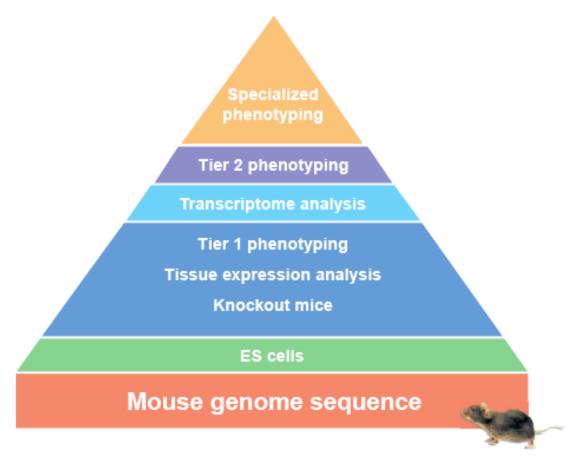


# Knockout Mouse Project (KOMP) and Knockout Mouse Production and Phenotyping (KOMP<sup>2</sup>)

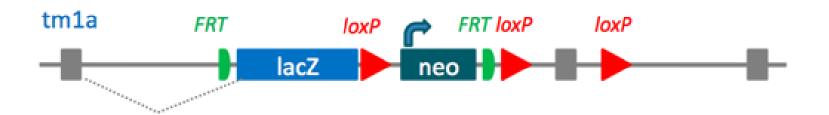
Colin Fletcher, Ph.D.
Common Fund
Apr. 9, 2013

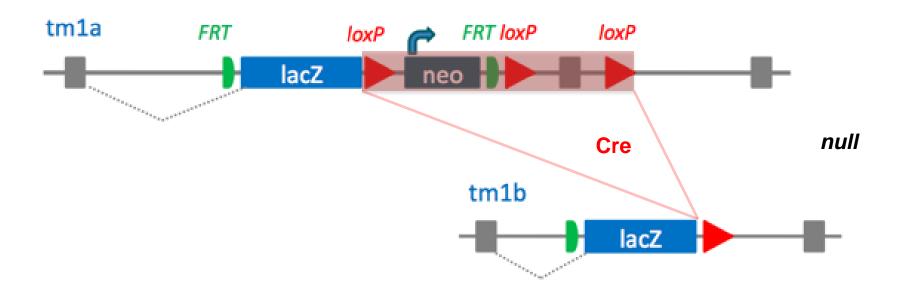


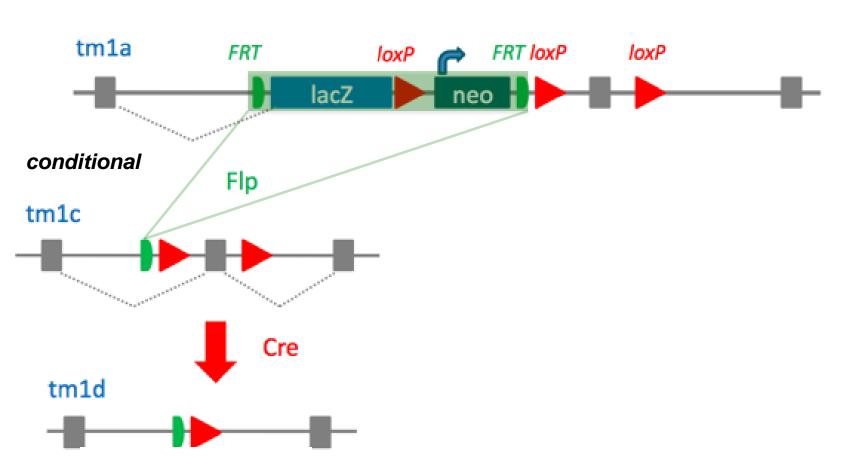
The vision for KOMP was articulated in a meeting at the Banbury Center, Cold Spring Harbor in 2003, calling for high throughput production of gene knockouts, and phenotyping, for every gene in the mouse genome.

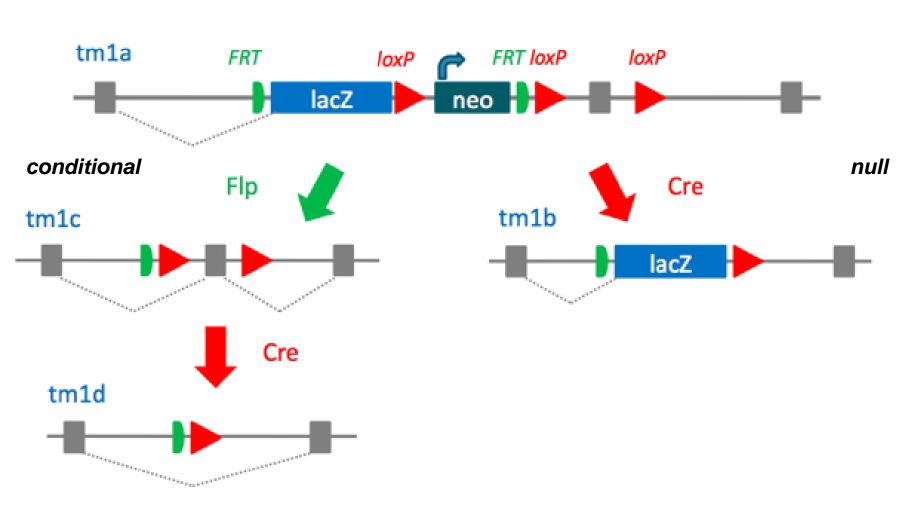
### **KOMP**

- "...a high-throughput international effort to produce...knockouts for all mouse genes, and place these resources into the public domain."
- The KOMP was launched in 2006 by NIH
  - \$56.6 million over 5 years from the ICs
  - a goal of creating 8,500 ES cell lines
  - alleles are nulls or conditional-ready, contain reporter
- The KOMP Research Network
  - Two production centers
  - A repository
  - A Data Coordination Center
  - Three ES cell development projects
- KOMP and EUCOMM along with other international efforts formed the International Knockout Mouse Consortium (IKMC) and have jointly produced > 17,000 mutant ES cell lines and made them available from public repositories.

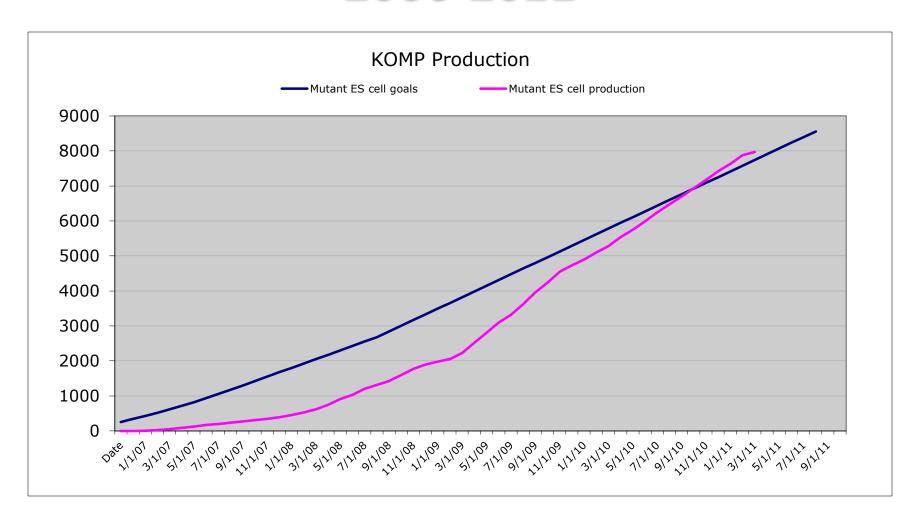








# Goals and Progress 2006-2011



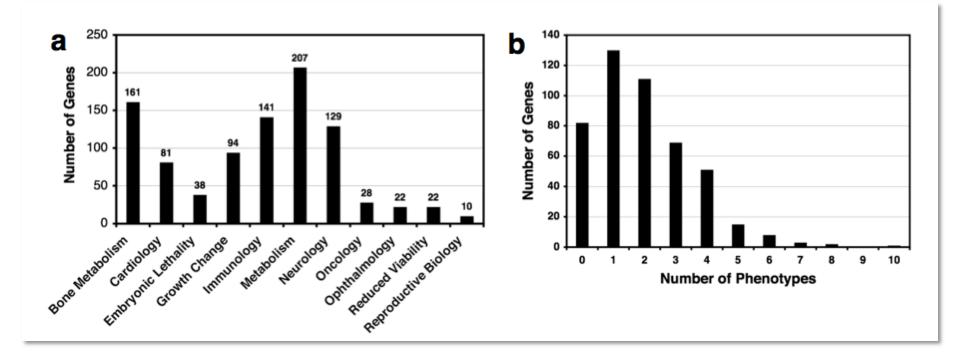
### Rationale for a Large-scale KOMP<sup>2</sup>

# Supporting a broad phenotyping effort would provide the following advantages:

- Eliminate the redundancy and waste inherent in the "cottage industry" approach
- Each mutant mouse will be characterized for a broad set of phenotypes to allow direct comparisons & result in a thorough description of gene function.
- Novel genes will be brought to light that would otherwise be ignored
- Quality standards will be established and maintained, so the data will be of the highest reliability.
- The risk of not finding a phenotype will be greatly reduced.
- Important, but unpublishable, negative results will be captured.
- Potential for breakthrough discoveries

## Genentech/Lexicon Mouse Phenotype Project

472 Mouse knockouts were broadly phenotyped



130 (27%) strains had 1 phenotype 245 (52%) strains had 2-5 phenotypes

Broad phenotyping shows that knockouts have pleiotropic effects

### Funding, Awards, and Coordination

#### Funding:

NIH Common Fund – 50% Participating NIH ICs – 50% \$110M over five years

#### **Common Fund Website:**

http://commonfund.nih.gov/KOMP2/

#### Production and Phenotyping Centers:

UCDavis (with Sick Kids and Charles River) Baylor (with MRC Harwell, Wellcome Trust Sanger)

The Jackson Laboratories

#### Data Coordination Center and Data Base:

European Bioinformatics Institute (with MRC Harwell)

#### Repository:

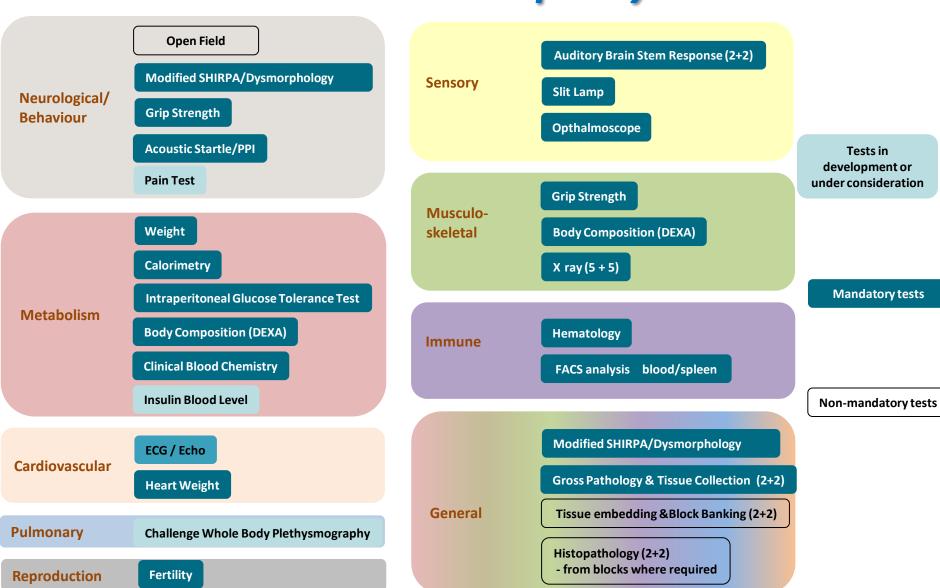
The KOMP Repository, UCDavis

NHGRI
NHLBI
OAR
NICHD
NINDS
NIDCR
NIDCR
NIDA
NIA
NCRR
NCI
NIGMS
NIMH
NIDCO
NIAID
NIA



Coordinating with The International Mouse Phenotyping Consortium

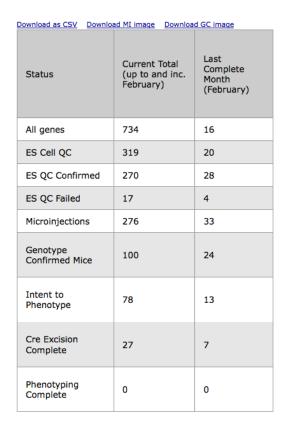
# **KOMP<sup>2</sup> Tests Multiple Systems**

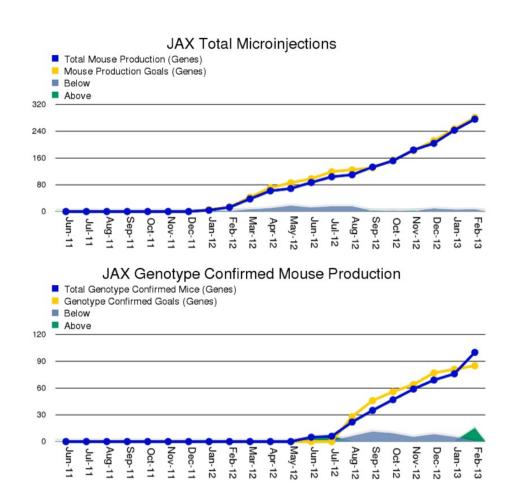


Coordinating with The International Mouse Phenotyping Consortium

### **Progress Tracking by DCC**

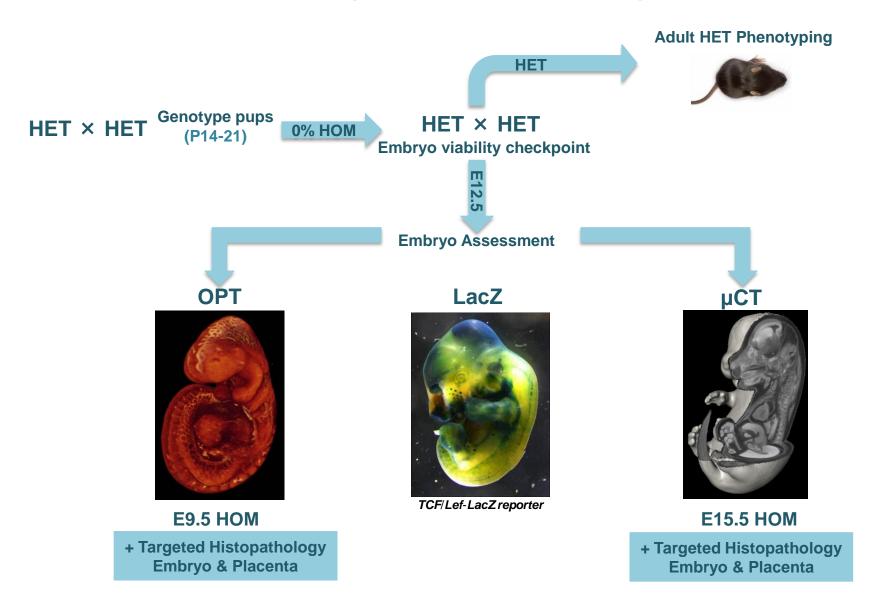
#### **JAX**





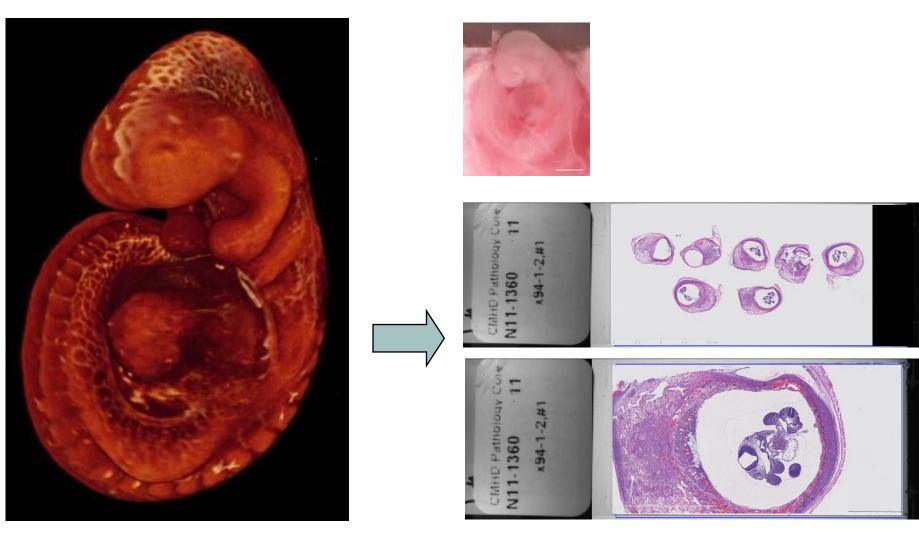
https://lims.mousebiology.org/dashboards/remote

### (New!) Embryonic Lethal Pipeline



### **Imaging Mouse Embryos**

**OPT** and Histopathology



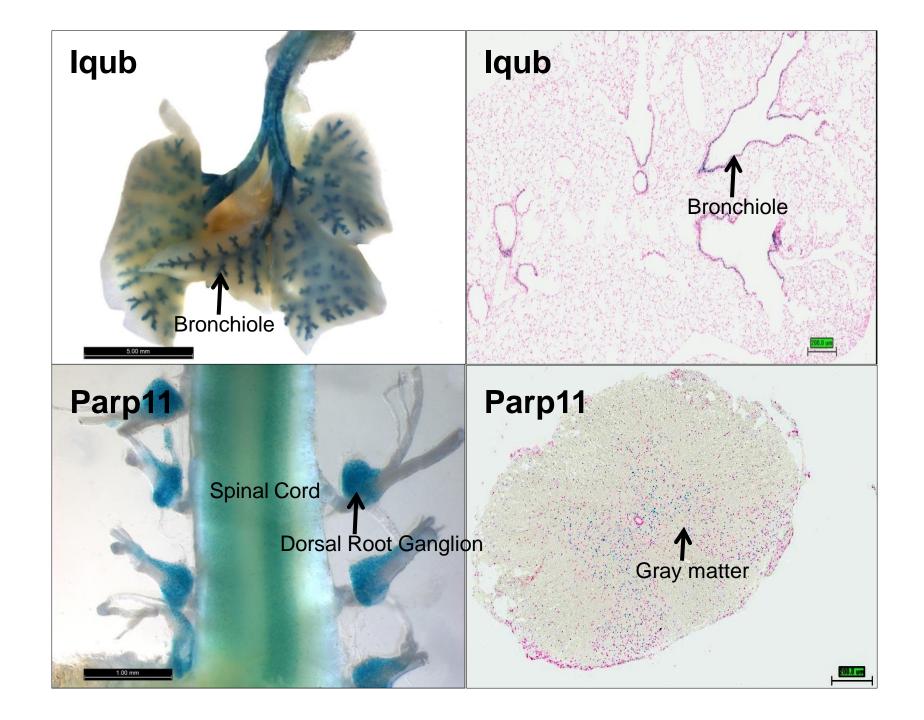
Automated analysis using image registration

Histological analysis of embryo and placenta

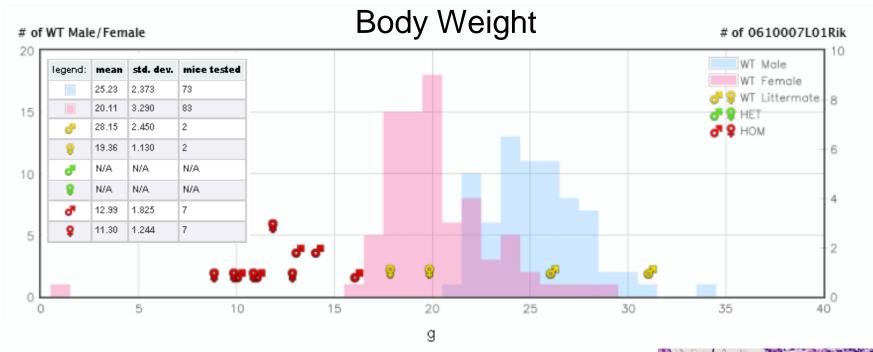
### Representation of Phenotype Data?



0810010K14RJK	0810037P05RJK	1100001G20Rk	1110008303mk	1110008P14RJK	119000ZHZ5RŘ	1500001M20Rk	1700009F17RJK	1700011 <b>r</b> 058k	1700012A03Rik	1700029115Rsk	1700034015Rik	1700108M19Rik	1810026325Rk	1810027010mk	1510049H13Rik
2010011120#sk	2010107G12Rk	2010305A19R/k	2310009815R/k	2510039H05Rik	2410016006/8k	Z410088E13RJk	Z4100761Z1Rik	2610002J02Rk	261001970370k	27000810158k	27000970099k	2810021807RJk	2900092E17Ruk	3110043021Rk	3110062M04Rik
4532428ND5RJK	4833420G17Rik	4855442319Rik	4930511M11Rik	4930524515RJk	4932414ND4RIK	A130010715Rik	AZ30050PZORIK	A830005F24Rik	A930001N09Rik	A930005104Rik	Aedec	Aard	A8124811	Abec10	Abd's
Abog1	Abhd13	APLI	Accord .	Acenii	Acc	Accl	Ady	Acoti	Acal 5	April April	Acvrlo	AdomZBo	Adamta15	Adomts9	AdarbZ
Addk5	Adig	Acbp1	Agex	Ahrr	Ahag	Alax5	Alx1	Alx3	Amx1	Ankrd1	Anp32c	Aox1	Ap4c1	Apof	Aqp4
Arapl	Artigap18	Artigap19	Artigop25	Arl10	ArmEZ	Aleti	eths .	Algab	ЯТр164	Alp2b1	RIptv1b1	AU023871	Asgp1	Azi1	Bgn
Bid1	Spife2	C130073F10Rik	C4bp	CodmZ	Colbz	Caldò	Car2	CaskinZ	Coap4	Casp7	CosqZ	Ccorl	Cede115	Code118	Cade141
Cede183	Cd2Z	Cels	Cort	C6200r3	Cd200r4	C6248	Cds	C670	Cq92	Cális	Cdknlo	Cdkn1c	Cdkn2a	ch ch	Cidn18
Clánz	CnnZ	Cnnm4	Cnot8	Cnr1	Colq	Сарс	Coq9	Corola	Crybbs	Coft .	데	CHR	C47	ClifapZ	culs
Cyb5r1	D130043K2ZRIŘ	D17Vau92c	DBn1	Det	Ddt	Defb1	Dgetzlő	Dgkg	Dgkq	DioZ	DipZa	Dkk1	Onesc1/2	Dnm1	Dram1
Dapp	Dafn	Dusp21	Dump3	Edo	Edar	edila	Efemp1	EMdz	Elf4cbp1	Erf4ebp3	elfs	Enom	Endog	Ephot	Ephx4
EpmZo	Brook	Erf .	Brg	EviS	Falip7	redd	reft .	Fam12Za	Fam123a	Fem176b	Fem52a2	Forp2	Postk	Place41	fbxc44
Fgs	rgiz		rin	Pox11	[ Fprl	ftyl	FronZ	Pus	rads	G8pc2	G8pdI	Gos2 1	Gdapl		Gknz
Glrx5	Gm129	Golge 7	Gpc2	Gpld1	Gpr119	Gpr182	Gpr20	Gpr35	Gpr85	Gpr88	GprcSb	Gpam3	Gpx1	Gridžip	G02a1
GucyZg	нз/зв	Haso	Hort	Head	Heyz	Hkz	Hmg20b	HmqnZ	Hogal	Hrosla	Had11b2	Htro4	1do2	1fi202b	1635
[fnor2	1fng		1827	1gfZbpZ	(gafil	1kbkap	[lists	1118bp	Litro	Infi	1qub	1(ga 9	10h4	Dan 2	Jakmip1
Josfi .	Kona b 3	Kon)3	Kosk15	Keld15	Kif12	10fSc	Nde1	Kifs	kihla	Klk7	Kmo	Kpnol	Krt18	10-01	KrIop17-1
Lama4	Lond2	Laprel 2	Ung	LporS	Lpin.3	Lrrk1		Lum	Lyss	Ly98	LyploZ	Lyplal1	Med1l1	Meob	McolnZ
Med1	Med24	Mcd29	Mogf10	MglZ	Wop2a	Mpdu1	Mars	Minrib	MyotSa	NfrgZ	Ndufez	Nogr1	w) 3	Nfebz	Nikbio
MedeZ	Mnjl	Nmc8	Nobex	Npax1	Мерь	Nptx1	Nug1	Nuck1	Nudits	Nat	Part2	O3fer1	Coslg	Oabpl7	Oxgr1
Panx1	Parp11	Pdk2	Post	Paskin	Pdc1c	Pepd	Pfkfb4	Phc1	Pib:1	Pichz	Plekhos	Pickhg4	Plin4	Plint	Pilp
Pnn	Podni1	Podxl2	PouZf3	PppZca	Pppdr3	Pprel	Pramcl6	Pramcl7	Prox	Prolid1	Prkab1	Prkedbp	PriSa1	PriSoS	Prr15
9117	Pasti	Pacn1 Riok1	Pamd10 Rin3	Pamc1 Ref10	Pipn14 Rof31	Plprt.	Reblifp1	Rob32	Rongop1 Smb1b28	Farres2	Read1 Scylz	Rbm3 Scc15a	Reg2 Sema4e	Reg3o Scot7	Rfc1 Scots
Rgs1Z	Roxibp						Sicle3	51pr4	<u> </u>						
Scrtad2	Sortad4 SloSZaZ	Sgpl1	Shabpal	Sidt.	51k1	5/c18a1		Slc20a1	5/c22a4	5lc25e22	Slc27e2	5/c30e9	5/c53e1	Slc3SeZ	5lc39e5
Sic3e1		Sinte S Sane 1	5/c7e13 5x0r4	5lc5c2 5tL4	Slfn1 Stard5	5(p) 5(b)3	5mpd4 5tbd1	Sno12 Stra	Snrk Sufu	Sex17	5nx27	5003	Spdef Tecr2	Spns2 Tef3	Spp2 The
Thell	Srgap1 Thr1	Thx4	Tonci	Tfcc	5/2 res	Tfei		Tjp1	Tiez	Tmem182	50903 Tmcm219	5ynm Tmcm248	Tecrz	Tmem70	Tmcm90a
Tmcm90b	Tmcm92	Tnfoip8l3	Trifaf11	Tna4	ТрррЗ	Tremi4	Trp53inp2	Talp	Tst	Ties	Tubb1	Truist2	Uhoz	Ubeshibb	UbeZeZ
Ubqini	UosZ	ulk4	Unclip	Unc13b	Usp48	urt.	Uts2r	Vex1	Voen	Vanit	Wdr16	Wfdea	Wattab	Well1	WDp
Yopl	Zesh18	zdhhe7	zibbs	Zfp12	Z/p487	Z/e538	Zfyve18			1281	Murro	MIDEL	HALLES		, wab



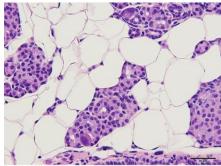
### K312 Phenotype Screen: 0610007L01Rik



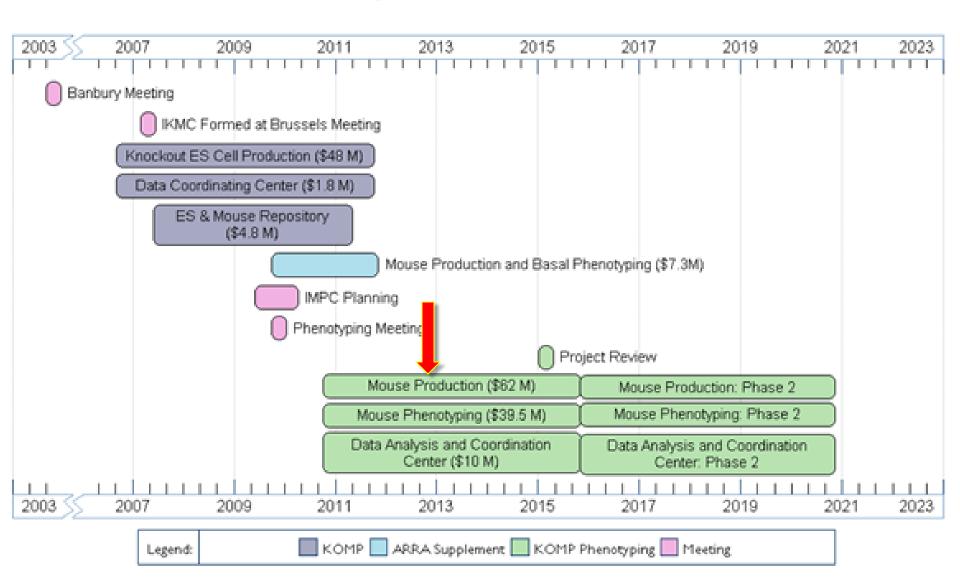
# Clinical Features 0610007LO1Rik:

- Stunted
- Little adipose tissue
- Distended cecum and colon
- Atrophied pancreas

Thymus has a decreased cortical:medullary distinction and medulla is slightly decreased in size. Pancreas is small with marked fatty infiltration. The pancreas consists predominantly of ducts and islets with only few individual acinar cells which are enlarged, some are binucleated, and distended with zymogen granules..



# **KOMP/KOMP<sup>2</sup> Timeline**



# Thank You!