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Genetically-engineered animal models of biliary tract cancers

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Genotype	Targeted cell type	Onset of transgene activity	Lesion	Latency period for CCA	Reference
<i>Alb-Cre/Smad4^{loxP/loxP}/Pten^{loxP/loxP}</i>	Hepatoblasts, hepatocytes, cholangiocytes, activated stellate cells	Prior birth; validated by recombination of <i>Rosa26R^{lacZ}</i> at P15	papillary dysplasia, iCCA, salivary gland tumor (rarely)	4-7 months	[52]
<i>Alb-Cre/Pten^{loxP/loxP}</i>			iCCA, HCC, salivary gland tumor (rarely)	1 year	
<i>Alb-Cre/Tp53^{loxP/loxP}loxP-stop-loxP-Kras^{G12D}</i>	Hepatoblasts, hepatocytes, cholangiocytes, activated stellate cells	Prior birth	iCCA, HCC, mixed HCC-CCA, IPNB, VMC	13-32 weeks	[53, 65]
<i>Alb-Cre/Tp53^{loxP/loxP}loxP-stop-loxP-Kras^{G12D}+DDC</i>			iCCA, mixed HCC-CCA, no HCC		
<i>Alb-Cre/Tp53^{loxP/+}loxP-stop-loxP-Kras^{G12D}</i>			iCCA, HCC, mixed HCC-CCA	32-62 weeks	
<i>Alb-Cre/Tp53^{+/+}loxP-stop-loxP-Kras^{G12D}</i>			iCCA (rarely)	36 weeks	
<i>Alb-Cre/ Pten^{loxP/loxP}loxP-stop-loxP-Kras^{G12D}</i>	Hepatoblasts, hepatocytes, cholangiocytes,	Prior birth	iCCA, papillary premalignant tumours	7 weeks	[54, 55]
<i>Alb-Cre/ Pten^{loxP/+}loxP-stop-loxP-Kras^{G12D}</i>			iCCA (unfrequent), hepatocellular dysplasia	6 months	
<i>Alb-Cre/Pten^{+/+}loxP-stop-loxP-Kras^{G12D}</i>			hepatocellular dysplasia		
<i>Alb-CreERT2/Pten^{loxP/loxP}loxP-stop-loxP-Kras^{G12D}</i>	Adult: hepatocytes, cholangiocytes (rarely) Newborn: hepatocytes, cholangiocytes	Starting from tamoxifen injection	Tamoxifen administered at 8 weeks:HCC Tamoxifen administered at P10: HCC, iCCA	2 months	

Table 1. continued					
<i>Alb-CreERT²/loxP-stop-loxP-Notch intracellular domain+ thioacetamide</i>	Hepatocytes	Starting from tamoxifen injection	iCCA	14 weeks	[17]
<i>K19-CreERT²/loxP-stop-loxP-Kras^{G12D}/Pten^{loxP/loxP}</i>	Cholangiocytes, adult progenitors, peribiliary glands	Starting from tamoxifen injection	Premalignant iCCA, papillary dysplasia in GB and EHBD; multiorgan defects	1 month	[54]
<i>Sox9-CreERT²/loxP-stop-loxP-Kras^{G12D}/Pten^{loxP/loxP}</i>	Cholangiocytes, periportal hepatocytes	Starting from tamoxifen injection	hyperplasia in IHBD, EHBD and GB; biliary adenoma of IHBD	3 months	[55]
<i>Sox9-CreERT²/loxP-stop-loxP-Kras^{G12D}/Tp53^{loxP/loxP}</i>	Cholangiocytes, periportal hepatocytes	Starting from tamoxifen injection	BillIN, iCCA, HCC (rarely)	30 weeks	[65]
<i>K19-CreERT²/loxP-stop-loxP-Kras^{G12D}/Tbr1^{loxP/loxP}/Cdh1^{loxP/loxP}</i>	Cholangiocytes, adult progenitors, peribiliary glands	Starting from tamoxifen injection	eCCA	1 month	[15, 56]
<i>K19-CreERT²/loxP-stop-loxP-Kras^{G12D}/Tbr1^{loxP/loxP}</i>			hyperplasia in EHBD		
<i>Alb-Cre/loxP-stop-loxP-Kras^{G12D}/Tbr1^{loxP/loxP}/Cdh1^{loxP/loxP}</i>	Hepatoblasts, hepatocytes, cholangiocytes, activated stellate cells	Prior birth	Hilar CCA, dysplasia of peripheral IHBD	2 months	
<i>Alb-Cre/loxP-stop-loxP-Kras^{G12D}/Cdh1^{loxP/loxP}</i>			HCC, iCCA, mixed HCC-iCCA		
<i>K19-CreERT²/loxP-stop-loxP-Kras^{G12D}</i>	Cholangiocytes, adult progenitors, peribiliary glands	Starting from tamoxifen injection	no biliary tumor		
<i>K19-CreERT²/Tbr1^{loxP/loxP}</i>			no biliary tumor		
<i>K19-CreERT²/Cdh1^{loxP/loxP}</i>			no biliary tumor		

Table 1. continued

<i>Alb-Cre/ loxP-stop-loxP-Idh2^{R172K}/ loxP-stop-loxP-Kras^{G12D}</i>	Hepatoblasts, hepatocytes, cholangiocytes, activated stellate cells	Prior birth	iCCA	47 weeks	[21]
<i>Alb-Cre/ loxP-stop-loxP-Kras^{G12D}</i>			HCC (rarely)	70 weeks	
<i>Alfp-Cre/ loxP-stop-loxP-Notch1 intracellular domain</i>	Hepatoblasts	Prior birth	iCCA after transplantation of Notch1 overexpressing cells in immunodeficient mice		[57]
<i>Ah-Cre/Pten^{loxP/loxP}</i>	Hepatocytes, cholangiocytes	Starting from tamoxifen and β -naphthoflavone injection	iCCA, HCC, mixed HCC-CCA, VMC, hyperplasia in IHBD, EHBD, GB; multiorgan defects		[58]
<i>Ah-Cre/ loxP-stop-loxP-Kras^{G12V}/ Pten^{loxP/loxP}</i>			GB adenocarcinoma, non-invasive papillary hyperplasia in GB and IHBD, multiorgan defects		
<i>Ah-Cre/ loxP-stop-loxP-Kras^{G12V}</i>			no lesion		
<i>Alfp-Cre/ p53^{loxP/loxP}</i>	Hepatoblasts	Prior birth	Mixed HCC-CCA, HCC	14-20 months	[59]
<i>Alb-Cre/ Hspd1^{loxP/loxP}</i>	Hepatoblasts, hepatocytes, cholangiocytes, activated stellate cells	Prior birth	BillIN, iCCA after transplantation of <i>Hspd1</i> ^{-/-} cells in immunodeficient mice		[60]
<i>Alb-Cre/ Nf2^{loxP/loxP}</i>	Hepatoblasts, hepatocytes, cholangiocytes, activated stellate cells	Prior birth	HCC, cholangiolocellular iCCA	30 weeks	[20]
<i>BK5-ErbB2A</i>	Hepatoblasts	Prior birth	GB adenocarcinoma iCCA cystic duct adenocarcinoma common bile duct adenocarcinoma	0.5 months 3 months 0.5 months 1 month	[61]
<i>Pdx1-Cre/ loxP-stop-loxP-Kras^{G12D}</i>	Extrahepatic and GB cholangiocytes, pancreas	Prior birth	GB adenoma		[62]
<i>Lxrb</i> ^{-/-} females			GB adenoma, GB adenocarcinoma	19 months	[70]

Table 1. continued					
<i>Prominin-CreER^{T2}/Pten^{fllox/fllox}/Tp53^{fllox/fllox}</i>	Postnatal progenitor cells	Starting from tamoxifen injection	HCC, iCCA after transplantation		[44]
Transposase-mediated expression of Notch intracellular domain	Hepatocytes	Starting from transposase-mediated integration in genome	iCCA	20 weeks	[18]
Transposase-mediated expression of Notch intracellular domain + Akt		Starting from transposase-mediated integration in genome	iCCA	4.5 weeks	
Transposase-mediated expression of Yap + p53 shRNA + Notch intracellular domain	Hepatocytes	Starting from transposase-mediated integration in genome	iCCA	6 weeks	[19]
Transposase-mediated expression of active Akt + β -catenin; inflammatory stimulus (DDC, CCl ₄)	Hepatocytes	Starting from transposase-mediated integration in genome	Hepatocellular adenoma, mixed HCC-CCA, hepatoblastoma (unfrequent)	11-17 weeks	[63]
Transposase-mediated expression of active Akt + N-Ras ^{G12V} ; inflammatory stimulus (DDC)		Starting from transposase-mediated integration in genome	HCC, iCCA, mixed HCC-iCCA	8-10 weeks	
Transposase-mediated expression of active Akt + YAP; inflammatory stimulus (IL33)	Cholangiocytes	Starting from transposase-mediated integration in genome	iCCA	10 weeks	[64]
<i>AAV8-TBG-Cre/Tp53^{loxP/loxP}/loxP-stop-loxP-Kras^{G12D}</i>	Hepatocytes	Starting from transposase-mediated integration in genome	HCC (rarely)	2 months	[65]
<i>AAV8-TBG-Cre/Tp53^{loxP/loxP}/loxP-stop-loxP-Kras^{G12D}</i> + inflammatory stimulus (DDC)			iCCA, HCC, mixed HCC-iCCA		