

# Johns Hopkins Engineering

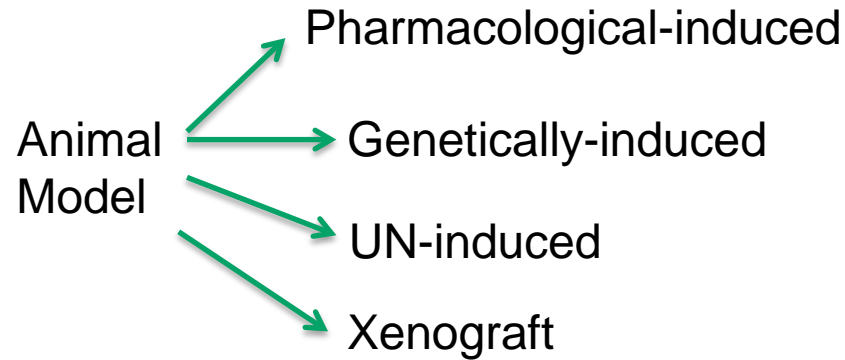
## Methods in Neurobiology

### Animal Models



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# Types of animal models used in biomedical research

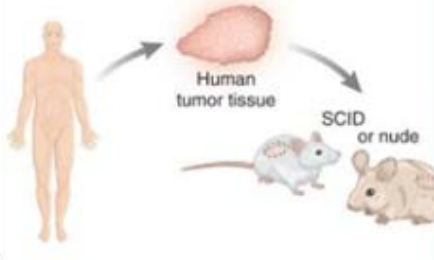
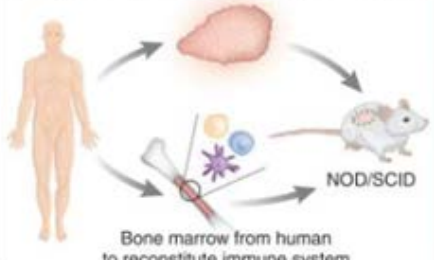
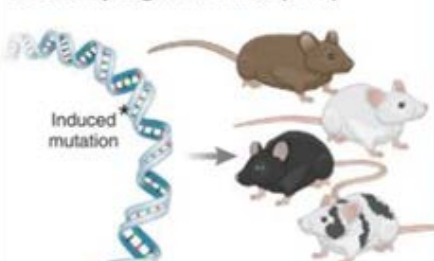


- Monkey
- Rat
- Mice
- Dog
- Pig
- Sheep
- Guinea Pig
- Nematode
- Drosophila
- ...

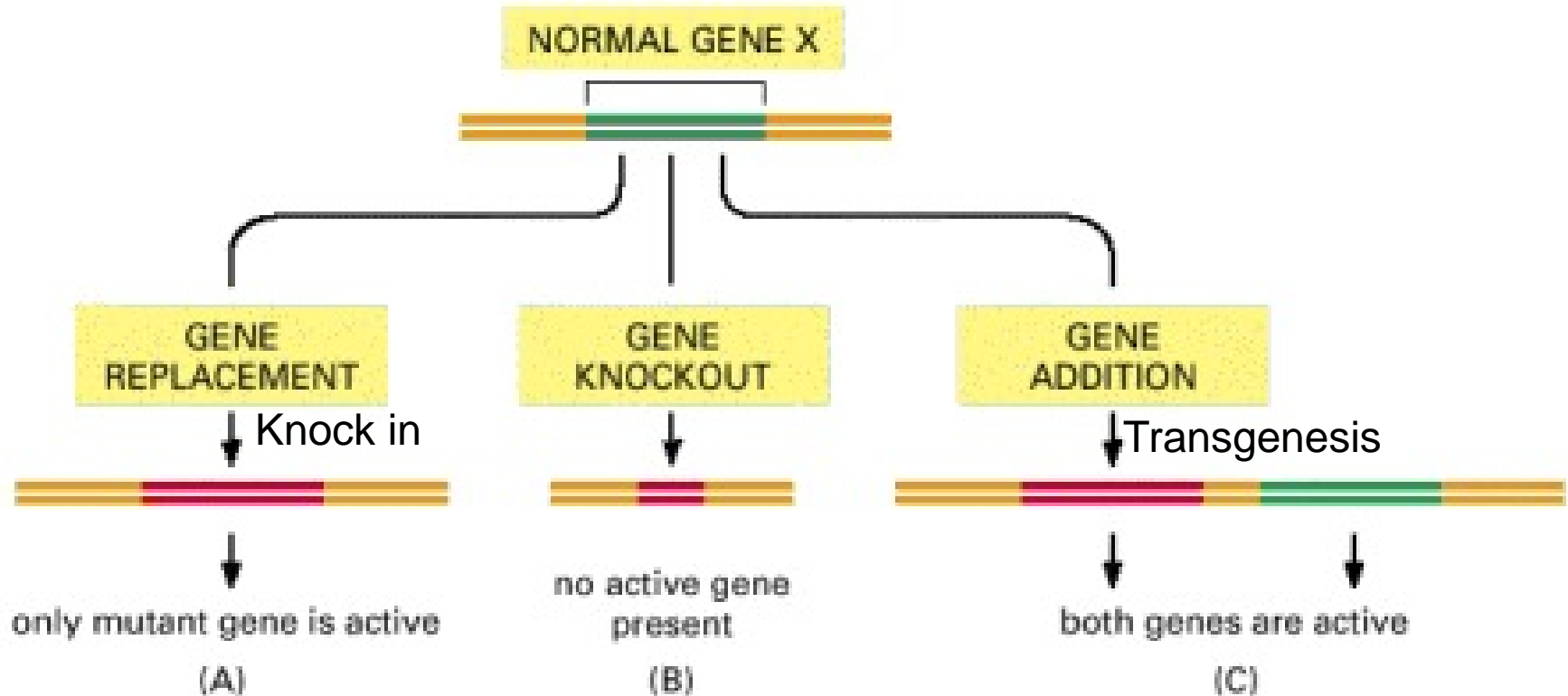
# Common animal models used for genetic engineering

Model Organism	Common Name	Research Applications
<i>Saccharomyces cerevisiae</i>	Yeast	Used for biological studies of cell processes (e.g., mitosis) and diseases (e.g., cancer)
<i>Pisum sativum</i>	Pea plant	Used by Gregor Mendel to describe patterns of inheritance
<i>Drosophila melanogaster</i>	Fruit fly	Employed in a wide variety of studies ranging from early gene mapping, via linkage and recombination studies, to large scale mutant screens to identify genes related to specific biological functions
<i>Caenorhabditis elegans</i>	Roundworm (nematode)	Valuable for studying the development of simple nervous systems and the aging process
<i>Danio rerio</i>	Zebra fish	Used for mapping and identifying genes involved in organ development
<i>Mus musculus</i>	House mouse	Commonly used to study genetic principles and human disease
<i>Rattus norvegicus</i>	Brown rat	Commonly used to study genetic principles and human

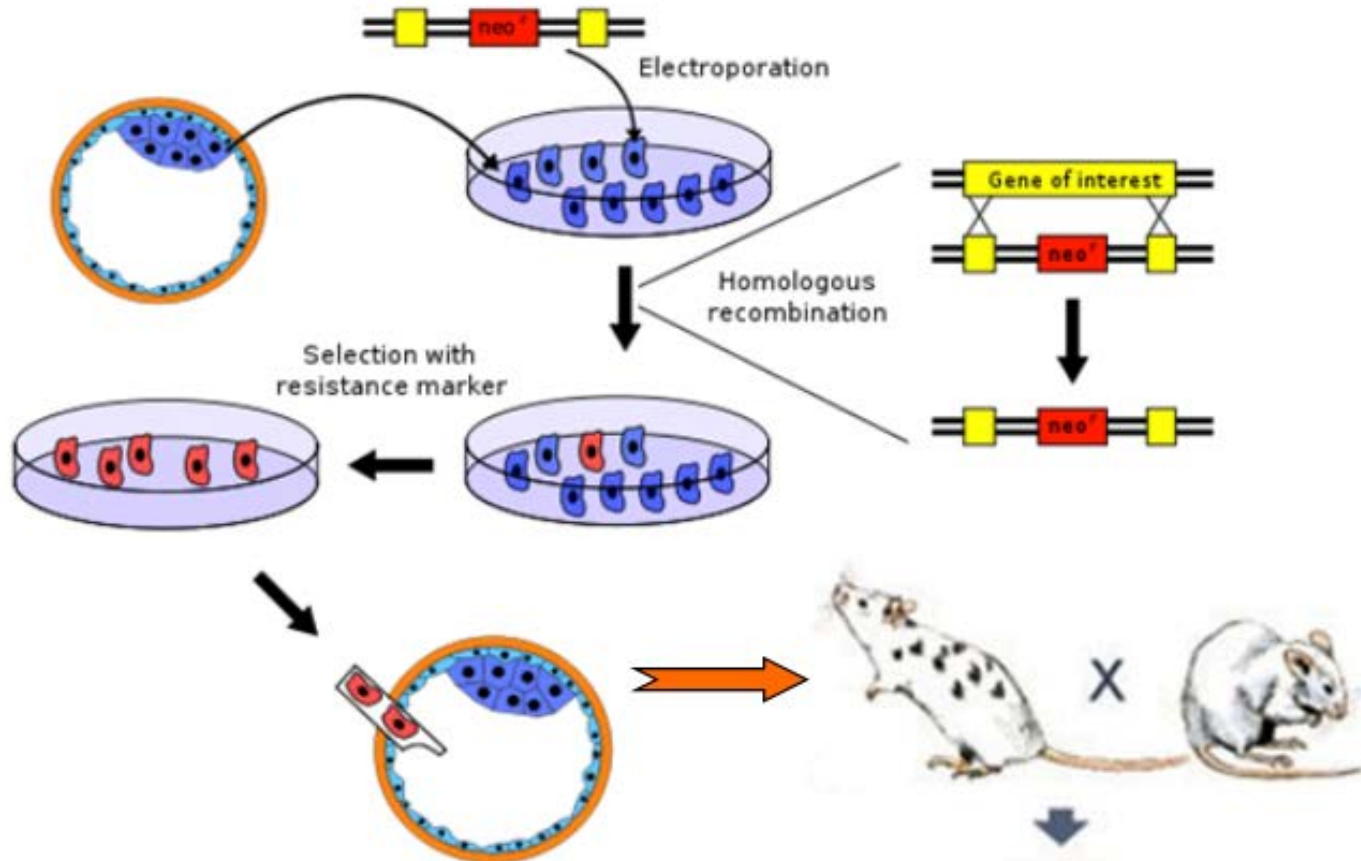
# Xenograft models for cancer research

	ADVANTAGES	DISADVANTAGES
<b>Orthotopic xenograft of human tumors</b>  <p>Human tumor tissue</p> <p>SCID or nude</p>	<ul style="list-style-type: none"> <li>- Can predict the drug response of a tumor in a human patient</li> <li>- Provides realistic heterogeneity of tumor cells</li> <li>- Allows for rapid analysis of human tumor response to a therapeutic regime</li> </ul>	<ul style="list-style-type: none"> <li>- Mice are immunocompromised, providing a less realistic tumor microenvironment</li> </ul>
<b>Xenograft of human tumor in humanized mice</b>  <p>Bone marrow from human to reconstitute immune system</p> <p>NOD/SCID</p>	<ul style="list-style-type: none"> <li>- Appropriately mimics human tumor microenvironment</li> <li>- Can predict the drug response of a tumor in a human patient</li> <li>- Provides realistic heterogeneity of tumor cells</li> </ul>	<ul style="list-style-type: none"> <li>- Expensive</li> <li>- Technically complicated</li> </ul>
<b>Genetically engineered mice (GEM)</b>  <p>Induced mutation</p>	<ul style="list-style-type: none"> <li>- Potential analysis of many genetic backgrounds by using a variety of mouse strains</li> <li>- Tumor exists in the presence of competent immune system (realistic microenvironment)</li> <li>- Defined mutations can mimic those identified in human tumors</li> <li>- Can follow tumor development from early time points</li> </ul>	<ul style="list-style-type: none"> <li>- Targets a limited number of genes which is usually not reflective of the complex heterogeneity of human tumor cells</li> <li>- Development is costly and time consuming, often requiring years of work before validation</li> <li>- Tumor development in animals is slow and variable</li> </ul>

# How to make animal models with genetic engineering

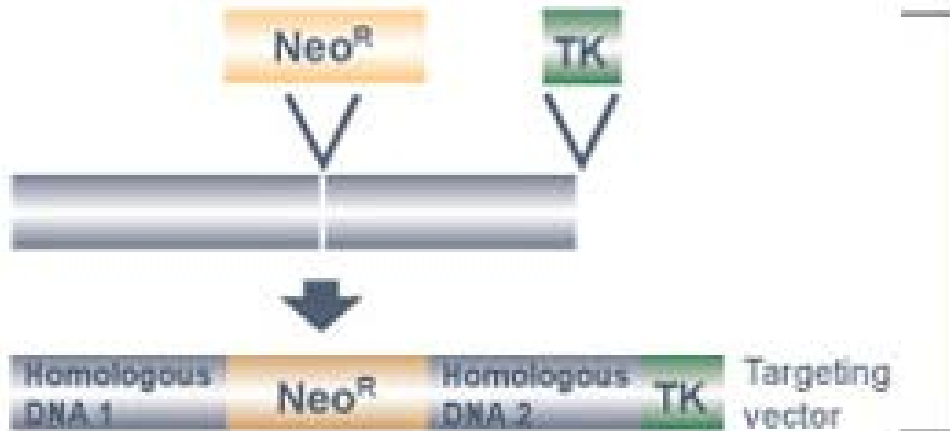


# How to make a Knock out (KO) or a Transgenic (Tg) mouse



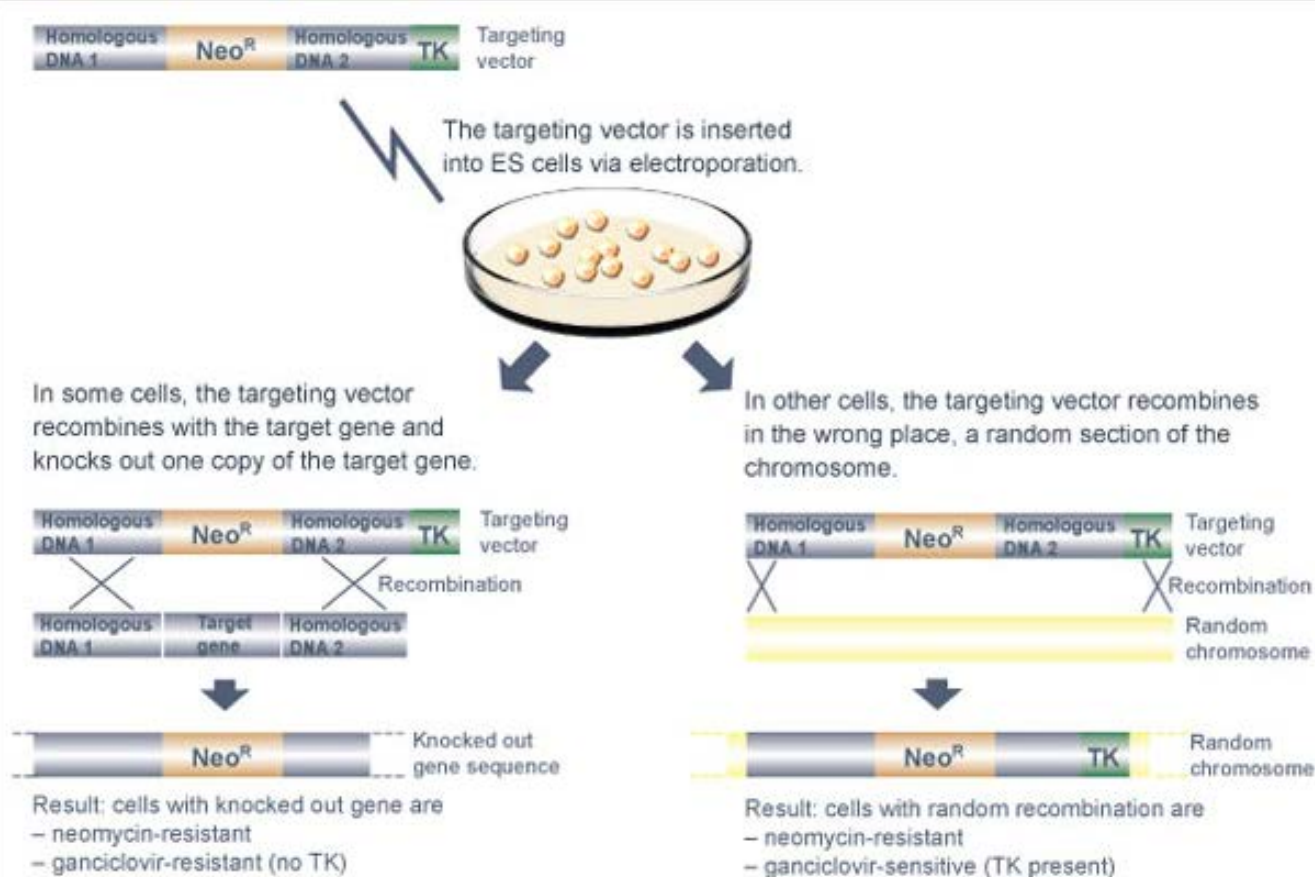
# Inserting genes with homologous recombination

Homologous DNA 1    Target gene    Homologous DNA 2    Target gene & flanking sequences



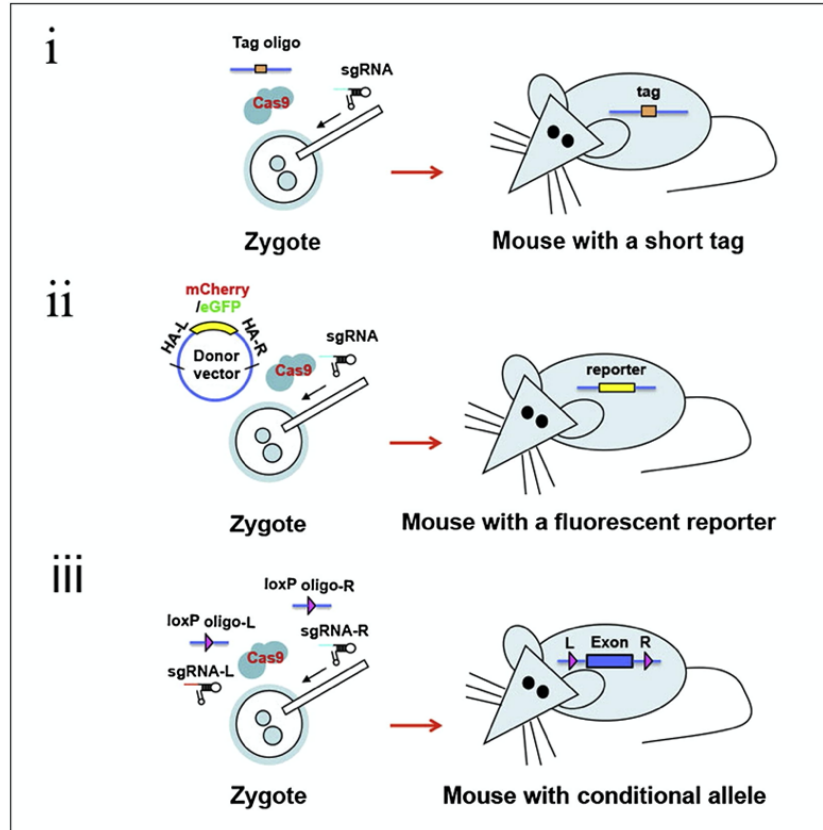
The markers Neo<sup>R</sup> and TK are inserted into the target gene sequence to make a targeting vector sequence.

# Inserting genes with homologous recombination

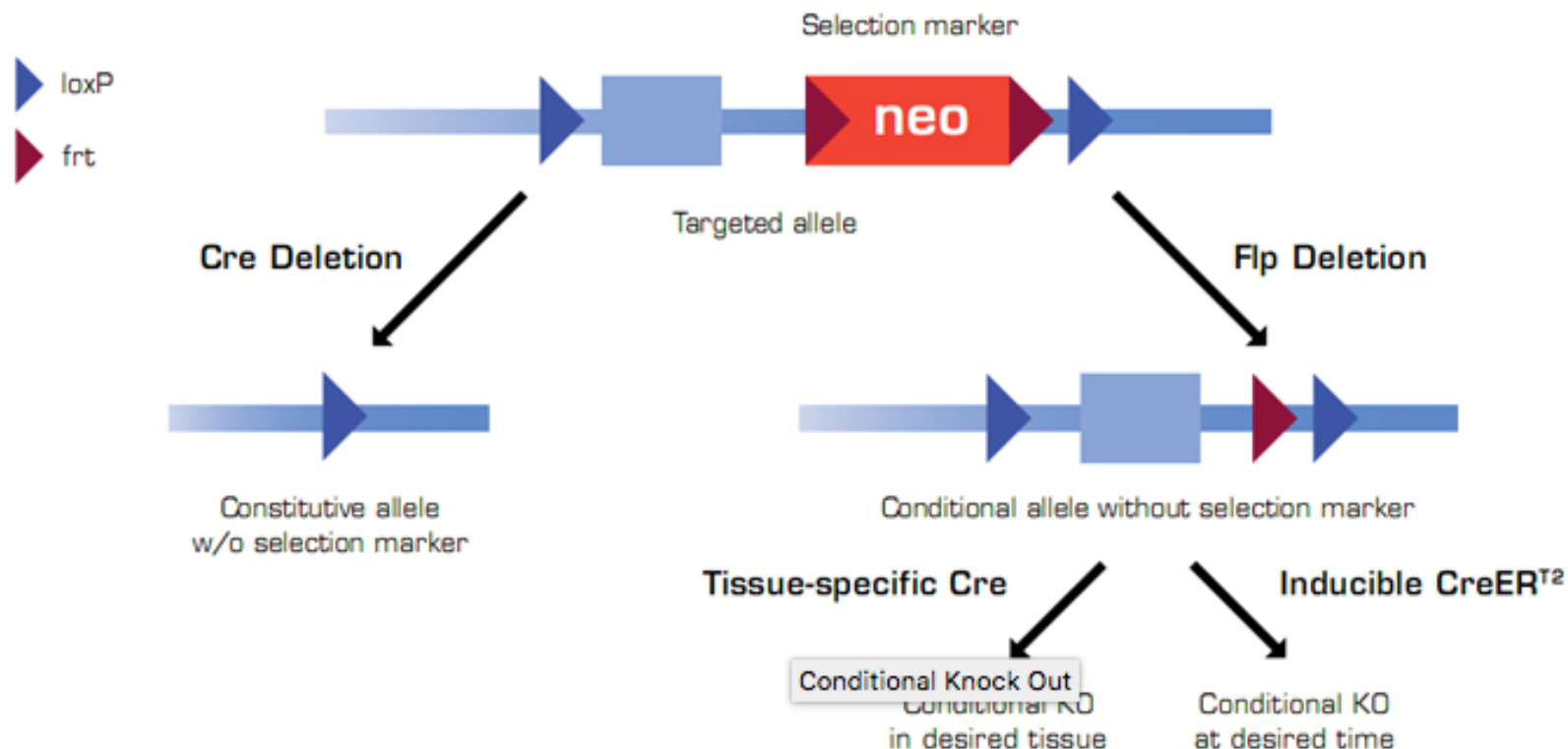




# How to make mouse models with CRISPR/Cas9



# Conditional KO mice



# References

Slide	Reference
2	Simmons, D. 2008. The Use of Animal Models in Studying Genetic Disease: Transgenesis and Induced Mutation. Scitable bynatureEDUCATION. <a href="https://www.nature.com/scitable/topicpage/the-use-of-animal-models-in-studying-855/">https://www.nature.com/scitable/topicpage/the-use-of-animal-models-in-studying-855/</a>
3	Wang Z, Wang SN, Xu TY, et al. 2017 Organoid technology for brain and therapeutics research. CNS Neuroscience & Therapeutics. 23(10):771-778.
4	Richmond, A., Su, Y. 2008 Mouse Xenograft Models vs GEM Models for Human Cancer Therapeutics. Dis Model Mech. 1(2-3): 78-82.
5	Lewis, J., Roberts, K., Morgan, D. 2002 Studying Gene Expression and Function. Molecular Biology of the cell. 4 <sup>th</sup> Ed., Garland Science. New York. <a href="https://www.ncbi.nlm.nih.gov/books/NBK26818/">https://www.ncbi.nlm.nih.gov/books/NBK26818/</a>
6	LinkedIn SlideShare. (Jul. 3, 2013) Knockout Mice. <a href="https://www.slideshare.net/priyananda12/knock-out-mice">https://www.slideshare.net/priyananda12/knock-out-mice</a>
7,8	Scitable bynatureEDUCATION. 2014 Scientists Can Analyze Gene Function by Deleting Gene Sequences. <a href="https://www.nature.com/scitable/topicpage/scientists-can-analyze-gene-function-by-deleting-6526138/">https://www.nature.com/scitable/topicpage/scientists-can-analyze-gene-function-by-deleting-6526138/</a>
9	Yang, H., Wang, H., Shivalila, C.S., Cheng, A.W., Shi, L., Jaenisch, R. 2013 CRISPR-Cas9 Mediated Mouse Model Creation and Transcription Regulation. Cell 154, 1370–1379
10	Taconic. (2020). Knockout Mice. Design Your Model. <a href="https://www.taconic.com/genetically-engineered-animal-models/knockout-mice/">https://www.taconic.com/genetically-engineered-animal-models/knockout-mice/</a>



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