Kras-LSL-G12D

Nomenclature	C57BL/6Smoc-*Kras*$^{em4(LSL-G12D)Smoc}$
Cat. NO.	NM-KI-190003
Strain State	Repository Live

Gene Summary

Gene Symbol **Kras**	**Synonyms**	Ki-ras; K-ras; Kras2; Kras-2
	NCBI ID	16653
	MGI ID	96680
	Ensembl ID	ENSMUSG00000030265
	Human Ortholog	KRAS

Model Description

野生型Kras激活/失活效应是受控的，而突变型Kras蛋白功能异常，持续处于激活状态，导致肿瘤细胞的持续增殖。将loxp-stop-loxp以及含有G12D的exon2替换Kras的exon2，建立Kras基因G12D条件性点突变小鼠品系，该小鼠与Cre小鼠交配后可获得G12D点突变小鼠。Kras(LSL-G12D/LSL-G12D);纯合子胚胎期即发生死亡。

Research Application：肿瘤研究

*Literature published using this strain should indicate: Kras-LSL-G12D mice (Cat. NO. NM-KI-190003) were purchased from Shanghai Model Organisms Center, Inc..

Disease Connection

膀胱癌 **Urinary Bladder Cancer**	**Phenotype(s)**	MGI:5790500 Note：该品系与Ctnnb1-Flox(NM-CKO-200154)和Upk2-cre工具鼠交配才可能获得预期表型
	Reference(s)	Ahmad I, Patel R, Liu Y, Singh LB, Taketo MM, Wu XR, Leung HY, Sansom OJ, Ras mutation cooperates with beta-catenin activation to drive bladder tumourigenesis. Cell Death Dis. 2011;2:e124

鳞状细胞癌 **Squamous Cell Carcinoma**	**Phenotype(s)**	MGI:5298084 Note：该品系与P53-Flox(2)(NM-CKO-190067)和KRT14-cre/ERT工具鼠交配才可能获得预期表型
	Reference(s)	Lapouge G, Youssef KK, Vokaer B, Achouri Y, Michaux C, Sotiropoulou PA, Blanpain C, Identifying the cellular origin of squamous skin tumors. Proc Natl Acad Sci U S A. 2011 May 3;108(18):7431-6
鳞状细胞癌 **Squamous Cell Carcinoma**	**Phenotype(s)**	MGI:5556259 Note：该品系与Smad4-Flox(NM-CKO-18011)和Krt1-15-cre工具鼠交配才可能获得预期表型
	Reference(s)	White RA, Neiman JM, Reddi A, Han G, Birlea S, Mitra D, Dionne L, Fernandez P, Murao K, Bian L, Keysar SB, Goldstein NB, Song N, Bornstein S, Han Z, Lu X, Wisell J, Li F, Song J, Lu SL, Jimeno A, Roop DR, Wang XJ, Epithelial stem cell mutations that promote squamous cell carcinoma metastasis. J Clin Invest. 2013 Oct 1;123(10):4390-404
卵巢癌 **Ovarian Cancer**	**Phenotype(s)**	MGI:5432224 Note：该品系与Ctnnb1-Flox(NM-CKO-200154)和CYP19A1-cre工具鼠交配才可能获得预期表型
	Reference(s)	Richards JS, Fan HY, Liu Z, Tsoi M, Lague MN, Boyer A, Boerboom D, Either Kras activation or Pten loss similarly enhance the dominant-stable CTNNB1-induced genetic program to promote granulosa cell tumor development in the ovary and testis. Oncogene. 2012 Mar 22;31(12):1504-20
卵巢癌 **Ovarian Cancer**	**Phenotype(s)**	MGI:5432231 Note：该品系与Ctnnb1-Flox(NM-CKO-200154)和Amhr2-Cre工具鼠交配才可能获得预期表型
	Reference(s)	Richards JS, Fan HY, Liu Z, Tsoi M, Lague MN, Boyer A, Boerboom D, Either Kras activation or Pten loss similarly enhance the dominant-stable CTNNB1-induced genetic program to promote granulosa cell tumor development in the ovary and testis. Oncogene. 2012 Mar 22;31(12):1504-20

前列腺癌 **Prostate Cancer**	**Phenotype(s)**	MGI:3836577 Note：该品系与Pbsn-cre工具鼠交配才可能获得预期表型
	Reference(s)	Pearson HB, Phesse TJ, Clarke AR, K-ras and Wnt signaling synergize to accelerate prostate tumorigenesis in the mouse. Cancer Res. 2009 Jan 1;69(1):94-101
前列腺癌 **Prostate Cancer**	**Phenotype(s)**	MGI:5300204 Note：该品系与Scrib-Flox(NM-CKO-2102030)和Pbsn-cre工具鼠交配才可能获得预期表型
	Reference(s)	Pearson HB, Perez-Mancera PA, Dow LE, Ryan A, Tennstedt P, Bogani D, Elsum I, Greenfield A, Tuveson DA, Simon R, Humbert PO, SCRIB expression is deregulated in human prostate cancer, and its deficiency in mice promotes prostate neoplasia. J Clin Invest. 2011 Nov 1;121(11):4257-67
前列腺癌 **Prostate Cancer**	**Phenotype(s)**	MGI:5705321 Note：该品系与Pten-Flox(NM-CKO-18004)和Pbsn-cre工具鼠交配才可能获得预期表型
	Reference(s)	Mulholland DJ, Kobayashi N, Ruscetti M, Zhi A, Tran LM, Huang J, Gleave M, Wu H, Pten loss and RAS/MAPK activation cooperate to promote EMT and metastasis initiated from prostate cancer stem/progenitor cells. Cancer Res. 2012 Apr 1;72(7):1878-89
神经纤维瘤病 **Neurofibromatosis**	**Phenotype(s)**	MGI:4849441 Note：该品系与Pten-Flox(NM-CKO-18004)和Gfap-cre工具鼠交配才可能获得预期表型
	Reference(s)	Gregorian C, Nakashima J, Dry SM, Nghiemphu PL, Smith KB, Ao Y, Dang J, Lawson G, Mellinghoff IK, Mischel PS, Phelps M, Parada LF, Liu X, Sofroniew MV, Eilber FC, Wu H, PTEN dosage is essential for neurofibroma development and malignant transformation. Proc Natl Acad Sci U S A. 2009 Nov 17;106(46):19479-84

胰腺癌 **Pancreatic Carcinoma**	**Phenotype(s)**	MGI:3032575 Note：该品系与Pdx1-cre工具鼠交配才可能获得预期表型
	Reference(s)	Hingorani SR, Petricoin EF, Maitra A, Rajapakse V, King C, Jacobetz MA, Ross S, Conrads TP, Veenstra TD, Hitt BA, Kawaguchi Y, Johann D, Liotta LA, Crawford HC, Putt ME, Jacks T, Wright CV, Hruban RH, Lowy AM, Tuveson DA, Preinvasive and invasive ductal pancreatic cancer and its early detection in the mouse. Cancer Cell. 2003 Dec;4(6):437-50
胰腺癌 **Pancreatic Carcinoma**	**Phenotype(s)**	MGI:3032576 Note：该品系与Ptf1a-Cre工具鼠交配才可能获得预期表型
	Reference(s)	Hingorani SR, Petricoin EF, Maitra A, Rajapakse V, King C, Jacobetz MA, Ross S, Conrads TP, Veenstra TD, Hitt BA, Kawaguchi Y, Johann D, Liotta LA, Crawford HC, Putt ME, Jacks T, Wright CV, Hruban RH, Lowy AM, Tuveson DA, Preinvasive and invasive ductal pancreatic cancer and its early detection in the mouse. Cancer Cell. 2003 Dec;4(6):437-50
胰腺癌 **Pancreatic Carcinoma**	**Phenotype(s)**	MGI:4940096 Note：该品系与Brca2-Flox(NM-CKO-200014)，P53-Flox(2)(NM-CKO-190067)和Pdx1-cre工具鼠交配才可能获得预期表型
	Reference(s)	Skoulidis F, Cassidy LD, Pisupati V, Jonasson JG, Bjarnason H, Eyfjord JE, Karreth FA, Lim M, Barber LM, Clatworthy SA, Davies SE, Olive KP, Tuveson DA, Venkitaraman AR, Germline Brca2 heterozygosity promotes Kras(G12D) -driven carcinogenesis in a murine model of familial pancreatic cancer. Cancer Cell. 2010 Nov 16;18(5):499-509
胰腺癌 **Pancreatic Carcinoma**	**Phenotype(s)**	MGI:5013917 Note：该品系与Pten-Flox(NM-CKO-18004)和Pdx1-cre工具鼠交配才可能获得预期表型
	Reference(s)	Hill R, Calvopina JH, Kim C, Wang Y, Dawson DW, Donahue TR, Dry S, Wu H, PTEN loss accelerates KrasG12D-induced pancreatic cancer development. Cancer Res. 2010 Sep 15;70(18):7114-24

胰腺癌 **Pancreatic Carcinoma**	**Phenotype(s)**	MGI:5441554 Note：该品系与Cdkn2a-Flox(2)(NM-CKO-200151)和Pdx1-cre工具鼠交配才可能获得预期表型
	Reference(s)	Singh M, Couto SS, Forrest WF, Lima A, Cheng JH, Molina R, Long JE, Hamilton P, McNutt A, Kasman I, Nannini MA, Reslan HB, Cao TC, Ho CC, Barck KH, Carano RA, Foreman O, Eastham-Anderson J, Jubb AM, Ferrara N, Johnson L, Anti-VEGF antibody therapy does not promote metastasis in genetically engineered mouse tumour models. J Pathol. 2012 Aug;227(4):417-30
胰腺癌 **Pancreatic Carcinoma**	**Phenotype(s)**	MGI:5635880 Note：该品系与P53-Flox(2)(NM-CKO-190067)和Pdx1-cre工具鼠交配才可能获得预期表型
	Reference(s)	Masso-Valles D, Jauset T, Serrano E, Sodir NM, Pedersen K, Affara NI, Whitfield JR, Beaulieu ME, Evan GI, Elias L, Arribas J, Soucek L, Ibrutinib exerts potent antifibrotic and antitumor activities in mouse models of pancreatic adenocarcinoma. Cancer Res. 2015 Apr 15;75(8):1675-81
胰腺导管腺癌 **Pancreatic Ductal Adenocarcinoma**	**Phenotype(s)**	MGI:2687217 Note：该品系与Cdkn2a-Flox(2)(NM-CKO-200151)和Pdx1-cre工具鼠交配才可能获得预期表型
	Reference(s)	Aguirre AJ, Bardeesy N, Sinha M, Lopez L, Tuveson DA, Horner J, Redston MS, DePinho RA, Activated Kras and Ink4a/Arf deficiency cooperate to produce metastatic pancreatic ductal adenocarcinoma. Genes Dev. 2003 Dec 15;17(24):3112-26
胰腺导管腺癌 **Pancreatic Ductal Adenocarcinoma**	**Phenotype(s)**	MGI:4941336 Note：该品系与P53-Flox(2)(NM-CKO-190067)和Pdx1-cre工具鼠交配才可能获得预期表型
	Reference(s)	Hingorani SR, Wang L, Multani AS, Combs C, Deramaudt TB, Hruban RH, Rustgi AK, Chang S, Tuveson DA, Trp53R172H and KrasG12D cooperate to promote chromosomal instability and widely metastatic pancreatic ductal adenocarcinoma in mice. Cancer Cell. 2005 May;7(5):469-83

胰腺导管腺癌 Pancreatic Ductal Adenocarcinoma	**Phenotype(s)**	MGI:5308946 Note：该品系与P53-Flox(2)(NM-CKO-190067)和Pdx1-cre工具鼠交配才可能获得预期表型
	Reference(s)	Bardeesy N, Aguirre AJ, Chu GC, Cheng KH, Lopez LV, Hezel AF, Feng B, Brennan C, Weissleder R, Mahmood U, Hanahan D, Redston MS, Chin L, Depinho RA, Both p16(Ink4a) and the p19(Arf)-p53 pathway constrain progression of pancreatic adenocarcinoma in the mouse. Proc Natl Acad Sci U S A. 2006 Apr 11;103(15):5947-52
胰腺导管腺癌 Pancreatic Ductal Adenocarcinoma	**Phenotype(s)**	MGI:5308951 Note：该品系与Cdkn2a-Flox(2)(NM-CKO-200151)，P53-Flox(2)(NM-CKO-190067)和Pdx1-cre工具鼠交配才可能获得预期表型
	Reference(s)	Bardeesy N, Aguirre AJ, Chu GC, Cheng KH, Lopez LV, Hezel AF, Feng B, Brennan C, Weissleder R, Mahmood U, Hanahan D, Redston MS, Chin L, Depinho RA, Both p16(Ink4a) and the p19(Arf)-p53 pathway constrain progression of pancreatic adenocarcinoma in the mouse. Proc Natl Acad Sci U S A. 2006 Apr 11;103(15):5947-52
胰腺导管腺癌 Pancreatic Ductal Adenocarcinoma	**Phenotype(s)**	MGI:6505560 Note：该品系与P53-Flox(2)(NM-CKO-190067)和Pdx1-cre工具鼠交配才可能获得预期表型
	Reference(s)	Poulin EJ, Bera AK, Lu J, Lin YJ, Strasser SD, Paulo JA, Huang TQ, Morales C, Yan W, Cook J, Nowak JA, Brubaker DK, Joughin BA, Johnson CW, DeStefanis RA, Ghazi PC, Gondi S, Wales TE, Iacob RE, Bogdanova L, Gierut JJ, Li Y, Engen JR, Perez-Mancera PA, Braun BS, Gygi SP, Lauffenburger DA, Westover KD, Haigis KM, Tissue-Specific Oncogenic Activity of KRAS(A146T). Cancer Discov. 2019 Jun;9(6):738-755
幼年型粒单核细胞白血病 Juvenile Myelomonocytic Leukemia	**Phenotype(s)**	MGI:3035835 Note：该品系与Mx1-cre工具鼠交配才可能获得预期表型
	Reference(s)	Chan IT, Kutok JL, Williams IR, Cohen S, Kelly L, Shigematsu H, Johnson L, Akashi K, Tuveson DA, Jacks T, Gilliland DG, Conditional expression of oncogenic K-ras from its endogenous promoter induces a myeloproliferative disease. J Clin Invest. 2004 Feb;113(4):528-38

幼年型粒单核细胞白血病 Juvenile Myelomonocytic Leukemia	**Phenotype(s)**	MGI:5582314 Note：该品系与Mx1-cre工具鼠交配才可能获得预期表型
	Reference(s)	Braun BS, Tuveson DA, Kong N, Le DT, Kogan SC, Rozmus J, Le Beau MM, Jacks TE, Shannon KM, Somatic activation of oncogenic Kras in hematopoietic cells initiates a rapidly fatal myeloproliferative disorder. Proc Natl Acad Sci U S A. 2004 Jan 13;101(2):597-602

Validation Data

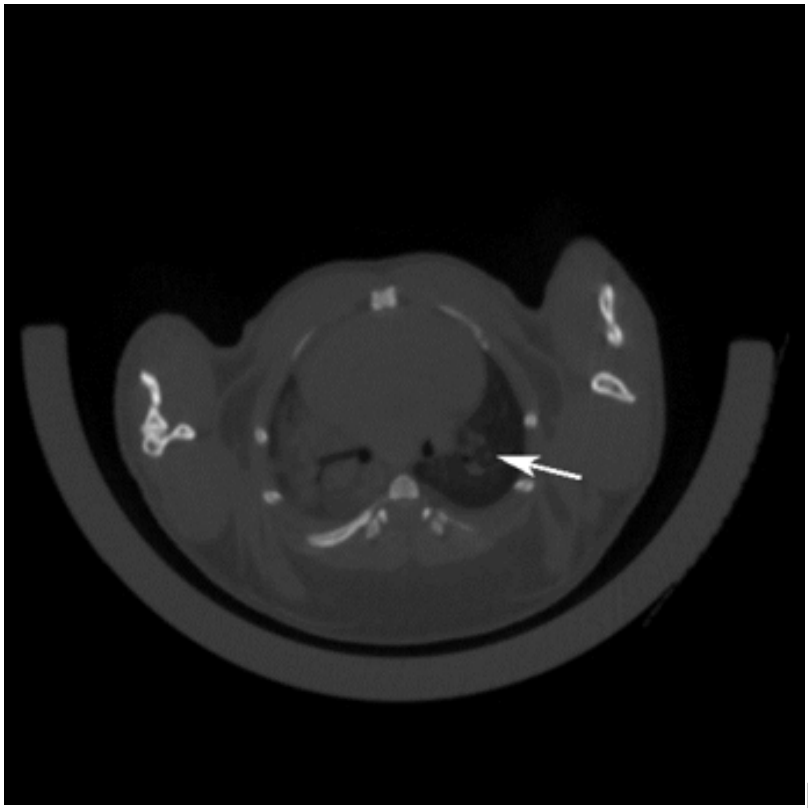


图1. 采用气管内注射的方法，将AAV-cre病毒注射到小鼠肺部，3个月后对小鼠肺部进行CT检测，CT结果显示有明显的肿瘤的形成。

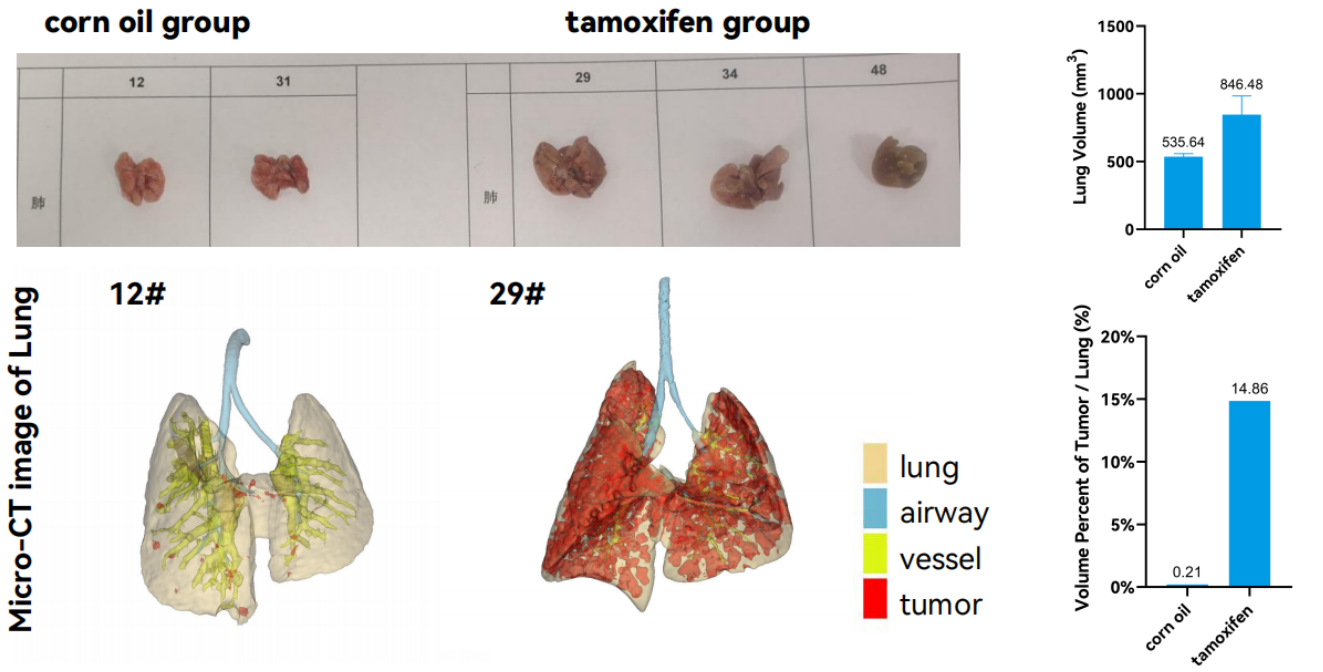


图2. Scgb1a1CreERT2/+; KrasG12D/+小鼠肺部CT检测结果。小鼠经腹腔注射玉米油/他莫西芬5次，5个月后对其肺部进行CT检测。

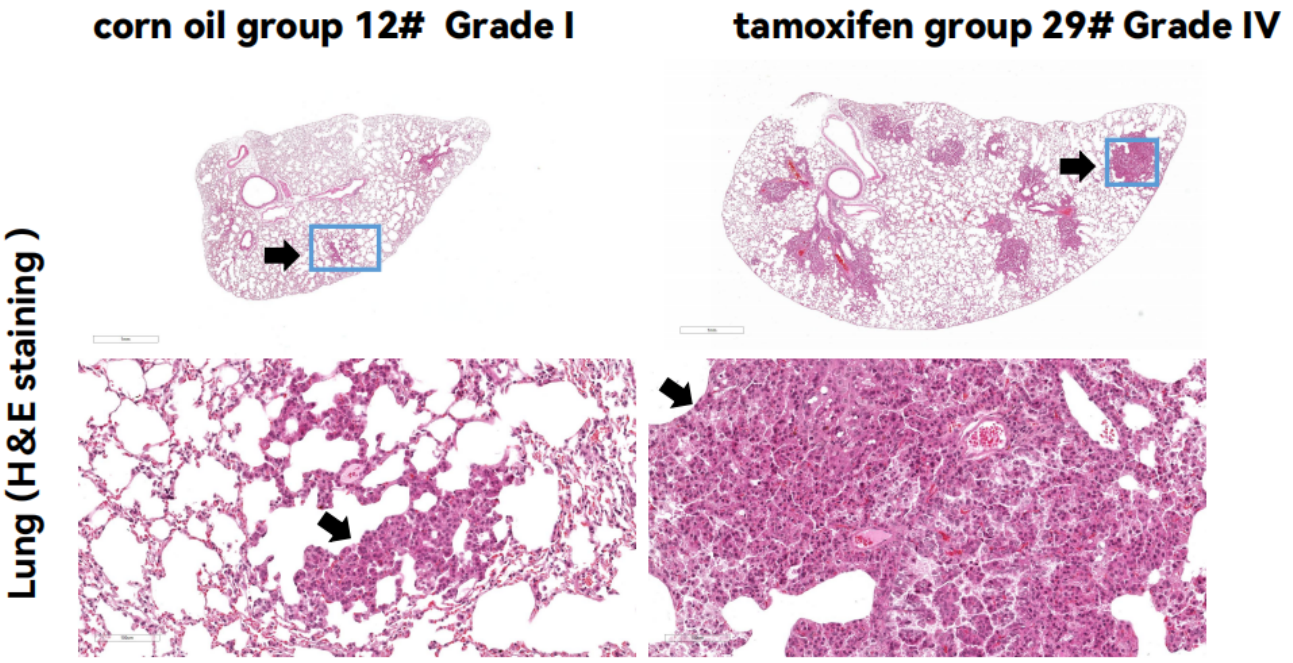


图3. Scgb1a1CreERT2/+; KrasG12D/+小鼠肺组织的H&E染色结果。肺部肿瘤均为肺腺癌，黑色箭头指示肿瘤组织。 Grade I和Grade IV： 动物肿瘤分级。

此外，我们还可以提供Kras(LSL-G12D/+)小鼠肿瘤细胞来源的荷瘤小鼠模型。肿瘤细胞可在受体小鼠体内快速增殖（如图2）。荷瘤小鼠模型可提高临床药效评价实验操作的简便性。

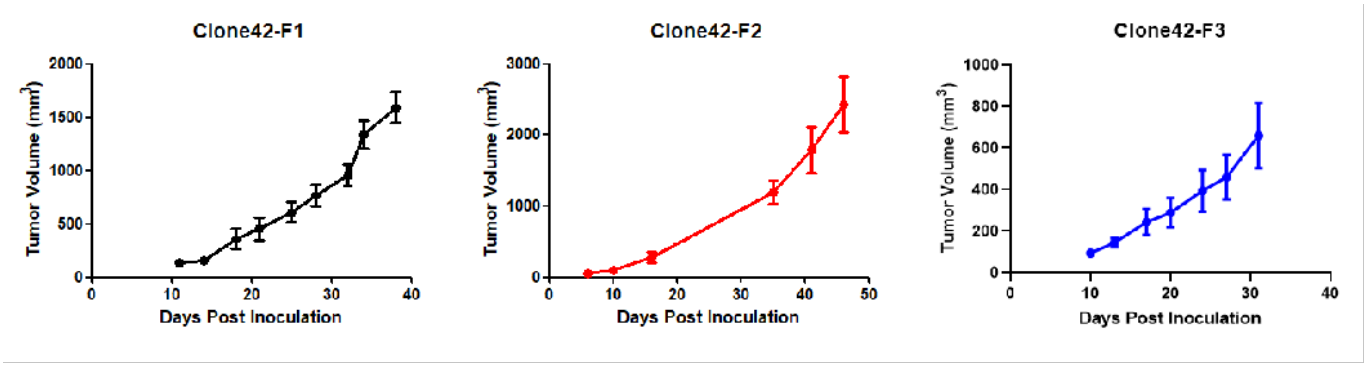


图4. 荷瘤小鼠体内肿瘤细胞体积随时间增长的变化。

KPC胰腺癌模型

小鼠是目前成功建立的一种胰腺导管腺癌模型小鼠，具有很多与人胰腺癌相似的特点，如胰腺内皮细胞瘤形成，强烈的免疫反应。80%的KPC小鼠出现了肝转移和肺转移的现象。KPC小鼠包含了KRAS和TP53基因突变，而在人胰腺癌的研究中发现，分别有80%和70%的患者表达这两种突变蛋白。

KPC小鼠的P53基因含有一个显性抑制性点突变（ TP53R172H ），KRAS基因含有一个条件性活化点突变（KRASG12D）。KRAS突变基因的上游含有lox-stop-lox终止序列，其在没有cre重组酶的条件下是不表达的。将Cre重组酶连接到PDX1的启动子后，其将在胰腺的腺泡、胰岛和导管中表达。在Cre介导的基因重组中，突变的KRAS基因含有的lox-stop-lox终止序列被切除，从而可在胰腺中表达KRASG12D蛋白。

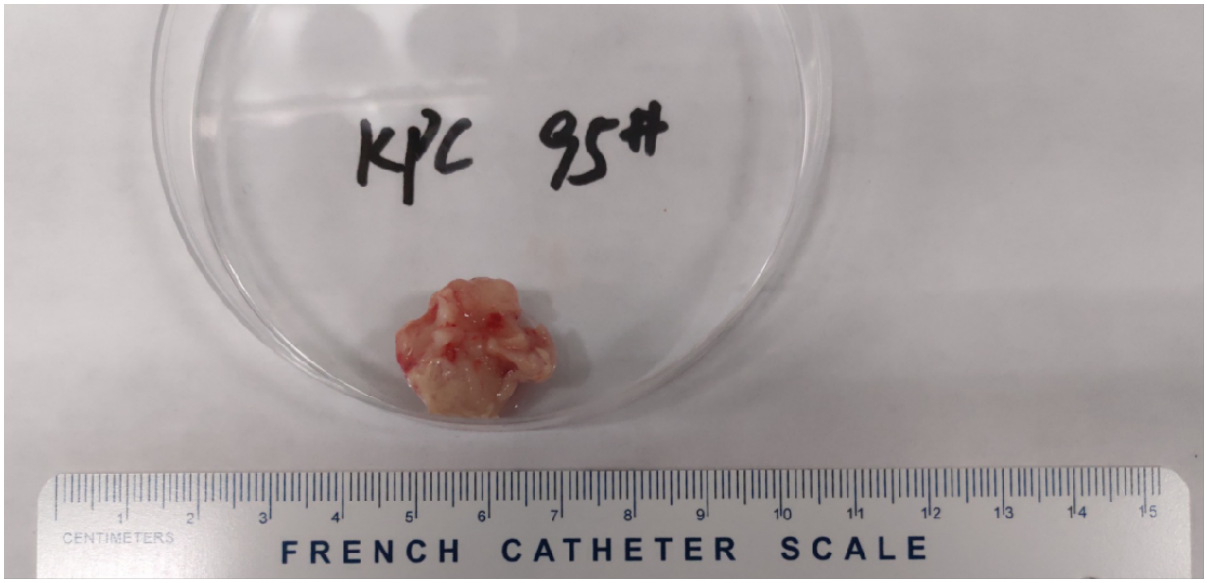
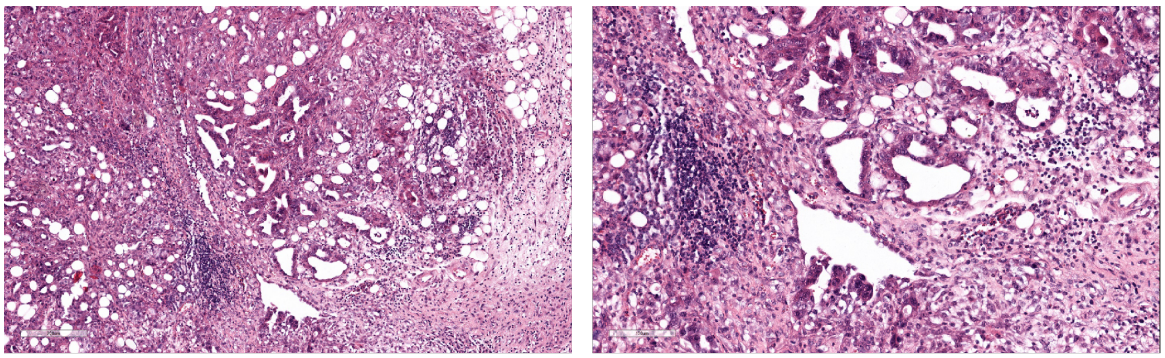


图1 KPC小鼠模型的自发式性胰腺癌体，体积较大，表面不平整，多个结节状突起。



10×　　20×

图2 KPC小鼠的胰腺癌体的HE染色结果。

胰腺细胞排列无序，组织结构呈不规则细胞团，可见胰腺导管增生，炎症细胞浸润，间质纤维形成，符合肿瘤组织结构特征。

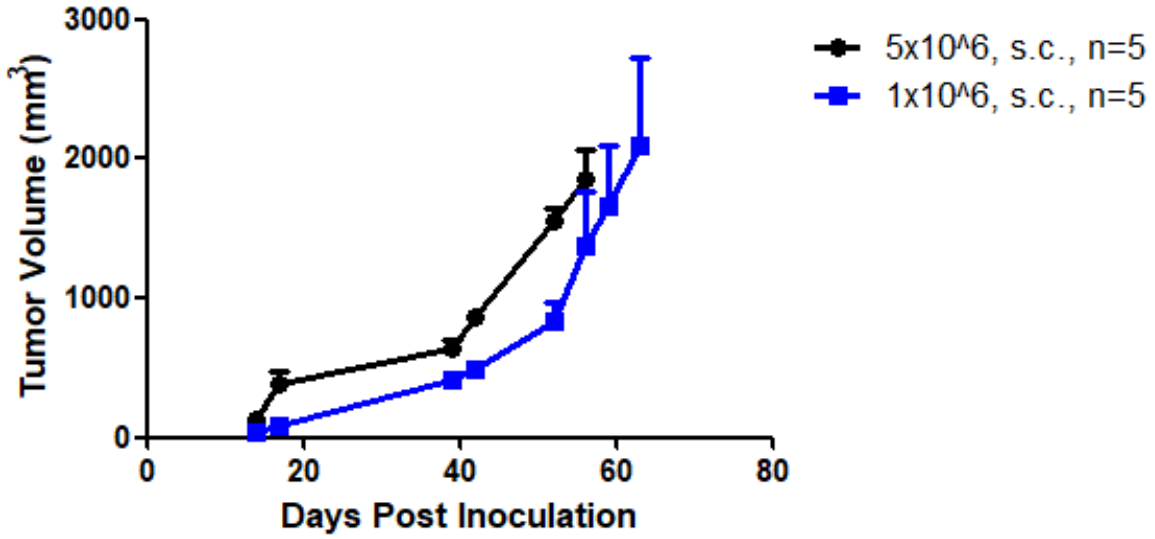


图3 荷瘤小鼠胰腺肿瘤体积的变化。

野生型小鼠接种了KPC小鼠的胰腺癌细胞，随着时间推移，胰腺肿瘤体积越来越大。

通过以下三个类型的小鼠模型，相互交配可以获得上文所述的KPC小鼠，这三类小鼠也可分别与其他感兴趣的模型小鼠交配以满足不同的研究需要。

Trp53-(R172H) NM-KI-18028

Kras-(LSL-G12D) NM-KI-190003

Pdx1-Cre-Tg

Publications