

Supplemental Table 1:

model	oncogene/ tumorsuppressor	conditional	promoter	genetic background/strain	phenotype	GEP-NEN location	tumor type	penetrance	metastasis	reference
MEN1										
Men1 ^{TSM/TSM} ; Men1 ^{TSM/+} ;	Men1			129, NIH Black Swiss	homozygotes: embryonic lethal, heterozygotes: multiple endocrine tumors	pancreas, stomach	adenoma, 1 islet cell carcinoma	20/71 pNEN 1/27 gastric NEN		Crabtree et al. 2001 [85]
Men1 ^{ΔN3-8/ΔN3-8} ; Men1 ^{ΔN3-8/+}	Men1			129, NIH Black Swiss	heterozygotes: hyperplastic islets, insulinomas	pancreas	insulinoma	5/6		
Men1 ^{ΔN/ΔN} ; RIP-cre(Men1 ^{tm1.2Ctre} /Men1 ^{tm1.2Ctre} Tg(Ins2-cre)25Mgn/0 Tg(Ins2-cre)1Heed/0 Tg(Ins2-cre)1Dh/0)	Men1	Men1	Rat insulin promoter (RIP)	129S6, SvEvTac; C57BL/6, FVB/N	NEN, pituitary adenomas (30% mice, higher incidence in females)	pancreas	insulinoma	> 80%		Crabtree et al. 2003 [90]
Men1 ^{T/T} ; Men1 ^{T/+} (Men1 ^{tm1Zqw} /Men1+)	Men1			129/Ola, 129/Sv	homozygotes: embryonic lethal heterozygotes: multiple endocrine tumors	pancreas, stomach, duodenum,	insulinoma, glucagonoma, coexpression of insulin and glucagon, islet cell carcinoma, extrapancreatic gastrinomas	37/61 carcinoma	3/50 LN	Bertolino et al. 2003 [83, 87]
Men1 ^{F/F} -RipCre+ (Men1 ^{tm1.2Zqw} /Men1 ^{tm1.2Zqw} Tg(Ins2-cre)23Herr/0)	Men1	Men1	RIP	129P2/OlaHsd; C57BL/6J; CBA/J	pNEN	pancreas	islet cell carcinoma	100 %		Bertolino et al. 2003 [91]
Men1 ^{loxP/loxP} Rip-cre+ (Men1 ^{tm1Gfk} /Men1 ^{tm1Gfk} Tg(Ins2cre)25Mgn)	Men1	Men1	RIP	C57BL/6	prolactinoma (60%), pNEN	pancreas	insulinoma	7/21		Biondile et al. 2004 [92]
Men1 ^{+/+} ; Rb1 ^{ΔX2/+} (Men1 ^{tm1Gfk} /Men1+Rb1 ^{tm1Tyj} /Rb1+)	Men1			129T2/SvEms; C57BL/6	normal lifespan	pancreas	insulinoma; rare glucagonoma and gastrinoma	90%		Loffler et al. 2007 [104]
Men1 ^{T/T}	Men1			C57BL/6	lethal, absence of α-cells at day 12.5					Fontaniere et al. 2008 [84]
				129S6/SvEv; C57BL/6		pancreas	insulinoma, 5% co-expression of insulin and glucagon	60%		Harding et al. 2009 [88]
Men1 ^{tm1Rvt} /Men1+	Men1			129S6/SvEv	reduced lifespan, tumours of the parathyroids, anterior pituitary, adrenal cortex and gonads, pNET; relative frequency and onset of tumors dependent on background strain	pancreas	insulinoma, 37% glucagonoma, co-occurrence of both types in 60% of mice	>85%		Lines et al. 2020 [89]
				C57BL/6		pancreas	insulinoma, 2 % glucagonoma, co-occurrence of both types in 1/15 mice	>85%		
Pdx1-Cre;Men1 ^{f/f} (Men1 ^{tm1Ctre} /Men1 ^{tm1Ctre} ; Tg(Pdx1-cre)89.1Dam/0)	Men1	Men1	pdx1	129S6, SvEvTac, C57BL/6, CBA, FVB/N	reduced lifespan, pNEN, exocrine pancreas not affected	pancreas	insulinoma	na		Shen et al. 2009 [97]
Men1 ^{L/L} /RIP2-CreER (Tg(Ins2-cre/ERT)1Dam/J, (RIP2-CreER), Men1 ^{tm1.1Ctre} /J)	Men1	Men1	RIP2	C57Bl/6, 129S	normal life span, pNEN	pancreas	insulinoma	100%		Lines et al. 2017 [98]

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Men1 ^{flox/flox} Pten ^{flox/flox} RIP-Cre (Men1 ^{tm1.2cre} , Pten ^{tm1Hwu} , Tg(Ins2-cre) 25Mgn)	Men1, Pten	Men1, Pten	RIP	129S; FVB	premature death from pituitary tumors, pNET	pancreas	insulinoma, G1/G2	100%		Wong et al. 2019 [100]
Men1 ^{flox/flox} Pten ^{flox/flox} MIP-Cre (Men1 ^{tm1.2cre} , Pten ^{tm1Hwu} ; Ins1 ^{tm1.1} (cre)Thor)	Men1, Pten	Men1, Pten	Mouse insulin promoter (MIP)	129S; FVB	pNET and hypoglycemia	pancreas	insulinoma, G1/G2	100%		
Men1 ^{F/F} -GluCre ⁺	Men1	Men1	rat glucagon		pNEN	pancreas	insulinoma, glucagonoma, mixed	10/14		Lu et al. 2010 [93]
Glu-Cre; Men1 ^{f/f}	Men1	Men1	rat glucagon		pNEN	pancreas	insulinoma	2/6		Shen et al. 2010 [94]
Villin-Cre; Men1 ^{loxP/loxP}	Men1	Men1	villin	C57BL/6J; SJL/J	NEN	stomach (antrum)	adenoma (not G-cell)	2/18		Veniaminova et al. 2012 [107]
VillinCre; Men1 ^{loxP/loxP} ; Sst ^{-/-}	Men1, SST	Men1	villin	C57BL/6J; SJL/J	NEN	stomach (corpus)	ECL cell tumor, accelerated by omeprazol	9/10		Sundaresan et al. 2017 [106]
ATP4A (ATPase H+/K+ Transporting Subunit Alpha)										
Atp4a ^{R703C/R703C}	Atp4aR703C			129S6/SvEv, C57BL/6J	normal lifespan, achlorhydria, hypergastrinemia	stomach (corpus)	dysplasia			Calvete et al. 2016 [108]
VHL										
Pdx1-Cre; Vhl ^{f/f} (Vhl ^{tm1Lss} /Vhl ^{tm1Lss} ; Tg(Pdx1-cre)89.1Dam/0)	Vhl		Pdx1	129X1/SvJ, C57BL/6, CBA	postnatal death due to exocrine pathology, pancreatic cysts and microadenomas in survivors	pancreas	adenoma (microcystic)			Shen et al. 2009 [110]
constitutive active Akt1										
RIP-MyrAkt1 (Tg(Ins2-Akt1*)3Mbb)	Akt1	Akt1	RIP	C57BL/6	pNEN	pancreas	insulinoma, islet cell carcinoma	19/23 insulinoma, 4/23 islet cell carcinoma	1/23, lung	Alliouachene et al. 2008 [111]
c-myc										
pIns-c-MycERTAM/RIP-Bcl-xL	c-myc, Bcl-xL	c-myc	RIP		pNEN	pancreas	islet cell carcinoma		LN, β cells in vessels	Pelengaris et al. 2002 [113]
Glucagon receptor, Prohormone convertase 2										
Gcgr ^{-/-}	unknown			C57BL/6	lean, NE hyperplasia	pancreas	α cell and exocrine hyperplasia	no NEN		Gelling et al. 2003 [114]
Gcgr ^{-/-} (Gcgr ^{tm1Jcp} /Gcgr ^{tm1Jcp})	unknown			DBA/1LacJ	hyperglucagonemia, reduced body weight, NE hyperplasia, pNEN	pancreas	islet hyperplasia, pNET, mostly glucagonoma, glucagon expressing cells budding from ductal epithelium	14/14	1/14, liver	Yu et al. 2011 [116]
Pc2 ^{-/-} (Pcsk2 ^{tm1Dfs} /Pcsk2 ^{tm1Dfs})	unknown			C57BL/6; 129	premature death (<20%), elevated circulating proglucagon and insulin, pNEN	pancreas	α-cell hyperplasia, adenoma, carcinoma; α-cell neogenesis associated with pancreatic duct(ule)s	60-90% adenoma, 5-35% carcinoma		Jones et al. 2014 [117]
Gcg ^{gfp/gfp}	unknown				reduced life span, pNEN, no hyperglycemia	pancreas	islet cell carcinoma, α-like cells, occasional coexpression of insulin	100%	> 95%, liver, lung	Takano et al. 2015 [118]

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p53, RB, p16/19, cdk4										
Tp53 ^{+/−} Rb ^{+/−} ; Tp53 ^{−/−} Rb ^{+/−}	p53, Rb			C57BL16, 129/Sv	premature death, pituitary adenoma, medullary thyroid carcinoma, pNEN, parathyroid tumors, lymphoma, osteo- and soft tissue sarcoma	pancreas	islet cell carcinoma	6-7%		Harvey et al. 1995 [102]
Tp53 ^{+/−} Rb ^{+/−} ; Tp53 ^{−/−} Rb ^{+/−}	p53, Rb			C57BL16, 129/Sv	premature death, pituitary tumors, medullary thyroid carcinoma, lymphoma, sarcoma, pNEN, pineal tumors,	pancreas	islet cell carcinoma	14-23%		Williams et al. 1994 [125]
RenCre;Tp53 ^{loxP/loxP} Rb ^{loxP/loxP}	p53, Rb	p53, Rb	renin	C57BL/6	pancreatic glucagonoma, subcutaneous vascular sarcoma like tumors (non NE)	pancreas	invasive glucagonoma	120/120	liver, LN	Glenn et al. 2014 [127]
Fabpl-Cre ^{tg/+} Rb ^{c/c} (Tg(Fabp1-cre)1Jig/Rb fl/fl)	Rb	Rb	fabp	FVB/N	mostly adenocarcinomas of small intestine and colon (11/26), few tumors with NE differentiation	small intestine, colon	NEC	2/26	LN, mesentery	Parisi et al. 2015 [140]
Cdk4 ^{R24C/R24C} (Cdk4 ^{tm1.1Bbd} /Cdk4 ^{tm1.1Bbd})	cdk4R24C (missense)			129X1/SvJ;129S1/Sv	premature death, tumors from different lineages, pNEN and sarcoma most frequent	pancreas	mostly insulinoma, occasionally PP or glucagon expression	53/155		Sotillo et al. 2001 [130]
elastase-tv-a; RCAS-c-myc; p16/p19 ^{−/−}	c-myc, p16/19	ALSV-A, c-myc,	elastase	FVB	lymphoma, sarcoma (limiting), NEN	pancreas	pNET, beta cell features	4/14		Lewis et al. 2003 [133]
elastase-tv-a; RCAS-PyMT; p16/p19 ^{−/−}	PyMT, p16/19	ALSV-A, PyMT,	elastase	FVB	lymphoma, sarcoma (limiting), pancreatic tumors	pancreas	progenitor (acinar, ductal lesions, SYP +PDX1 positive)	8/11		
RIP7-rtTA;tet-o-MT; p48-Cre; p16/p19 ^{loxP/loxP}	PyMT, p16/19	PyMT, p16/19	RIP; Ptf1a (p48)	C57BL/6, FVB, ICR	pNEN	pancreas	pNET	12/16	5/12	
RIP7-rtTA;tet-o-MT; p48-Cre;p53 ^{loxP/loxP}	PyMT, p53	PyMT, p53	RIP; Ptf1a (p48)	C57BL/6, FVB, ICR	pNEN	pancreas	pNET	2/12	0/2	Azzopardi et al. 2016 [132]
Pdx1-tTA; tet-o-MT; p48-Cre; p16/p19 ^{lox/lox}	PyMT, p16/19	PyMT, p16/19	Pdx1; Ptf1a (p48)	C57BL/6, FVB, ICR	pancreatic tumors, mostly acinar cell carcinoma, few pNEN	pancreas	pNET	4/35		
Pdx1-tTA; tet-o-MT; p48-Cre;p53 ^{lox/lox}	PyMT, p53	PyMT, p53	Pdx1; Ptf1a (p48)	C57BL/6, FVB, ICR	pancreatic tumors, mostly acinar cell carcinoma (ACC)	pancreas	mixed ACC/NE	4/20	4/4	
HR-HPV										
bK6-HPV16e	HPV-16 early region	HPV16e	bovine keratin 6 (bk6)	CBA; C57BL/6	premature death, gastric NEN, occasional hyperplastic squamous skin lesion	glandular stomach	poorly differentiated NEN	100	LN, liver, rare lung	Searle et al. 1994 [142]
SV40										
RIP-Tag2 (Tg(RIP1-Tag)2Dh)	SV40-Tag	SV40-Tag	RIP	C57BL/6, DBA/2	premature death (hypoglycemia), pNEN with adenoma-carcinoma sequence, rare intestinal NEN	pancreas	pNEN: insulinoma/invasive carcinoma intestinal NEN: invasive carcinoma, polyhormonal, mostly secretin	pNEN: 100% intestinal NEN: 2/8	<5%	Hanahan 1985 [154] Rindi et al. 1990 [170] Grant et al. 1991 [169]
RIP-Tag5 (Tg(RIP1-Tag)5Dh)	SV40-Tag	SV40-Tag	RIP	C3HeB/FeJ	extended lifespan compared to RIP1-Tag2 mice due to delayed Tag expression	pancreas	insulinoma/invasive carcinoma			Onrust et al. 1996 [149]

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RipTag-IRES-Luciferase (RTL1) (Tg(Ins1-Tag,-luc)1Gcr)	SV40-Tag	SV40-Tag	RIP	FVB/N	phenocopies RIP1-Tag2, luciferase reporter	pancreas	insulinoma/invasive carcinoma	comparable to RIP1- Tag2		Zumsteg et al. 2010 [150]
RIP-Tag (Tg(RIP1-Tag)2Dh)	SV40-Tag	SV40-Tag	RIP	C57BL/6 C3HeB/Fe	phenocopies RIP1-Tag2 phenocopies RIP1-Tag2	pancreas pancreas	insulinoma/invasive carcinoma (IC) insulinoma/invasive carcinoma (IC)	100% insulinoma, >50% of lesions IC 100% insulinoma, <15% of lesions IC		Chun et al. 2010 [166]
RIP-TβAg (Tg(Ins2-Tag*,-flpe)#Gne)	SV40-Tag	SV40-Tag	RIP	na	phenocopies RIP1-Tag2	pancreas	insulinoma/invasive carcinoma	comparable to RIP1- Tag2		Singh et al. 2012 [147]
				AB6(F1)	reduced early mortality compared to B6 background, no hypoglycemia	pancreas	pNET, non functioning	comparable to RIP1- Tag2	65%	Kobayashi et al. 2019 [167]
RIP-Tag (Tg(RIP1-Tag)2Dh)	SV40-Tag	SV40-Tag	RIP	B6A(F1)	pancreatic and intestinal NEN, pancreatic tumor load and metastasis reduced compared to AB6 background,	pancreas, small intestine	pNET and siNET	comparable to RIP1- Tag2 100 % (pNEN) 12/30 (siNEN)	20%	Contractor et al. 2020 [168]
RIP-Tag/RIPPyST	SV40-Tag, PyST1	SV40-Tag, PyST1	RIP	C57BL/6, DBA/2	pancreatic NEN as in RIP1-Tag2 mice, in addition small intestinal NEN	pancreas, small intestine	invasive carcinoma, polyhormonal, mostly secretin expression	15/15	8/11, liver, mesentery	Rindi et al. 1990 [170] Grant et al. 1991 [169]
Glu2-Tag	SV40-Tag	SV40-Tag	rat glucagon	C57BL/6	premature death around 10 months, pNEN, Tag expression in CNS	pancreas	hyperplastic islets, glucagonoma, invasive carcinoma	100%		Efrat et al. 1988 [172]
GLUTag-Y Tg(Gcg-TAg)25Ddr	SV40-Tag	SV40-Tag	rat glucagon	CD-1	early premature death, reduced body weight, transgene expression in CNS, pancreas, stomach, small and large intestine, NEN	pancreas, colon	invasive carcinoma, mostly glucagon expression or loss of hormon expression	consistently	LN	Lee et al. 1992 [174] Asa et al. 1996 [175]
VT-C (Avp-Tag)	SV40-Tag	SV40-Tag	vasopressin	C57BL/10; CBA	premature death, pituitary tumors, pNEN	pancreas	insulinoma	7/8		Murphy et al. 1987 [176]
SV-202	SV40-Tag	SV40-Tag	metallo-thionein1	C57BL/6	premature death (hyperinsulinemia), HCC and pNEN,	pancreas	insulinoma	100%		Dyer et al. 1989 [180]
Secretin-Tag	SV40-Tag	SV40-Tag	secretin	B6D2F1	premature death, NEN, non NE neoplasias in liver, spleen and thymus	pancreas, small intestine, colon	NEC in the small intestine, pancreatic insulinoma, well differentiated colonic NET with glucagon expression			Lopez et al. 1995 [171]
ELSV (Tg(Ela-I,SV4OE)Bril8)	SV40-Tag	SV40-Tag	rat elastase 1		premature death due to acinar cell carcinoma (73%), pNEN	pancreas	insulinoma, D-cell hyperplasia	insulinoma 15/48 D-cell hyperplasia 28/33		Bell et al. 1990 [179]
GP1.5 Tag, GP10.5 Tag	SV40-Tag	SV40-Tag	human gastrin		bile duct cancer, HCC, pNEN, antral G cell hyperplasia	pancreas	insulinoma, pancreatic ductal hyperplasia with focal insulin expression in ductal cells,	full penetrance in GP1.5, sporadic in GP10.5		Montag et al. 1993 [177]
ITF-Tag	SV40-Tag	SV40-Tag	ITF (intestinal trefoil factor)	C57BL/6, BALB/c	premature death, invasive small cell colon cancer, dysplastic duodenal villi	proximal colon	NEC	50/50		Gum et al. 2004 [183]

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<i>Atp4b</i> -SV40 Tag	SV40-Tag	SV40-Tag	Atp4b	FVB/N	metastatic gastric cancer; targeting of Tag to parietal cells and their precursors confirmed in Atp4b-Cre, R26R mice	stomach	NEC	53/53	60% LN, 20% liver	Syder et al. 2004 [182]
Vil-Cre-ER ^{T2} LoxP-Tag (Tg (Vil-cre) 997Gum/J)	SV40-Tag	SV40-Tag	stochastic, tissue-specific activation of Cre recombinase	C57BL/6	rare colon carcinoma and NEC in aging mice	small intestine and colon	invasive carcinoma, neuroendocrine, glandular, or mixed	GI cancer in 17/21 mice 4/19 tumors NEC 11/19 tumors MINEN	6/19	Czéh et al. 2010 [186]
CEA424-SV40-Tag (Tg(CEACAM5-Tag)L5496Wzm/Cnrm)	SV40-Tag	SV40-Tag	CEA minimal	C57BL/6	premature death due to pyloric obstruction from NEN, enlarged cecum	pyloric region of the stomach	dysplastic lesions, multi-focal carcinomas	100%	local invasive growth into duodenum	Ihler et al. 2012 [184]
L-PK/Tag (Tg(Pklr-Tag)Ak)	SV40-Tag	SV40-Tag	L-type pyruvate kinase	C57BL/6, DBA	hepatocellular carcinoma, diet dependent pNEN	pancreas	islet cell carcinoma (α, β, δ lineage)			Cartier et al. 1992 [181]
other										
<i>Prdx1</i> ^{-/-} (Prdx1 ^{tm1Rave} /Prdx1 ^{tm1Rave})	Prdx1				severe haemolytic anaemia, impaired NK cell function, islet cell adenoma, lymphoma, histiocytic malignancy, HCC, sarcoma, lung cancer	pancreas	adenoma	9%		Neumann et al. 2003 [138]
Cul9 ^{tm1.2Yxi} /Cul9+	Cul9			129P2/OlaHsd, C57BL/6, FVB/N	wide tumor spectrum in 17/23 heterozygous mice, 1 pNEN	pancreas	insulinoma	1/23		Pei et al. 2011 [139]

Supplemental Table 1: Overview of GEMMs for GEP-NEN. Model names refer to the designation in the original publications. If available, the exact symbol for the targeted allele(s) is given in parenthesis below the model name. Values for NEN incidence generally refer to the percentage or fraction of tumor bearing mice by the end of the observation time. Description of phenotypes has been reduced to NEN related features. Please refer to references for full phenotypes. Numbers in parenthesis in the reference column refer to reference numbers in the current manuscript. For the purpose of the current review, we focused on monogenic and multigenic models with a de novo NEN phenotype. In depth coverage of additional multigenic phenotype variants is available from reviews that more specifically cover menin or SV40-Tag induced mouse tumors [1, 2]. Abbreviations are: pNEN pancreatic neuroendocrine neoplasia; RIP rat insulin promoter; LN lymph nodes; Atp4b, ATPase H⁺/K⁺ Transporting Subunit Beta; TVA, receptor for ALSV-A; ALSV-A, Avian Leucosis Sarcoma Virus; Fabp1, Fatty Acid Binding Protein 1; Prdx1, Peroxiredoxin 1, Ptf1a, Pancreas Associated Transcription Factor 1a.

References:

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- 2 Hudson AL, Colvin EK. Transgenic Mouse Models of SV40-Induced Cancer. ILAR journal. 2016;57(1):44-54.