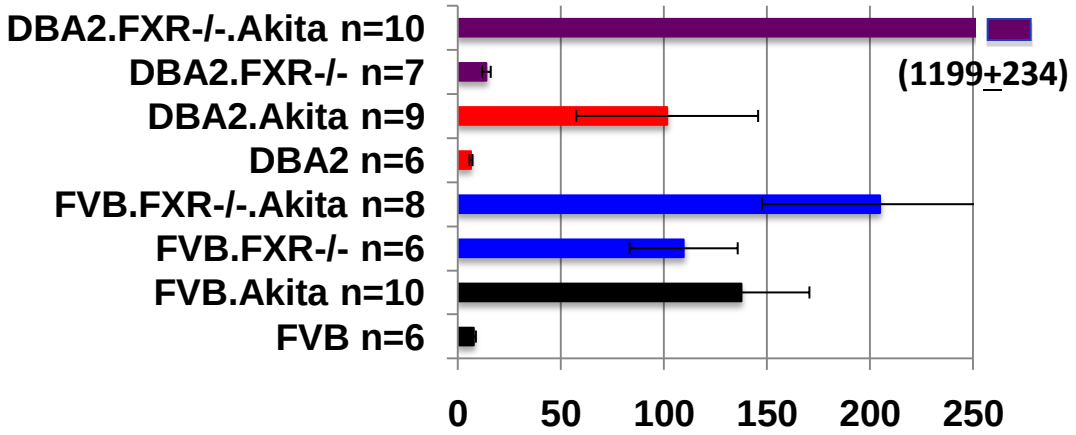
Males



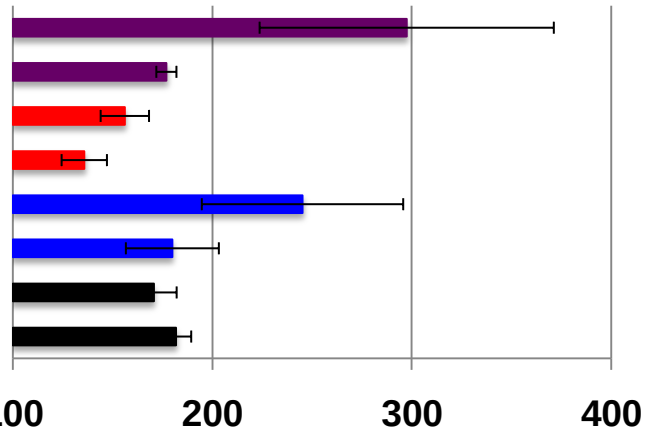
Females

Exacerbated Hyperlipemia in Diabetic FXR^{null} Males

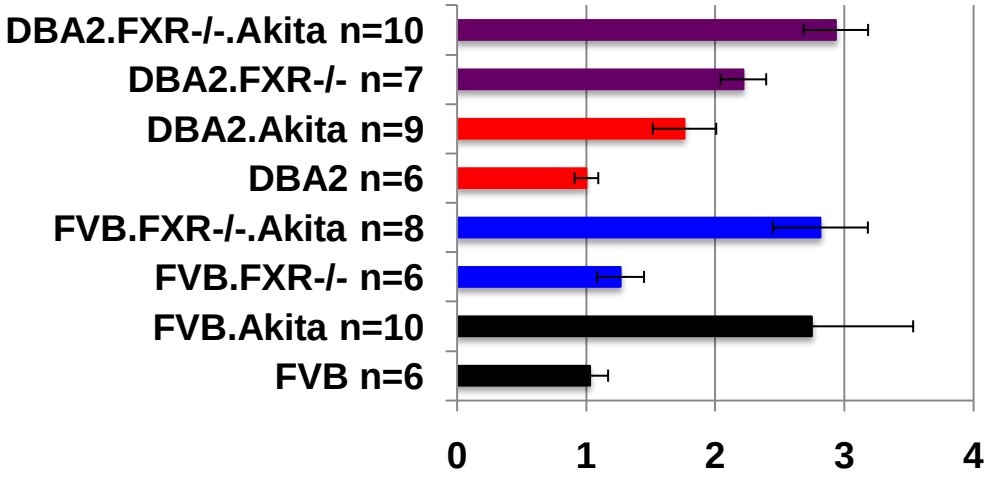
Glutamate Dehydrogenase (GLDH, IU/L)



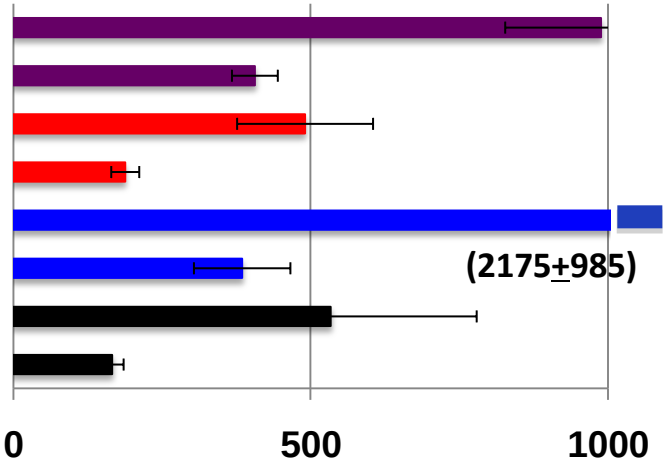
Cholesterol (mg/dl)



Non-Esterfied Fatty Acids (mEq/L)

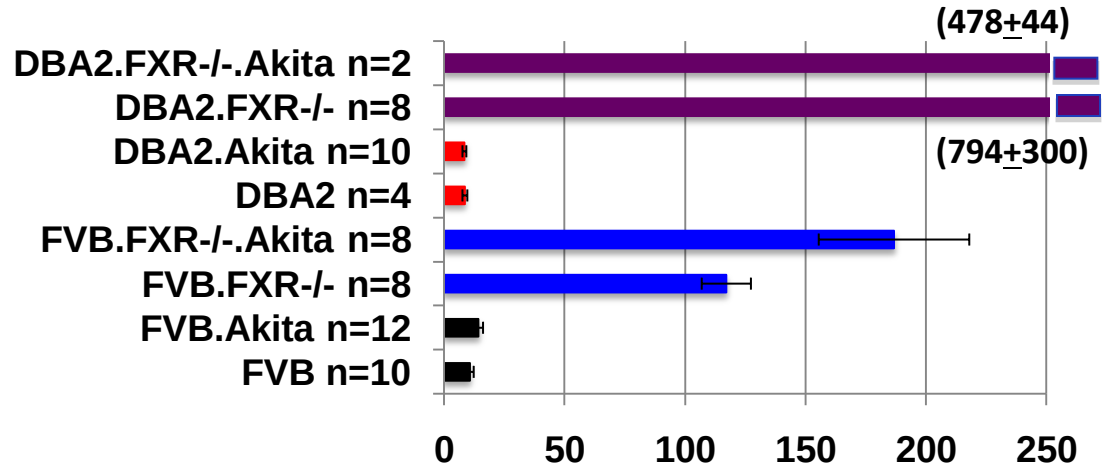


Triglycerides (mg/dl)

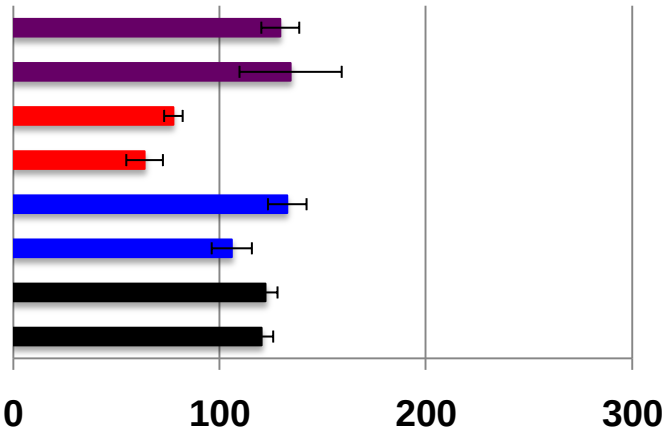


Plasma Chemistry, 26 wks, Females

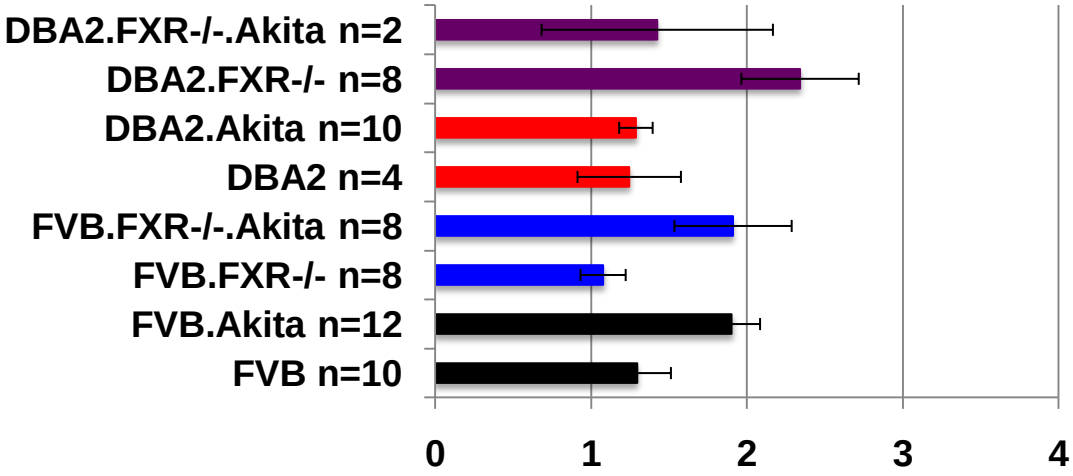
Glutamate Dehydrogenase (GLDH, IU/L)



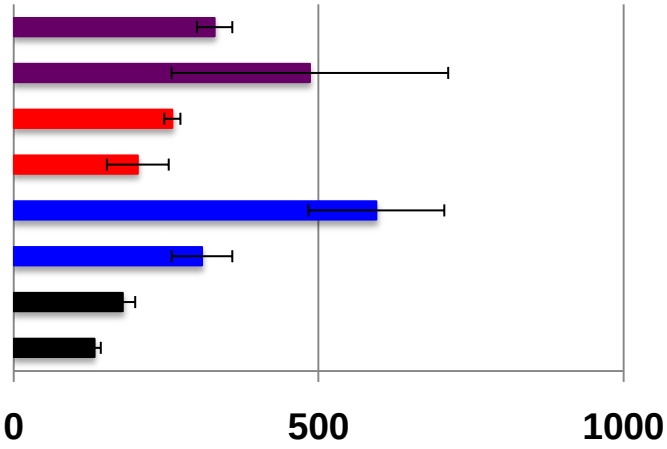
Cholesterol (mg/dl)



Non-Esterfied Fatty Acids (mEq/L)

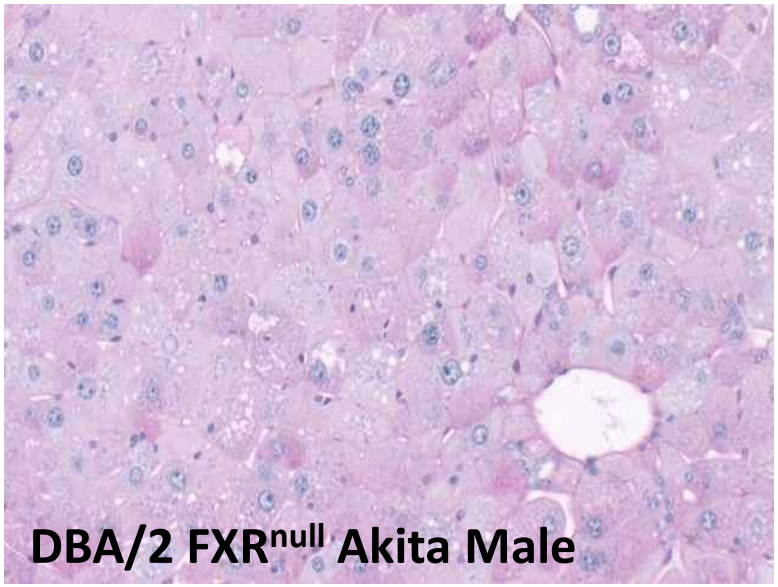


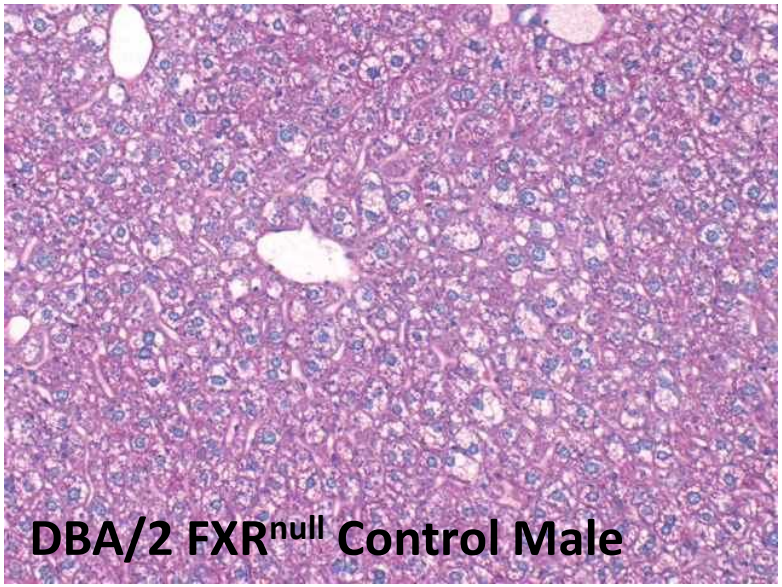
Triglycerides (mg/dl)

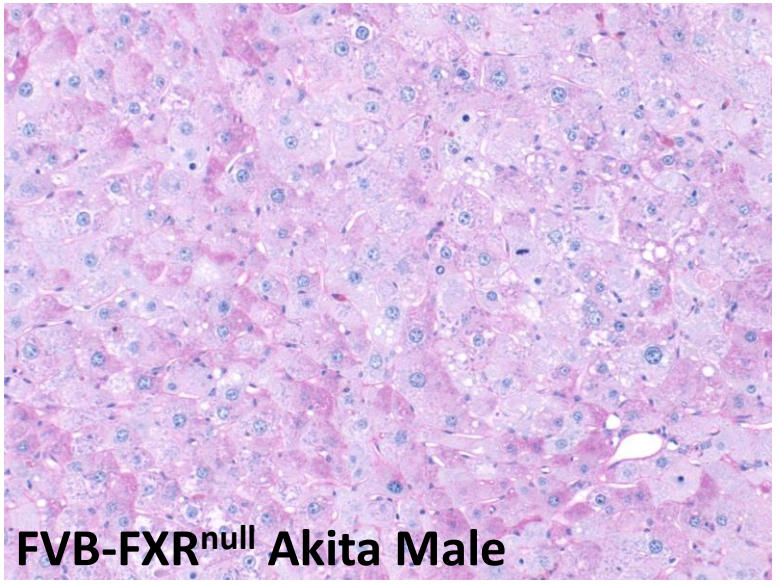


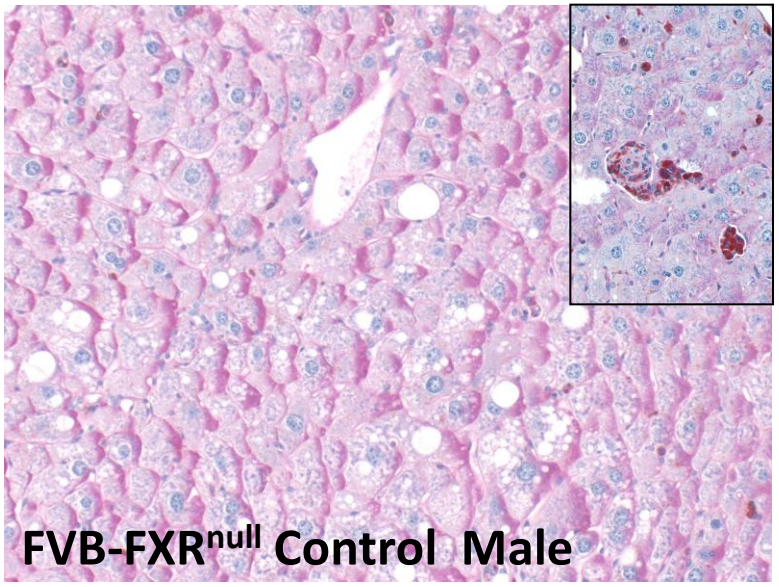
Effects of FXR Nullizygosity: Liver

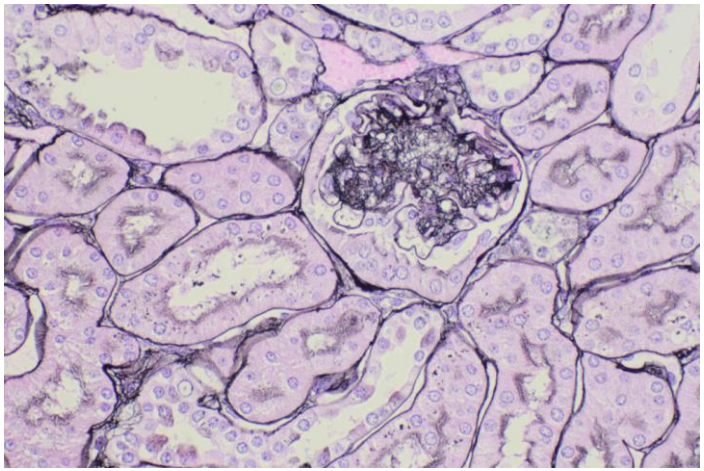
Histopathology assistance of Dr. Anoop Kavirayani (JAX)



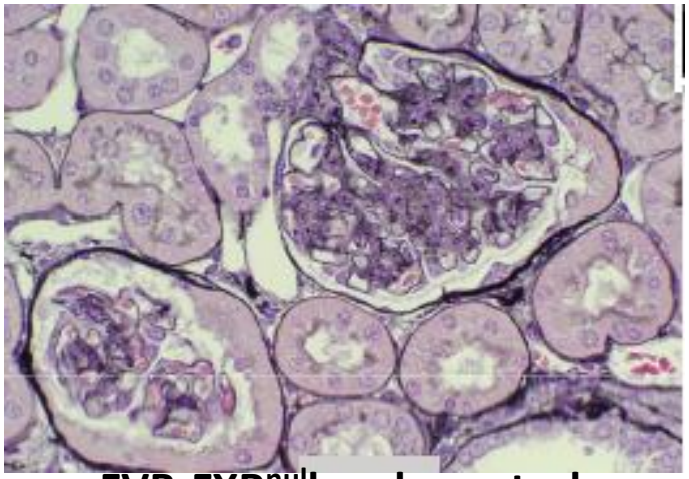




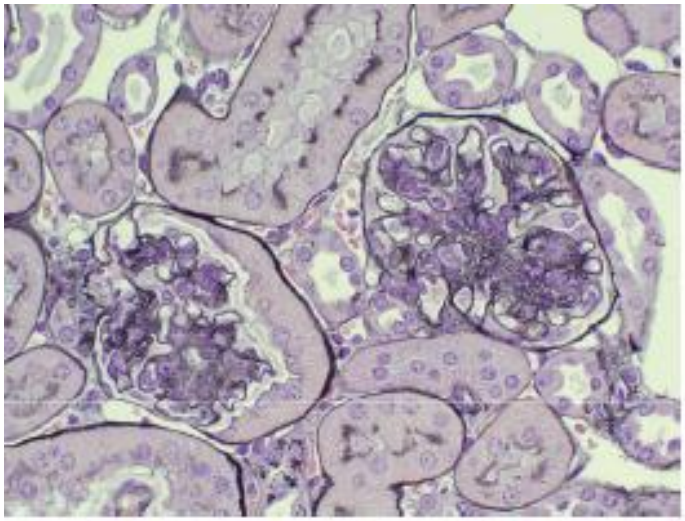




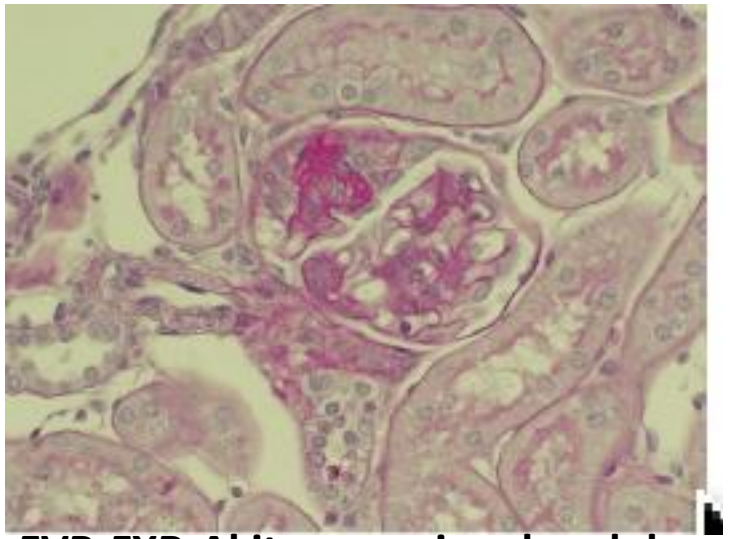
D2-FXRnull Akita male, mesangial expansion, silver methenamine.



FVB-FXR^{null}l male control



FVB-FXRnull Akita male, mesangial expansion, silver methenamine



FVB-FXR-Akita, occasional nodular lesion, PAS

Morphometry – silver methenamine stained slides, area of mesangium including areas of mesangiolysis

COURTESY OF DR. KELLY HUDKINS IN THE ALPERS LAB

	Glomerular Size, um^2	% Mesangial Matrix
DBA2.FXR-/-. Ins2 Akita (n=4)	3781.64 ± 182.26	15.17 ± 1.46
DBA2.FXR-/-. WT (n=3)	2804.32 ± 160.48	8.97 ± 0.53
	ns	p=0.057
FVB Cg.Ins2 Akita.FXR -/- (n=3)	6917.43 ± 478.79	16.52 ± 0.71
FVB Cg.WT. FXR-/- (n=3)	5727.96 ± 972.21	17.25 ± 2.95
	ns	ns

Summary

Ablation of an important gene function such as a transcription factor regulating multiple metabolic pathways, when combined with a diabetic syndrome, makes it difficult to identify what is truly a diabetic complication versus a consequence of the genetic targeting.

In the time frame studied, we cannot confirm that FXR deficiency coupled with diabetes produced by the Akita mutation produces more severe renal lesions on the DBA/2J vs the FVB/NJ background.

FXR nullizygosity elicits pathologic changes in the liver independent of the Akita mutation.

AMDCC

The Jackson Laboratory

In Progress…

Ove26 Projects in Progress
Spot ACR

FVB.Ove26

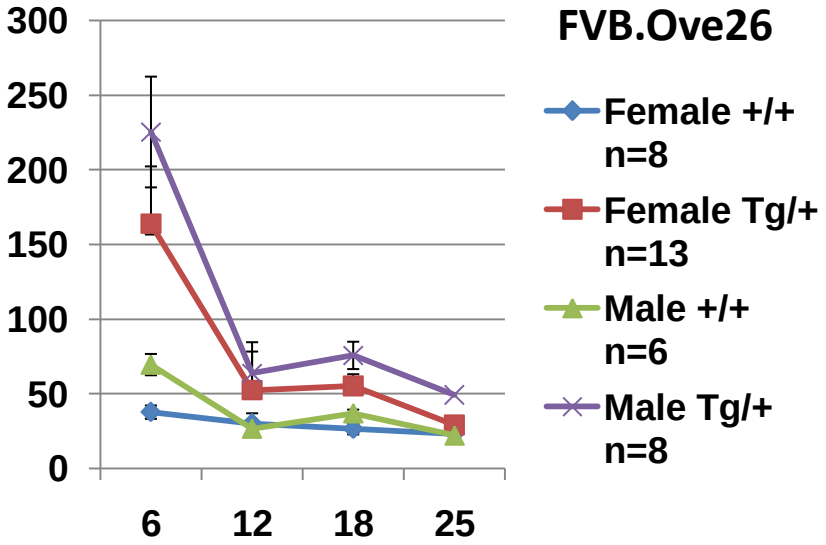
FVB.Ove26 on medicated water

(PWKxFVB)F1.Ove26

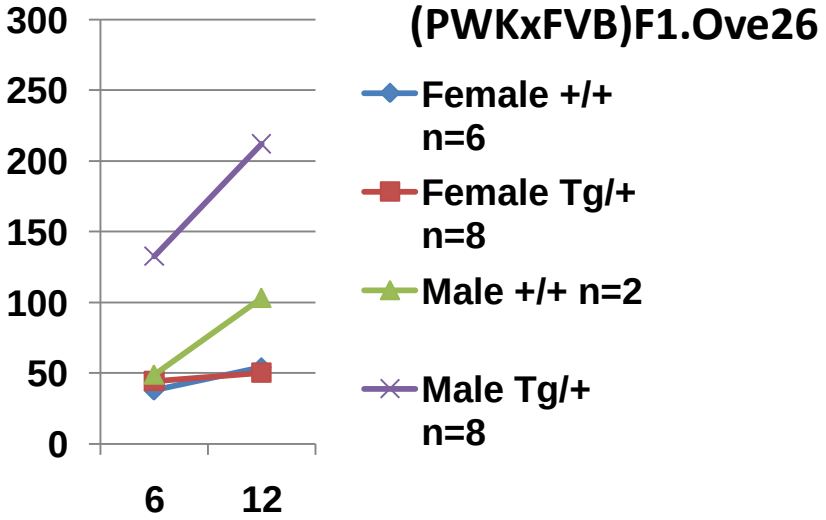
(NONxFVB)F1.Ove26

(ALRxFVB)F1.Ove26

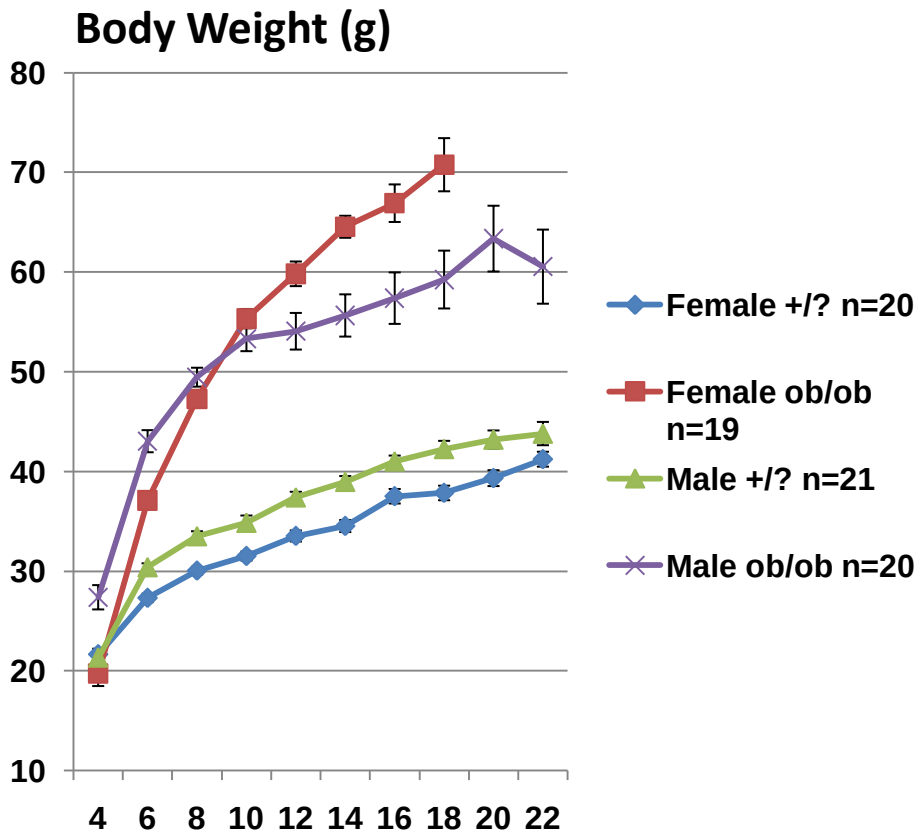
(µg/mg)

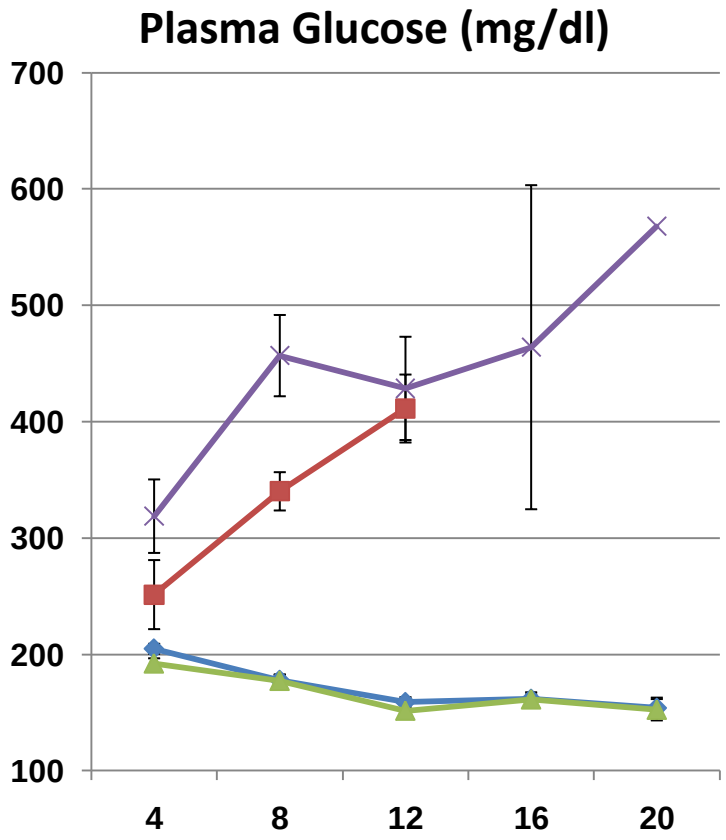


(µg/mg)



BTBR-ob/ob


Body Weight (g)
80
70
60
50
40
30
20
10
4
6
8
10
12
14
16
18
20
22
Female +/? n=20
Female ob/ob n=19
Male +/? n=21
Male ob/ob n=20


Plasma Glucose (mg/dl)
700
600
500
400
300
200
100
4
8
12
16
20

BTBR.ob/ob, Spot ACR at 17 & 21 wks