opportunities, please contact Elizabeth M. Denholm, Ph.D. at *denholme@niehs.nih.gov*.

Treatment of Acute and Chronic Neurological Disorders Using GLP–1, Exendin-4 and Analogs

Description of Technology: Glucagon-like peptide-1 (GLP–1) and related peptides, including exendin-4 and liraglutide, are incretin mimetics that enhance glucose-dependent insulin secretion following food ingestion as a regulator of glucose homeostasis. Exendin-4 and liraglutide are used clinically in the safe and effective treatment of type 2 diabetes to enhance insulin secretion and maintain a euglycemic state. These actions are primarily mediated at the level of the GLP–1 receptor in the pancreas; however, these compounds are known to enter the brain where the GLP–1 receptor also is expressed.

Researchers at the NIH have discovered the novel use of GLP–1 and exendin-4 analogs in the treatment of acute and chronic neurological disorders and neurodegenerative diseases. Studies conducted in extensive cell culture and in mouse models using these analogs have demonstrated significant neurotrophic and neuroprotective actions in models of several disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS, stroke, head trauma and peripheral neuropathy. These studies have now been extensively published and independently validated by other scientific groups. Furthermore, clinical studies are ongoing to evaluate the use of GLP–1 receptor agonists for the treatment of early Alzheimer's disease, Parkinson's disease and diabetic neuropathy by several groups within the US and Europe.

Potential Commercial Applications: Therapeutics for:

- Neurodegenerative diseases—Alzheimer's, Huntington's, Parkinson's, ALS
- Stroke
- Head trauma (traumatic brain injury)
- Peripheral neuropathies

Competitive Advantages:

- Compounds reduce neuronal cell death, amyloid deposition and neuroinflammation while promoting neurogenesis.
- Compounds in this class have already been shown to be safe and effective for other indications.
- Extensive in vitro and animal data are available, and clinical studies are ongoing.
- There are extensive publications in the literature, both from the inventors and independent groups.

Development Stage:

- Pre-clinical
- Clinical
- In vitro data available
- In vivo data available (animal)
- In vivo data available (human)

Inventors: Nigel Greig, Harold Halloway, Maire Doyle, Josephine Egan (all of NIA).

Publications:

1. Li Y, et al. Exendin-4 ameliorates motor neuron degeneration in cellular and animal models of amyotrophic lateral sclerosis. PLoS One. 2012;7(2):e32008. [PMID 22384126]
2. Li Y, et al. Enhancing the GLP–1 receptor signaling pathway leads to proliferation and neuroprotection in human neuroblastoma cells. J Neurochem. 2010 Jun;113(6):1621–1631. [PMID 20374430]
3. Li Y, et al. GLP–1 receptor stimulation reduces amyloid-beta peptide accumulation and cytotoxicity in cellular and animal models of Alzheimer's disease. J Alzheimers Dis. 2010;19(4):1205–1219. [PMID 20308787]
4. Li Y, et al. GLP–1 receptor stimulation preserves primary cortical and dopaminergic neurons in cellular and rodent models of stroke and Parkinsonism. Proc Natl Acad Sci USA. 2009 Jan 27;106(4):1285–1290. [PMID 19164583]
5. Martin B, et al. Exendin-4 improves glycemic control, ameliorates brain and pancreatic pathologies and extends survival in a mouse model of Huntington's disease. Diabetes. 2009 Feb;58(2):318–328. [PMID:18984744]
6. Perry T, et al. Evidence of GLP–1-mediated neuroprotection in an animal model of pyridoxine-induced peripheral sensory neuropathy. Exp Neurol. 2007 Feb;203(2):293–301. [PMID 17125767]
7. Perry T, Greig NH. Enhancing central nervous system endogenous GLP–1 receptor pathways for intervention in Alzheimer's disease. Curr Alzheimers Res. 2005 Jul;2(3):377–385. [PMID 15974903]
8. Greig NH, et al. New therapeutic strategies and drug candidates for neurodegenerative diseases: p53 and TNF-alpha inhibitors, and GLP–1 receptor agonists. Ann NY Acad Sci. 2004 Dec;1035:290–315. [PMID 15681814]
9. Perry TA, Greig NH. A new Alzheimer's disease interventive strategy: GLP–1. Curr Drug Targets. 2004 Aug;5(6):565–571. [PMID 15270203]

Listing of additional related publications available upon request.

Intellectual Property: HHS Reference No. E–049–2001/0—

- U.S. Patent 7,576,050 issued 18 Aug 2009
- U.S. Patent Application No. 12/317,042 filed 18 Dec 2008
- Foreign counterparts in Australia, Canada, Europe, India, and Japan

Licensing Contact: Tara L. Kirby, Ph.D.; 301–435–4426; *tarak@mail.nih.gov*.

Collaborative Research Opportunity: The National Institute on Aging, Drug Design and Development Section, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate or commercialize this technology. For collaboration opportunities, please contact Vio Conley at *conleyv@mail.nih.gov*.

Dated: April 18, 2012.

Richard U. Rodriguez,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

[FR Doc. 2012–9776 Filed 4–23–12; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing: Mouse Models

AGENCY: National Institutes of Health, Public Health Service, HHS.

ACTION: Notice.

SUMMARY: The inventions listed below are owned by an agency of the U.S. Government and are available for licensing in the U.S. in accordance with 35 U.S.C. 207 to achieve expeditious commercialization of results of federally-funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing.

FOR FURTHER INFORMATION CONTACT: Licensing information for the technologies listed below may be obtained by writing to the indicated licensing contact at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–

3804; telephone: 301–496–7057; fax: 301–402–0220.

Smad4 Knockout (Smad4^{tm1Cxd}) Mouse Model for Developmental Biology Studies

Description of Mouse: Smad4 knockout: Smad4 is essential for epiblast proliferation, egg cylinder formation and mesoderm induction in early embryogenesis.

The TGF-beta-related superfamily plays an important role in multiple biological systems including embryogenesis. TGF-beta ligands activate specific receptors, which interact with specific Smad proteins, which in turn form a complex with a common partner, Smad4, that conveys the signal to downstream targets. Exon 8 of the *Smad4* gene was disrupted using homologous recombination in embryonic stem cells. Exon 8 encodes the C-terminal domain of *Smad4* that is essential for the formation of heteromeric complexes with the other Smads. Mice heterozygous for the Smad4 mutation are phenotypically normal. Homozygotes, however, die early in embryonic development (day E6.5–8.5). *Smad4* is required for three essential functions in early embryogenesis: epiblast proliferation, egg cylinder formation, and mesoderm induction.

Potential Commercial Application: Study of developmental biology in conjunction with compounds.

Development Status: Pre-clinical.

Developer of Mouse: Chu-Xia Deng, Ph.D. (NIDDK).

Relevant Publication: Yang X, et al. The tumor suppressor SMAD4/DPC4 is essential for epiblast proliferation and mesoderm induction in mice. Proc Natl Acad Sci U S A. 1998 Mar 31;95(7):3667–72. [PMID 9520423].

Intellectual Property: HHS Reference No. E–133–1999/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Charlene A. Sydnor, Ph.D.; 301–435–4689; *sydnorc@mail.nih.gov*.

Fgfr4 Knockout Mouse Model for Respiratory System Studies

Description of Mouse: FGFR4 knockout: Lung alveoli fail to develop normally in double mutant with FGFR4 and FGFR3 knockouts.

The fibroblast growth factor receptor 4 (*fgfr-4*) gene was inactivated by targeted disruption and homozygous recombination to study its possible role in lung development. FGFR–4 is expressed in postnatal lung, and FGFR–4 null mice have no obvious abnormalities. However, mice that are doubly homozygous for targeted disruptions of FGFR3 and FGFR4 display novel phenotypes, including pronounced dwarfism and lung abnormalities. The lungs of the double knockout mice are normal at birth, but they fail to develop secondary septae that delimit alveoli and increase the surface area of the lung. Although lung function is impaired, the double homozygous knockout mice are viable but sickly.

Potential Commercial Application: Model for the study of respiratory system and potential treatments.

Development Status: Pre-clinical.

Developer of Mouse: Chu-Xia Deng, Ph.D. (NIDDK).

Relevant Publication: Weinstein M, et al. FGFR–3 and FGFR–4 function cooperatively to direct alveogenesis in the murine lung. Development. 1998 Sep;125(18):3615–23. [PMID 9716527].

Intellectual Property: HHS Reference No. E–125–2000/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Charlene A. Sydnor, Ph.D.; 301–435–4689; *sydnorc@mail.nih.gov*.

M5 Muscarinic Receptor Knockout (Chrm5^{tm1Jwe}) Mouse Model for Neurological Studies

Description of Mouse: M5 muscarinic receptor knockout: Deficiency of M5Rs reduces drug-seeking behavior.

The five Muscarinic Acetylcholine (ACh) receptors are G-protein coupled receptors (M1R–M5R). M1R, M3R and M5R selectively couple to Gq/G11; M2R and M4R selectively couple to Gi/Go. M5R knockout mice are viable and fertile, and have no major morphological abnormalities.

M5 muscarinic ACh receptors are located in the central nervous system and may contribute to the cognitive-enhancing effects of ACh. M5R knockout mice show deficits in two hippocampus-dependent cognitive tasks, and exhibit reduced cerebral blood flow in the cerebral cortex and hippocampus, consistent with the observation that M5Rs mediate ACh-mediated dilation of cerebral blood vessels. M5R agonists or agonists for mixed M1/M5 receptors may be effective in the treatment of Alzheimer's disease and related memory disorders. The M5R knockout mutation also appears to exert a stabilizing effect on sensorimotor gating in intact mice, which is decreased in schizophrenia. Analysis of M5R knockout mice also has shown that the lack of M5Rs reduces drug-seeking behavior.

Potential Commercial Application: Mouse model for use in neurological studies.

Development Stage: Pre-clinical.

Developer of Mouse: Jürgen Wess, Ph.D. (NIDDK).

Relevant Publication: Yamada M, et al. Cholinergic dilation of cerebral blood vessels is abolished in M(5) muscarinic acetylcholine receptor knockout mice. Proc Natl Acad Sci U S A. 2001 Nov 20;98(24):14096–101. [PMID 11707605].

Intellectual Property: HHS Reference No. E–110–2012/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Charlene A. Sydnor, Ph.D.; 301–435–4689; *sydnorc@mail.nih.gov.*

Stat5a LoxP/Stat5b LoxP (Stat5a/Stat5b^{tm2Mam}) Mouse Model for Mammopoietic and Lactogenic Signaling Studies

Description of Mouse: Conditional knockout of Stat5a and Stat5b: Combined deletion of conserved Stat5a and Stat5b in mammary epithelium at different times during pregnancy reveal multiple distinct functions.

The signal transducer and activator of transcription (STAT) family of transcription factors conveys signals from membrane receptors to the nucleus, where they activate diverse genetic programs. Stat5a and Stat5b are highly conserved proteins that are activated by many cytokines, erythropoietin, prolactin and growth hormone. Despite their similarities, they have many unique functions. Stat5a deficiency results in the loss of prolactin-dependent mammary gland development, but does not affect body growth. Inactivation of Stat5b does not adversely affect mammary development and function, but leads to severe growth retardation. To study the effects of combined deficiency of Stat 5a and 5b before and during pregnancy, loxP was added to the ends of a DNA fragment that contains the two genes which are located within a stretch of 110 kb on chromosome 11 in a head to head orientation with no other genes between them. The loxP-flanked fragment was introduced into the genome using homologous recombination, and deleted using two transgenic lines expressing Cre in mammary epithelium at different times. Deletion of Stat 5 before pregnancy prevents epithelial proliferation. Ductal characteristics are retained but differentiation into secretory alveoli does not occur. When deletion of Stat5 occurs late in pregnancy after differentiation has started, differentiation is halted and premature death occurs.

Potential Commercial Application: Mouse model to study mammopoietic and lactogenic signaling.

Development Stage: Pre-clinical.

Developer of Mouse: Lothar Hennighausen, Ph.D. (NIDDK).

Relevant Publication: Cui Y, et al. Inactivation of Stat5 in mouse mammary epithelium during pregnancy reveals distinct functions in cell proliferation, survival, and differentiation. Mol Cell Biol. 2004 Sep;24(18):8037–47. [PMID 15340066].

Intellectual Property: HHS Reference No. E–114–2012/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Suryanarayana (Sury) Vepa, Ph.D., J.D.; 301–435–5020; *vepas@mail.nih.gov.*

Stat5a Knockout (Stat5a^{tm1Mam}) Mouse Model for Mammopoietic and Lactogenic Signaling Studies

Description of Mouse: Stat5a Knockout: Stat5a deficiency results in the loss of prolactin-dependent mammary gland development and lactogenesis.

Prolactin induces mammary gland development and lactogenesis. Binding of Prolactin to its receptor leads to the phosphorylation and activation of STAT (signal transducers and activators of transcription) proteins. Two Stat proteins, Stat5a and Stat5b, are expressed in mammary tissues during pregnancy. Stat5a null mice developed normally, and were indistinguishable from hemizygous and wild-type littermates in size, weight and fertility. Mammary lobulo-alveolar outgrowth during pregnancy was reduced and females failed to lactate after parturition. Stat5b, despite 96% similarity to Stat5a, could not compensate for the loss of Stat5a. Stat5a is the principal and obligate mediator of mammopoietic and lactogenic signaling.

Potential Commercial Application: Mouse model to study mammopoietic and lactogenic signaling.

Development Stage: Pre-clinical.

Developer of Mouse: Lothar Hennighausen, Ph.D. (NIDDK).

Relevant Publication: Liu X, et al. Stat5a is mandatory for adult mammary gland development and lactogenesis. Genes Dev. 1997 Jan 15;11(2):179–86. [PMID 9009201].

Intellectual Property: HHS Reference No. E–116–2012/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Suryanarayana (Sury) Vepa, Ph.D., J.D.; 301–435–5020; *vepas@mail.nih.gov.*

Gs Alpha LoxP (Gnas^{tm1Lsw}) Mouse Model for Metabolism Studies

Description of Mouse: Generation of a floxed *Gnsa* gene for the G-protein G_s alpha ($G_s\alpha$) for the construction of conditional knockout mice.

The heterotrimeric G protein $G_s\alpha$ couples many receptors to adenylyl cyclase and is essential for hormone-stimulated cAMP generation. Previous mouse models with germ-line mutations in *Gnas,* the gene that encodes $G_s\alpha$ had limited usefulness in trying to decipher the role of $G_s\alpha$ pathways in specific tissues since only heterozygotes were viable and could be analyzed. Analysis was further complicated by the fact that $G_s\alpha$ is imprinted expressed in many metabolically active tissues.

$G_s\alpha$-floxed mice were generated so that the metabolic effects of $G_s\alpha$ deficiency could be examined in specific tissues. Exon1, which is specific for $G_s\alpha$, was surrounded with loxP recombination sites. Liver-specific knockouts of $G_s\alpha$ were obtained by mating the $G_s\alpha$-floxed mice with albumin promoter-Cre-transgenic mice. $G_s\alpha$ exon1 was efficiently deleted. These mice have been used successfully to generate other tissue-specfic $G_s\alpha$ knockout mice.

Potential Commercial Application: Mouse model to study metabolism.

Development Stage: Pre-clinical.

Developer of Mouse: Lee Weinstein, M.D. (NIDDK).

Relevant Publication: Chen M, et al. Increased glucose tolerance and reduced adiposity in the absence of fasting hypoglycemia in mice with liver-specific Gs alpha deficiency. J Clin Invest. 2005 Nov;115(11):3217–27. [PMID 16239968].

Intellectual Property: HHS Reference No. E–117–2012/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Suryanarayana (Sury) Vepa, Ph.D., J.D.; 301–435–5020; *vepas@mail.nih.gov.*

Sirt6 LoxP (Sirt6$^{tm1.1Cxd}$) Mouse Model for Liver Studies

Description of Mouse: Generation of floxed Sirtuin 6 for the construction of conditional knockout mice.

The Sirtuins (Sirt1–7), a family of seven proteins related to yeast Sir2, are histone deacetylases that regulate many critical biological processes including genomic stability, adaptation to calorie restriction and aging. Mice with a targeted disruption of Sirt6 had very low levels of blood glucose (and paradoxically, low insulin levels) and died shortly after weaning. Hypoglycemia, attributed to increased sensitivity to insulin, was the major cause for lethality.

Because of the post-weaning mortality of Sirt6 null mice, liver-specific Sirt6 conditional knockout mice were constructed using Cre-Lox technology to study the effects on glucose and lipid metabolism. Hepatic-specific Sirt6 deficient mice exhibited increased glycolysis and triglyceride synthesis, resulting in the development of fatty liver. Sirt6 is a potential therapeutic target for treating fatty liver disease, the most common cause of liver dysfunction.

Potential Commercial Application: Mouse model to study the liver.

Development Stage: Pre-clinical.

Developer of Mouse: Chuxia Deng, Ph.D. (NIDDK).

Relevant Publication: Kim HS, et al. Hepatic-specific disruption of SIRT6 in mice results in fatty liver formation due to enhanced glycolysis and triglyceride synthesis. Cell Metab. 2010 Sep 8;12(3):224–36. [PMID 20816089].

Intellectual Property: HHS Reference No. E–121–2012/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Lauren Nguyen-Antczak, Ph.D., J.D.; 301–435–4074; *Lauren.Nguyen-Antczak@nih.gov.*

Sirt1 LoxP (Sirt1^{tm1Cxd}) Mouse Model for Metabolism and Hepatology Studies

Description of Mouse: Generation of floxed Sirtuin 1 Exon5–Exon6 for the construction of conditional knockout mice.

Sirtuin 1 (Sirt1), a homolog of yeast Sir 2, is an NAD-dependent histone and protein deacetylase. It has a wide range of biological functions, ranging from DNA damage repair to effects on glucose metabolism. Sirt1 null mice die before birth due to chromosomal aberrations and impaired DNA damage repair. Sirt1 is thought to affect energy metabolism, but the mechanism remains poorly understood. In order to study tissue-specific metabolic effects of Sirt1, floxed Sirt1 was constructed so that exons 5 and 6 would be deleted using the Cre-Lox strategy. In contrast to a previously reported deletion of Sirt1 exon4, no truncated (and potentially active) Sirt1 forms were detected when exons 5 and 6 were deleted.

Hepatic exon 5–6 null Sirt1 mice were generated when Floxed Sirt1 exon 5 and 6 mice were mated with mice that expressed the Cre-recombinase in liver. The hepatic exon 5–6 null Sirt1 mice developed fatty liver under normal feeding conditions. This was accompanied by increased expression of the carbohydrate responsive element binding protein, which is a major

regulator of lipid synthesis. Sirt1-deficient liver also has an impaired insulin response, primarily due to reduced phosphorylation of the serine-threonine kinase Akt in the presence of insulin.

Potential Commercial Application: Mouse model to study metabolism and hepatology.

Development Stage: Pre-clinical.

Developer of Mouse: Chuxia Deng, Ph.D. (NIDDK).

Relevant Publications:

1. Wang RH, et al. Liver steatosis and increased ChREBP expression in mice carrying a liver specific SIRT1 null mutation under a normal feeding condition. Int J Biol Sci. 2010 Nov 16;6(7):682–90. [PMID 21103071].
2. Wang RH, et al. Hepatic Sirt1 deficiency in mice impairs mTorc2/Akt signaling and results in hyperglycemia, oxidative damage, and insulin resistance. J Clin Invest. 2011 Nov 1;121(11):4477–90. [PMID 21965330].

Intellectual Property: HHS Reference No. E–122–2012/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Lauren Nguyen-Antczak, Ph.D., J.D.; 301–435–4074; *Lauren.Nguyen-Antczak@nih.gov.*

Fgfr3 Knockout Mouse Model for Developmental Biology Studies

Description of Mouse: FGFR3 knockout. Complete knockout of the FGFR3 gene, the gene in which missense mutants cause short statue achondroplasia, fails to restrain cartilage growth at the bone growth plate, allowing bones to elongate excessively but fail to ossify.

Endochondral ossification is a major mode of bone formation. Cartilage proliferates, undergoes hypertrophy, begins to calcify, undergoes a program of cell death, and is replaced by osteoblasts. Fibroblast Growth Factor Receptor 3 (FGFR3) is expressed in cartilage rudiments of a wide variety of bones, and dominant missense mutations in the human FGFR3 gene cause achondroplasia, a common form of human dwarfism characterized by minimal proliferation of the growth plate cartilage in long bones. To determine the effect of complete absence of FGFR3 on bone development in mice, targeted disruption of the FGFR3 gene was accomplished by homologous recombination in embryonic stem cells. Remarkably, the vertebral column and long bones of FGFR3 null mice were extremely long, suggesting that in normal development, FGFR3 restrains cartilage promotion and limits bone elongation so that the endochondral ossification program can proceed. Restraint of cartilage growth by FGFR3 provides a plausible explanation for the role of FGFR3 missense mutations in human achondroplastic dwarfs.

Potential Commercial Application: Mouse model to study developmental biology.

Development Stage: Pre-clinical.

Developer of Mouse: Chuxia Deng, Ph.D. (NIDDK).

Relevant Publication: Deng C, et al. Fibroblast growth factor receptor 3 is a negative regulator of bone growth. Cell. 1996 Mar 22;84(6):911–21. [PMID 8601314]

Intellectual Property: HHS Reference No. E–123–2012/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Lauren Nguyen-Antczak, Ph.D., J.D.; 301–435–4074; *Lauren.Nguyen-Antczak@nih.gov*.

Fgfr2 Knockout (Fgfr2 ^{tm1Cxd}) Mouse Model for Developmental Biology Studies

Description of Mouse: FGFR2 knockout is an embryonic lethal mutation and blocks limb bud initiation.

Fibroblast Growth Factor Receptor 2 (FGFR2) is a high affinity receptor for several members of the FGF family. The FGFR2 gene was inactivated by deleting the entire immunoglobulin-like domain of the receptor which is critical for FGF binding and FGFR2 activity. Embryos that lack this domain die at E10–11.5 owing to a failure in chorioallantoic fusion or placental formation. The deletion also blocks limb bud initiation, establishing FGFR2 as the major receptor that mediates FGF signals during limb induction.

Potential Commercial Application: Mouse model to study developmental biology.

Development Stage: Pre-clinical.

Developer of Mouse: Chuxia Deng, Ph.D. (NIDDK).

Relevant Publication: Xu X, et al. Fibroblast growth factor receptor 2 (FGFR2)-mediated reciprocal regulation loop between FGF8 and FGF10 is essential for limb induction. Development. 1998 Feb;125(4):753–65. [PMID 9435295].

Intellectual Property: HHS Reference No. E–124–2012/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Lauren Nguyen-Antczak, Ph.D., J.D.; 301–435–4074; Lauren.Nguyen-Antczak@nih.gov.

Alb-tTA (Tg(Alb1-tTA)3123Lng) Mouse Model for Liver Function Studies

Description of Mouse: Tetracycline-responsive transcriptional activator driven by the liver-specific mouse albumin promoter (Alb-tTA).

The E. Coli tetracycline operon regulatory system was used to generate a liver-specific transcription activation system that was inhibited by tetracycline. The transcription activator was a fused protein consisting of a tetracycline repressor gene (tetR) that was only active in the presence of tetracycline and a herpes simplex virus protein (VP–16) transcription activating domain. Transcription was induced only in the absence of tetracycline (Tet-Off). A liver-specific promoter such as mouse albumin determined that the tetracycline-regulated transcriptional activator (tTA) would be expressed specifically in liver. To study the effect of the transcription activator on a target gene (for example, Simian Virus 40 (SV4) large tumor (T) antigen (TAg)) specifically in liver, Alb-tTA mice were mated with transgenic mice in which the Target gene (TAg) was controlled by the E. Coli Tetracycline Operator (Tet-O). In this example, TAg was expressed in hepatocytes in the absence of Tetracycline, leading to hepatoma formation. When the mice were treated with tetracycline, TAg was not expressed and hepatomas did not form.

Potential Commercial Application: Mouse model to liver function.

Development Stage: Pre-clinical.

Developer of Mouse: T. Jake Liang, M.D. (NIDDK).

Relevant Publication: Manickan E, et al. Conditional liver-specific expression of simian virus 40 T antigen leads to regulatable development of hepatic neoplasm in transgenic mice. J Biol Chem. 2001 Apr 27;276(17):13989–94. [PMID 11278564]

Intellectual Property: HHS Reference No. E–125–2012/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Lauren Nguyen-Antczak, Ph.D., J.D.; 301–435–4074; *Lauren.Nguyen-Antczak@nih.gov*.

MUP-tTA Mouse Model for Liver Function Studies

Description of Mouse: Tetracycline-responsive transcriptional activator driven by the liver-specific mouse major urinary protein promoter (MUP-tTA).

The E. Coli tetracycline operon regulatory system was used to generate a liver-specific transcription activation system that was inhibited by tetracycline. The transcription activator was a fused protein consisting of a

tetracycline repressor gene (tetR) that was only active in the presence of tetracycline and a herpes simplex virus protein (VP–16) transcription activating domain (Tet-Off). Transcription was induced only in the absence of tetracycline (Tet-Off). A liver-specific promoter such as the mouse major urinary protein (MUP) promoter determined that the tetracycline-regulated transcriptional activator (tTA) would be expressed specifically in liver. To study the effect of the transcription activator on a target gene (for example, beta-galactosidase, LacZ) specifically in liver, MUP-tTA mice would be mated with transgenic mice in which the TAg Target gene was controlled by the E. Coli Tetracycline Operator (Tet-O). The Tet technology may require a separate license.

Potential Commercial Application: Mouse model to study liver function.

Development Stage: Pre-clinical.

Developer of Mouse: T. Jake Liang, M.D. (NIDDK).

Relevant Publication: Manickan E, et al. Conditional liver-specific expression of simian virus 40 T antigen leads to regulatable development of hepatic neoplasm in transgenic mice. J Biol Chem. 2001 Apr 27;276(17):13989–94. [PMID 11278564]

Intellectual Property: HHS Reference No. E–126–2012/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Lauren Nguyen-Antczak, Ph.D., J.D.; 301–435–4074; *Lauren.Nguyen-Antczak@nih.gov*.

mEpoR Knockout/Tg(hEpoR) Mouse Model for Anemia and Renal Function Studies

Description of Mouse: mEpoR−/−hEpoR+: The mouse Erythropoietin Receptor knockout that contains a human Erythropoietin Receptor transgene can be used to define the potency of recombinant erythropoietin preparations used to treat anemia associated with chronic kidney disease.

Erythropoietin, acting by binding to Erythropoietin receptors (EpoR) on erythroid progenitor cells, is required for erythropoiesis. Absence of erythropoietin or the EpoR in mice interrupts erythropoiesis in the fetal liver and results in death at embryonic day 13.5. An 80-kb human EpoR transgene bred onto a mouse EpoR null background (provided by F. Constantini of Columbia University) restored effective erythropoiesis in the EpoR null mouse. Erythropoietin preparations made utilizing recombinant DNA technology are used in the treatment of anemia in chronic kidney disease and other critical illnesses. The mouse EpoR null mouse containing the human EpoR transgene can be used to define the potency of erythropoietin preparation in humans.

Potential Commercial Applications: Model for study of anemia and renal function and possible drug screening.

Developer of Mouse: Constance Noguchi, Ph.D. (NIDDK).

Relevant Publication: Yu X, et al. The human erythropoietin receptor gene rescues erythropoiesis and developmental defects in the erythropoietin receptor null mouse. Blood. 2001 Jul 15;98(2):475–7. [PMID 11435319].

Intellectual Property: HHS Reference No. E–127–2001/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Jennifer S. Wong; 301–435–4633; *wongje@mail.nih.gov*.

Sirt3 Knockout (Sirt3$^{tm1.1Cxd}$) Mouse Model for Cardiology and Metabolism Studies

Description of Mouse: Sirt3 knockout: Sirt3 is a mitochondrial-localized tumor suppressor that maintains mitochondrial integrity and metabolism during stress. Sirt3 is a mitochondrial protein that is a member of the Sirtuin family of NAD-dependent protein deacetylases. Sirt3(−/−) mice are phenotypically normal, but exhibit many proteins whose acetylation is increased. They generate more reactive oxygen species and are more susceptible to mammary tumors than normal mice. Sirt3 is inactivated in a large percentage of human breast and ovarian cancers, suggesting that Sirt3 may be a mitochondria-localized tumor suppressor by maintaining mitochondrial integrity and efficient oxidative metabolism.

Potential Commercial Applications: Cardiology, Metabolism.

Developer of Mouse: Chuxia Deng, Ph.D. (NIDDK).

Relevant Publication: Kim HS, et al. SIRT3 is a mitochondria-localized tumor suppressor required for maintenance of mitochondrial integrity and metabolism during stress. Cancer Cell. 2010 Jan 19;17(1):41–52. [PMID 20129246].

Intellectual Property: HHS Reference No. E–119–2012/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Jennifer S. Wong; 301–435–4633; *wongje@mail.nih.gov*.

Sirt1 Knockout (Sirt1$^{tm1.1Cxd}$) Mouse Model for Oncology and Metabolism Studies

Description of Mouse: Sirt1 knockout: Sirt1, a protein deacetylase, is a tumor suppressor that promotes genome stability and regulates proteins involved in energy metabolism.

Yeast Sir2, a nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylase, has been implicated in chromatin silencing, longevity and genome stability. Mammals contain a family of related deacetylases, the sirtuins, of which 7 have been identified. Sirt1 is the closest mammalian orthologue of yeast Sir 2. The Sirt1 gene in mice was disrupted by homologous recombination in embryonic stem cells. The majority of Sirt1 (−/−) embryos die between E9.5 and E14.5, displaying altered histone modification, increased chromosomal aberrations, and impaired DNA damage repair. Tumor formation was increased in mutant tissues in Sirt1(+/−): p53(+/−) double heterozygotes, indicating that full levels of Sirt1 are necessary for tumor suppression. Tumorigenesis is reduced by treatment with the polyphenol, resveratrol, which activates Sirt1. Sirt1 may act as a tumor suppressor by promoting DNA damage repair and maintaining genome integrity. Sirt1also is involved in the regulation of proteins involved in energy metabolism, and components of the circadian clock.

Potential Commercial Applications: Oncology, Metabolism.

Developer of Mouse: Chuxia Deng, Ph.D. (NIDDK).

Relevant Publication: Wang RH, et al. Impaired DNA damage response, genome instability, and tumorigenesis in SIRT1 mutant mice. Cancer Cell. 2008 Oct 7;14(4):312–23. [PMID 18835033]

Intellectual Property: HHS Reference No. E–120–2012/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Jennifer S. Wong; 301–435–4633; *wongje@mail.nih.gov*.

Stat1LoxP (Stat1^{tm1Mam}) Mouse Model for Oncology and Immunology Studies

Description of Mouse: Selective inactivation of Stat1 in mammary cells indicates that its effect as a tumor suppressor in breast is direct.

STAT1 is considered a tumor suppressor, but it is not known if this effect occurs directly in mammary cells or secondarily by disrupting interferon signaling through the JAK/STAT1 pathway to induce immune responses. ERBB2/neu-induced breast cancer appeared sooner in mice lacking STAT1 only in mammary cells than in wild-type mice, indicating that STAT1 tumor suppression was intrinsic to mammary cells and not secondary to an induced immune response.

Potential Commercial Applications: Oncology, Immunology.

Developer of Mouse: Lothar Hennighausen, Ph.D. (NIDDK).

Relevant Publication: Klover PJ, et al. Loss of STAT1 from mouse mammary epithelium results in an increased Neu-induced tumor burden. Neoplasia. 2010 Nov;12(11):899–905. [PMID 21076615].

Intellectual Property: HHS Reference No. E–111–2012/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Mojdeh Bahar, J.D., CLP; 301–435–2950; *baharm@mail.nih.gov*.

Tg(Wap-cre)11738Mam Mouse Model for Developmental Biology Studies

Description of Mouse: Cre-recombinase under the control of the whey acidic acid protein was only detected in alveolar epithelial cells of mammary tissue during lactation, and transcription occurred at all stages of mammary development.

The Cre recombinase from bacteriophage P1 excises intervening DNA sequences located between two unidirectional lox sites positioned on the same linear DNA segment, leaving one lox site behind. Through insertion of lox sites via homologous recombination into the gene of interest and targeting Cre recombinase expression to a specific cell type using a tissue-specific promoter, it is possible to introduce predetermined deletions into the mammalian genome. To delete genes specifically from mammary gland, transgenic mice were created carrying the Cre gene under the control of the whey acidic protein (WAP) gene promoter. Expression of WAP–Cre was only detected in alveolar epithelial cells of mammary tissue during lactation. Recombination mediated by Cre under control of the WAP gene promoter was largely restricted to the mammary gland but occasionally was observed in the brain. High-level transcriptional activity of WAP-based transgenes can be obtained at every stage of mammary development.

Potential Commercial Application: Developmental Biology.

Developer of Mouse: Lothar Hennighausen, Ph.D. (NIDDK).

Relevant Publication: Wagner KU, et al. Cre-mediated gene deletion in the mammary gland. Nucleic Acids Res. 1997 Nov 1;25(21):4323–30. [PMID 9336464].

Intellectual Property: HHS Reference No. E–112–2012/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Mojdeh Bahar, J.D., CLP; 301–435–2950; *baharm@mail.nih.gov*.

Tg(MMTV–Cre)#Mam Mouse Model for Developmental Biology, Hepatology, and Oncology Studies

Description of Mouse: Cre-recombinase under the control of mouse mammary tumor virus long terminal repeat (MMTV) was expressed in the salivary gland and mammary epithelial cells of adult mice, and induced recombination in all tissues.

The Cre recombinase from bacteriophage P1 excises intervening DNA sequences located between two unidirectional lox sites positioned on the same linear DNA segment, leaving one lox site behind. Through insertion of lox sites via homologous recombination into the gene of interest and targeting Cre recombinase expression to a specific cell type using a tissue-specific promoter, it is possible to introduce predetermined deletions into the mammalian genome. To delete genes specifically from mammary gland, transgenic mice were created carrying the Cre gene under the control of the mouse mammary tumor virus (MMTV) long terminal repeat (LTR). In adult MMTV–Cre mice, expression of the transgene was confined to striated ductal cells of the salivary gland and mammary epithelial cells in virgin and lactating mice. In contrast to WAP–Cre, however, Cre expression under control of the MMTV LR resulted in recombination in all tissues.

Potential Commercial Applications: Developmental Biology, Hepatology, Oncology.

Developer of Mouse: Lothar Hennighausen, Ph.D. (NIDDK).

Relevant Publication: Wagner KU, et al. Cre-mediated gene deletion in the mammary gland. Nucleic Acids Res. 1997 Nov 1;25(21):4323–30. [PMID 9336464].

Intellectual Property: HHS Reference No. E–113–2012/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Mojdeh Bahar, J.D., CLP; 301–435–2950; *baharm@mail.nih.gov*.

Bcl-x LoxP (Bcl2l1$^{tm1.1Mam}$) Mouse Model for Developmental Biology Studies

Description of Mouse: Floxed Bcl-x: Conditional knockout of pro-survival Bcl-x in primordial germ cells was used to study the balance between pro-apoptotic Bax during embryogenesis.

Bcl-x is a pro-survival protein that opposes the pro-apoptotic action of Bax which interacts with mitochondria to activate the caspase 9 pathway. Mice in which the Bcl-x gene is inactivated die at E12.5. To be able to study lineage-specific activities of Bcl-x at different stages of development, the Cre-LoxP recombination system was used. Homologous recombination was used to flank the promoter, exon1, and major coding exon2 of the Bcl-x gene with loxP sites. The targeted allele contained a loxP flanked (or floxed) neomycin cassette in the Bcl-x promoter, and an additional loxP site in intron 2. Floxed Bcl-x has been used to study the balance between Bcl-x and Bax in primordial germ cells that undergo controlled levels of cell reduction due to apoptosis, the induction of hemolytic anemia and splenomegaly following conditional deletion of the Bcl-x gene from erythroid cells, the protection of hepatocytes from apoptosis and ensuing fibrotic response by Bcl-x, and the demonstration that Bcl-x is critical for the survival of dendritic cells, important regulators of immune function.

Potential Commercial Application: Developmental Biology.

Developer of Mouse: Lothar Hennighausen, Ph.D. (NIDDK).

Relevant Publication: Rucker EB 3rd, et al. Bcl-x and Bax regulate mouse primordial germ cell survival and apoptosis during embryogenesis. Mol Endocrinol. 2000 Jul;14(7):1038–52. [PMID 10894153].

Intellectual Property: HHS Reference No. E–115–2012/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Mojdeh Bahar, J.D., CLP; 301–435–2950; *baharm@mail.nih.gov*.

UTX LoxP Mouse Model for Oncology Research

Description of Mouse: UTX-flox. Conditional knockout mice for the histone demethylase UTX (Kdm6a) conditional knockout will help understand its role as a tumor suppressor.

Di- and tri-methylations on histone H3 lysine 27 (H3K27me2 and H3K27me3) are epigenetic marks for gene repression. UTX (ubiquitously transcribed X chromosome protein), also known as Kdm6a (lysine (K)-specific demethylase 6a) is a histone demethylase that specifically removes H3K27me2 and H3K27me3. UTX knockout mice are embryonic lethal, so we have generated UTX conditional knockout mice (UTX-flox) in which exon 24 is flanked with loxP sites. UTX has been found to be a tumor suppressor gene mutated in a wide variety of human cancers. The UTX-flox mice provide a valuable tool to study how

UTX functions as a tumor suppressor and as an epigenetic regulator of gene expression.

Potential Commercial Application: Mouse model for Oncology research.

Development Stage: Pre-clinical.

Developer of Mouse: Kai Ge, Ph.D. (NIDDK).

Relevant Publication: Unpublished. Gene ID: 22289.

Intellectual Property: HHS Reference No. E–118–2012/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Contact: Mojdeh Bahar, J.D., CLP; 301–435–2950; *baharm@mail.nih.gov*.

Dated: April 18, 2012.

Richard U. Rodriguez,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

[FR Doc. 2012–9775 Filed 4–23–12; 8:45 am]

BILLING CODE 4140–01–P

ADVISORY COUNCIL ON HISTORIC PRESERVATION

ACHP Quarterly Business Meeting

AGENCY: Advisory Council on Historic Preservation.

ACTION: Notice.

SUMMARY: Notice is hereby given that the Advisory Council on Historic Preservation (ACHP) will meet Thursday, May 10, 2012. The meeting will be held in the Caucus Room of the Russell Senate Office Building at Constitution and Delaware Avenues NE., Washington, DC at 8:30 a.m.

The ACHP was established by the National Historic Preservation Act of 1966 (16 U.S.C. 470 et seq.) to advise the President and Congress on national historic preservation policy and to comment upon federal, federally assisted, and federally licensed undertakings having an effect upon properties listed in or eligible for inclusion in the National Register of Historic Places. The ACHP's members are the Architect of the Capitol; the Secretaries of the Interior, Agriculture, Defense, Housing and Urban Development, Commerce, Education, Veterans Affairs, and Transportation; the Administrator of the General Services Administration; the Chairman of the National Trust for Historic Preservation; the President of the National Conference of State Historic Preservation Officers; a Governor; a Mayor; a Native American; and eight non-federal members appointed by the President.

Call to Order—8:30 a.m.

I. Chairman's Welcome
II. Chairman's Award
III. Chairman's Report
IV. ACHP Management Issues
  A. Credentials Committee Report and Recommendations
  B. Alumni Foundation Report
  C. Recodification of the National Historic Preservation Act
V. Forum Discussion-Federal Budget Austerity and Historic Preservation-Part II
VI. Historic Preservation Policy and Programs
  A. Building a More Inclusive Preservation Program
  B. Legislative Agenda
  C. Rightsizing Task Force Report
  D. Sustainability Task Force Report
VIII. Section 106 Issues
  A. Guidance on Coordinating and Substituting NEPA and Section 106 Compliance
  B. Section 3 Report Submission and Follow up
  C. Traditional Cultural Landscapes Forum Action Plan Implementation
  D. Section 106 Training Initiatives-Webinars
  E. Executive Order on Infrastructure Projects
  F. Post Office Closures and Disposal
IX. New Business
X. Adjourn

Note: The meetings of the ACHP are open to the public. If you need special accommodations due to a disability, please contact the Advisory Council on Historic Preservation, 1100 Pennsylvania Avenue NW., Room 803, Washington, DC 202–606–8503, at least seven (7) days prior to the meeting. For further information: Additional information concerning the meeting is available from the Executive Director, Advisory Council on Historic Preservation, 1100 Pennsylvania Avenue NW., #803, Washington, DC 20004.

Dated: April 18, 2012.

John M. Fowler,

Executive Director.

[FR Doc. 2012–9783 Filed 4–23–12; 8:45 am]

BILLING CODE 4310–K6–P

DEPARTMENT OF HOMELAND SECURITY

Federal Emergency Management Agency

[Docket ID FEMA–2012–0007]

Hazard Mitigation Assistance for Wind Retrofit Projects for Existing Residential Buildings

AGENCY: Federal Emergency Management Agency, DHS.

ACTION: Notice of availability; request for comments.

SUMMARY: The Federal Emergency Management Agency (FEMA) is accepting comments on *Hazard Mitigation Assistance for Wind Retrofit Projects for Existing Residential Buildings*.

DATES: Comments must be received by June 25, 2012.

ADDRESSES: You may submit comments, identified by Docket ID FEMA–2012–0007, by one of the following methods:

Federal eRulemaking Portal: http://www.regulations.gov. Search for docket ID FEMA–2012–0007 and follow the instructions for submitting comments. Please note that this proposed policy is not a rulemaking and the Federal Rulemaking Portal is being utilized only as a mechanism for receiving comments.

Mail/Hand Delivery/Courier: Office of Chief Counsel, Federal Emergency Management Agency, 500 C Street SW., Room 835, Washington, DC 20472–3100.

FOR FURTHER INFORMATION CONTACT: Cecelia Rosenberg, Federal Insurance and Mitigation Administration, Federal Emergency Management Agency, 1800 South Bell Street, Room 608, Arlington, VA 20598–3015, (phone) 202–646–3321, or email *cecelia.rosenberg@fema.dhs.gov*.

SUPPLEMENTARY INFORMATION:

I. Public Participation

Instructions: All submissions received must include the agency name and docket ID. Regardless of the method used for submitting comments or material, all submissions will be posted, without change, to the Federal eRulemaking Portal at *http://www.regulations.gov,* and will include any personal information you provide. Therefore, submitting this information makes it public. You may wish to read the Privacy Act notice which can be viewed by clicking on the ''Privacy Notice'' link in the footer of *www.regulations.gov*.

Docket: The proposed policy is available in docket ID FEMA–2012–0007. For access to the docket to read background documents or comments received, go to the Federal eRulemaking Portal at *http://www.regulations.gov* and search for the docket ID. Submitted comments may also be inspected at FEMA, Office of Chief Counsel, Room 835, 500 C Street SW., Washington, DC 20472.

II. Background

The Pre-Disaster Mitigation program (PDM) and the Hazard Mitigation Grant