Optogenetic calcium sensor, voltage indicator and chemogenetic mouse models available from The Jackson Laboratory.

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ABSTRACT

Understanding neural circuitry in both normal and disease states is a priority of the biomedical community. To facilitate this, The Jackson Laboratory offers an impressive array of genetically-engineered tools enabling scientists to monitor the neural activity of intact mouse brain. Top most in this tool box are mouse lines using optogenetic and transient-sensing (calcium-, voltage-) technologies. Opsins are light-activated proteins that alter membrane potential in neurons, so that stimulation with light allows rapid control of neuronal activity. Several mouse lines express improved/optimized opsins fused to fluorescent proteins. These include mice with channelrhodopsin expression directed by specific promoters. Additional control is available in mice with Cre- or Tet-dependent expression of channelrhodopsin or halorhodopsin.

GCaMP fluorescence in response to calcium is an indicator of cell activation. These include Thy1-promoter driven GCaMP6 transgenic lines and Cre or Tet-dependent GCaMP6 variants. Both cytosolic- and membrane-targeted GCaMP6 mice are available. Furthermore, mice with GCaMP8 expression in capillaries allow studying the blood/brain barrier.

Several intersectional strains utilize both Cre-lox and Tet-On/-Off function. Removal of a floxed-STOP allows Tet-dependent expression of channelrhodopsin (ReaChR/EYFP, ChR2*H134R/EYFP), GCaMP6s, GCaMP6f, RCaMP1.07, voltage-sensor (ASAP2s) or bicistronic QuasAr voltage-indicator CheRiff channelrhodopsin (OptoPatch).

This set includes mice created by the Allen Institute for Brain Science, the Genetically-Encoded Neuronal Indicator and Effector (GENIE) Project (Janelia/HHMI), Duke/MIT and several others.

Designer receptors exclusively activated by designer drugs (DREADDs) are mutant G-protein coupled receptors activated by the pharmacologically-inert molecule clozapine-N-oxide. Several chemogenetic strains have Cre- and/or FLP-inducible expression of DREADDs.

JAX Repository receives support from NIH, HHMI and private foundations.

Search The Jackson Laboratory Repository / JAX® Mice Database
www.jax.org/mouse-search

www.jax.org/donate-a-mouse
Donating a Strain to The Jackson Laboratory

The Jackson Laboratory Resources for Optogenetics, Cre-dependent Optogenetic Tools and Cre Strains for Neurobiology
www.jax.org/optogenetics

MMRRC
Mutant Mouse Resource & Research Centers supported by NIH

Mutant Mouse Resource and Research Center at JAX

Human APP / PS1 mice with Alzheimer's mutations

MMRRC#	COMMON NAME	Donated By
034830-JAX	3xTg-AD	Dr. Frank LaFerla (Univ of California, Irvine)
034840-JAX	5xFAD	Dr. Robert Vassar (Northwestern University)
034829-JAX	APPswe/PSEN1dE9	Dr. David Borchelt (Univ of Florida)

AD-BxD panel

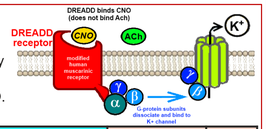
As extensions of MMRRC-JAX 5xFAD mouse line utility, recently available are the **AD-BXD** panel of F1 hybrid mice - an isogenic resource useful for studying the effect of genetic background/diversity on the 5xFAD transgenic model of Alzheimer's disease.

This panel allows for the monitoring of phenotype in individual mice harboring identical high-risk *FAD* mutations in human *APP* and *PSEN1* genes, but whose allelic contributions differ across the remainder of the genome.

25 lines available - search JAX® Mice Database for "AD-BXD"

CHEMOGENETICS

DREADD: "Designer Receptors Exclusively Activated by Designer Drugs" are mutant G protein-coupled receptors activated by *CNO*.



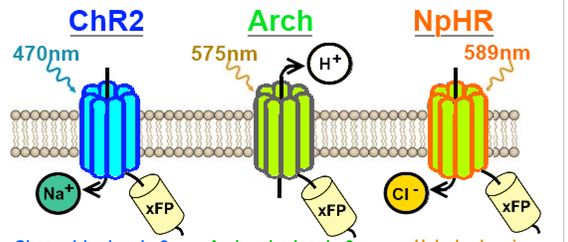
PROMOTER	EFFECTOR	EXPRESSION	NAME	JAX#
R26 :: CAG	hM3Dq	Cre-inducible mCitrine ; then CNO-inducible Gq	R26-LSL-Gq-DREADD	026220
R26 :: CAG	hM3Dq	Cre-inducible mCherry ; then CNO-inducible Gq	RC::L-hM3Dq	026943
R26 :: CAG	hM4Di	Cre-inducible mCitrine ; then CNO-inducible Gi	R26-LSL-Gi-DREADD	026219
R26 :: CAG	hM4Di	FLP-inducible mCherry ; then Cre- & CNO-inducible Gi	RC::FPDi	029040

OPTOGENETICS

A. **OPTOGENETICS**: control of cellular functions in genetically modified cells using opsins - transmembrane, retinal-binding proteins that combine a light-sensitive domain with an ion channel or pump. Upon absorption of light, the protein is activated and provides ion transport, membrane potential alteration and sensory functions to bacteria.

By exogenously expressing light-activated proteins that alter membrane potential in neurons, addition or removal of specific wavelengths of light can be used for rapid control of neuronal activity.

B. **OPSINS**



Channelrhodopsin-2 (ChR2)
cation channel
depolarizes cell - causes action potentials in response to **blue** light.

Archaerhodopsin-3 (Arch)
outward proton pump
hyperpolarizes cell - prevents action potentials in response to **yellow-green** light

Halorhodopsin (NpHR)
inward chloride ion pump
hyperpolarizes cell - prevents action potentials in response to **yellow** light

C. **APPLICATION**

Fiber optic electrode delivers specific wavelengths of light
= opens the ion channel
= light controls neuronal signaling

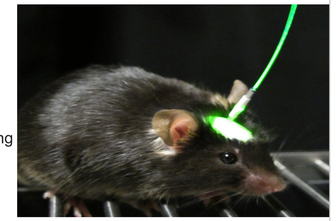


Image from Williams and Deisseroth 2013 PNAS 110:16287

Specific Promoters *drive expression of opsins, xFPs, Ca+ sensors and photoactivatable GFP*

PROMOTER	EFFECTOR	EXPRESSION	COMMON NAME	JAX#
thymus cell antigen 1	ChR2 / EYFP	widespread brain	Thy1-ChR2-EYFP line 18	007612
thymus cell antigen 1	ChR2 / EYFP	widespread brain	Thy1-ChR2-EYFP line 9	007615
choline acetyltransferase	mhChR2 / EYFP	cholinergic neurons	ChAT-ChR2(H134R)-EYFP line 6	014546
vesicular GABA transporter	mhChR2 / EYFP	GABAergic interneurons	VGAT-ChR2(H134R)-EYFP	014548
olfactory receptor 160	ChR2*H134R / EYFP	M72+ olfactory sensory neurons	M72-IRES-ChR2-YFP	021206
TRE	GCaMP6s	Tet-inducible	TRE-GCaMP6s line G6s2	024742
synaptosomal-assoc. protein 25	GCaMP6s	widespread brain	Snap25-2A-GCaMP6s-D	025111
cadherin 5	GCaMP8	blood/brain barrier (endothelial cells)	Cdh5-GCaMP8	033342
thymus cell antigen 1	jRGECO1a	brain (denser cortex)	Thy1-jRGECO1a-WPRE line GP8.20	030525
thymus cell antigen 1	jRGECO1a	brain (sparser cortex)	Thy1-jRGECO1a-WPRE line GP8.31	030526
thymus cell antigen 1	jRGECO1a	brain	Thy1-jRGECO1a-WPRE line GP8.58	030527
thymus cell antigen 1	jRGECO1a	brain	Thy1-jRGECO1a-WPRE line GP8.62	030528
Cx3cr1 :: Snap25 :: Mobp :: Aldh1L1	EGFP :: YFP :: Cerulean :: DsRedMax	microglia, neurons, oligodendrocytes, astrocytes	PrismPlus	031478
CAG	mKate2	widespread mitochondria	mito::mKate2	032188
human ubiquitin C	PA-GFP	widespread	UBC PA-GFP	022486

IMAGES

	Thy1-GCaMP6s		Thy1-GCaMP6f		
Line	GP4.3	GP4.12	GP5.5	GP5.11	GP5.17
JAX#	024275	025776	024276	024339	025393
Olf. bulb	+	++	++	++	++
M1	++	+++	++	++	+++
Piriform	+	++	+	+	+
Amygdala	+	+++	++	+	+++
S1	++	+++	++	++	+++
Hippocamp	+++	+++	+++	++	+++
Thalamus	+	+	+	+	+
Hypothal	-	+	+	+	+
V1	++	++	++	++	+++
Cerebellum	-	-	-	+	-
Midbrain	+	+	-	-	+
Pons	+	+	+	+	++
Medulla	+	-	-	-	+

hhmi janelia Research Campus

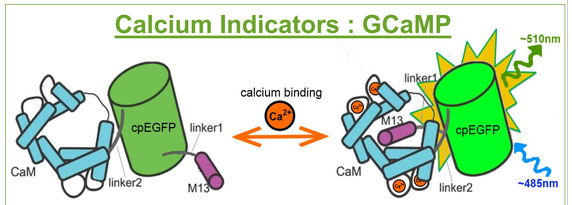
GENIE

Thy1-GCaMP6

Founder line-specific, brain expression of GCaMP6 variants
[Dana et al. 2014 PLoS One. 9:e108697 - Table 1]

TRANSIENT-SENSORS

Calcium Indicators : GCaMP

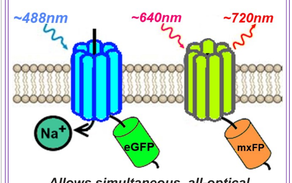


- Ca2+ binding (neuron activation) → EGFP fluorescence (~510 nm)
- Optimized dynamic range, baseline fluorescence, sensitivity & function

GCaMP illustration adapted from Akerboom et al. 2012 J Neurosci 32:13819

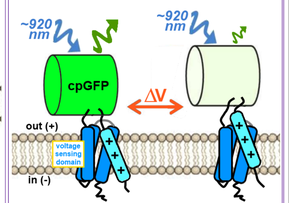
Voltage Indicators : OptoPatch and ASAP2s

OptoPatch2 / OptoPatch3
CheRiff-eGFP::QuasAr-mxFP



Allows simultaneous, all-optical electrophysiology

ASAP2s



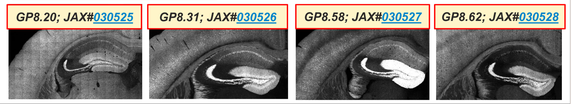
Allows imaging of voltage dynamics

CheRiff : sensitive blue light-activated ChR variant; fused to eGFP
QuasAr2: near infrared-activated, Arch-derived, enhanced voltage indicator; fused to a membrane-targeted dark Orange2
QuasAr3: improved *in vivo* trafficking; fused to membrane-targeted Citrine
ASAP2s: high-sensitivity variant of green fluorescent voltage indicator accelerated sensor of action potentials

PROM	EFFECTOR	EXPRESSION	NAME	JAX#
R26 :: CAG	CheRiff-eGFP:: QuasAr2-mOrange2	Cre-inducible	Floxopatch, Optopatch2	028678
TIGRE :: TRE	CheRiff-eGFP:: QuasAr3-mCitrine	Cre-inducible & Tet-control	Optopatch3 Ai155	029679
TIGRE :: TRE2 + CAG	ASAP2s + tTA2s	Cre-inducible & Tet-control	Ai169D	031569

Thy1-jRGECO1a

Cortical imaging of Thy1-jRGECO1a-WPRE
Courtesy of Drs. Hod Dana and Douglas Kim



Cre:Tet-Inducible Lines

ALLEN INSTITUTE for BRAIN SCIENCE *Fueling Discovery*

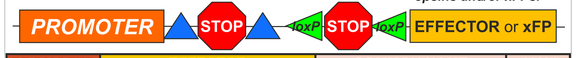
Cre-inducible and dox-inducible / reversible expression of opsins, xFPs, Ca2+ sensors, etc.

TIGRE locus (*Igs7*)
~21.54 Mbp on Chr.9

PROMOTER	EFFECTOR	COMMON NAME	JAX#
TIGRE :: TRE ; CaMK2a	*GCaMP6f* + tTA	Ai93D;CaMK2a-tTA	024108
TIGRE :: TRE2 + CAG	*GCaMP6s* + tTA2s	Ai162D	031562
TIGRE :: TRE2 + CAG	*GCaMP6f* + tTA2s	Ai148D	030328
TIGRE :: TRE ; CaMK2a	*GCaMP6s* + tTA	Ai94D;CaMK2a-tTA	024115
TIGRE :: TRE	*RCaMP1.07*	Ai143D	030217
TIGRE :: TRE2 + CAG	*EGFP* + tdT + tTA2s	Ai139D	030219
TIGRE :: TRE2 + CAG	*EGFP* + tTA2	Ai140D	030220

Cre:FLP Dual Inducible Lines

Multiple STOP cassettes prevent transcription of opsins and/or xFPs.



PROMOTER	EFFECTOR	COMMON NAME	JAX#
R26 :: CAG	CatChR2^{L132C} / EYFP	Ai80D	025109
R26 :: CAG	ReaChR / mCitrine	Rosa26 CAG-FSF-LSL-ReaChR-mCit	024846
R26 :: CAG	Synaptophysin / EGFP + tdTom	RC::FPSit	030206
R26 :: CAG	tdT	Ai65D	021875
R26 :: CAG	tdT ; EGFP	RC::FLTG	026932

Cre-Inducible Lines

A floxed-STOP cassette prevents transcription

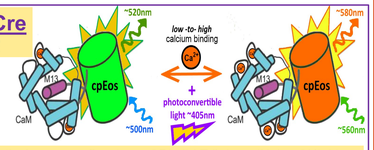
PROMOTER	EFFECTOR	COMMON NAME	JAX#
R26 :: CAG	Arch / GFP	Ai35D	012735
R26 :: CAG	ArchT / EGFP	Ai40D	021188
R26 :: CAG	ChETA/ChR2*H134R ; tdT	2xChETA-tdT	017455
R26 :: CAG	ChR2*H134R / EYFP	Ai32	024109
R26 :: CAG	hChR2*H134R / tdT	Ai27D	012567
R26 :: CAG	GtACR1 / FusionRed	R26-CAG-LNL-GtACR1-ts-FRed-Kv2.1	033089
R26 :: CAG	ReaChR / mCitrine	Rosa26 CAG-LSL-ReaChR-mCit	026294
R26 :: CAG	eNpHR3.0 / EYFP	Ai39	014539
R26 :: CAG	CaMPARI2	R26-CAG-lsl-CaMPARI2	034240
RNA pol II :: CAG	GCaMP5G ; tdT	PC::G5-tdT	024477
R26 :: CAG	GCaMP6f	Ai95D	028865
R26 :: CAG	GCaMP6f [membrane]	R26-Lck-GCaMP6f^{flox}	029626
R26 :: CAG	GCaMP6f / tdTom (Salsa6f)	LSL-Salsa6f	031968
R26 :: CAG	GCaMP6s	Ai96	028866
R26 :: CAG	Mb2-mYFP*A206K ; Mb2-tdTomato ; Mb2-mTFP1 :: H2B-mCherry ; H2B-EGFP ; H2B-mCerulean	iMb2-Control-Mosaic:: iChr2-Control-Mosaic	031298 031301 031302
R26 :: CAG	INDIA (mNeonGreen-aCasp3-mRuby2)	Rosa26^{LSL}-INDIA apoptosis indicator	032068
H11 :: CAG	H2B-mTagBFP + tTA2	TB (tTA2-BFP)	031776
R26 :: CAG	mKate2 + rtTA3	Rosa26-CAGs-LSL-RIK	029633
R26 :: CAG	^{T}Epac^{VV}	CAMPER (cAMP FRET sensor)	032205
R26 :: CAG	SunTag / superfolder GFP	CAG-Sun1/sfGFP	030952
R26 :: CAG	SunTag(BFP) / dCas9	Rosa26-LSL-dCas9/SunTag	031925
CAG	SunTag-p65-HSF1	SPH	031645
R26 :: CAG	Synaptophysin / tdT	Ai34D	012570
R26 :: CAG	tdTomato	Ai14	007914

IMAGES

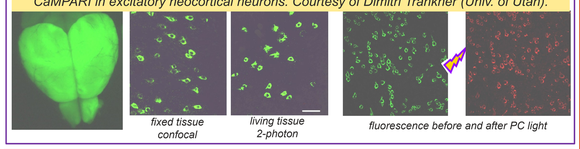
CaMPARI2 ; Emx1-Cre

JAX#s 034240 x 005628

CaMPARI changes from green-to-red fluorescence with high intracellular calcium and photoconversion light



CaMPARI in excitatory neocortical neurons. Courtesy of Dimitri Tränkner (Univ. of Utah).

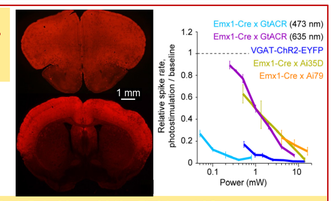


fixed tissue confocal | *living tissue 2-photon* | *fluorescence before and after PC light*

GtACR1-ts-FRed-Kv2.1 ; Emx1-Cre

JAX#s 033089 x 005628

Soma-localized anion channel rhodopsin 1 with FusionRed allows:
[i] FRed fluorescence and
[ii] strong photoinhibition
in cortical excitatory neurons

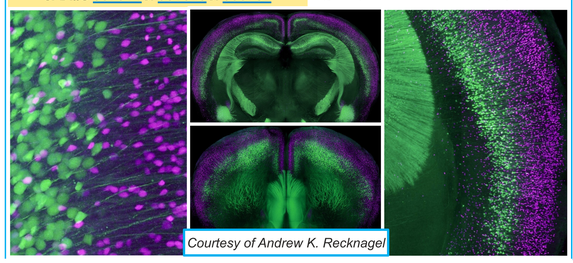


Data from Li et al. 2019 bioRxiv 20may2019 - Fig2A and 2C.

Ai14; VIP-IRES-Cre ; Thy1-YFP-H

JAX#s 007914 x 031628 x 003782

GABAergic (magenta) & pyramidal neurons (green) of neocortex + axon projections



Courtesy of Andrew K. Recknagel

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