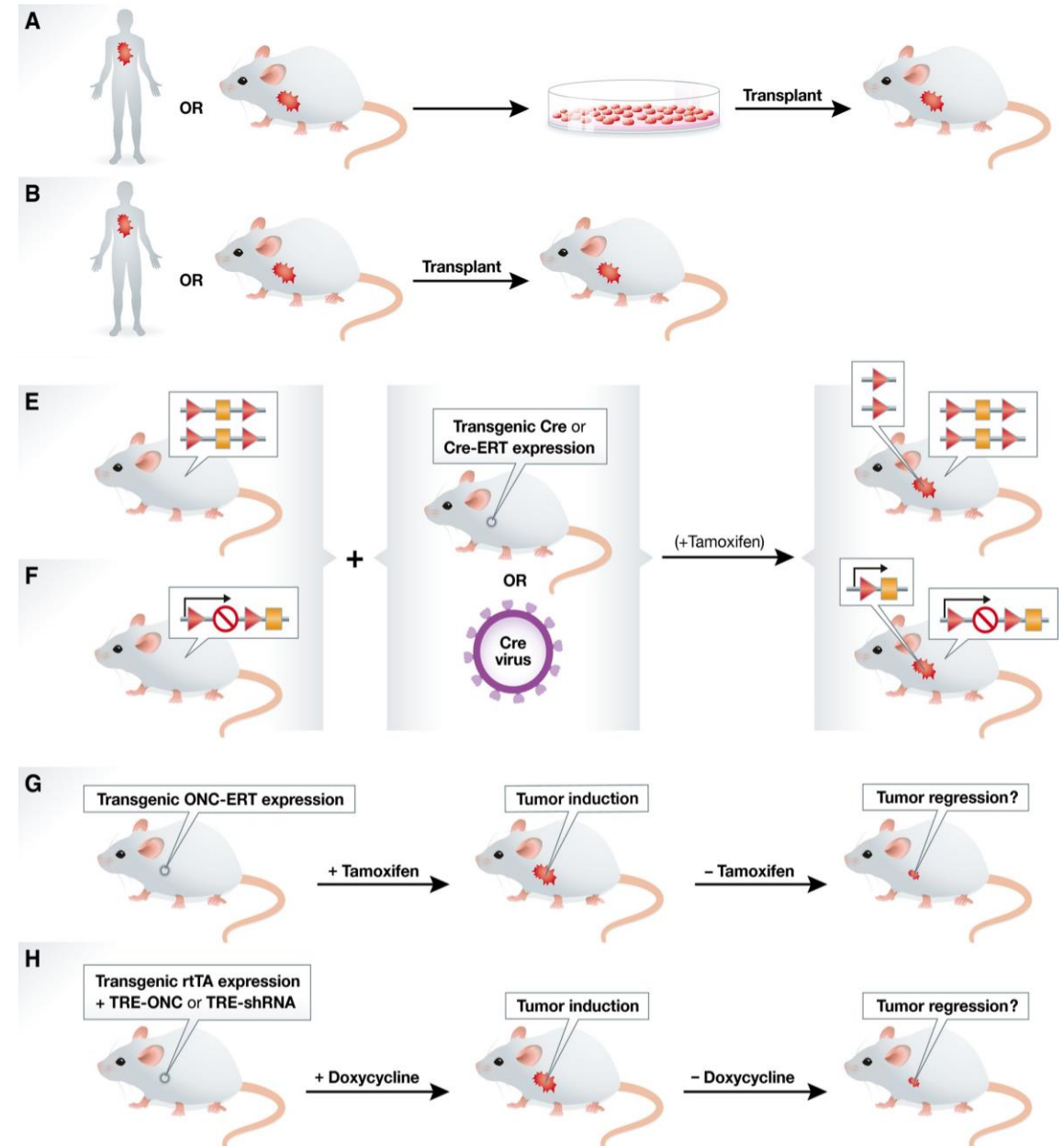


Mouse Models for Cancer Research – An NCI Resource

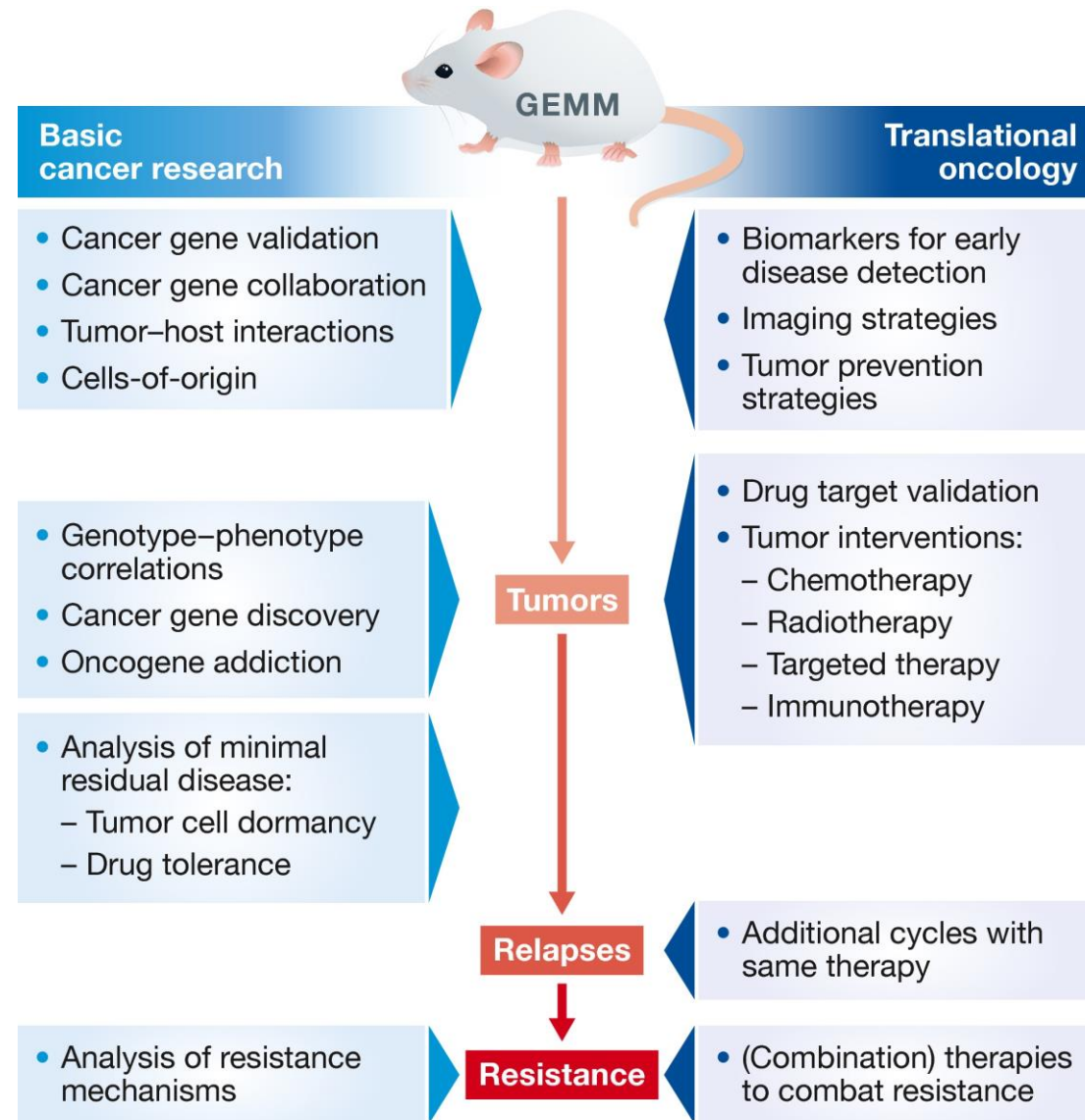
Joanna M. Watson, PhD
Division of Cancer Biology
National Cancer Institute

Mouse Models Used In Cancer Research

- Cell line-derived transplantation models
- Patient-derived xenograft models
- Genetically engineered models
 - Oncomice
 - TSG KO
 - Tissue-specific Cre-loxP*
 - inactivate conditional TSG alleles
 - activate conditional oncogenes
- * Tissue-specific expression of Cre-recombinase achieved by crossbreeding with:
 - Cre-transgenic mice
 - Tamoxifen-inducible Cre-ERT transgenic
 - Or by local administration of Cre-encoding lenti- or adenoviruses
- Tamoxifen- or doxycycline-inducible gene expression



Uses of GEMM for Cancer Research



The NCI Division of Cancer Biology Mouse Models of Human Cancers Consortium



Purpose:

- “To accelerate the pace at which mice with heritable malignancies that are accurate, reproducible models of human cancer are made available to the research community”
 - To develop and validate mouse models with heritable malignancies that parallel human disease
 - To make those models available easily and readily to the cancer research community

Establishment of the Mouse Models of Human Cancers Consortium (MMHCC)

- RFA CA98-013 was issued in July 1998, with awards made September 1999.
 - 18 U01 grants and 1 intramural project; 1 DOD-funded project was added.
 - Eight organ sites were represented: breast, CNS, GI, hematopoietic, lung, ovary, prostate, and skin.
 - Funding approximately \$15M.
- Program was renewed in 2003 (RFA-CA04-002) and in 2008 (RFA-CA08-018), each time bringing in new investigators and models.
- Program ended officially in 2013.

MMHCC Involved Investigators from across the US

Founding Investigators

C Abate Shen

D Albertson

A Balmain

R Coffey

R DePinho

W Dove

J Green

N Greenberg

J Groden

T Hamilton

M Israel

T Jacks

R Kucherlapati

E Lee

D Medina

P Pandolfi

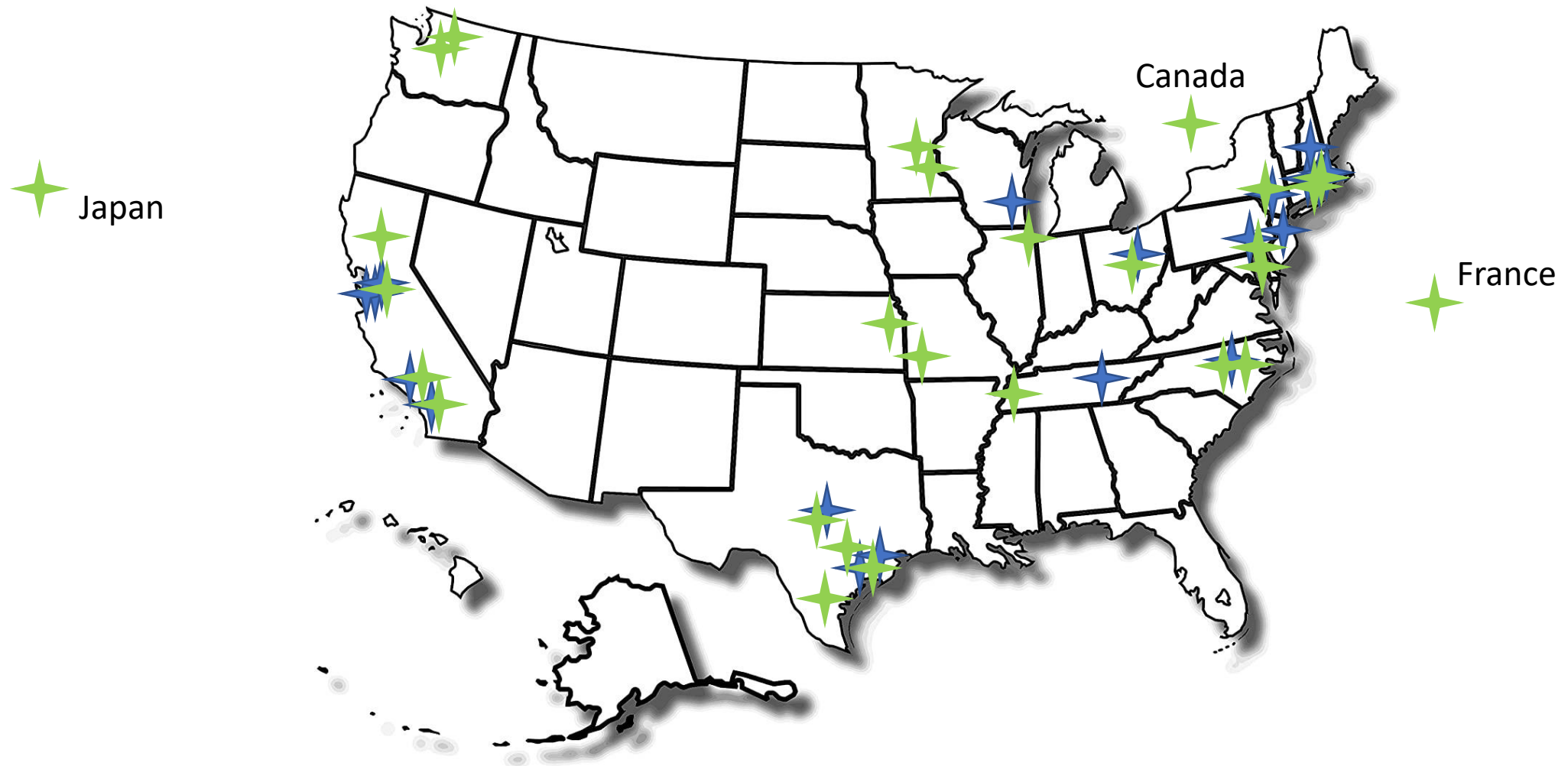
C Sawyers

K Shannon

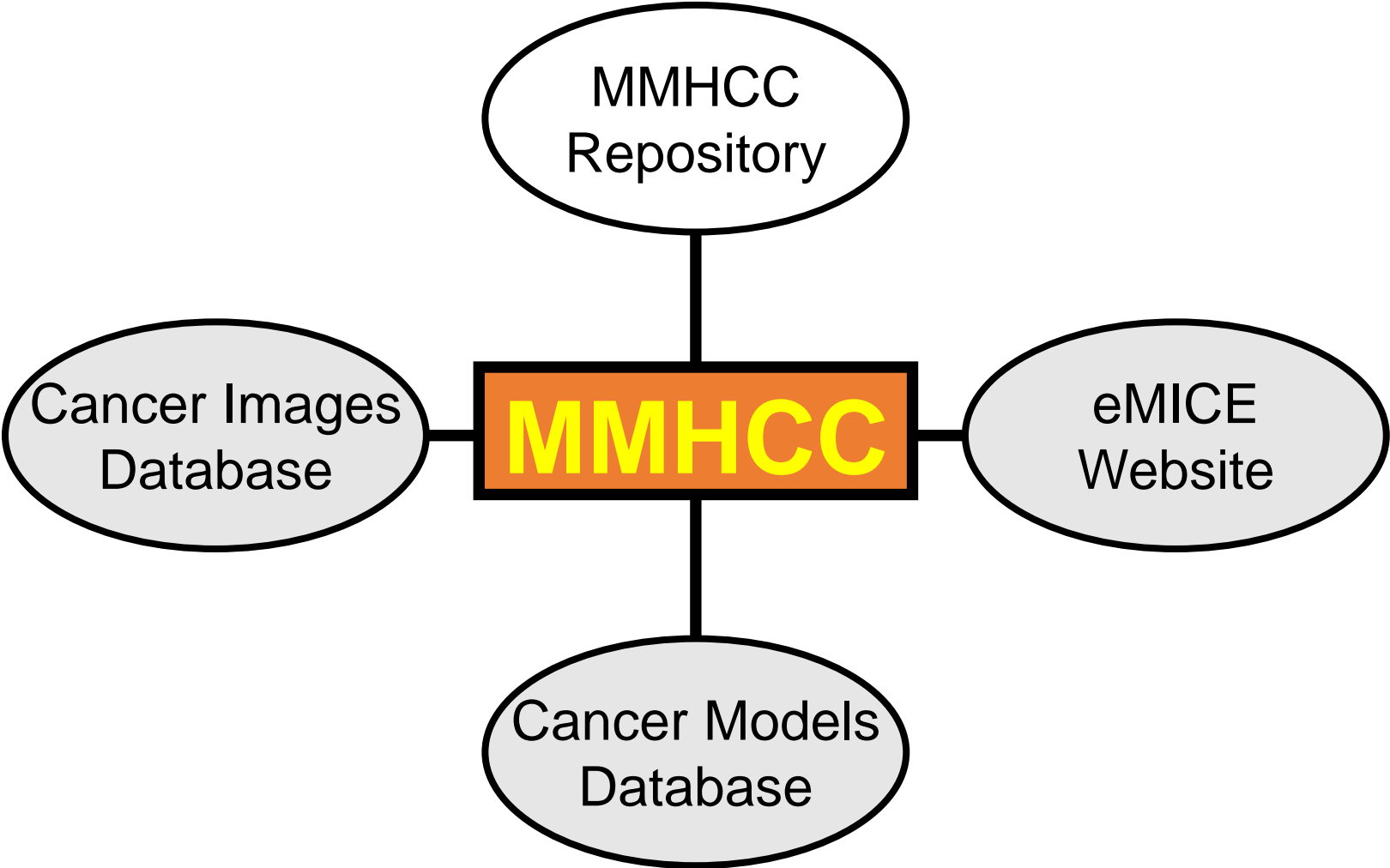
T Van Dyke



MMHCC Created a Community of Mouse Modelers through Collaborations across the US and Internationally

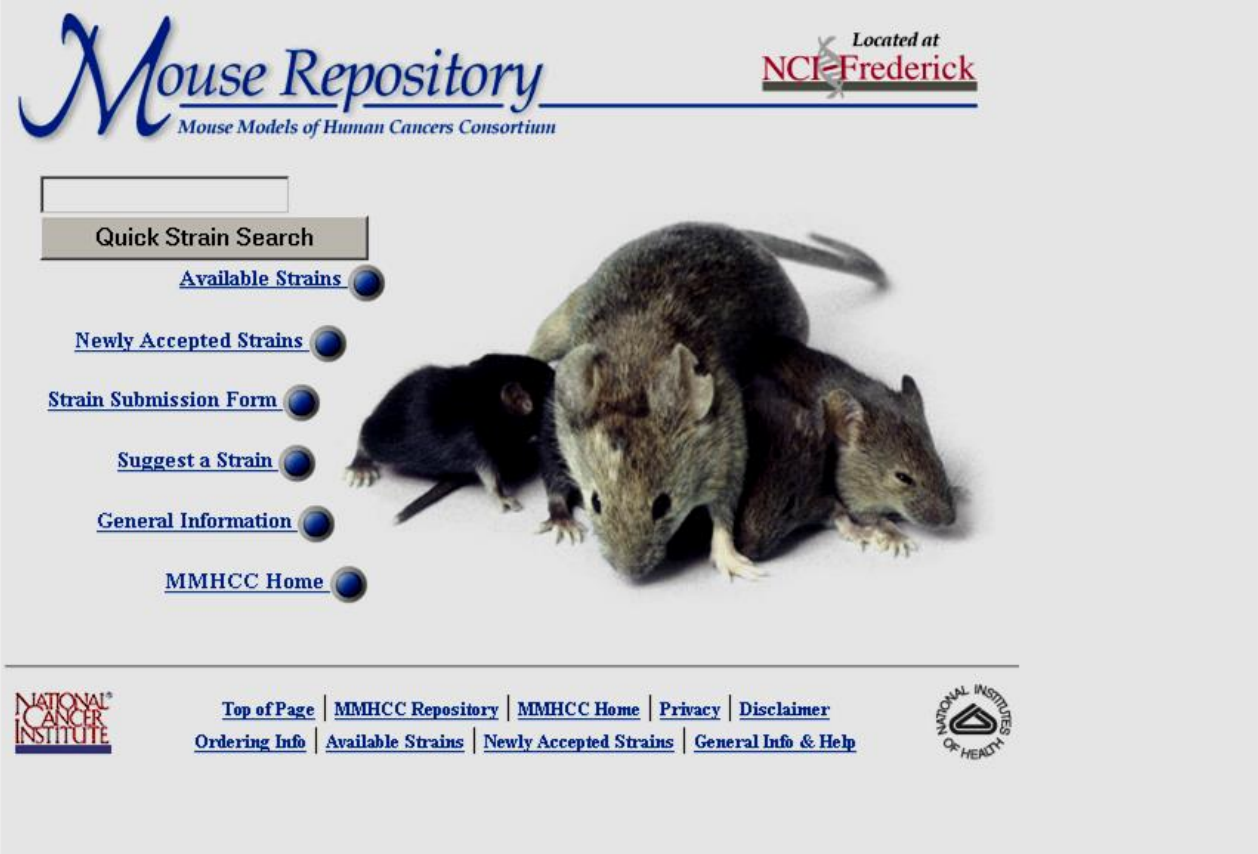


Structure and Goals of the MMHCC:



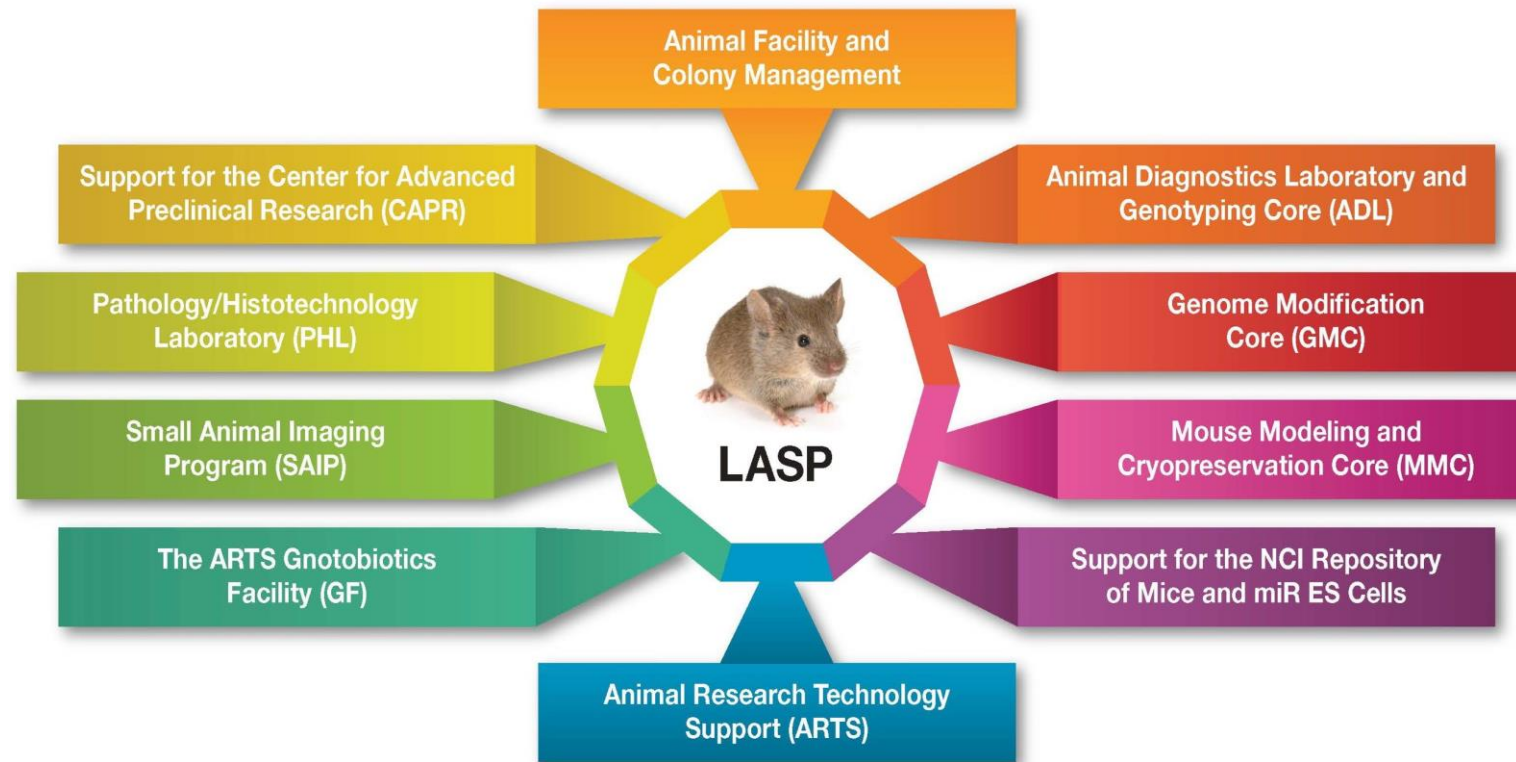
MMHCC Mouse Repository

- Housed at NCI Frederick (FNLCR)
- Provided the community rapid access to newly generated mouse models.
- Designed to receive, quarantine, rederive, cryopreserve, produce, genotype and distribute reposed mouse strains.
- Although MMHCC ended in 2013, the mouse repository continues.



The screenshot shows the Mouse Repository website. At the top left, the logo reads "Mouse Repository" in a large blue script font, with "Mouse Models of Human Cancers Consortium" in a smaller black font below it. To the right, it says "Located at NCI Frederick" with a small mouse icon. Below the logo is a search bar and a "Quick Strain Search" button. A vertical list of links includes "Available Strains", "Newly Accepted Strains", "Strain Submission Form", "Suggest a Strain", "General Information", and "MMHCC Home", each with a blue circular icon. A photograph of several mice is positioned to the right of these links. At the bottom left is the National Cancer Institute logo, and at the bottom right is the National Institutes of Health logo. A horizontal menu of links is located between the logos, including "Top of Page", "MMHCC Repository", "MMHCC Home", "Privacy", "Disclaimer", "Ordering Info", "Available Strains", "Newly Accepted Strains", and "General Info & Help".

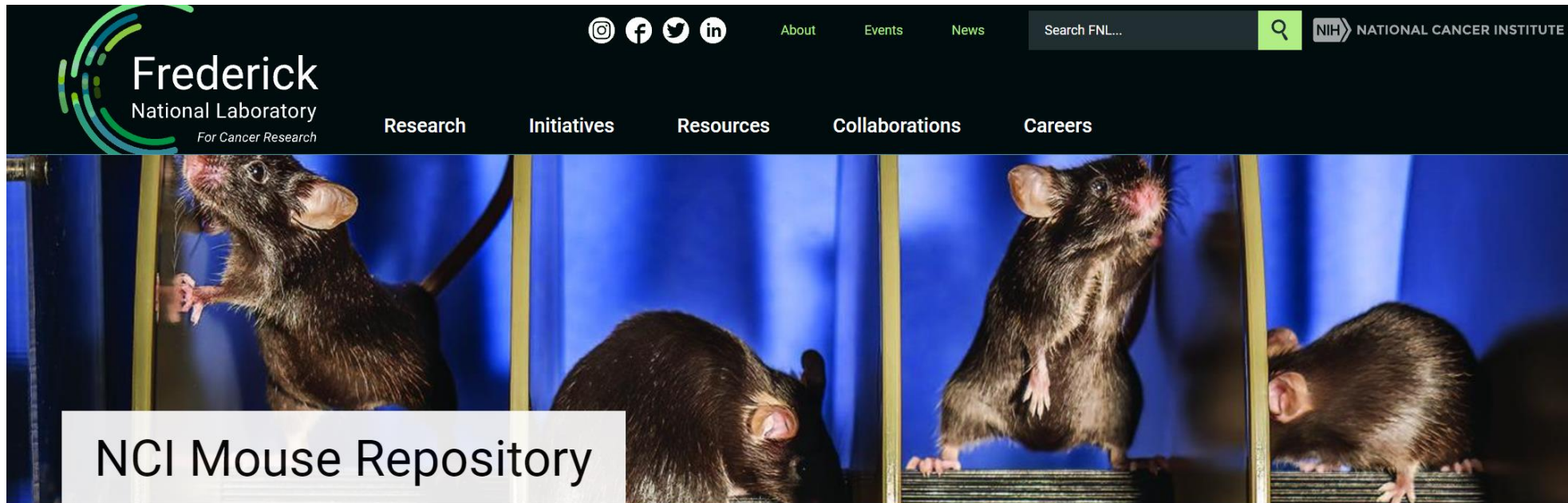
Laboratory Animal Sciences Program at FNLCR oversees the NCI Mouse Repository



LASP serves as a comprehensive resource for FNLCR and NCI scientists performing animal-based pre-clinical research by providing the highest level of animal care, by offering robust and cutting edge scientific support for animal studies, and by ensuring that all investigators' animals are cared for and studied in a humane and highly professional manner (and in full accordance with regulatory guidelines).

Mouse miRNA Embryonic Stem Cell Library

- KH2 (C57BL/6 x 129/Sv) mES cells conditionally express each known murine miRNA.
- In genetically engineered mice, these lines will produce a tet-inducible, reversible system
 - Clones controlled by tetracycline response element (TRE) or TRE-tight, which reduces leakiness and increases restricted expression
 - All clones have a GFP fluorescent reporter
- ***1. mES cell lines with mature microRNAs embedded in a miR30 precursor, designed to control the effect microRNA processing might have on overall expression***
 - a) 509 mESC lines expressing the miR controlled by TRE-tight promoter.
 - b) 299 mESC lines expressing the major miR controlled by TRE promoter.
- ***2. mES cell lines with mature microRNA species in their endogenous context (referred to as: Primary-miRNAs)***
 - a) 261 mESC lines expressing the miR controlled by TRE-tight promoter.
 - b) 432 mESC lines expressing the miR controlled by TRE promoter.
- Distribution restricted to US, with nominal fee for ES cell line processing.



Mouse models

The repository distributes more than 150 mouse models for human cancers. The models are archived as cryopreserved germplasm (embryos and/or sperm) and are available to the scientific community at no charge. The requestor is responsible for all shipping fees and must provide the liquid nitrogen dry shipper for the transport of the material.

Learn More

Mouse Models

[General Information](#)[Ordering Information](#)[Pricing Information](#)[Available Strains](#)[Newly Accepted Strains](#)[Strains Submission Form](#)[FAQs](#)[Contacts](#)[NCI Mouse Repository Home Page](#)

NCI Mouse Repository

General Information about the NCI Mouse Repository

The Repository

The NCI Mouse Repository is an NCI-funded resource for mouse cancer models and associated strains. The repository makes strains available to all members of the scientific community (academic, non-profit, and commercial). **NCI Mouse Repository strains are cryoarchived and distributed as frozen germplasm (embryos and/or sperm).**

For a complete list of available strains, [click here](#).

Researchers are encouraged to submit their cancer models to the NCI Mouse Repository for archiving and distribution. [Submission requests](#) are reviewed and evaluated by the NCI Mouse Repository.

Distribution Conditions

Strains may not be transferred to third parties. The donating institution sets the distribution terms for each strain by designating a "Release Category" in an incoming Material Transfer Agreement (MTA).

Release Categories

- **Category A:** Mouse stocks may be used for research or commercial purposes without an agreement with the donor.
- **Category B:** Recipient may use mouse stocks for research purposes and must sign an agreement with the Donor's institution for commercial use* before using or incorporating the mouse stocks for commercial purposes.
- **Category C:** Mouse stocks may be used for research purposes only. Recipient must not use or incorporate the mouse stocks for commercial purposes.*

Mouse Models

General Information

Ordering Information

Pricing Information

Available Strains

Newly Accepted Strains

Strains Submission Form

FAQs

Contacts

NCI Mouse Repository Home Page

NCI Mouse Repository

Available Strains

The following strains are currently being distributed from the NCI information on the process of ordering mouse models from the details on that strain. You can sort on selected columns by

STRAIN NUMBER	COMMON STRAIN NAME	GENE/TRANSGENE SYMBOL	OR
01BM1	Bloom homolog mutant	Blm	All
01BM2	K-rasLA1	Kras	Lung
01BM3	K-rasLA2	Kras	Lung
01BQ0	B6.Cg-macroH2A1.2 KO	Macroh2a1	whole
01BZ0	Ovyp1-iCreERT2	Cre	ovidu
01CMM	miR-10b KO	miR-10b	Whole
01CXG	IDH2_R140Q	IDH2	

NCI Mouse Repository

Available Strain Details

Strain Information

Strain Number: 01BM2
Common Strain Name: K-rasLA1
Strain Nomenclature: B6.129S2-Kras^{tm2Tyj}
Animal State: Frozen Embryo & F
Release Category (Required for MTA B₁ form):

[Sample MTA for this Strain](#)

Strain Description: This strain carries a can be activated by ('run'). One half of the normal K-ras allele (rasG12D). Mice can death/sacrifice of 30. The most frequent c tumors are present similar to human no Immunohistochemis II cell lineage. Metas other visceral organ sites include the thy (papillomas). A com recombines to the a

Mutation Information

Mutation Type: Targeted

Mutation Information

Mutation Type: Targeted
Gene Name: Kirsten rat sarcoma oncogene, 2 expressed
Gene Symbol: Kras
Transgene Name:
Transgene Symbol:
Promotor Name:
Promotor Symbol:
Current Genetic Background: B6.129S2
Approx. Generation: 21
Organ Site: Lung

Additional Information

Cryopreservation Mating Scheme: EMBRYOS: The cryopreservation mating scheme is C57BL/6 females x heterozygous males. SPERM: Sperm was obtained from heterozygous males. When maintained as a live colony, breeder pairs were supplied as a heterozygote (male or female) x wildtype C57BL/6 (male or female).
Protocol 1: [Allele: Kras<tm2Tyj>](#)

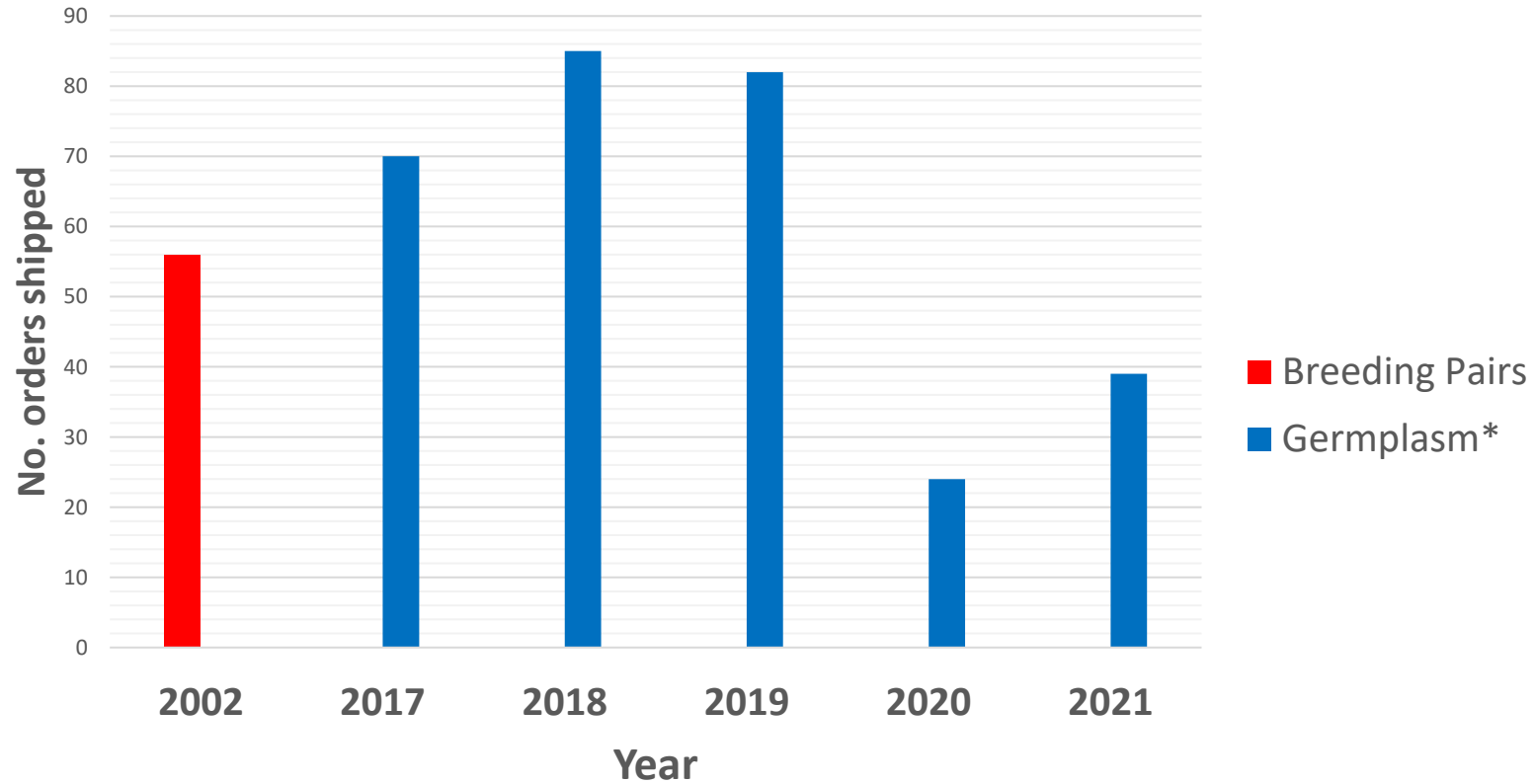
Donating Investigator: Dr. Tyler Jacks

Key Reference: Johnson L, Mercer K, Greenbaum D, Bronson RT, Crowley D, Tuveson DA, Jacks. 2001. Somatic activation of the K-ras oncogene causes early onset lung cancer in mice. Nature 410:1111-6. PMID: 11323676
[\[PubMed Abstract\]](#)

Related Reference: Huarte M1, Guttman M, Feldser D, Garber M, Koziol MJ, Kenzelmann-Broz D, Khalil AM, Zuk O, Amit I, Rabani M, Attardi LD, Regev A, Lander ES, Jacks T, Rinn JL. A large intergenic noncoding RNA induced by p53 mediates global gene repression in the p53 response. Cell. 2010 Aug 6;142(3):409-19. PMID: 20673990 PMCID: PMC2956184

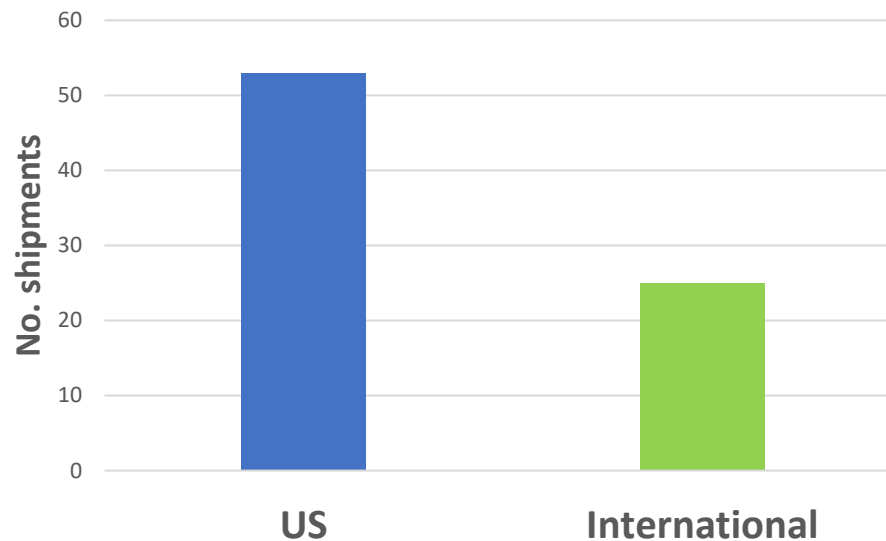
Strains are unique to the NCI Mouse Repository and not available elsewhere!

NCI Mouse Repository – Orders Shipped (2017 – 09/2021)

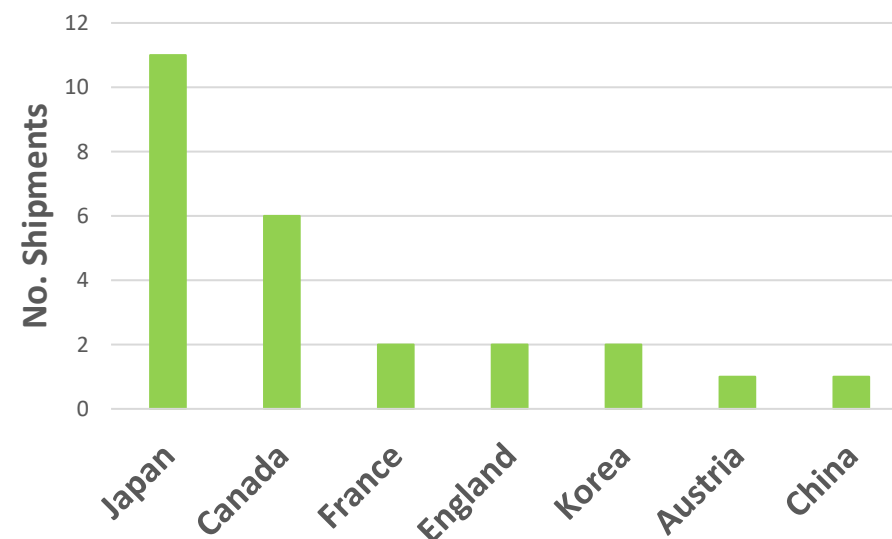


*Germplasm – embryos, sperm

NCI Mouse Repository: Orders Shipped Across the US and Internationally (Q4 2019 – Q3 2021)



Baylor	Moffitt	UC Berkeley	UT SW
Cincinnati Children's Hosp.	MUSC	UCLA	U Utah
City College NY	NIH/NHGRI	U Colorado	U Washington
Dartmouth	Penn State	U Maryland	Vanderbilt
Duke	Rockefeller	U Michigan	Washington Univ
Mass Gen. Hosp.	Rutgers	U Oklahoma	Weill Cornell
MD Anderson	Sanford Burnham	U Penn	West Virginia U
Mich. State	Stanford	U Pittsburgh	



Frequently Requested Strains (09/2017 – 09/2021)

Common Strain	Common Description
LSL-p53 R172H	Point-mutant allele of Trp53, activated by Cre-mediated recombination. Functions as null mutation.
p16-luc	Luciferase knockin mouse, faithfully reports expression of p16 (INK4a).
Ink4a/Arf null (B6)	Targeted deletion of exons 2/3 of the INK4a/ARF locus, eliminating both p16 and p19.
Hi-Myc	Express human c-Myc in mouse prostate uses the rat probasin promoter.
Brca2 floxed	Conditional mutation in the endogenous Brca2 gene. LoxP sites surround exon 11. Creates same phenotype as Brca2-null mutation.
EGFR-L858R	Cross with appropriate rtTA strain for inducible expression of EGFR L858R allele.
ED-L2/Cre	Cre expression in epithelia of tongue, esophagus, forestomach.

Original Article

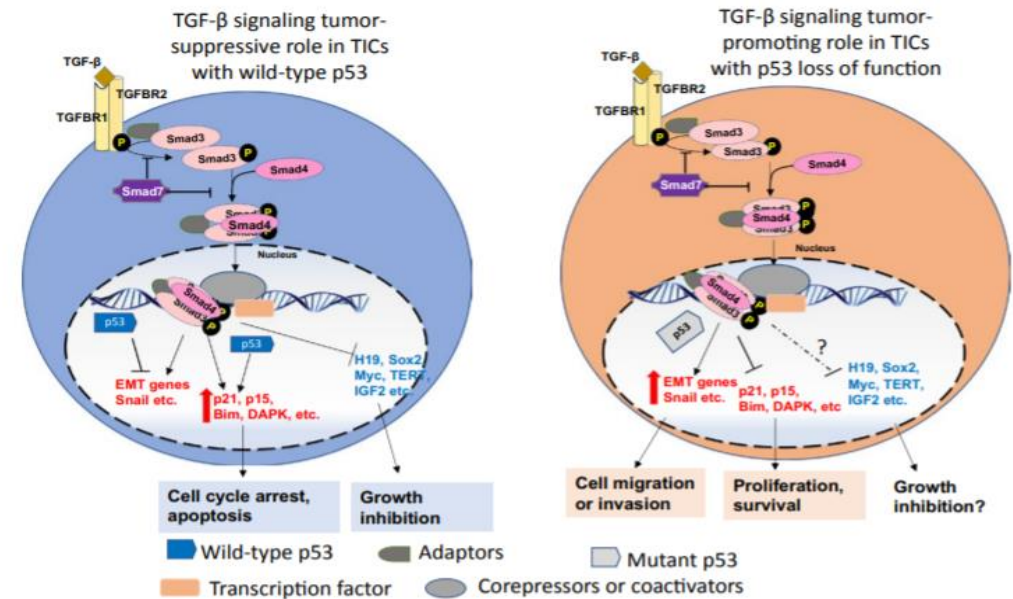
A Transforming Growth Factor- β and H19 Signaling Axis in Tumor-Initiating Hepatocytes That Regulates Hepatic Carcinogenesis

Jinqiang Zhang, Chang Han, Nathan Ungerleider, Weina Chen, Kyoungsub Song, Ying Wang, Hyunjoo Kwon, Wenbo Ma, Tong Wu✉

2019; 69:1549-63

Mouse model:

B6.129S6-Tgfbr2^{tm1Hlm} (Tgfbr2 flox)

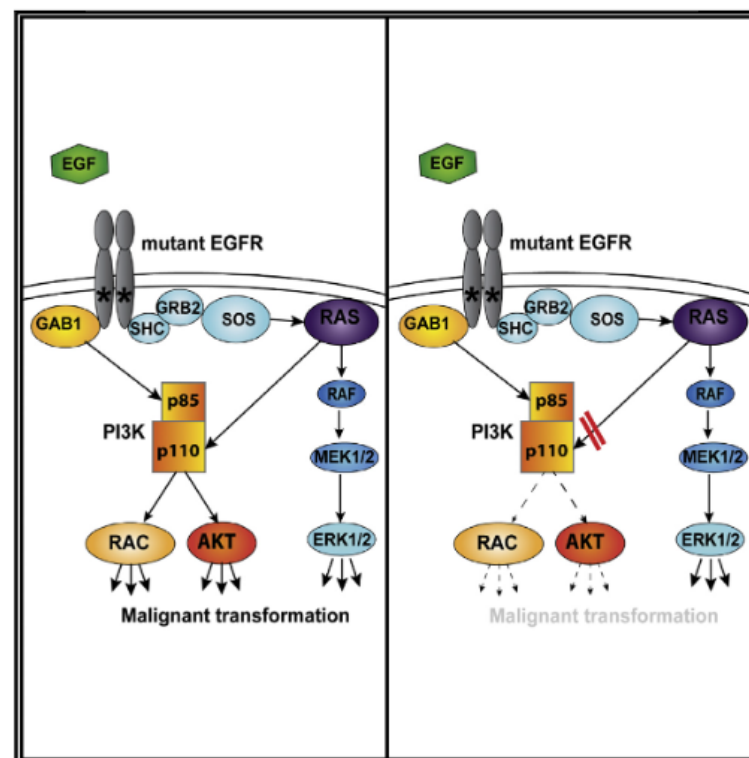


Cell Reports

Disruption of the Interaction of RAS with PI 3-Kinase Induces Regression of EGFR-Mutant-Driven Lung Cancer

2018; 25:3545-3553.e2

Graphical Abstract



Authors

Miguel M. Murillo, Sareena Rana, Bradley Spencer-Dene, Emma Nye, Gordon Stamp, Julian Downward

Correspondence

julian.downward@crick.ac.uk

In Brief

The interaction between RAS and PI 3-kinase is essential for RAS-mutant-induced carcinogenesis. Murillo et al. show that in EGFR-mutant-driven lung cancer, disruption of the interaction of PI 3-kinase with normal RAS proteins blocks tumor initiation and promotes regression of existing tumors, highlighting an unexpected vulnerability of EGFR-driven lung cancer.

Mouse model:
B6;CBA-Tg(tetO-EGFR*L858R)56Hev/Nci
(Tet-inducible EGFR-L858R)

ARTICLE

<https://doi.org/10.1038/s41467-021-21160-0>

OPEN



Malignant subclone drives metastasis of genetically and phenotypically heterogenous cell clusters through fibrotic niche generation

Sau Yee Kok¹, Hiroko Oshima^{1,2}, Kei Takahashi³, Mizuho Nakayama^{1,2}, Kazuhiro Murakami⁴, Hiroki R. Ueda^{5,6}, Kohei Miyazono³ & Masanobu Oshima^{1,2}

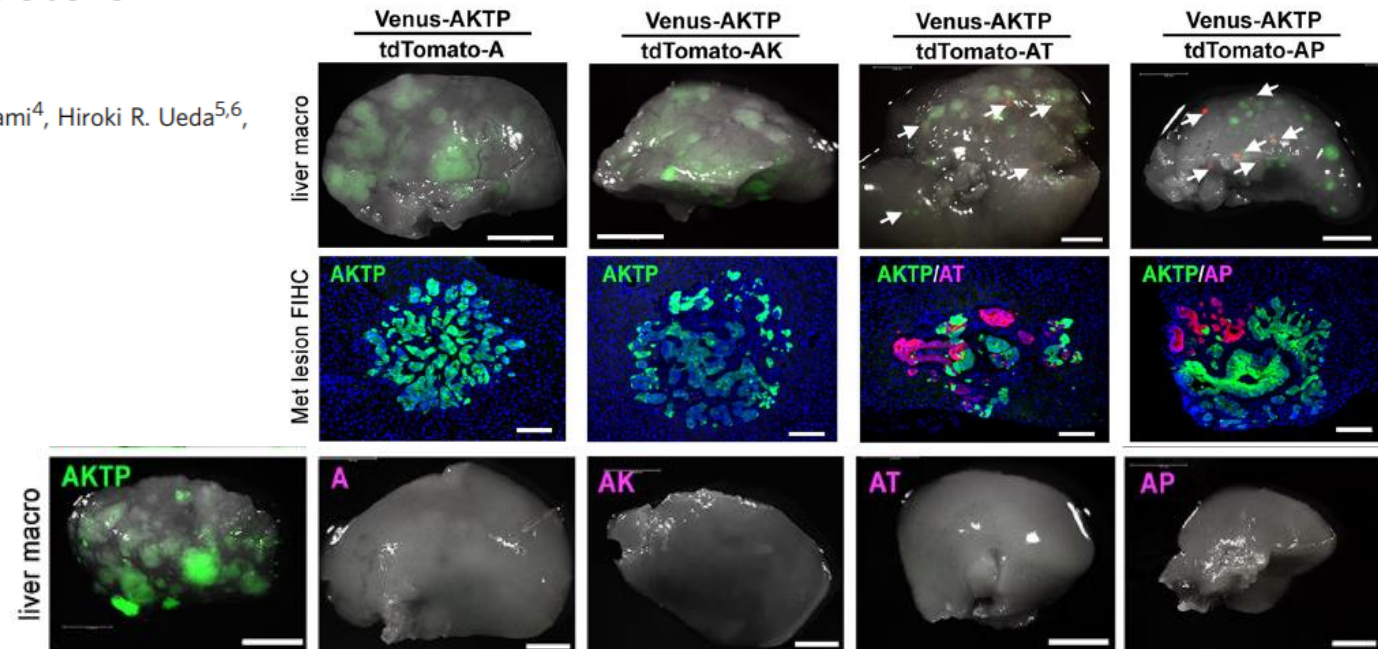
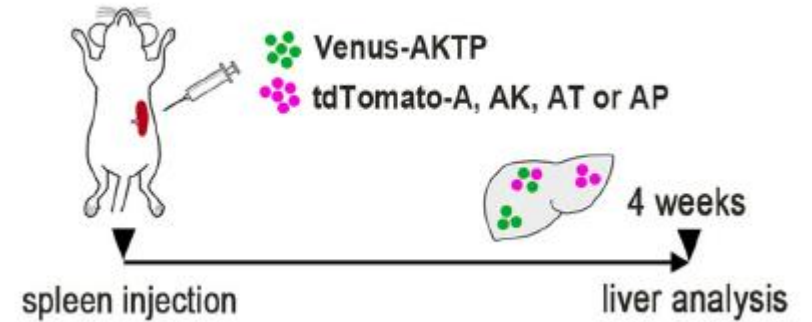
2021; 12:863 doi: 10.1038/s41467-021021160-0

Mouse models:

B6.129S6-Tgfb^{r2}^{tm1Hlm} (Tgfb^{r2} flox)

129S4-Trp53^{tm3Tyj/Nci} (Trp53 LSL R270H)

B6;129-Gt(ROSA)26Sor^{tm1(cre/Esr1)Tyj/Nci} (ROSA-CreER)



ARTICLE OPEN

Therapeutic targeting of *BRCA1* and *TP53* mutant breast cancer through mutant p53 reactivation

Bing Na^{1,2}, Xin Yu^{1,2}, Tracy Withers², John Gilleran^{3,4}, Ming Yao², Tzeh Keong Foo^{2,5}, Chunxia Chen^{2,6}, Dirk Moore^{2,6}, Yong Lin^{2,6}, S. David Kimball^{2,3,4,7}, Bing Xia^{2,5}, Shridar Ganesan^{2,8,9} and Darren R. Carpizo^{1,2,8,10}

2019; 5:14

Mouse models:

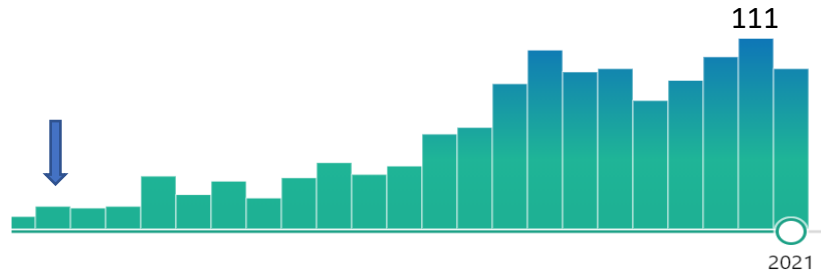
B6.Cg-Tg(Wap-Cre)11738Mam/Nci (Wap-Cre)

129S4-Trp53^{tm2Tyj/Nci} (Trp53 LSL 172H)

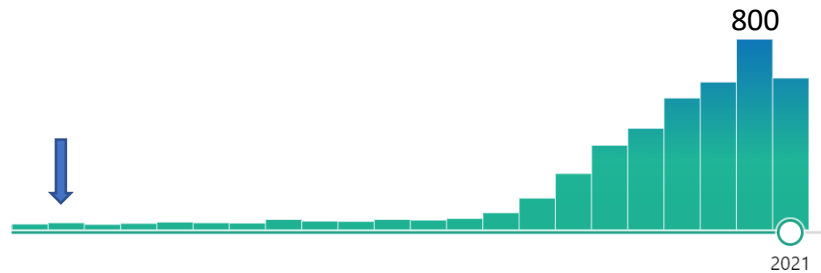
B6;129-Gt(ROSA)26Sor^{tm1(cre/Esr1)Tyj/Nci} (ROSA-CreER)

Mouse Models In Cancer Research Publications Since 2000

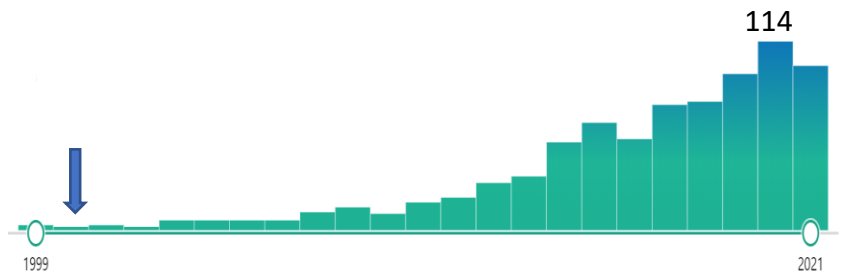
PubMed records



Genetically Engineered Mouse Models



Patient-Derived Mouse Models



Humanized Mouse Models

Outreach for the NCI Mouse Repository

General Efforts:

- DCB Public Website (Research Resources)
- DCB New Grantee Workshop
 - NCI Resources for Investigators
- DCB social Media Platforms
- Annual AACR meetings
- Seminars given by LASP Director

Targeted Efforts:

- Oncology Models Forum
 - Annual Meeting
 - Quarterly Seminar Series
- International Society for Transgenic Technologies meetings (LASP)



Summary:

- NCI Mouse Repository was developed as part of the MMHCC more than 20 years ago.
- NCI Mouse Repository accepts and provides validated mouse models to the research community at minimal cost (just shipping) domestically and internationally.
- With the exception of 2020, requests for mouse models are consistent from year to year.
- The repository is a valuable, unique resource of mouse models relevant to cancer research.

Questions?

- Questions about deposition or acquisition of mouse strains or miRNA ESC cells
 - MouseRepository@mail.nih.gov
- Information about the repository can be found:
 - <https://Frederick.cancer.gov/resources/repositories/nci-mouse-repository>
- Questions about Division of Cancer Biology:
 - <https://www.cancer.gov/about-nci/organization/dcb>