

Newly available JAX[®] Mice strains

Below is a partial list (13) of newly available JAX[®] Mice strains. For a complete list, see www.jax.org/jaxmice/newstrains.

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Transgenic Strains

B6.Cg-Tg(CAG-Ub*G76V/GFP)1Dant/J 008111
B6.Cg-Tg(CAG-Ub*G76V/GFP)2Dant/J 008112

Both ubiquitin/proteasome system reporter lines, UbG76V-GFP/1 (008111) and UbG76V-GFP/2 (008112), may be used to monitor the role of ubiquitin/proteasome-dependent proteolysis in diverse disorders, and to test the efficacy of compounds on the ubiquitin/proteasome system.

B6.Cg-Tg(tetO-cre)1Jaw/J 006234
FVB.Cg-Tg(tetO-cre)1Jaw/J 008244

Transgenic tetO-cre mice express Cre recombinase under the control of a tetracycline-responsive promoter element (TRE or tetO). When bred with a transgenic strain expressing a reverse tetracycline-controlled transactivator protein, or (r) tTA, they produce bitransgenic offspring in which Cre-mediated recombination can be regulated with the tetracycline analog doxycycline. These strains are an effective tool for generating inducible, tissue-specific-targeted mutants for studying cell lineage during development.

C57BL/6-Tg(Thy1-APP^{SwDutIowa})BWevn/J 007027

This transgenic strain expresses the human amyloid beta-precursor protein, APP gene, 770 isoform, with the Swedish K670N/M671L, Dutch E693Q and Iowa D694N mutations, under the direction of the mouse thymus cell antigen 1, theta, Thy1, promoter. Plaque-like deposits of amyloid beta, similar to those observed in people with the Dutch and Iowa familial disorders, are initially detected at approximately three months in the subiculum, hippocampus and cortex. Amyloid beta deposits are detected throughout the forebrain by 12 months. The strain may be used to study Alzheimer's.

C57BL/6j-Tg(Itgax-cre,-EGFP)4097Ach/J 007567

CD11c-Cre-GFP transgenic mice may be used to study the immune system or protein expression in dendritic cells.

STOCK Tg(tetO-DTA)1Gfi/J 008168

This tet-DTA strain expresses diphtheria toxin A (DTA) under the control of a tetracycline operator (tetO or TRE) and a cytomegalovirus minimal promoter. It may be used to generate

bi-transgenic mutant mice for the reversible, inducible deletion of specific groups of cells.

Targeted Mutants

B6.Cg-Dicer1^{tm1Bdh}/J 006366

This Dicer1 strain contains *loxP* sites flanking exon 23 of the Dcr-1 homolog (Drosophila) gene. It can be used to generate cell/tissue-specific deletions of the endogenous gene for applications in embryonic development, translation, protein processing, and miRNA/siRNA regulation of gene expression.

B6.129S6(FVB)-Ptgs2^{tm1.1Fun}/J 008101

This strain has an amino acid substitution that inactivates the cyclooxygenase but not the peroxidase activity of the enzyme. Homozygotes exhibit abnormal kidney function and elevated systolic blood pressure. This strain may be used to research thrombogenesis and hypertension.

B6.Cg-Mirn155^{tm1.1Rsky}/J 007745

This bic/mir-155 strain may be used to study the role of miR-155 and its target genes (including those encoding cytokines, chemokines and transcription factors) in homeostasis and functions of the immune system.

B6;129S4-Pou5f1^{tm1Jae}/J 008204

This Oct4-neo mutant strain may be used to select induced pluripotent stem (iPS) cells.

B6;129S4-Pou5f1^{tm2Jae}/J 008214

This Oct4-EGFP mutant strain may be used to select induced pluripotent stem (iPS) cells or, more generally, to fluorescently label embryonic stem cells.

STOCK Gli1^{tm3(cre/ESR1)Alj}/J 007913

When this Gli1-CreER^{T2} strain is bred with one containing a *loxP*-flanked sequence of interest, it produces offspring in which tamoxifen-inducible, Cre-mediated recombination deletes the flanked sequences in Gli1-expressing cells. The strain may be used to study axis patterning, proliferation, and cell fate specification of hedgehog-responding cells at different stages of embryogenesis.

JAX-engineered NSG mouse, an innovative cancer research tool

In the winter issue of JAX® NOTES, we explained how the NOD.Cg-Prkdc^{scid} Il2rg^{tm1Wjl}/SzJ (005557) mouse, nicknamed “NSG” (for NOD *scid* gamma), is enabling cutting-edge HIV research (Kumar *et al.* 2008). In this issue, we call attention to the superior ability of this mouse to engraft human cells and tissues. As a result, new insights into the pathophysiology and development of therapies for several cancer types have been unveiled.

NSG mouse has superior xenografting capability

In the last decade, several immunodeficient mouse strains have been constructed to facilitate the engraftment of foreign tissues and cells (Shultz *et al.* 2007). However, these strains maintain a residual immune system that mounts a substantial host-vs-graft innate immune response that may completely reject the xenograft. In contrast, the NSG mouse, developed by JAX Professor Leonard D. Shultz, lacks mature T cells, B cells, and is deficient for several high-affinity receptors for cytokines (including IL2, IL4, IL7, IL9, IL15, and IL21) that block the development of NK cells and further impair innate immunity. Consequently, the NSG mouse engrafts human cells and tissues better than any other published mouse strain (Shultz *et al.* 2005).

Tumorigenic melanoma cells are common

The superior engrafting ability of the NSG mouse allowed a University of Michigan research team to partly answer a fundamental question in cancer biology: How common are human cancer stem cells, which have the ability to initiate new tumors? Previous studies in which human cancer cells were transplanted into NOD.CB17-Prkdc^{scid}/SzJ (001303, commonly called NOD *scid*) and other strains of immunodeficient mice had indicated that these cells are rare, comprising no more than approximately 0.1% of all human cancer cells. These findings support the “cancer stem cell” model – that only a few tumor cells have autonomous tumorigenic potential.

However, the University of Michigan team found that approximately 25% to 27% of human melanoma cells transplanted in NSG mice are tumorigenic, suggesting that, at least in some cancers, cancer stem cells are more common than previously thought (Quintana *et al.* 2008).

CD19 expression defines tumorigenic B-ALL cells

Recently, xenograft studies using the NSG mouse helped clarify the nature of tumorigenic stem cells in primary human B-precursor acute lymphocytic leukemia (B-ALL), the most common type of childhood cancer. A European research team in collaboration with Professor Shultz transplanted cells from human B-ALL tumors into NSG mice and found that B



The NSG mouse is helping scientists solve many puzzling aspects of cancer.

cell precursors at different stages of maturation can engraft, initiate leukemia and continue to engraft and initiate leukemia in subsequent NSG mice over four serial transplantations spanning a 12-month period (leViseur *et al.* 2008). A second collaboration among Professor Shultz and Japanese and Chinese researchers showed that only the CD19-expressing cells can initiate B-ALL and have self-renewal capacity upon secondary transplantation (Kong *et al.* 2008). By shedding new light on B-ALL tumorigenesis, these results are helping researchers understand the mechanisms of chemotherapy resistance and may lead to the development of drugs that prevent B-ALL relapse or drug resistance.

Human lung cancer xenograft retains microenvironmental integrity

The NSG mouse’s superior engrafting ability may yield new insights into another dreaded disease – lung cancer. Collaborating with Professor Shultz, researchers from State University of New York- (SUNY-)Buffalo found that non-disrupted pieces of human primary lung tumor transplanted into NSG mice can retain their cancerous architecture (including tumor-associated leukocytes, stromal fibroblasts and tumor cells) with limited host-vs-graft interference for up to nine weeks. Additionally, tumor-associated T cells from the spleens of xenografted mice can be maintained and expanded after adoptive transfer into tumor-free NSG mice. For the first time, a lung cancer model is providing scientists with an opportunity to study human tumor and tumor-stromal cell interactions *in situ* for prolonged periods (Simpson-Abelson *et al.* 2008).

These results of collaborative cancer research using the NSG mouse are significantly improving our understanding of human cancer. As Professor Shultz states, “Interdisciplinary collaboration among clinicians and basic researchers using the NSG mouse and other newly developed models holds great

promise in accelerating our understanding of basic processes underlying cancer growth and resistance to treatment". As an NCI-designated cancer center since 1983, JAX provides important resources to researchers, such as the NSG strain and is continually striving to fight against cancer through supporting investigator-initiated research.

References

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JAX[®] Research News

New JAX cancer researcher studies heat shock response

The most recent addition to The Jackson Laboratory's scientific staff, cancer researcher Chengkai Dai, M.D., Ph.D, is armed with a mission – to better understand the heat shock or stress response – a highly conserved adaptive mechanism that normally protects healthy cells from environmental stresses but sometimes changes allegiance to protect cancer cells. Dr. Dai hopes that clarifying the heat shock response's beneficial and detrimental effects will lead to improved cancer therapies.



Dr. Dai hopes his research will lead to more effective cancer therapies.

The heat shock response and cancer

Understanding how the heat shock response functions during the dynamic, multi-stage process of tumor formation may revolutionize our knowledge of cancer evolution and ultimately translate into ground-breaking cancer prevention and therapies. Dr. Dai's laboratory is concentrating on the study of stress response, and investigating its role in the malignancy associated with neurofibromatosis type I (NF1), the most common human cancer-predisposition syndrome afflicting one in 3,500 people worldwide. NF1 patients frequently develop multiple types of malignancy, including neurofibromas, brain tumors and myeloid leukemia. Dr. Dai's research clearly indicates that inhibiting the stress response markedly suppresses the tumorigenic process associated with NF1 and impairs the growth and survival of human NF1 tumor cells (Dai *et al.* 2007). These studies provide strong evidence that targeting the stress response is an innovative and promising strategy to treat tumors in NF1 patients.

Based on his experience, Dr. Dai concludes that the main obstacle to treating established cancers is their extraordinary complexity and incredible ability to evolve. He hopes his research on the stress response will help overcome that obstacle and ultimately lead to innovative ways of fighting cancer.

The heat shock response and aging

Another area of Dr. Dai's study is the relationship between the heat shock response and aging. Although the response has a fascinating role in prolonging the lifespan of lower organisms, its influence on mammalian longevity is elusive. Particularly in humans, aging is associated with two major diseases — cancer and neurodegeneration — and the response is involved in both. While the heat shock response protects neurons from death and antagonizes neurodegeneration, the very same mechanism promotes cancer. Dr. Dai is devoted to understanding how this ancient mechanism's effects on cancer and neurodegeneration are balanced and how they impact longevity in mammals. These studies may ultimately lead to new ways of fighting aging and increasing longevity.

Dr. Dai earned his M.D. and M.S. degrees from Tianjin Medical University and received his Ph.D. from the University of Texas—Houston Health Science Center. Dr. Dai recently finished a postdoctoral appointment at the Whitehead Institute for Biomedical Research, an independent institution affiliated with MIT.

He has co-authored 17 research and review articles (seven as first author) in peer-reviewed journals, including *Cell* and *Genes & Development*. In 2006, he received The Children's Tumor Foundation Young Investigator Award.

Reference

(Author in bold is a Jackson Laboratory scientist.)

Dai C, Whitesell L, Rogers AB, Lindquist S. 2007. Heat shock factor 1 is a powerful multifaceted modifier of carcinogenesis. *Cell* 130:986-8.

JAX® ocular research produces eye-catching results



The eyes have it. JAX professors Naggert, Nishina and John each contributed chapters to the new reference book on the mouse eye. Professor Nishina recently received a grant from the National Eye Institute to identify and study gene mutations associated with retinal diseases in mouse models, and Professor John recently received a grant from the Howard Hughes Medical Institute to develop wireless sensors for monitoring the intraocular pressure (IOP) of a mouse eye.

JAX scientists contribute to book on mouse eye

It's hard to imagine a 750+ page book written on the mouse eye, but that's exactly the subject matter of "Eye, retina and visual system of the mouse" (edited by Leo M. Chalupa and Robert W. Williams, MIT Press, Cambridge, MA) JAX scientists Simon John, Ph.D., Gareth Howell, Ph.D., Juergen Naggert, Ph.D., and Patsy Nishina, Ph.D., each contributed to the tome. John and Howell co-authored "Mouse models: a key system in revolutionizing the understanding of glaucoma", and Nishina and Naggert co-authored "Beyond positional cloning of single gene mutations: use of mouse models to examine allele variance and to identify genetic modifiers".

Dr. J. Anthony Movshon of New York University praises the book highly: "Twenty years ago, most visual neuroscientists studied cats or monkeys, and the idea of using the mouse for vision research was preposterous – everyone 'knew' that mice could hardly see at all, so why would one bother? Now, the genetic revolution has utterly changed the landscape, and

the growth of mouse vision research has been explosive. This comprehensive and well-produced volume collects our essential knowledge of mouse vision into a single extraordinarily useful volume. It will be the standard reference for years to come."

JAX Professor Nishina awarded \$3 million grant

The National Eye Institute awarded Professor Patsy Nishina, Ph.D., a five-year grant of \$3,032,659 to identify and study gene mutations associated with retinal diseases in mouse models. Dr. Nishina explains: "Knowing more about the genes and molecular pathways that are associated with retinal diseases may provide insights to new treatment regimens, and the models can then be used not only to identify the time frame in which treatment might be most effective but also a resource in which to test therapies. The eventual goal is to identify patients with the genetic variations that are associated with these diseases and then provide treatment early enough to prevent vision impairment and loss."

JAX glaucoma researcher presented HHMI Collaborative Innovation Award

JAX Professor and Howard Hughes Medical Institute (HHMI) Investigator, Simon John, Ph.D., one of the nation's leading researchers of glaucoma, has been awarded an HHMI Collaborative Innovation Award. The Innovation Awards are part of a new, \$40 million HHMI initiative to spur scientists "to devote substantial time and energy to pursuing collaborative, transformative research" (www.hhmi.org/news/20081120).

Professor John will lead a team to develop wireless sensors for monitoring the intraocular pressure (IOP) of a mouse eye. Dr. Pedro Irazoqui and Dr. William Chappel, both engineers at Purdue University, are key team members. If successful, the sensors could have a wide range of applications in human medicine, particularly for monitoring and treating glaucoma, one of the leading causes of blindness affecting some 70 million people worldwide. Currently, one of the most common ways to treat glaucoma is to reduce harmfully high IOP, a major but little understood cause of the disease. The sensors that Professor John will help develop could be used to continually monitor IOP in glaucoma patients, thereby helping scientists better understand how IOP arises, leading to optic nerve damage.

Professor John is determined to find a cure for glaucoma. He and his lab recently discovered that, inexplicably, a full-body radiation treatment prevents glaucoma from developing in some mice. "We're now working with a machine that lets us irradiate just the mouse eye, testing to see if you can stop glaucoma that way. It could hold potential for treating humans at risk for the disease, and it's very exciting... I get the most heartrending emails from mothers of children with glaucoma, asking for my help. I tell them I can't give medical advice, but it's hard. Connections like that remind you that people need hope. That keeps me working" (www.jax.org/news/simon_john).

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Courses

Below is a partial listing of upcoming courses. Go to our website (www.jax.org/courses) for a full listing of all courses.

March 17-20 *Advanced Surgical Techniques in Mice:*

Jugular Vein & Carotid Artery
Catheterizations (March 17)

Thymectomy, Nephrectomy & Kidney
Capsule Implant (March 18)

Jugular Vein & Carotid Artery
Catheterizations—Second Session (March 19)

Thymectomy, Nephrectomy & Kidney
Capsule Implant—Second Session (March 20)

Apr 13-17 Colony Management: Principles and Practices

Apr 28-May 1 Workshop on Embryo Transfer

May 4-7 Workshop on Cryopreservation of
Mouse Germplasm

May 17-22 Workshop on Surgical Techniques in
the Laboratory Mouse

June 11-13 Colony Management:
Principles and Practices, at Emory University

June 21-26 Comprehensive Approaches to the *in vivo*
Assessment of Cardiovascular Function in Mice

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