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

exon2 of Kras were replaced by loxp-stop-loxp and exon2 containing G12D. When crossed with a Cre recombinase-expressing strain, this strain is useful in studies of cancer and development.
Research Application: cancer research
*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

Squamous Cell Carcinoma	**Phenotype(s)**	MGI:5556259 Note: The expected phenotype(s) may be observed in the above-mentioned mice that bred with Smad4-Flox(NM-CKO-18011) and Krt1-15-cre mice.
	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

Prostate Cancer	**Phenotype(s)**	MGI:5300204 Note: The expected phenotype(s) may be observed in the above-mentioned mice that bred with Scrib-Flox(NM-CKO-2102030) and Pbsn-cre mice.
	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
Pancreatic Carcinoma	**Phenotype(s)**	MGI:3032576 Note: The expected phenotype(s) may be observed in the above-mentioned mice that bred with Ptf1a-Cre mice.
	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
pancreatic carcinoma	**Phenotype(s)**	MGI:5013917 Note: The expected phenotype(s) may be observed in the above-mentioned mice that bred with Pten-Flox(NM-CKO-18004) and Pdx1-cre mice.
	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
Prostate Cancer	**Phenotype(s)**	MGI:5705321 Note: The expected phenotype(s) may be observed in the above-mentioned mice that bred with Pten-Flox(NM-CKO-18004) and Pbsn-cre mice.
	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

Neurofibromatosis	**Phenotype(s)**	MGI:4849441 Note: The expected phenotype(s) may be observed in the above-mentioned mice that bred with Pten-Flox(NM-CKO-18004) and Gfap-cre mice.
	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
Pancreatic Carcinoma	**Phenotype(s)**	MGI:3032575 Note: The expected phenotype(s) may be observed in the above-mentioned mice that bred with Pdx1-cre mice.
	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
Prostate Cancer	**Phenotype(s)**	MGI:3836577 Note: The expected phenotype(s) may be observed in the above-mentioned mice that bred with Pbsn-cre mice.
	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
Pancreatic Carcinoma	**Phenotype(s)**	MGI:5635880 Note: The expected phenotype(s) may be observed in the above-mentioned mice that bred with P53-Flox(2)(NM-CKO-190067) and Pdx1-cre mice.
	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

Pancreatic Ductal Adenocarcinoma	**Phenotype(s)**	MGI:4941336 Note：The expected phenotype(s) may be observed in the above-mentioned mice that bred with P53-Flox(2)(NM-CKO-190067) and Pdx1-cre mice.
	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
pancreatic ductal adenocarcinoma	**Phenotype(s)**	MGI:5308946 Note：The expected phenotype(s) may be observed in the above-mentioned mice that bred with P53-Flox(2)(NM-CKO-190067) and Pdx1-cre mice.
	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
pancreatic ductal adenocarcinoma	**Phenotype(s)**	MGI:6505560 Note：The expected phenotype(s) may be observed in the above-mentioned mice that bred with P53-Flox(2)(NM-CKO-190067) and Pdx1-cre mice.
	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

Squamous Cell Carcinoma	**Phenotype(s)**	MGI:5298084 Note：The expected phenotype(s) may be observed in the above-mentioned mice that bred with P53-Flox(2)(NM-CKO-190067) and KRT14-cre/ERT mice.
	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
Juvenile Myelomonocytic Leukemia	**Phenotype(s)**	MGI:3035835 Note：The expected phenotype(s) may be observed in the above-mentioned mice that bred with Mx1-cre mice.
	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
juvenile myelomonocytic leukemia	**Phenotype(s)**	MGI:5582314 Note：The expected phenotype(s) may be observed in the above-mentioned mice that bred with Mx1-cre mice.
	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
Urinary Bladder Cancer	**Phenotype(s)**	MGI:5790500 Note：The expected phenotype(s) may be observed in the above-mentioned mice that bred with Ctnnb1-Flox(NM-CKO-200154) and Upk2-cre mice.
	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

Ovarian Cancer	**Phenotype(s)**	MGI:5432224 Note：The expected phenotype(s) may be observed in the above-mentioned mice that bred with Ctnnb1-Flox(NM-CKO-200154) and CYP19A1-cre mice.
	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
ovarian cancer	**Phenotype(s)**	MGI:5432231 Note：The expected phenotype(s) may be observed in the above-mentioned mice that bred with Ctnnb1-Flox(NM-CKO-200154) and Amhr2-Cre mice.
	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
Pancreatic Ductal Adenocarcinoma	**Phenotype(s)**	MGI:5308951 Note：The expected phenotype(s) may be observed in the above-mentioned mice that bred with Cdkn2a-Flox(2)(NM-CKO-200151)，P53-Flox(2)(NM-CKO-190067) and Pdx1-cre mice.
	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
Pancreatic Carcinoma	**Phenotype(s)**	MGI:5441554 Note：The expected phenotype(s) may be observed in the above-mentioned mice that bred with Cdkn2a-Flox(2)(NM-CKO-200151) and Pdx1-cre mice.
	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

Pancreatic Ductal Adenocarcinoma	**Phenotype(s)**	MGI:2687217 Note：The expected phenotype(s) may be observed in the above-mentioned mice that bred with Cdkn2a-Flox(2)(NM-CKO-200151) and Pdx1-cre mice.
	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
Pancreatic Carcinoma	**Phenotype(s)**	MGI:4940096 Note：The expected phenotype(s) may be observed in the above-mentioned mice that bred with Brca2-Flox(NM-CKO-200014)，P53-Flox(2)(NM-CKO-190067) and Pdx1-cre mice.
	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

Validation Data

Pancreatic ductal adenocarcinoma

The KPC mouse is an established and clinically relevant model of pancreatic ductal adenocarcinoma (PDAC) which develops many key features observed in human PDAC including pancreatic intraepithelial neoplasia alongside a robust inflammatory reaction including exclusion of effector T cells. Metastases are observed in around 80% of KPC animals located primarily in the liver and lungs. Mutations in both KRAS and TP53 genes are found in around 80% and 70% of all human PDACs respectively.

Trp53-(R172H) (NM-KI-18028)、Kras-(LSL-G12D) (NM-KI-190003)were crossed with Pdx1-Cre-Tg to generate KPC mice.

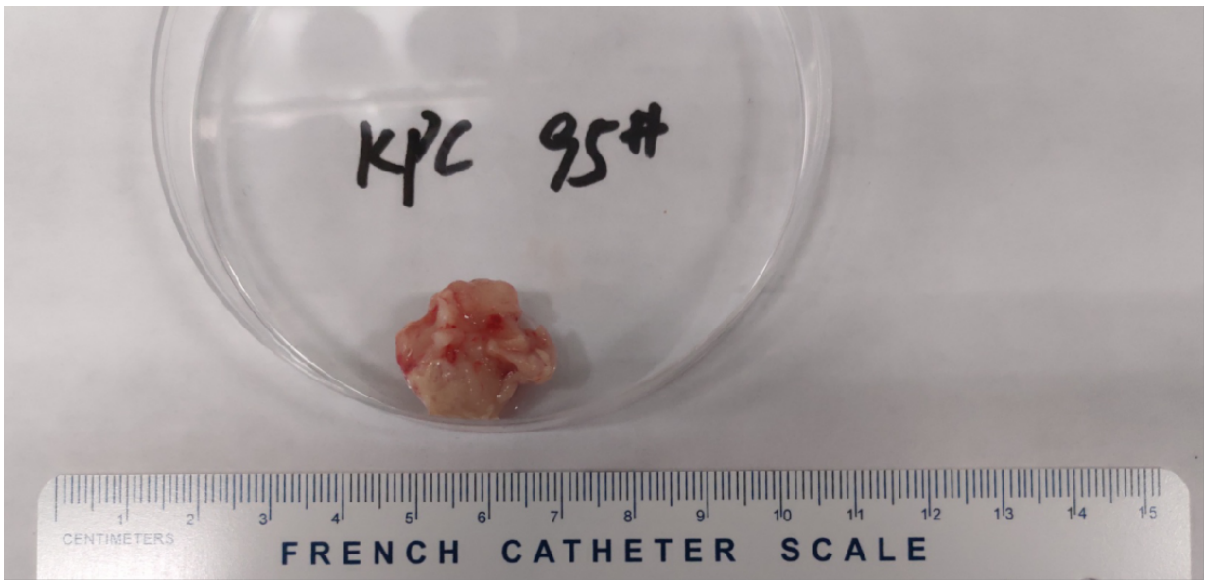
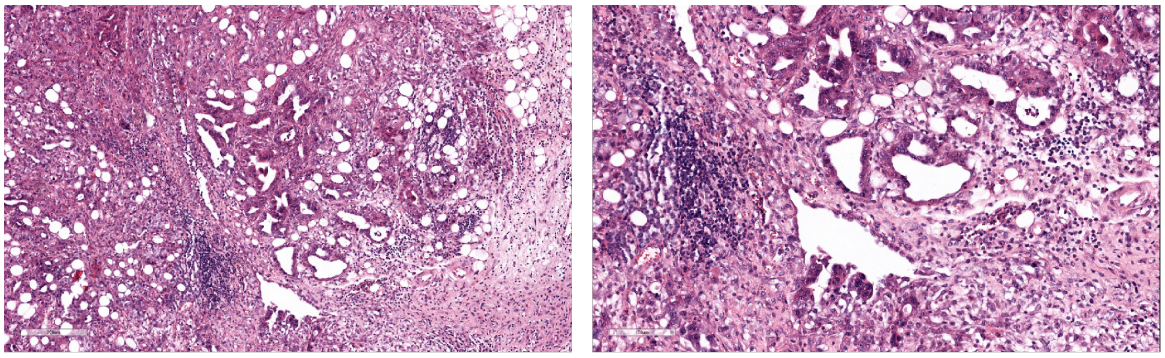


Fig1. The spontaneous pancreatic tumor of KPC mouse model with large volume, uneven surface and multiple nodular projections.



10× 20×

Fig2. H&E staining of pancreatic tumor from KPC mouse model.

The tumor cells from KPC mouse model demonstrated disorderly arranged pancreatic cells, irregular tissue structure, dilated pancreatic ducts, inflammatory cells infiltration and stromal fibrosis as was seen in pancreas adenocarcinoma.

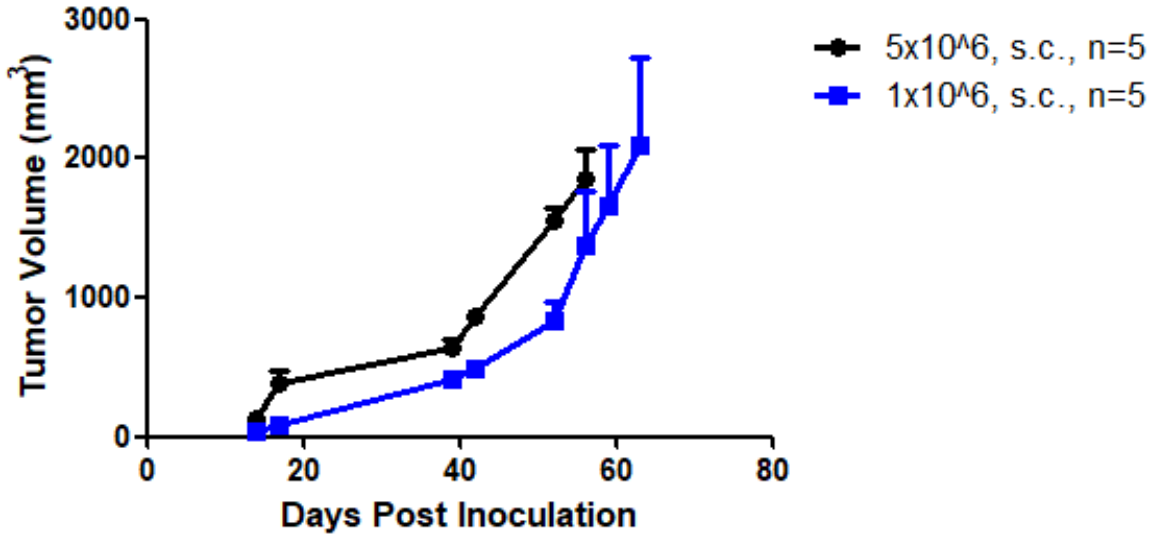


Fig3. Changes in pancreatic tumor volume of tumor-burdened mice.

Wild-type mice were inoculated with pancreatic tumor cells from KPC mice, and pancreatic tumors grew in size over time.

lung cancer model

Lung tumors in mice can be genetically induced by the expression of oncogenes in pulmonary cells. A popular model is $Kras^{LSL\text{-}G12D/+}$ mice that express the Kras G12D oncogene in pulmonary cells after Adeno-Cre or Lenti-Cre inhalation.

This $Kras^{LSL\text{-}G12D/+}$ strain of SMOC carries a point mutation (G12D) whose expression is blocked by the presence of a loxP-flanked stop codon. Homozygotes die in utero.

Cre-mediated recombination can excise the stop codon and permit the oncogenic protein to be expressed. Lung infection with an adenovirus encoding Cre results in a very high frequency of lung tumors(Fig. 1). This strain may be useful in studies of lung cancer and development.

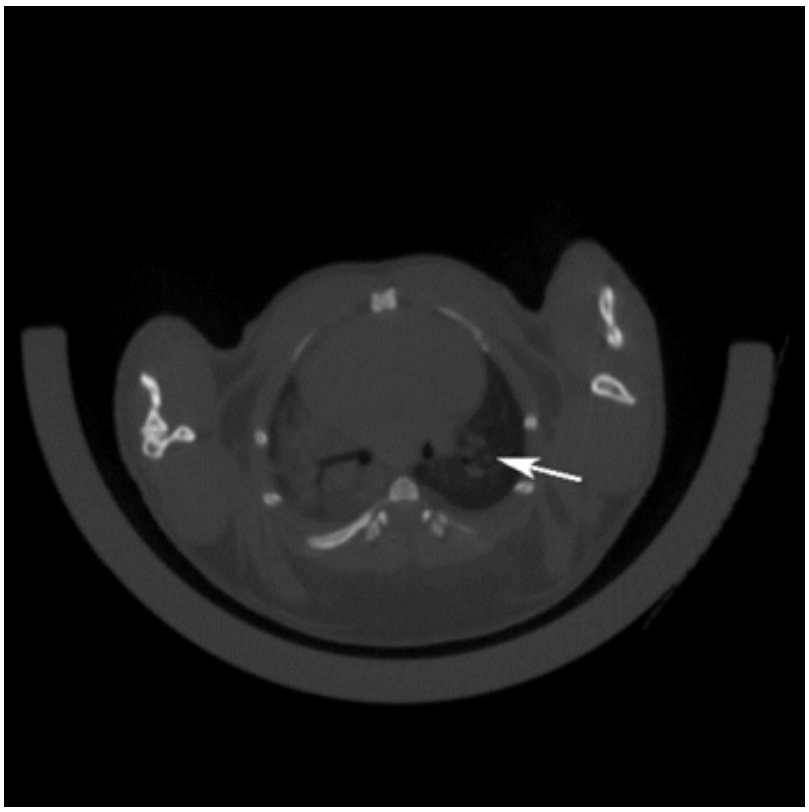


Fig1. Mice were anesthetized and administered AAV-Cre virus by intratracheal injection.

After 3 months, CT scan analysis of the lungs revealed significant tumor formation (arrow marks) in 42# mice.

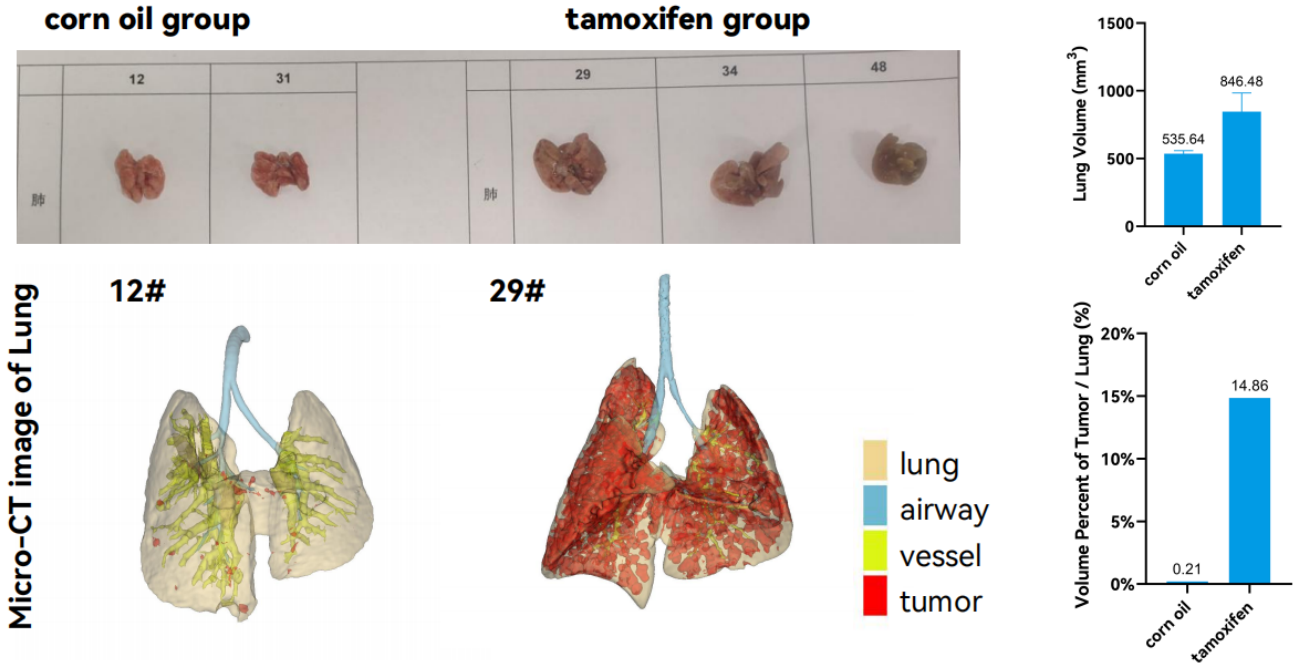


Fig2. CT scan analysis of Scgb1a1$^{CreERT2/+}$; Kras$^{G12D/+}$mice.

The mice were intraperitoneally injected with corn oil/tamoxifen 5 times, and their lungs were examined by CT 5 months later.

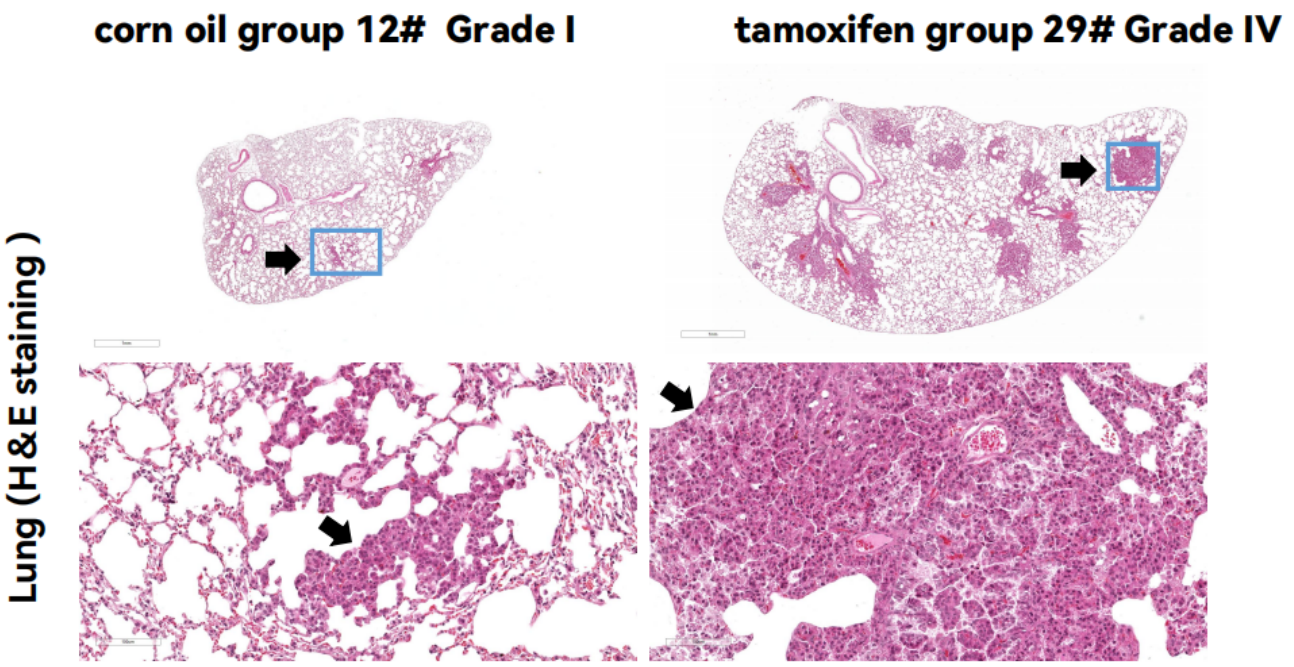


Fig3. H&E staining results of lung tissue of Scgb1a1$^{CreERT2/+}$; Kras$^{G12D/+}$mice.

The tumors are lung adenocarcinoma (Indicated by black arrow). Grade I and Grade IV : grading of animal tumor.

We have developed the mouse allograft lung cancer model (Fig. 4) from Kras$^{(LSL-G12D/+)}$ mice administered with AAV-Cre virus by intratracheal injection (Fig. 1). The mouse allograft lung cancer model grew robustly (Fig. 4) and it can provide improved operational simplicity needed for efficacy studies .

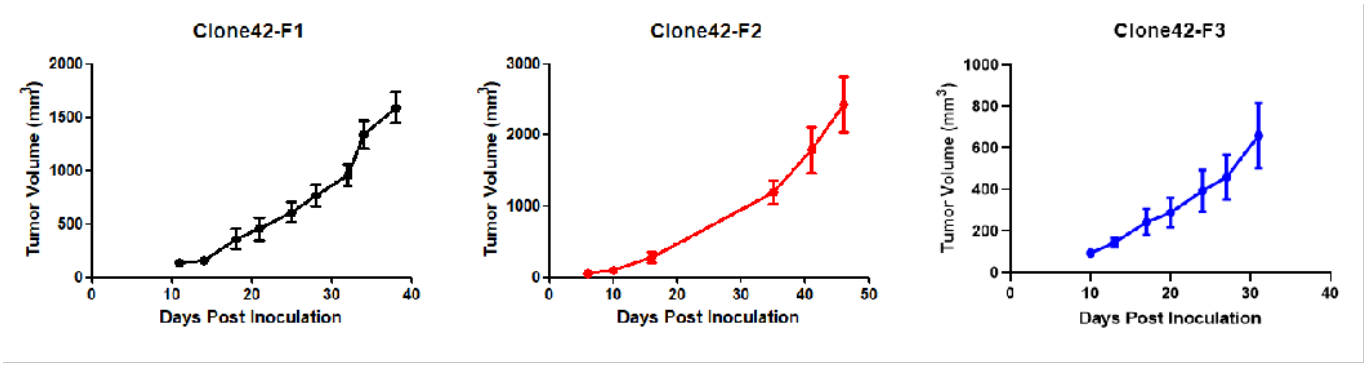


Fig4. The growth of tumors in C57BL/6 mice inoculated with lung cancer tumor from 42# mice.