Supplementary Table 1 Tissue targeted animal models evaluating the independent effects of tissue-specific insulin receptor knock-out, or GLUT4 knock-out, or the induction of steatosis or inflammation on metabolic outcomes, including liver steatosis, endogenous glucose production, glucose tolerance and body weight.

Primary defect	Model	Target	Age	Liver size / function	Liver Steatosis	Liver inflammation/fibrosis	EGP	Whole body IR-IS	Food intake	Insulin	Leptin	TG-FFA	F-glucose	Glu-Intolerance	Body weight	Adipos ity	Other	Ref
Peripheral insulin resistance	Mouse	MIRKO	2-11 months				Normal (clamp)	Moderate IR (GU low in muscle,		Normal-high	Normal	High	Normal	Absent or only at 10 months	Normal-low	High		Bruning Mol Cell 1998, Kim J Clin

							high in fat with low oxidation)										Invest 2000, Ealey Am J Physiol 2008
Mouse	FIRKO 50 or 90%	0.5-12 months	FIRKO-90% hepatomegaly, dysplastic	FIRKO-50% absent, FIRKO-90% severe	FIRKO-50% absent, FIRKO-90% low PEPCK, G6P	FIRKO-90% high IS, FIR	FIRKO-50% high	FIRKO-50 % normal	FIRKO-50% low, FIRKO-90%	FIRKO-50 % normal	Low fasting, high	FIRKO-50% normal, FIR	FIRKO-50% better than cont	FIRKO-50% low, FIRKO-90%	Low-absent, small adi	FIRKO-50% live longer. FIRKO-90%	Bluher devcell 2002, Bau

	nodules, high enzymes, ROS, lipid perox, high glycogen	90% severe	ase	KO-90% severe IR (GU low in muscle, fat)	l, high FIR KO-90% high	l, fed FIR KO-90% very low	90% high, reduced by HFD	rols, FIR KO-90% severe	normal-high, reduced by HFD	pocytes (muscle mass transiently reduced at 3 mo)	high RER, glycolysis at 12 months	cher Diabetes 2016, Softic Diabetes 2016

	Mouse	GLUT4-KO-M, GLUT4-KO-M+AT	2-12 months	High glucokinase	Absent (greater lipogenesis, DNL gene expr., VLDL production) in M+AT	High during clamp (high PEPCK, G6Pase) at 5 months	Present IR with ITT and clamp (GU always low in muscle, AT hig	Normal in M, high in M+AT	Normal	Normal tg, ffa (high clearance, low RQ)	High at 5 mo in M, early in M+AT KO	Present with GTT but milder than expected	Normal-low	Normal	No blood proinflammatory profile. Phorizin or AT GLUT4 overexpr. Reverse effects in M	Carvalho AJP 2005, Zisman Nat Med 2000, Kim JCI 2001, Kotani

	h GU in you ng M- KO but IR late r, low in M+ AT)	GLUT 4 KO	JCI 2004

	Mouse	GLUT4-null	Short lived	Normal glycogen, high GLUT2, GU gene-expr., normal fa-ox	Absent (higher lipogenesis, DNL gene expr., tg-export)	Absent	Normal PEPCK, G6Pase in fed	IR present with ITT	Normal-high	Normal-low	Normal-slightly high	Normal	Low	Low	Heterozigous worse than homozigous. Restoration in brain or muscle, brain+muscle,	Lin and Accili J Biol Chem 2011, Ran allet ta Diabetes 2005 and AJP

		brain+ muscle+adipose tissue = steatosis in all, very high insulin, tg-ffa, glucose, low BW (not in	2007, Katz Nature 1995

muscl e). Blood proinf lamm atory profile in muscl e+brai n, mild in muscl e restor ed

Insulin resistance in liver, brain, intestine	Mouse	LIRKO	2-12 months	Small-dark liver, focal dysplasia, low glycogen, low albumin, high blood enzymes	Absent 2-3 mo (more cholesterol), moderate from 6 mo (low lipogenesis, DNL gene	No fibrosis	High (clamp), high PEPCK, low PK	Severe (but normal lipolysis)	Normal (high leptin sensitivity)	Very high (low clearance, high production)	Very high (low free)	Low tg, low-normal ffa	High 2-3 mo, low in old	Severe with GTT (not fed state)	Normal	Normal, High WAT leptin receptor	Resistant to ob/ob and diet induced steatosis. Acute downregulation of insulin receptor norma	Michael Mol Cell 2000, Fisher & Kahn JCI 2003, Buettner JCI 2005,

	expr)	l profile	Coen J Biol Chem 2007, Bidding er Cell Metab 2008, Haas Cell

																	Metab 2012
Mouse	LGSKO (impaired liver glycogen synthesis in inducing insuli	4, 7, 15 months	Lighter liver	Moderate increase from 7 months with normal lipid expo	Normal inflammtory markers in liver	Normal with clamp, abnormal ins. Sign., high fast	Normal with ITT dose-response and with h	Normal food intake	Low	Normal	Normal tg	Low fast and fed	Present with GTT	Normal	Normal-high at 4 and 14 months (high		Irimia J Biol Chem 2010, 2017

	n resistance and liver fat overaccumulation)	rt, high lipogenesis and DNL gene expr, high glucokinase (present in perip heral insuli	PEPCK, G6Pase, GNG (low glycogenolysis)	cla mp, nor mal GU in mu scle, WAT, brai n								fat pads at 4 months)		
Mouse	NIRKO (or ins. Infusions,	(present in peripheral insuli	Normal, but reduced in	Present only in females	Normal int	Tendency in males,	High in both sex	High-low tg rep	Normal in both sexes	Normal in both sexes	Normal in mal es, high	High-normal rep ort	Reduced fertility	Bruning Science 2000,

or WB ins. Receptor deletion or sparing brain)	n infusion; peripheral and central insulin balance each other, by VLDL expo	severe hypoglycemia due to low epinephrine	ake in males, high in females	in	es	ort ed	in females (and HFD males/females)	ed, higher in females	Diggs-Andrews Diabetes 2010, Sherer Diabetes 2016

		rt)									
Mouse	Brain specific GLUT4 KO + chow or HFD	3 months	High during clamp	Normal by ITT, low GIR in clamp due to EGP (normal	Normal fast and fed, normal secretion in GTT	Normal fast and fed	Present with GTT	Normal	KO do not respond differently to HFD. Altered brain glucose sensing glucag	Reno Diabetes 2017

				GU in muscle, fat, heart, low in brain)								on-epinephrine in hypoglycemia		
Mouse	Intestinal-IRKO	1-2 months±3-6 month	Normal liver weight	Intestinal G6Pase expred	Normal with ITT (low	Normal	Normal	Normal-better (low oral gluc	Normal	Normal	Normal intestinal structure & micro	And res Am J Physiol 2014

			s HFD (diet-matched comparison)			uced	GU in intestine)					ose absorption)		biota, low GIP. In HFD, lower EEC, blood cholesterol	, Ussar Diabetes 2017
Hepatic steatosis±inflammation	Mouse	Hepatic DGAT2 or MTTP	1.5-4 months	Hepatomegaly, normal-high liver	3-7 folds increase (high lipog	No (high linolieic acid, DAG,	Normal-high (normal PEP	Normal ITT and clamp	Normal food int	Normal DGAT2, low MTT	Normal	Normal-low	Normal DGAT2, low	Normal	Normal	Normal	Slightly low RQ, in adipose norma	Monetti Cell Metab 2007

	overx press ion	enzym es, low glycog en	enesi s, norm al-high CPT1 gene expr, norm al tg secre tion, fa-ox))	cerami de)	CK, G6P ase)	wid e dos e ran ge	ake P		MT TP	l tg synthe sis, DNL. No proinf lamm atory blood profile . Overe xpr DGAT 2 also in brain- kidne	, Min ehir a J Lip Res 2008 (Raa be JCI 1999), Bjor kegr en J Biol Che m

											y worsens liver steatosis, ER stress, increases G6Pase	2002, Jornayvaz PNAS 2011
Mouse	MTTP overexpr+ LPS or cona	1.5 months	Mild hepatomegaly, normal liver enzym	Moderate 3-folds	Normal, with LPS high macrophage		Low	Low tg, normal ffa	Low	Slightly high (ns)		Bjorkegren J Biol Chem 2002

		or PEA		es (increase with toxins)		inflammatory protein, high lip perox, ox stress											
Microbiota±inflammation	Mouse	Gut microbiota KO (Germ-free)	1.5-4 months	Low liver weight, low glycogen in fast	Low (reduced gene expr. Lipogenic enzy	High transcripts against bacterial compo	High GP6ase in fast	High IS with ITT, high insu	Low	Low	Normal tg, ffa	Low	Better with GTT	Low	Low	11-folds higher caecum weight. Adipo	Rabot FASEB J 2010, Back hea

	mes, slightly higher cholesterol synthesis/ content)	nents, low acute phase response transcripts	lin sign alin g in fat, AM PK in mu scle		se tnfa, IL6, IL1b low in fat, low plasma tnfa, antibacterial ifng, antiinflammatory IL-10 in GF mice	d PNAS 2007, Caesar Gut 2012

Mouse, rat	LPS, effects of microbiota in chow or HFD	3-4 months (few measures at 2 weeks)	Increase in normal weight, increase in GU (liver, spleen =macrophage-rich organs)	Increase (but ns, higher in HFD)	Very high markers at 2 wks (modestly increased later in fat, muscle)	High during clamp (opposite to HFD)	Normal (opposite to HFD), 68% increase in fasting GU	Normal food intake	High fast	Mild elevation	Very mild only at 15 min of GTT	High	High	CD14 mutant mice resisted most LPS and HFD effects. In GF mice inoculated with producing and	Mesarros J Biol Chem 1987, Cani Diabetes 2007, Caesar Gut 2012

non-LPS escherichia coli strains showed only fat inflammation and non other metabolic or liver abnor

														mality vs GF	
Inflammation-targeting	Mouse, rat	NSAID (cox-inhib, aspirin, indomethacin, IL1Ra) effect	1-6 months intervention in 2-5 months old	Reduction of liver weight, blood liver enzymes (aspirin, celecoxib)	Reduction (aspirin, celecoxib, indomethacin), selective reduction	Reduced by all drugs, fibrosis and HSC PG production (celecoxib), high	Reduced PEPCK (IL1Ra) or not reported	Improved HOMA and/or ITT	Normal or not reported food intake	Reduced hyperinsulinemia (celecoxib, IL1Ra)	Reduced hyperglycemia (celecoxib, IL1Ra)	Reduced hyperglycemia (celecoxib)	Reduced in diabetic (celecoxib)	Normal or not reported	Celecoxib had effect in diabetic model but not in treated control	Madrigal-Perez Int J Clin Exp Med 2015, Paik Gut

	in high-risk models	of macrovescicular (mefenamate), high DGAT1, FASN (indomethacin)	CPT1, PXR, low ABCD3, ACOT3 (indomethacin)	ls. Fish oil added to indomethacin superior effects	2009, Tian Plos One 2014, Murali J Lip Res 2012, Ehses PNAS 2009