

Supplementary Materials

Supplementary Table S1. Fibrosis fraction for each animal in %.

ID	Group	Fibrosis fraction [%]
5	Control	1.718
10	Control	1.203
31	Control	1.358
32	Control	1.097
45	Control	1.322
56	Control	1.644
2	NASH	10.413
9	NASH	7.925
11	NASH	6.219
20	NASH	5.700
41	NASH	6.162
65	NASH	8.480

Table S2. Normalized enrichment scores for the Reactome pathways in common between preclinical models and HNASH2 dataset. See fig. 4F for a graphical overview of guinea pig and HNASH2 pathways. NES: normalized enrichment score. HNASH2: GSE49541, DIAMOND: GSE67680, WD1: GSE52748, WD2: GSE38141.

Pathway	HNASH2 NES	DIAMOND NES	WD1 NES	WD2 NES	Guinea pig
COMPLEX 1 BIOGENESIS	-1.9	-1.9			-2.3
RESPIRATORY ELECTRON TRANSPORT	-1.9	-1.9			-2.6
RESPIRATORY ELECTRON TRANSPORT ATP SYNTHESIS BY CHEMIOSMOTIC COUPLING AND HEAT PRODUCTION BY UNCOULING PROTEINS	-1.9	-1.8			-2.5
THE CITRIC ACID TCA CYCLE AND RESPIRATORY ELECTRON TRANSPORT	-1.9	-1.7			-2.4
CHEMOKINE RECEPTORS BIND CHEMOKINES	1.8	1.9			
GLYOXYLATE METABOLISM AND GLYCINE DEGRADATION	-1.9	-1.9			-2.1
MITOCHONDRIAL TRANSLATION	-2.0	-1.6			-2.4
METABOLISM OF AMINO ACIDS AND DERIVATIVES	-2.1	-1.8	-2.2		
BIOLOGICAL OXIDATIONS	-1.9		-1.7		
MITOCHONDRIAL FATTY ACID BETA OXIDATION	-1.8		1.9		
FATTY ACID METABOLISM					-2.0
CHOLESTEROL BIOSYNTHESIS	-1.8	-2.3	-2.5	-2.6	-2.6
PEROXISOMAL LIPID METABOLISM					-2.5
PEROXISOMAL PROTEIN IMPORT					-2.6
ECM PROTEOGLYCANS	2.1	1.8	2.2	1.9	
ASSEMBLY OF COLLAGEN FIBRILS AND OTHER MULTIMERIC STRUCTURES	1.9	1.7	2.0		
COLLAGEN FORMATION	1.8	1.7	2.0		
CLASS A 1 RHODOPSIN LIKE RECEPTORS	1.7		1.5		
COLLAGEN CHAIN TRIMERIZATION	1.9		1.9		
COLLAGEN DEGRADATION	1.9		1.9		
COLLAGEN BIOSYNTHESIS AND MODIFYING ENZYMES	1.8		2.0		
ELASTIC FIBRE FORMATION	1.8		1.9	1.9	
INTEGRIN CELL SURFACE INTERACTIONS	2.9		2.1		
SIGNALING BY PDGF	1.8		1.9		
DEGRADATION OF THE EXTRACELLULAR MATRIX	2.0		1.9		
EXTRACELLULAR MATRIX ORGANIZATION	2.0		2.1	1.9	
NON-INTEGRIN MEMBRANE ECM INTERACTIONS	1.9		2.0		
MOLECULES ASSOCIATED WITH ELASTIC FIBRES	1.7		1.9	1.9	
O GLYCOSYLATION OF TSR CONTAINING MOLECULES	1.8		1.8		
MET ACTIVATES PTK2 SIGNALING	1.8		1.9		
NCAM SIGNALING FOR NEURITE OUT GROWTH					1.7
PHASE I FUNCTIONALIZATION OF COMPOUNDS					-2.1
PROTEIN LOCALIZATION					-2.5

Supplementary Table S3. Hallmark gene set in guinea pig, including leading edge genes. Genes included in the manuscript are highlighted (in yellow). Pval: p-value, Padj: p-adjusted, ES: enrichment score, NES: normalized enrichment score.

Pathway	Pval	Padj	ES	NES	Leading Edge
TNFA SIGNALING VIA NFKB	0.00010 3	0.00086 2	0.66316 2	1.92328	CCL2, SERPINE1, CCL20, ABCA1, CCN1, EGR2, EGR3, TNFAIP6, PFKFB3, CCL4, TNFAIP2, NR4A3, MYC, CD83, SLC2A6, GPR183, DUSP4, GPTP2, CLCF1, RELB, L1B, GADD45A, KLF6, JAG1, SLC16A6, NR4A1, F2RL1, IL7R, EGR1, PHD2A, TLR2, NFKBIE, SPSB1, CDKN1A, LIF, PLAU, TNF, FOSL1, CD44, IFNGR2, NFKB2, DRAM1, OLR1, ATF3, ACKR3, SQSTM1, PHD1A1, TRAF1, RCAN1, DUSP2, F3, FOSL2, PLEK, TNFAIP3, SOD2, BIRC3, CCND1, RNF19B, EDN1, TRIP1, BCL3, ZC3H12A, PLAUR, GEM, TIPARP, SMAD3, BTG3, PTGER4, ETS2, BTG1
HYPOXIA	0.01457 9	0.02803 7	0.47502 8	1.38449 4	SERPINE1, CCNS, CCN1, PFKFB3, DTNA, TGFB3, S100A4, PPFA4, COL5A1, SLC6A6, PDGFB, CSR2, STC2, TMEM45A, AMPD3, STC1, KLF6, PLIN2, CXCR4, HK2, CHST3, PGM2, CDKN1A, TPBG, SDC3, TES, ATF3, ACKR3, NAGK, SRPX, PFKP, GPC1, F3, PGF, FOSL2, CAVIN3, PIM1, TNFAIP3, CAVIN1, PDK3, PLAUR, ALDOA, MYH9, TIPARP, KIF5A, HS3ST1, CASP6, STBD1, BTG1, WSB1, HMOX1, NDRG1, CCN2, MAP3K1, LNX, ENO3
CHOLESTEROL HOMEOSTASIS	0.55988 4	0.65102 7	0.35227 7	0.95799 9	FABP5, LGALS3, LPL, TNFRSF12A, FADS2, ANXA5, CD9, FASN, S100A11, JAG1, CHKA, ATF3, GPX8, CLU, DPK3, PLAUR
MITOTIC SPINDLE	0.00010 2	0.00086 2	0.63451 6	1.85235 2	ECT2, KIF2C, DLGAP5, CCNB2, ANLN, BUB1, KIF15, KIF4A, NDC80, TOP2A, CENPE, FBXO5, RACGAP1, PRC1, KIF11, NEK2, TPX2, KIF22, SASS6, CD2AP, SYNPO, CENPF, RHOF, ESP1, LLGL1, CDC42EP1, GSN, PI1, KIF20B, BIRC5, DOCK2, SPTAN1, ABR, EZR, BCR, ARHGEF2, NEDD9, INCENP, ARHGEF27, FSCN1, EPB41L2, FLNA, MYO9B, PREX1, NF1, PLEKHG2, MYH9, NIN, MID1P1, LMNB1, KIF3C, ARHGEF3, PCNT, VCL, RICTOR, MYO1E, DYNC1H1, PKD2, ALMS1, EPB41, CDC42BPA, BCAR1, HOOK3, ARL8A, KNTC1, ARF6, SORBS2, OPHN1, ARHGEF10, ARHGDIA, KIF5B
WNT BETA CATENIN SIGNALING	0.48646 9	0.59923 6	0.41228 8	0.99873 1	MYC, JAG1, CSNK1E, WNT5B, PPARD, TP53, HEY1, ADAM17, NKD1, RBPJ
TGF BETA SIGNALING	0.15787 5	0.24612 5	0.48534 2	1.25636	LTBP2, THBS1, SERPINE1, SKIL, IFNGR2, TGFB1, WWTR1, HDAC1, SMAD3, PMEPA1, XIAP, HIPK2, SLC20A1, CDH1
IL6 JAK STAT3 SIGNALING	0.00336 8	0.01052 4	0.59121 3	1.60356 2	CCL7, TNFRSF12A, ACVR1B, ITGA8, TNFRSF21, CD9, TLR2, TNF, CD44, CCR1, ITGB3, IFNGR2, TNFRSF1B, CSF3R, TGFBI, PIM1, BAK1, CNTFR, IL12RB1, ACVR1L, OSMR, HMOX1, MAP3K8, IL10RB, IL17RA, CD36, TNFRSF1A, STAT1, PTPN1, IFNGR1, PTPN11, IL13RA1, IL2RG, IL4R, FAS, IL1B, IL6ST
DNA REPAIR	0.97724 4	0.97724 4	0.22230 8	0.64085 2	RAD51, TYMS, CDA, TAF1C, HCLS1, BCAM, ZWINT, POLD1, REV3L, POLA2, ADA, RFC4, VPS37B, RALA, NRP2, AGO4, CMPK2, VPS37D, SMAD5, TP53, POLA1, RFC5
G2M CHECKPOINT	0.00010 3	0.00086 2	0.72342 3	2.11143 4	KIF2C, CCNB2, CDC45, CDC20, BUB1, KIF15, KIF4A, NDC80, EXO1, TOP2A, CDC6, TROAP, CCNA2, URBK, POLE, CENPE, CENPA, FBXO5, UCK2, RACGAP1, RAD54L, PRC1, KNL1, KIF11, PTTG1, SLC38A1, HMMR, PBK, NEK2, HMG83, MCM2, MVC, TACC3, TPX2, MYBL2, KIF22, MCM3, TRAIP, BARD1, STMN1, CKS2, CHAF1A, CENPF, ESL1, SLC7A5, E2F2, CDKN2, CDKN2C, KIF20B, BIRC5, SLC7A1, SMC2, TGFBI, MCM6, NSD2, INCENP, CCND1, CDC25A, CDCT, CHEK1, PRIM2, BCL3, ODC1
APOPTOSIS	0.01000 7	0.02084 9	0.49626 2	1.42828 8	LGALS3, TOP2A, TNFRSF12A, EMP1, ANXA1, EGR3, IGFBP6, TIMP1, MMP2, IL18, GADD45A, PAK1, PDGFRB, CDKN1A, PLCB2, GSN, TNF, CD44, TIMP2, HMGB2, ATF3, SQSTM1, SPTAN1, CASP4, GPX3, KRT18, PMAPI1, LUM, NEDD9, CLU, SOD2, BIRC3, CCND1, ERBB2, BCL2L1, TGFBI2, IGF2R, BTG3, CASP6, WEE1, HMOX1, ANKH, CASP2, CDC25B, CASP8, CFLAR
NOTCH SIGNALING	0.25779 5	0.36827 8	0.49235 2	1.18466 3	JAG1, DTX4, MAML2, ARRBI, FZD7, HEYL, NOTCH3, CCND1, PRKCA, PPARD, FBXW11, NOTCH2, WNT5A, KAT2A
ADIPOGENESIS	0.00434 8	0.01087	-0.32836	-1.41819	CIDEA, DHCR7, GPAM, PHYH, MARC2, ITGA7, FAH, ARL4A, ACOX1, PIM3, TOB1, ATL2, SOD1, CAT, TST, DDT, QDPR, FZD4, ECHS1, DECRI, CMLB, DHR57, ALDH2, REEP6, HADH, CYP4B1, LIPE, ETFB, ACADS, MGLL, SLC25A1, ACADM, SORBS1, PRDX3, PPP1R15B, RIOK3, DBT, POR, NDUFAS, SDHC, CAVIN2, DNAJB9, UQCRC11, IDH1, CRAT, ACAA2, CHCHD10, AIFM1, COX6A1, ANGPTL4, GRPELI, ATP5PC1, PGM1, NDUFB7, NKR1A1, MGST3, NDUF53, COX7B, HIBCH, DHR57B, GPX4, GPAT4, AK2, UQCRC10, DRAM2, SUCLG1, COQ5, MCC1, STOM, NDUFAB1, COX8A, PFKL, GBE1, MDH2, ADIPOR2, SLC19A1, UQCRC1, ESRA, COQ3, UBQLN1
ESTROGEN RESPONSE EARLY	0.06602 8	0.11004 7	0.43794 8	1.27431 4	CLDN7, SLC1A4, CCNS, MREG, THSD4, MYOF, GAB2, EGR3, INHBB, OLFML3, HR, GIA1, MYC, IGF1R, ANXA9, STC2, NPY1R, ZNF185, FASN, SFN, SLC7A5, FHL2, TPBG, SLC26A2, KRT19, CD44, ALDH3B1, NAV2, LAD1, SYT12, KRT8, KRT18, CISH, P2RY2, PMAPI1, ELF3, TGFIF2, CCND1, ABUM1, FCMR1, WWC1, MLPH, TIPARP, CBAF23
ESTROGEN RESPONSE LATE	0.04714 3	0.08600 3	0.44844 2	1.30248	KIF20A, CDC20, FABP5, TOP2A, CDC6, SLC1A4, CCNS, MYOF, EGR3, ST14, LAMC2, CPE, MDK, CA2, HR,AGR2, SLC2A8, MAPK13, ANXA9, CD9, TFP12, NPY1R, ATP2B4, S100A9, SFN, SLC7A5, TPBG, SLC26A2, KRT19, CD44, ALDH3B1, DLG5, NAB2, CISH, GIB3, DUSP2, RNASEH2A, LTF, CCND1, CKB
ANDROGEN RESPONSE	0.7539 1	0.80202 7	0.30409 6	0.84426 1	ABC4, SLC6A8, COL1A1, COL6A3, DTNA, BDKRB2, PPFIA4, COL4A2, COL6A2, APOD, STC2, AEBP1, ITGB4, COL3A1, KLF5, MAPK12, CDKN1A, PTG1, GSN, TNNI2, ATP2A1, SPARC, LAMA2, NAV2, SPTAN1, GPX3, TGFB1, PFKM, FABP3, SOD3, CLU, SORBS3, WWTR1, IGFBP7, CFD, ABLIM1, AGRN, CKB, CACNA1H, SSPN, EFS, MYH9, FST, RYR1, ITGB5, EPHB3, TNNT1
MYOGENESIS	0.00208 5	0.00744 6	0.52880 6	1.52195 3	ACHE, SLC6A8, COL1A1, COL6A3, DTNA, BDKRB2, PPFIA4, COL4A2, COL6A2, APOD, STC2, AEBP1, ITGB4, COL3A1, KLF5, MAPK12, CDKN1A, PTG1, GSN, TNNI2, ATP2A1, SPARC, LAMA2, NAV2, SPTAN1, GPX3, TGFB1, PFKM, FABP3, SOD3, CLU, SORBS3, WWTR1, IGFBP7, CFD, ABLIM1, AGRN, CKB, CACNA1H, SSPN, EFS, MYH9, FST, RYR1, ITGB5, EPHB3, TNNT1
PROTEIN SECRETION	0.87343 5	0.89972 7	0.26870 8	0.75276	ABCA1, SCRN1, TSPAN8, CD63, KRT18, ICA1, SSPN, IGF2R, ADAM10, CLCN3, VAMP3, GLA, ARFGEF2, SEC24D, RAB22A, YKT6, RPS6KA3, KIF1B, ARFGEF1, STX7, DOP1A, GALC, SNAP23, STAM, COG2
INTERFERON ALPHA RESPONSE	0.58259 4	0.66203 7	0.34379 5	0.94584	LY6E, MX1, SAMD9, IFI30, RSAD2, ISG15, SAMD9L, IRF7, DDX60, LGALS3BP, SELL, CASP8, PARP14, OASL, CD74, ISG20, CMPK2, ELF1, UBE2L6, IL4R, CD47, PARP12, CASP1, DHX58, BATF2
INTERFERON GAMMA RESPONSE	0.00857 8	0.01864 8	0.49253 4	1.42843 2	CCL7, MTHFD2, CCL2, TNFAIP6, TNFAIP2, UPP1, OAS2, CDKN1A, LY6E, CD86, MX1, IFI30, SAMHD1, CD274, CMKL1, FGL2, CAPSP, SLAMF7, BPGM, STAT4, PFKP, LYSM2D, RSAD2, ST8SIA4, PIN1, TNFAIP3, SOD2, IL10RA, ISG15, SAMD9L, SELP, CIITA, SSPN, IDO1, IRF7, DDX60, LGALS3BP, VAMP8, BTG1, OAS3, LCP2, CASP8, ITGB7, PARP14, OASL, IRF4, CD74,

					ISG20 , CMPK2 , STAT1 , PML , NOD1 , PTPN1 , ZNF1X , ST3GAL5 , RIPK1 , NUP93 , UBE2L6 , PSMB10 , I4R , FAS , IL18BP , NFKB1 , PTPN6 , VAMP5 , CSF2RB , HIF1A , PARP12 , CD40 , CASP1 , RAPGEF6 , JAK2 , DHX58 , ZBP1 , BATF2 , PLA2G4A , NFKBIA , ARIOS5		
APICAL JUNCTION	0.00124	0.00518	0.53452	1.54450	CLDN7 , COL16A1 , CLDN4 , LAMC2 , MDN , THBS3 , MAPK13 , CD276 , ITGA3 , ZYX , MMP2 , ITGB4 , FLNC , RHOF , SDC3 , SYK , ADRA1B , CNN2 , NRTN , CD86 , CX3CL1 , VWF , NECTIN2 , SRC , YWHAH , CD274 , CD34 , VASP , TRAF1 , RRAS , TMEM88 , SORBS3 , FSCN1 , EPB41L2 , LAYN , NF1 , ACTB , MYH2 , EVL , BAIAP2 , ADAM9 , ARHGEF6 , PTPRC , FYB1 , CTNNA1 , VCL , MAPK11 , GNAI2 , MSN , ACTN1 , SLIT2 , NECTIN1		
APICAL SURFACE	0.48427	0.59923	0.40736	1.00123	ATP6V0A4 , PKHD1 , SULF2 , SLC2A4 , CX3CL1 , AFAP1L2 , SRPX , DCBLD2 , TMEM8B , PLAUR		
	5	6	9	1	6	8	9
HEDGEHOG SIGNALING	0.04816	0.08600	0.62263	1.45786	ACHE , NRP2 , CDK6 , ADGRG1 , CNTFR , NF1 , MYH9 , DPYSL2 , ETS2 , OPHN1 , PML , HEY1		
	2	3	8	8			
COMPLEMENT	0.00361	0.01061	0.50472	1.46650	MMP12 , LGALS3 , SERPINE1 , CPM , PRSS36 , CA2 , COL4A2 , PDGFB , ME1 , FCN1 , ANXA5 , TIMP1 , TFP12 , DOCK9 , \$100A9 , MT3 , ITGAM , CDA , CTSH , TIMP2 , SRC , PIK3CG , LIPA , CTSD , PRKCD , OLR1 , CASP4 , CASP5 , ZFPM2 , PLA2G7 , F3 , CTSP , CLU , PLEK , PIM1 , LTF , TNFAIP3 , FCFER1G , CTSS , GDP2 , CTSV , WAS , PLAUR , MMP15 , CSRP1 , IRF7 , DOCK10 , ADAM9 , GCA , GN48 , KIF2A , CBLB , PRCP , GNAI2 , LCP2		
	8	5	6				
UNFOLDED PROTEIN RESPONSE	0.05210	0.08984	0.47406	1.33682	MTHFD2 , DNAJA4 , CHAC1 , CCL2 , SLC1A4 , STC2 , SLC7A5		
	8	1	2	3			
PI3K AKT MTOR SIGNALING	0.24373	0.35842	0.41487	1.15104	RPS6KA1 , CXCR4 , SFN , MAP2K6 , CDKN1A , VAV3 , PRKCB , SLA , SQSTM1 , AKT1 , THEM4 , ACTR3 , RALB , TNFRSF1A , NOD1 , ARHGDIA , PTPN11 , RIPK1 , SMAD2 , IL2RG , DAPP1 , RPS6KA3 , NCX1		
	6	5	3				
MTORC1 SIGNALING	0.49137	0.59923	0.34309	1.00485	MTHFD2 , RRM2 , BUB1 , FADS2 , SLC1A4 , MCM2 , SLC6A6 , ME1 , CD9 , NUPR1 , FADS1 , SLC1A5 , STC1 , CXCR4 , G6PD , HK2 , SLC7A5 , CDKN1A , EGLN3 , TES , SLA , IFI30 , SERPINH1 , FGL2 , SQSTM1		
	3	6	3	7			
E2F TARGETS	0.00010	0.00086	0.71619	2.09316	MTHFD2 , KIF2C , DLGAP5 , CDCA3 , CCNB2 , UBE2T , RRM2 , CDC20 , TRIP13 , KIF4A , DEPDCC1 , CDCAB8 , TOP2A , AURKB , POLE , CENPE , MELK , RACGAP1 , TK1 , PTTG1 , DCK , GINS4 , CCNE1 , HMMR , HMGB3 , MCM2 , MYC , WDR90 , TACC3 , MYBL2 , KIF22 , SPC25 , CTPS1 , SPAG5 , MCM3 , GINS3 , BARD1 , STMN1 , CKS2 , MXD3 , ESLP1 , CDKN3 , TCF19 , CDKN1A , E2F8 , CDKN2C , TUBB , RAD51AP1 , HMGB2 , BIRC5		
	2	2	1	7			
MYC TARGETS V1	0.53145	0.63268	0.33876	0.98821	CDC45 , CDC20 , CCA1 , MCM2 , MYC , TYMS , CTPS1		
	2	1	2	7			
MYC TARGETS V2	0.88173	0.89972	0.26999	0.71172	MYC , HK2 , DUSP2 , RRP9 , MCM5 , PPRC1 , MCM4 , MYBBP1A , TCOF1 , RRP12 , PLK1 , LAS1L , CBX3 , UTP20 , NOP56 , BYSL , PRMT3 , WDR43 , SRM , DDX18 , GNL3 , CDK4 , MRT04 , TBRG4		
	3	7	5	5			
EPITHELIAL MESENCHYMAL TRANSITION	0.00010	0.00086	0.67044	1.94383	SPOCK1 , SLC6A8 , COL16A1 , RGS4 , COL1A1 , THBS1 , TNFRSF12A , SERPINE1 , PMP22 , FMOD , CCN1 , LGALS1 , COL6A3 , LAMC2 , MGP , CXCL8 , LOXL1 , THBS2 , GJA1 , DPYSL3 , COL1A2 , COL8A2 , CAPG , COL4A1 , COL5A1 , COL4A2 , COL6A2 , SLT3 , FSTL3 , TIMP1 , QSOX1 , TFP12 , COL12A1 , MMP2 , COL3A1 , GADD45A , SPP1 , NID2 , FBLN2 , PDLM4 , TPM1 , FBLN5 , PDGFRB , GLIPR1 , COL5A2 , CD44 , EMP3 , SPARC , LAMA2 , ITGB3 , ABIBP1 , VIM , SERPINH1 , LOXL2 , EFEMP2 , TGFBI , GPC1 , PLD2 , LUM , LAMC1 , ACT2A , TNFAIP3 , APLP1 , ITGAV , FNLA , PLAUR , SGCB , GEM , SERPINE2 , ITGB5 , COMP		
	3	2		2			
INFLAMMATORY RESPONSE	0.00010	0.00086	0.60926	1.76545	CC17 , CCL2 , HAS2 , ITGB8 , RG51 , SERPINE1 , CCL20 , ABCA1 , TNFAIP6 , CCL22 , RGS16 , CXCL8 , ACVR1B , MYC , KCNA1 , CLECSA , TIMP1 , GPR183 , SLC28A2 , CSAR1 , IL18 , KLF6 , IL7R , TLR2 , CDKN1A , TPBG , LY6E , LIF , CYBB , CX3CL1 , SGMS2 , EMP3 , FFAR2 , ITGB3 , IFNGR2 , CMKLRL1 , ORL1 , SLC7A1 , NLRP3 , LPAR1 , TNFRSF1B , P2RY2 , CSF3R , P2RX7 , DCBLD2 , F3 , MSR1 , NOD2 , IL10RA , EDN1		
	3	2	9	3			
XENOBIOTIC METABOLISM	0.00420	0.01087	-0.53052	-2.287	CYP1A2 , PTGDS , SERPINA6 , CYP26A1 , G6PC , CYP2E1 , BCAT1 , CRP , ADH1C , TTPA , RBP4 , GCH1 , FM03 , FAH , CROT , KYNU , DCXR , ITH1 , ACOX1 , CYP1A1 , FETUB , CAT , ARG1 , TD02 , TAT , FM01 , ATOH8 , DDT , IGHF1 , ITH4 , MAOA , DDC , MBL2 , GNMT , ALA51 , MPP2 , PGRCMC1 , DHR57 , ALDH2 , IGFBP4 , ALDH9A1 , AOX1 , UPB1 , CYB5A , CSAD , ENTPD5 , TPST1 , ENPEP , HRG , LPIN2 , LCAT , BPHL , HACL1 , HSDB1B1 , CDO1 , ACOX2 , F10 , IL1R1 , AHCV , IGFBP1 , F11 , POR , NFS1 , ASL , GSTO1 , TMBIM6 , NQO1 , BLVRB , VTN , IDH1 , AKR1C3 , ACPP2 , RAP1GAP , SHMT2 , LEAP2 , SAR1B , PLG , GSTM4 , MTHFD1 , HGFC4 , ABHD6		
	2						
FATTY ACID METABOLISM	0.00269	0.00898	-0.51307	-2.12865	DHCR24 , IDE , HSD1B7 , CPOX , NSDHL , ADHC1 , ALDH1A1 , GDP1 , ID1 , HSD17B4 , ACOX1 , CYP1A1 , CRY2 , EC1 , TDO2 , HMGCS1 , FM01 , MAOA , GST1 , ECHS1 , CPT1A , HSD17B11 , DECR1 , REEP6 , ALDH9A1 , ACSL1 , EC1 , HMGC22 , HADH , ACOT2 , ACAA1 , ALDH3A2 , ACADS , MGLL , BCKDHB , HPGD , ACADM , BPHL , CYP4A22 , CYP4A11 , AOC3 , SUCLG2 , HMGLC , BLVRA , NTHL1 , AUH ,AADAT , ACAT2 , GRHPR , PCBD1 , SDHC , FH , SDHD , MCEE , IDH1 , GCDH , METAP1 , CRAT , ACAA2 , RDH11 , ALAD , OSTC , HIBCH , MLYCD , ETFDH , PDHB , SUCLA2 , PSME1 , SUCLG1 , D2HGDH , SLC22A5 , MDH1		
	5	5					
OXIDATIVE PHOSPHORYLATION	0.00510	0.01214	-0.59473	-2.56985	PHY , TIMM10 , ATP5MC2 , ECHS1 , SLC25A11 , CPT1A , ALA51 , DECR1 , ALDH6A1 , EC1 , CYB5A , ACAA1 , IDH2 , ETFB , ACADM , OAT , PRDX3 , FDX1 , GLUD1 , ETFA , SLC25A4 , NDUF2 , MAOB , POR , NDUF1 , NDUFA5 , SDHC , ACAT1 , SLC25A20 , FH , SDHD , UQCRC1 , IDH1 , COX411 , NDUFA2 , NDUFA3 , ISCU , ATP5MG , COX5A , ATP1B1 , ATP5PD , ACA2 , NDUFS2 , UQCRCB , NDUFB5 , AIFM1 , COX11 , PDK4 , COX6A1 , COX6B1 , TIMM13 , GRPEL1 , COX5B , ATP5PO , MPC1 , COX7A2 , NDUFB7 , MGST3 , NDUFB6 , ATP5ME , NDUFA4 , ATP5MC1 , NDUFS3 , COX7B , NDUFB4 , NDUFB5 , GPX4 , COX7C , UQCRC10 , NDUF56 , NDUFA9 , COX6C , RHO1 , ETFDH , ATP5PF , PDHB , SUCLA2 , NDUFS4 , SUCLG1 , MTRF1 , UQCRC , MDH1 , NDUF57 , NDUFA7 , NDUFA8 , HADHB , BDH2 , COX8A , MRPS15 , MDH2 , UQCRC2 , IDH3B , UQCRC1 , CYB5R3 , NDUFB8 , POLR2F , PDK1 , ATP5F1E , MRPS12 , SDHA , ATP5PB , NDUFB3 , NDUFA8 , NDUFA6 , SURF1 , ATP5F1A , NDUFB2 , MRPS30 , CYC1 , MRPL15 , DLAT , ATP5F1D , ACADS , MRPS22 , SDHB , MRPL11 , PMPCA , AFG3L2 , MRPS11		
	2	8					
GLYCOLYSIS	0.16244	0.24612	0.40294	1.17544	MIOX , KIF20A , DEPDCC1 , CENPA , HMMR , PPFA4 , COL5A1 , ME1 , B3GNT3 , STC2 , QSOX1 , STC1 , STMN1 , CAPNS1 , CXCR4 , G6PD , HK2 , PGM2 , TPBG , SDC3 , SRD5A3 , EGLN3 , PKM , CD44 , DSC2 , FUT8 , PFKF , GPC1 , ELF3 , B4GALT4 , PLD2 , AGRN , CACNA1H , PDK3 , ALDOA , B4GALT2 , KIF2A , CASP6		
	2	5	3	1			
REACTIVE OXYGEN SPECIES PATHWAY	0.68578	0.75636	0.33783	0.86251	PRDX2 , PDLM1 , G6PD , SRXN1 , GPX3 , PFKP , SOD2 , CDKN2D , ABCC1 , SBNO2		
	6	2	5				
PS3 PATHWAY	0.14681	0.23680	0.40831	1.19006	INHBB , ST14 , RGS16 , S100A4 , UPP1 , ACVR1B , GM2A , NUPR1 , ABCC5 , ITGB4 , GADD45A , RRAD , SFN , CDKN1A , LIF , GPX2 , RAP2B , IFI30 , CTSD , DRAM1 , ATF3 , TGFBI , PTPN14 , APAF1 , CCND3 , PDGFA , RALGDS , BAK1 , RNF19B , LRMP , DGKA , TAX1BP3 , AEN , BAIAP2 , VAMP8 , BTG1 , HMOX1 , NDRG1 , PLK2 , ADA		
	7	2	9	7			

UV RESPONSE UP	0.30606 9	0.41360 7	0.38485 8	1.10186 7	SLC6A8 , HSPA2 , EPCAM , CA2 , CCNE1 , PLCL1 , RRAD , NR4A1 , CHKA , PRKCD , ATF3 , ABCB1 , SQSTM1 , GPX3 , CCND3 , BAK1 , SOD2 , CTSV , AGO2 , ALDOA , BTG3 , BTG1 , AMD1 , HMOX1 , TYRO3 , TFRC , RFC4 , RASGRP1
UV RESPONSE DN	0.00780 5	0.01773 9	0.51260 6	1.46290 8	HAS2 , RG54 , COL1A1 , SERPINE1 , PMP22 , CCN1 , RUNX1 , GJA1 , COL1A2 , MYC , IGF1R , GCNT1 , ATP2B4 , COL3A1 , FBLN5 , PDGFRB , FHL2 , COL5A2 , EFEMP1 , ITGB3 , MAP1B , SLC7A1 , KIT , LPAR1 , F3 , LAMC1 , ERBB2 , PIK3CD , ICA1 ,CACNA1A , SMAD3 , CDON , ABCC1
ANGIOGENESIS	0.00427 9	0.01087 6	0.67947 6	1.64597	LPL , S100A4 , TNFRSF21 , TIMP1 , COL3A1 , STC1 , SPP1 , JAG1 , FGFR1 , COL5A2 , OLR1 , LUM , PDGFA , ITGAV , SLC02A1
HEME METABOLISM	0.00112 9	0.00513 3	0.52832 9	1.53984 3	SPTA1 , KEL , SLC4A1 , GATA1 , XK , SLC6A8 , ADD2 , TRIM58 , ALAS2 , CA1 , SLC6A9 , SNCA , RHAG , HBQ1 , TRIM10 , TMCC2 , CA2 , PRDX2 , KLF1 , RBM38 , AGPAT4 , NFE2 , ACP5 , E2F2 , ARL2BP , UCP2
COAGULATION	0.27932	0.38794	0.39498	1.12028	THBS1 , SERPINE1 , ANXA1 , MMP11 , CAPN2 , PDGFB , CD9 , TIMP1 , TFP12 , MMP2 , CAPNS , GSN , PLAU , CTSH , VWF , SPARC , ITGB3 , OLR1 , F3 , CTSB , CLU , PLEK , CFD , CTSV , MMP15 , CSRP1 , COMP , ADAM9
IL2 STAT5 SIGNALING	0.00082 5	0.00412 4	0.54191 8	1.57601 3	GATA1 , ITIH5 , CDC6 , UCK2 , EMP1 , CAPN3 , RGS16 , ETV4 , CA2 , CCNE1 , CAPG , SYT11 , MYC , IGF1R , CD83 , TNFRSF21 , TLR7 , SLC1A5 , SPP1 , KLF6 , CKAP4 , GLIPR2 , PLIN2 , HK2 , CD79B , LIF , CD86 , CD44 , GPR65 , FGL2 , ABCB1 , TNFRSF1B , CISH , PHLDA1 , TRAF1 , CCND3 , PIM1 , APL1 , IL10RA , SELP , ITGAV , BCL2L1 , ODC1 , CDCP1 , IGF2R , ENPP1 , NDRG1 , SELL , SERPINB6 , ENO3 , MYO1E , ADAM19 , ITGAE , TNFRSF4 , MAP3K8
BILE ACID METABOLISM	0.00146	0.00561 5	-0.55295	-2.21076	DHCR24 , SERPINA6 , AKR1D1 , TTR , HSD3B7 , PECR , CYP8B1 , PHYH , ALDH1A1 , NUDT12 , IDI1 , CROT , ALDH8A1 , HSD17B4 , AMACR , HSD17B6 , SOD1 , SLC27A2 , CAT , ABCA2 , PEX11G , GNMT , HSD17B11 , PRDX5 , SLC27A5 , ALDH9A1 , ACSL1 , GC , RXRA , ABCD1 , IDH2 , HA01 , ABCA6 , LIPE , AGXT , LONP2 , HACL1 , GSTK1 , PEX16 , APOA1 , SLC23A1 , PEX11A , NR3C2 , IDH1 , ABCG8 , ISOC1 , BBOX1 , NR112 , PEX19
PEROXISOME	0.01156 8	0.02313 6	-0.38524	-1.50922	DHCR24 , SERPINA6 , TTR , HSD3B7 , ALDH1A1 , IDI1 , HSD17B4 , ACOX1 , SOD1 , SLC27A2 , CAT , EC12 , ALB , HSD17B11 , PRDX5 , ALDH9A1 , ACSL1 , ACAA1 , ABCD1 , IDH2 , LONP2 , HMGCL , GSTK1 , CRABP1 , FDPS , SLC25A4 , PEX11A , DHR53 , IDH1 , ISOC1 , CRAT , NR12
ALLOGRAFT REJECTION	0.00020 8	0.00129 9	0.57744 6	1.66623 7	CCL7 , CCL2 , ACHE , CCL22 , INHBB , CCL4 , IGSF6 , CAPG , CCR2 , CCR5 , TIMP1 , GCNT1 , IL18 , LY75 , TLR2 , ELF4 , MAP4K1 , LIF , TNF , CD86 , PRKCB , ITK , CD79A , CCR1 , GPR65 , IFNGR2 , SP1 , CD8A , NLRP3 , STAT4 , TGFBI , APPBB1 , CCND3 , HCLS1 , ST8SIA4 , CTSS , ITGAL , FLNA , BCL3 , WAS , SRGN , IL12RB1 , TGFBI2 , IRF7 , AKT1 , TLR6 , PTPRC , FYB1 , EIF4G3 , LCP2 , ITGB2 , NCF4 , PRKCG , IRF4 , CD74
SPERMATOGENESIS	0.00033 6	0.00186 6	0.63675 8	1.73162 8	KIF2C , DDX4 , CCNB2 , BUB1 , NPY5R , TNNI3 , HSPA2 , CFTR , ACE , NEK2 , PACRG , NCAPH , CDKN3 , PCSK4
KRAS SIGNALING UP	0.00020 7	0.00129 9	0.56508 1	1.63658	ADAMDEC1 , ADAM8 , HKDC1 , CCL20 , EMP1 , MMP11 , TMEM100 , GPNMB , CPE , RGS16 , GPRC5B , ETV4 , CA2 , EPB41L3 , ACE , MMD , APOD , GFP72 , IL1R2 , SPP1 , SPARCL1 , KIF5C , CXCR4 , F2RL1 , IL7R , PRDM1 , MAP4K1 , LIF , PLAU , LAPTM5 , LCP1 , TLR8 , DOCK2 , CMKL1 , ABCB1 , BPGLM , TNFRSF1B , TRAF1 , IKZF1 , DCBLD2 , CD37 , TNFAIP3 , BIRC3 , IL10RA , TRIB2 , FCER1G , CTSS , PLAUR , NIN , ETV5 , STRN , SPON1 , ANKH , MAP3K1
KRAS SIGNALING DN	0.38337 7	0.50444 4	0.38625 3	1.06226 4	EFH1 , TNNI3 , SCN10A , HSD1B2 , SYNPO , BARD1 , SKIL , MFSD6 , MX1 , RSAD2 , SLC29A3 , ATP4A , EDN1 , CNTFR , MAST3 , TGFB2 , RYR1 , MYO15A , SPTBN2
PANCREAS BETA CELLS	0.69585 1	0.75636	0.36915	0.83425 9	ABCC8 , AKT3

Supplementary Table S4. Reactome “Fatty Acid Metabolism” gene set in each model. Genes included in the manuscript are highlighted (in yellow). Pval: p-value, Padj: p-adjusted, ES: enrichment score, NES: normalized enrichment score.

	Pval	Padj	ES	NES	Leading Edge
Guinea pig	0.00314	0.04460	-0.47078	-1.97238	THRSP, CYP1A2, ELOVL2, PTGDS, PECR, PON3, CYP8B1, HSD17B3, PHYH, PON1, CROT, ACOT12, HSD17B4, ACOX1, AMACR, ACSL3, CYP1A1, SLC27A2, DECR2, EC12, ECHS1, CPT1A, DECR1, ACSL1, EC1, HADH, CYP4B1, ACOT4, ACOT2, ACOT1, ACAA1, ALDH3A2, RXRA, ABCD1, ACADS, ACAD11, HPGD, SLC25A1, ACADM, HACL1, PTGR2, CYP4F11, CYP4A22, CYP4A11, ACOX2, ACAD10, MMAA, PCCA, PON2, SLC27A3, SLC25A20, ACBD5, MCEE, AKR1C3, PTGS1, CPT1B, CRAT, ACAA2
HNASH 2	0.00347	0.06584	-0.55709	-1.73678	CYP2C19, CYP1A2, THRSP, ACSM3, SCD, HAO2, HADH, ACADS, ACSL5, CYP1A1, RXRA, PECR, EPHX2, EC1, CYP4F11, SLC25A1, HADHA, ACOX2, CYP8B1, HSD17B8, EC12, ACSL1, PTGR1, MLYCD, ACAA2, HPGD, MCEE, MECR, SLC27A2, FASN, FADS2, ACOT13, MCAT, TECR, CRAT, ACACA, ACADL, PON3, ACSF2, CYP2C8, ALDH3A2, ACOT4, ECHS1, HACD3, ACOX1, NDUFAB1, CPT2, FAAH, CYP2C9, DECR1, ACAA1, CYP2J2, PCCB, NUDT19, AKR1C3, PON1, DECR2, HACL1, CPT1A, SLC25A20, CBR1, GPX4, AMACR, SLC25A17, ACBD4, GPX1, ELOVL5, PTGES2, ACACB, CYP4F3, DPEP2, ELOVL6, ACOT8
HNASH 1	0.85866	0.95272	0.194743	0.81625	ACSL4, PRKAA2, PTGDS, CYP4F22, GPX2, ELOVL2, THRSP, SCD, ACOT12, ACSL6, FASN, ACOT1, ELOVL6, FADS2, AKR1C3, DBI, PRXL2B