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Introduction to laboratory animal science

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Master 1 D2HP, Development of Drugs and Health Products

January 23rd, 2025

moods
une équipe du cesp

Improve the understanding, prevention, and treatment of depression, anxiety, psychotrauma, and suicide.

teaching
& pre-clinical research

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Pr. D. DAVID

Translational

Clinic ➡ Preclinic ➡ Clinic

Multi-disciplinary

Psychiatrist, Psychology,
Pharmacologist, Biology, Neurobiologie,
Imaging,

Teaching
& Clinical research

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Pr. E.Corruble

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The Moods Team (Pre-clinic)

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+PhD Students +MSc Students

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PhD Student, 1st yr

Makiath ADEBO,
PhD Student, 1st yr

Salma ABDENNEBI
Msc Student

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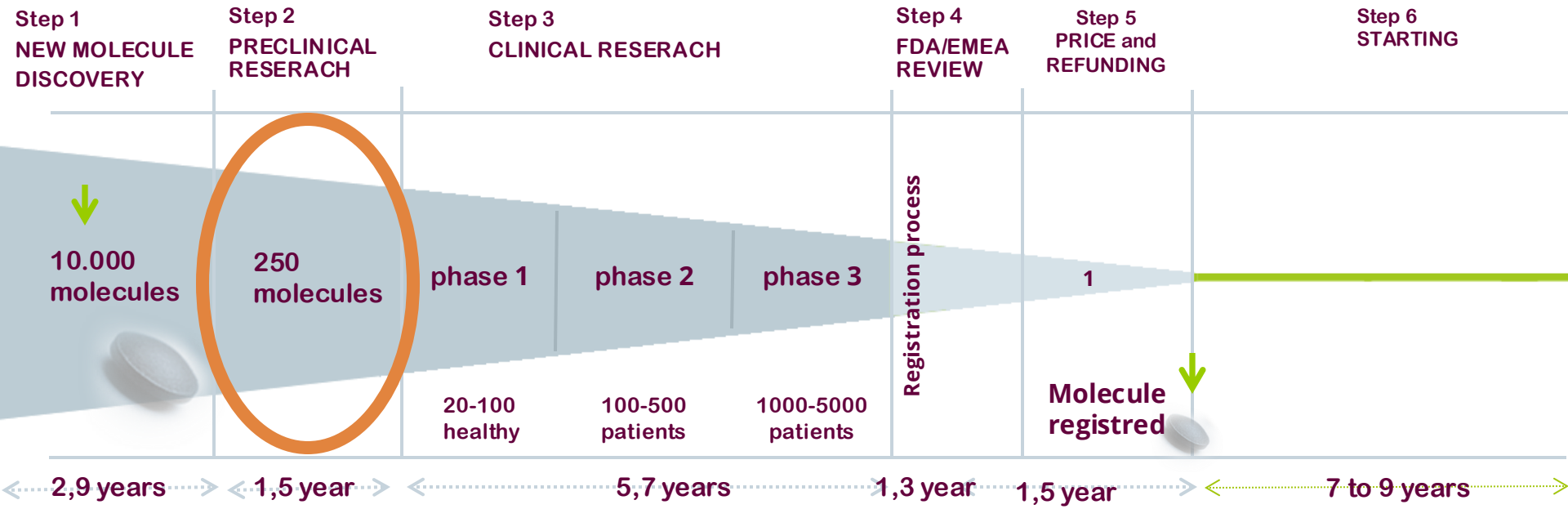
The Tragedy of the Elixir, 1937, USA

- Sulfanilamide Elixir: 10% sulfanilamide, 72% diethylene glycol, 16% water.
- Treating different ailments
- From gonorrhea to sore throats.
- Poison 105 patients
- 1930: Food, Drug, and Cosmetics Act,
- The FDA has the power to monitor the safety of new molecules.
- In 1962, the U.S. Congress passed the Kefauver-Harris Drug Amendments.
- Need for the pharmaceutical industry to prove the efficacy and safety of molecules

The important role preclinical research in the development of a new molecule

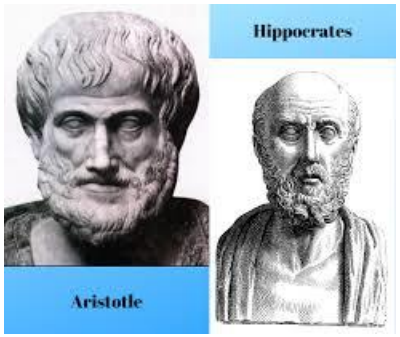


A new medication

1 000 000 000	Invest
7 000 874	Hours of
6 587	Experiments
423	Researchers
1	Medication

Adapted from CMR International Factbook 2004 (Centre for Medicines Research International)

History of Laboratory Animals



- Investigated the structure and function of the human body
  - see their respective *Historia Animalium* and *Corpus Hippocraticum*

Galen

- Conducted physiological experiments on pigs, monkeys and dogs

Claude Barnard

- Imperative to use animals to make medical discoveries, teach, test

Animal Experimentation

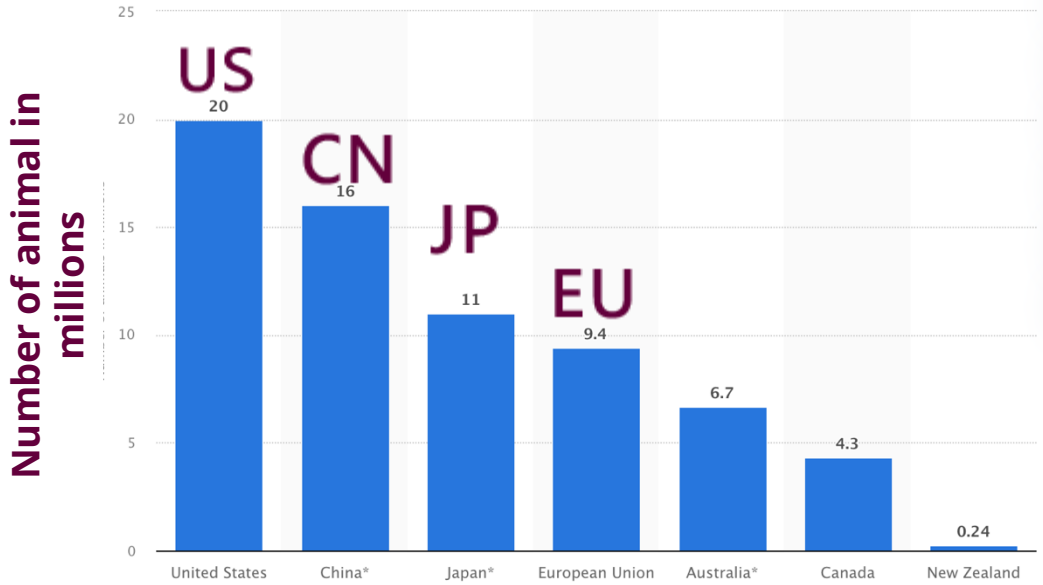
- Similar physiology betweens animals and humans

vs.

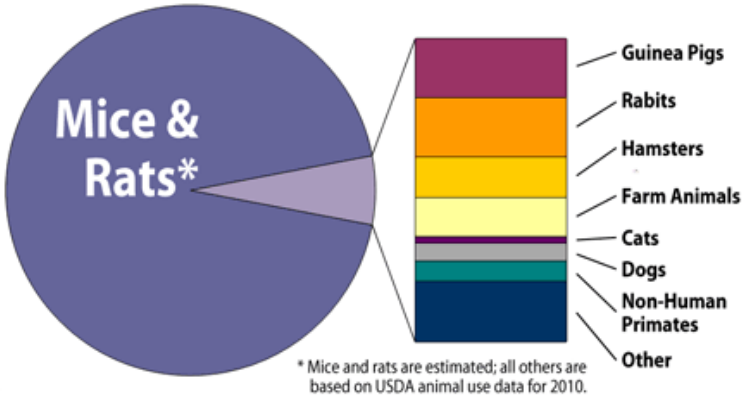
- Important to find treatment for many diseases
  - Can help to cure diseases
    - New vaccines
- Not only useful for humanity
- Lack of suitable alternative testing methods

The use of Laboratory Animals

- ~70 million animal species in the world in 2020 (Matej Mikulic , Oct 28, 2021)



- The majority are mammalian animals
  - 80% of all vertebrates are rodents



vs.

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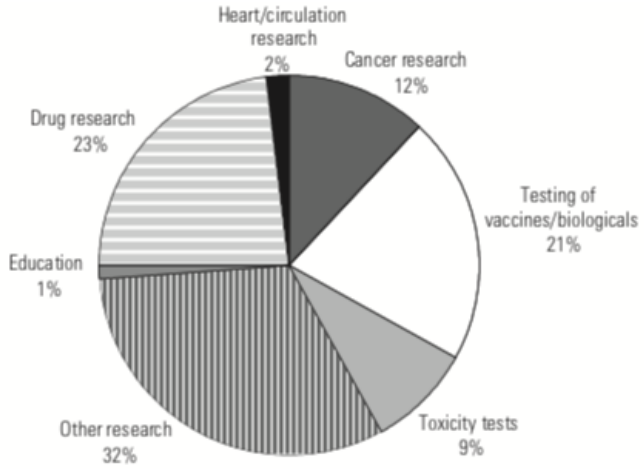
Species of Laboratory Animals

- Few animals are used for scientific research and animal experimental study in nature.
- Drug research, testing of vaccines, cancer research account for about 70% of the animals used



Laboratory Mouse

Education

Caltech, Oxford, Stanford, Harvard, MIT, Princeton, Cambridge, Imperial, Berkeley, Chicago, Yale, ETH Zurich, Columbia, UPenn, John Hopkins, UCL, Cornell, Northwestern, UMichigan, Toronto, Carniege Mellon, Duke, UWashington, UTexas at Austin, GA Tech, Tokyo, Melbourne, Singapore, UBC, Wisconsin-Madison, Edinburgh, McGill, Hong Kong, Santa Barbara, Karolinska Institute, UMinnesota, Manchester ... and just about every other major university, medical school & research institution in the world.

Nobel Prizes

1905 - Transmission and treatment of TB
1906 - Structure of Nervous System
1907 - Role of protozoa in disease
1908 - Immunity to infectious diseases
1928 - Investigations on typhus
1929 - Importance of dietary vitamins
1939 - Discovery of antibacterial agent, Prontosil
1945 - Discovery of penicillin
1951 - Yellow fever vaccine
1952 - Discovery of streptomycin
1954 - Culture of the polio virus
1960 - Understanding of immunity
1970 - Understanding of neurotransmitters
1974 - Structural & functional organisation of cells
1975 - Tumour-viruses and genetics of cells
1977 - Hypothalamic hormones
1984 - Techniques of monoclonal antibody formation
1986 - Nerve growth factor and epidermal growth factor
1990 - Organ transplantation techniques
1992 - Regulatory mechanisms in cells
1996 - Immune-system detection of virus-infected cells
1997 - Discovery and characterisations of prions
1999 - Discovery of signal peptides
2000 - Signal transduction in the nervous system
2004 – Odour receptors and organisation of olfactory systems
2008 - Role of HPV and HIV in causing disease
2010 - Development of in vitro fertilization
2011 - Discoveries around innate and adaptive immunity
2012 - Reprogramming mature cells to pluripotent ones

Overview

- Involved in around 75% of research
- Short life-span and fast reproductive rate means mice are suitable for studying disease across whole life cycle
- 98% of genes have comparable genes in humans
- Similar reproductive and nervous systems and suffer many of the same diseases as humans including cancer diabetes and anxiety
- Can be genetically modified to include human genes in enhance biological relevance
- Can act as an avatar for a human cancer to allow drug therapies to be trialled safely

Research Areas

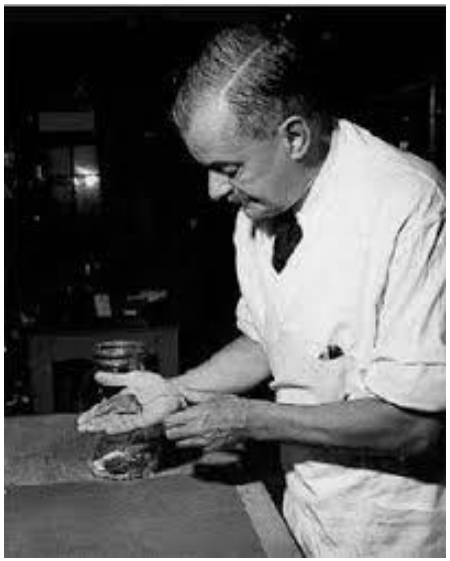
Alzheimer's disease, anaesthetics, AIDS & HIV, anticoagulants, antidepressants, asthma, blindness, bone and joint disease, brain injury, breast cancer, cardiac arrest, cystic fibrosis, deafness/hearing loss, Down's sndrome, drugs for high blood pressure, transplant rejection, Hepatitis B, C & E, Huntington's disease, influenza, leukaemia, malaria, motor neurone disease, multiple sclerosis, muscular dystrophy, Parkinson's disease, prostate cancer, schistomiasis, spinal cord injury, stroke, testicular cancer, tuberculosis,

CV of a Lifesaver

Contact

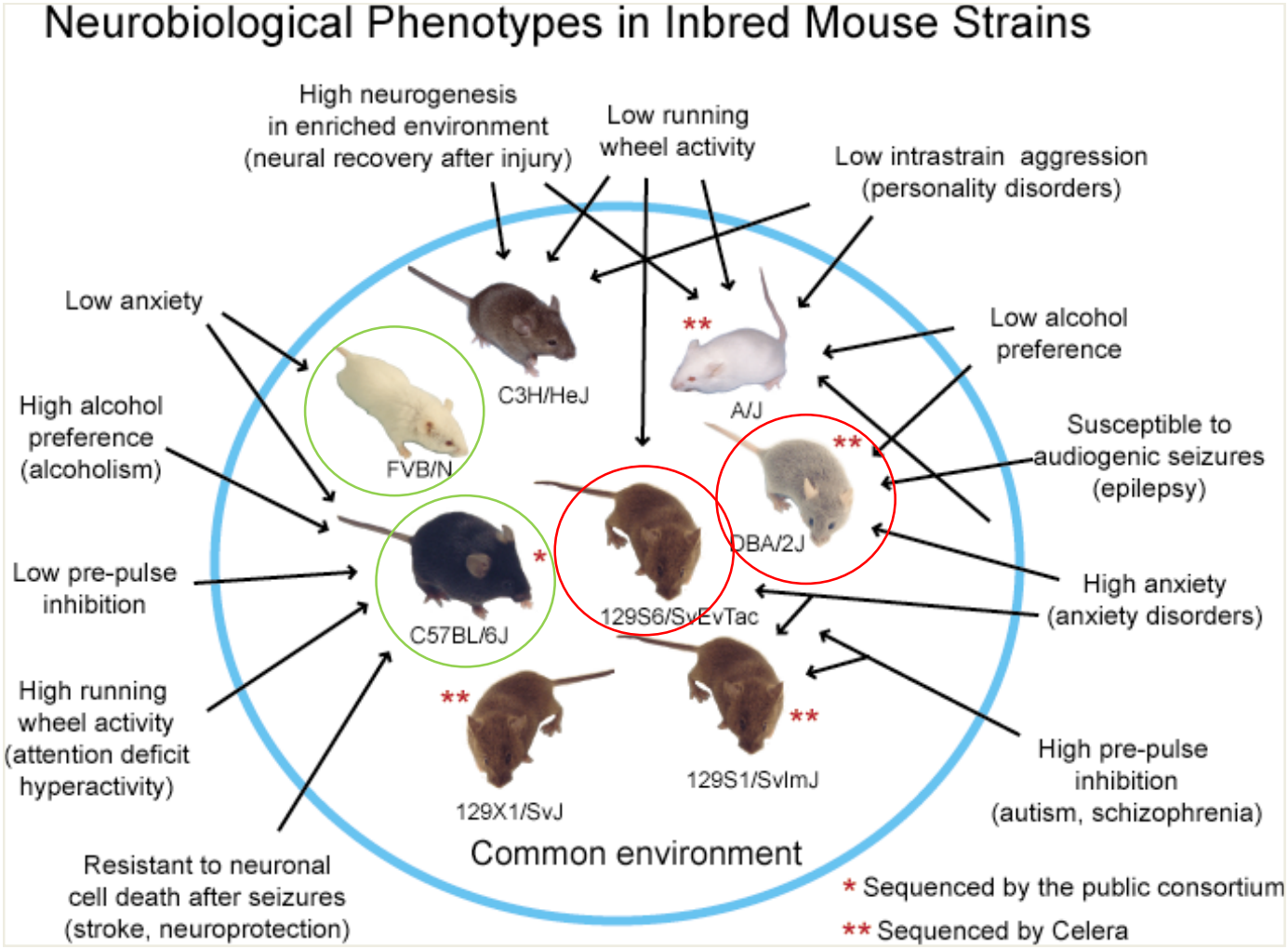
www.understandinganimalresearch.org.uk
www.animalresearch.info
www.amprogress.org
www.speakingofresearch.com

The use of mouse in scientific research

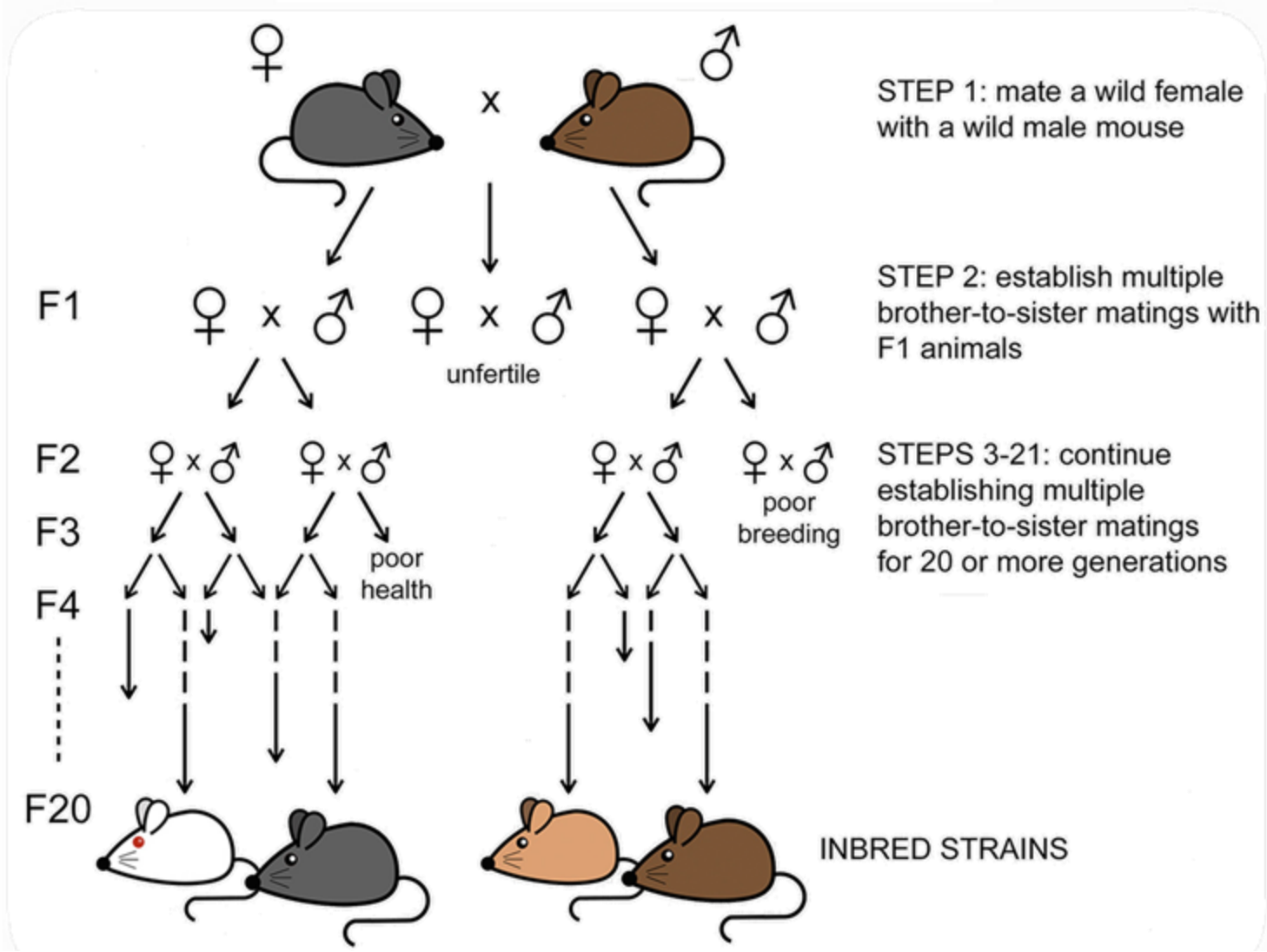


- In 1902, William Castle
  - started to breed and use mice for biomedical research.
- In 1909, Clarence Little
  - utilized consecutive inbreeding (sibmating) and created the world's first inbred strain mice DBA.

The use of mouse in scientific research

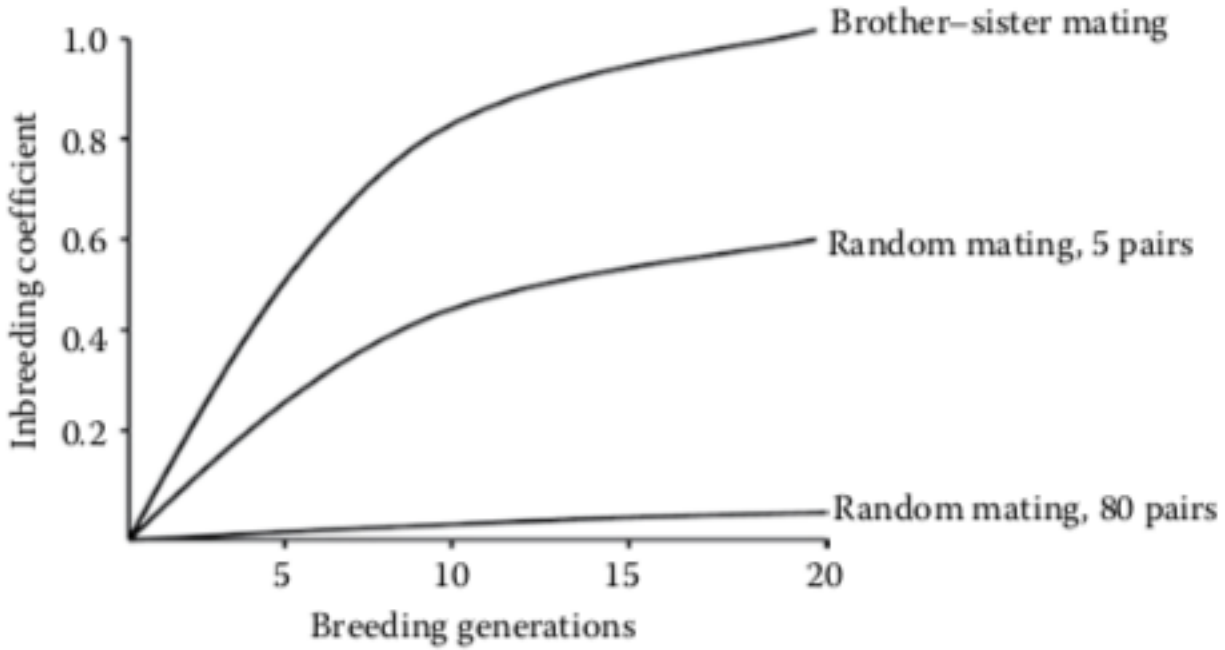


Generation of inbred strains



Adapated from M. J Garcia-Garcia, A History of Mouse Genetics: From Fancy Mice to Mutations in Every Gene

Inbreeding coefficients in different mating and breeding schemes.



Classification of experimental animals

Experimental animals

- Rodent (Mouse, Rat, Guinea pig, Gerbil, Hamster)
- Non Rodent (Rabbit, Dog, Cat, Monkey, Pig)
- Miscellanous (Frog, Pigeon, Zebra, fish, chicken)

Mouse (*Mus musculus*)

- Normal temperature: 37.4
- Pulse rate: 120
- Estrous cycle: 4-5 days
- Gestation period: 19-21 days
- Weaning age: 19-21 days
- Mating age: 6-8 weeks
- Litters size: 6-12
- Lifespan: 1,5-2,5 yrs

Application mouse

- Toxicological studies
- Teratogenicity studies
- Bioassay of insulin, screening of analgesic and anticonvulsant drugs
- Screening of chemotherapeutic agents
- Studies related to genetics and cancer research

Rabbit (*Oryctolagus cuniculus*)

- Rectal temperature: 38.7°-39.1°C
- Normal respiratory rate: 55/min
- Pulse rate: 135 per min
- Gestation period: 28-31 days
- Weaning age: 6-8 weeks
- Mating age: 6-9 months
- Weight adult: 0.9-6.75 kg

Application Rabbit

- Commonly used for toxicity and safety testing of substances.
  - Used in skin and eye irritation studies (even though less and less)
- A number of rabbit models have been developed to study human diseases
  - cardiovascular disease, cancer and AIDS.
  - used as bioreactors for the production of pharmaceutical proteins.
- A breed of choice for polyclonal antibody production.

Dogs (*Canis familiaris*)

- Rectal temperature: 38°-39°C
- Normal respiratory rate: 20-30/min
- Pulse rate: 50-150/min
- Gestation period: 63-67 days
- Litter size: 3-6
- Weaning age: 6-7 months
- Weight – adult: 10-80 kg

Application Dogs

- Pharmacokinetics, alternative drug delivery systems, and cardiovascular pharmacology
- Dental, and periodontal disease and surgery, orthopedic surgery and skeletal physiology, and radiation oncology.

Nonhuman Primates

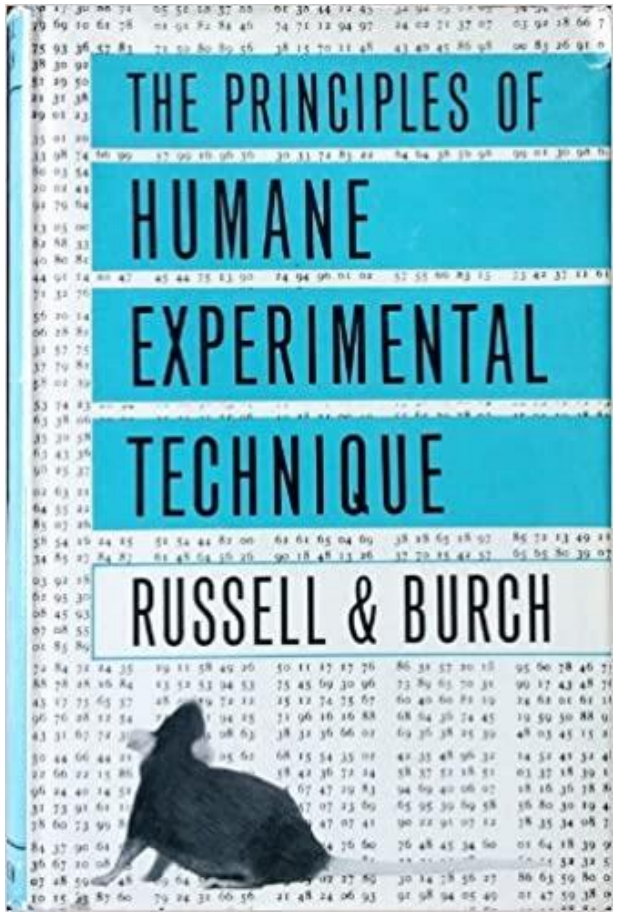
- Rectal temperature: 36-40°C
- Normal respiratory rate: 40-65/min
- Pulse rate: 100-150/min
- Gestation period: 155-170 days
- Litter size: 1
- Weaning age: 12-16 months
- Weight – adult: 10-80 kg
- Lifespan: 20-30 yrs

the rhesus monkey

Nonhuman Primates

- Structurally and fonctionally similar to man
- Uterus resembles humans and exhibiting regular menstrual periods
- Best for studying drugs acting on CNS, CVS, GIT and fertility
- used to investigate, develop, and produce the polio vaccine.
- Rhesus monkeys are currently the models of choice for human immunodeficiency virus infection/acquired immune deficiency syndrome (HIV/AIDS) vaccine development and stud

Laboratory Animal Science: A Resource to Improvethe Quality of Science



- Russell and Burch (1959):
  - « humane science is good qualityscience and that it is achievable by application of the three Rs »
- 3Rs: replace, reduce, refine
  - Use justified if the benefit to people outweighs the cost paid by the animals

The 3Rs

(Russell & Burch, 1959; Fenwick et al., 2009)

- 3 Rs in OIE *Terrestrial Animal Health Code*, Chapter 7.8 (OIE, 2011)
  - Relative Replacement:
    - use cells, tissues, organs
  - Absolute replacement:
    - use inanimate systems (e.g. computer modelling)
  - Reduction:
    - use fewer animals
  - Refinement:
    - minimize pain etc. and enhance welfare,
  - Use species with less capacity for suffering or distress
  - Consider welfare throughout the animal's life – husbandry, transport and death, as well as during the procedures

Animal welfare

- Animal experiments should only be performed
  - when no alternative is available ,
  - when the benefit of the experiment outweighs the suffering of the animal.
- Legal and moral obligation to safeguard welfare and minimise discomfort,
  - beneficial for both the animal and the experimental outcome.

What is good animal welfare?

- 1st definitions of welfare was published as minimal standards for farm animals in 1965 by the Brambell Committee and known as the 'five freedoms'
  - Freedom from hunger and thirst
  - Freedom from discomfort
  - Freedom from pain, injury and disease
  - Freedom to express normal behaviour
  - Freedom from fear and distress

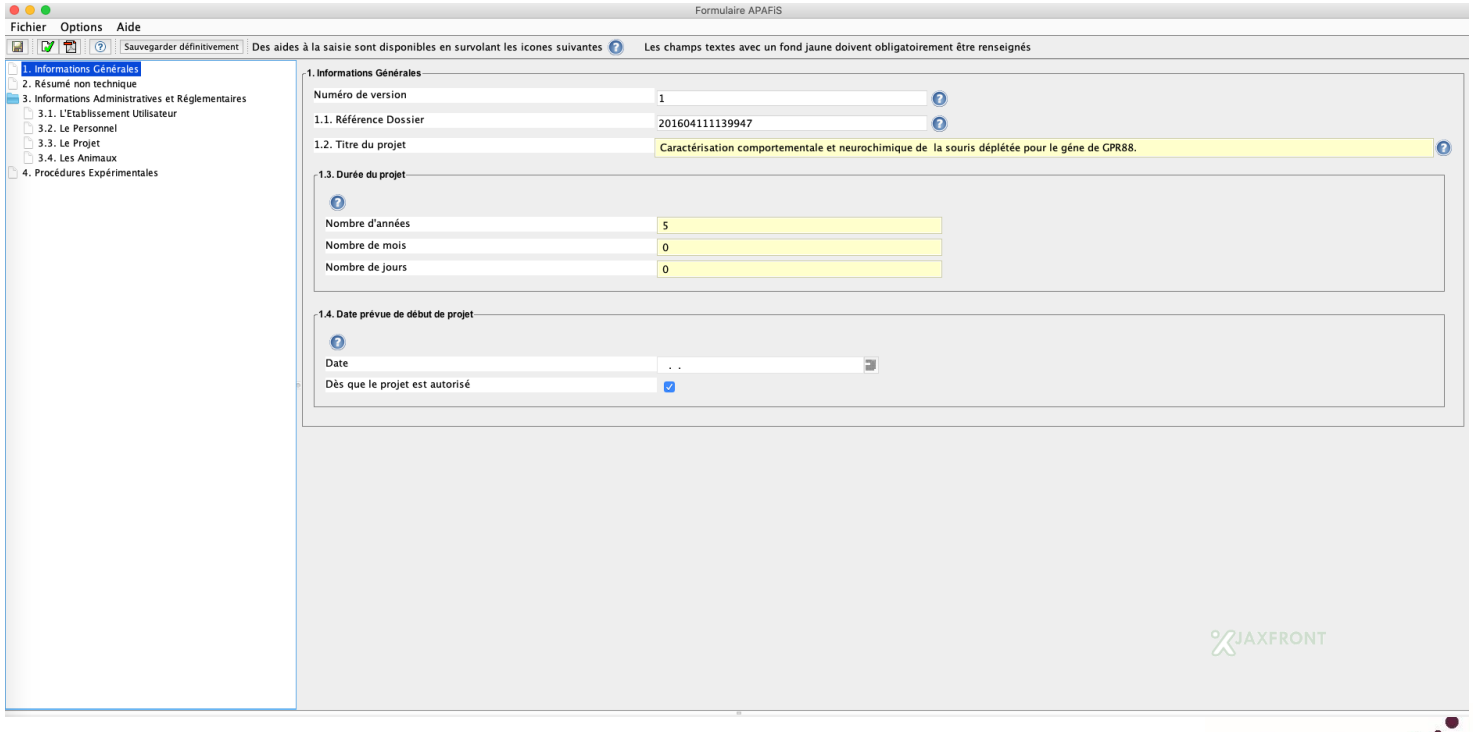
- Legislative aspects of housing and care of laboratory animals
  - Environmental conditions
  - Environmental enrichment

What is good animal welfare?

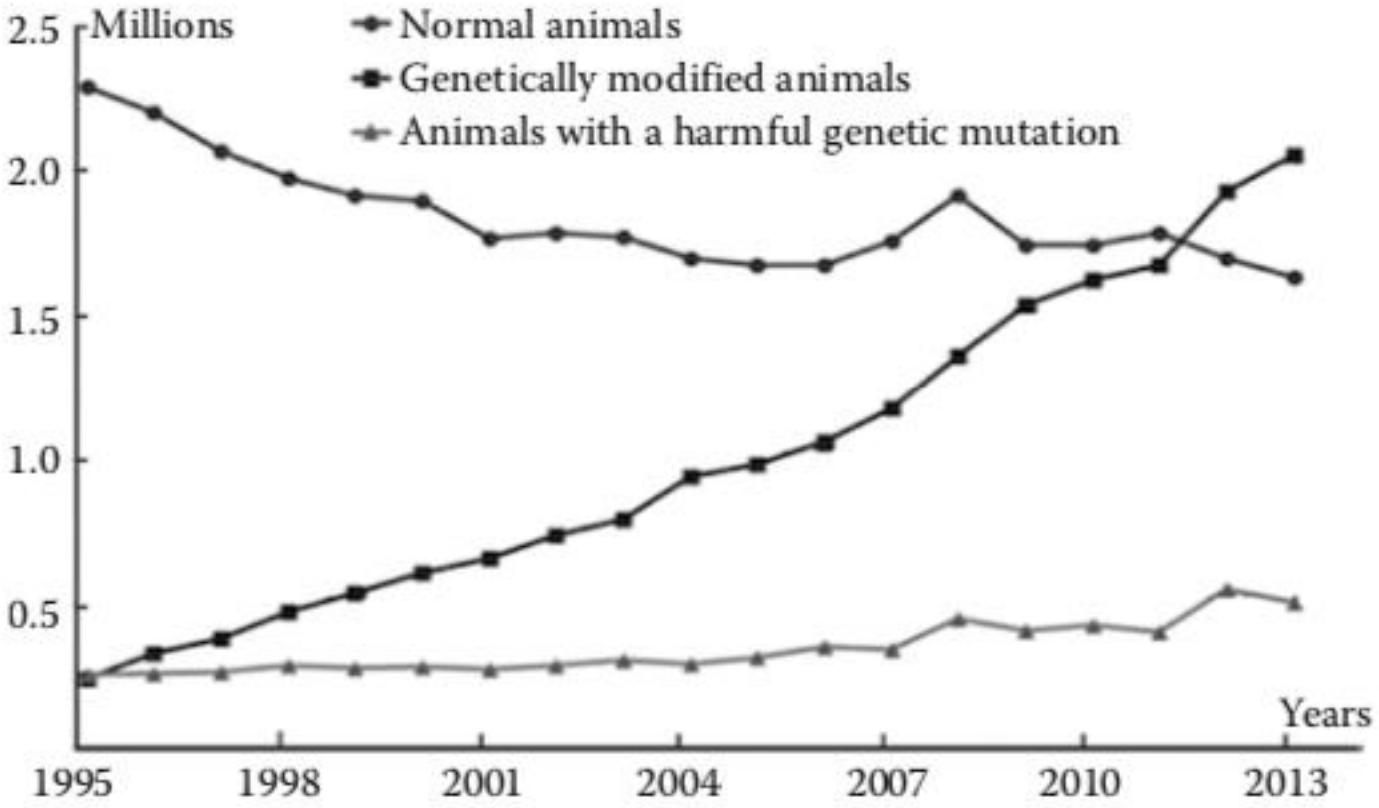
- Legislative aspects of housing and care of laboratory animals
  - Environmental conditions
  - Environmental enrichment

Legislative aspects of housing and care of laboratory animals

- National and international laws and policies
  - Council directive #87-848, October 19, 1987, Ministère de l'Agriculture et de la Forêt, Service Vétérinaire de la Santé et de la Protection Animale,
  - Institutional Animal Care and Use Committee



Genetically Modified Laboratory Animals



- Use of transgenic animals will help us to better understand human disease & improve health care

What is an animal model ?

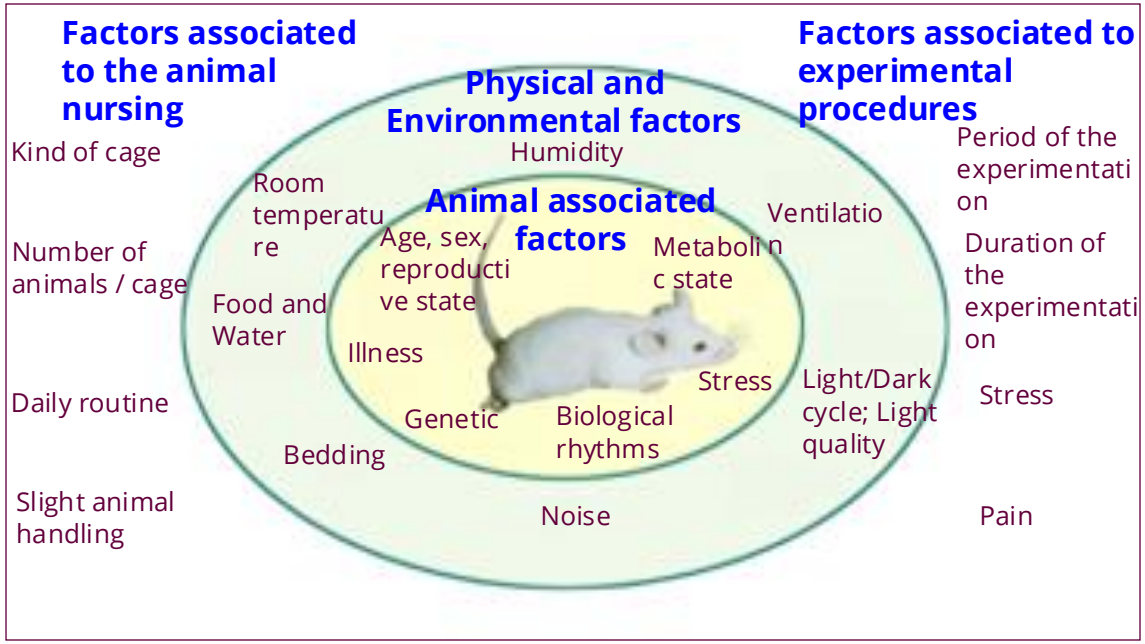
- An experimental simulation in which a simple system represents another system, more complex, with a less accessibility to the experimentation
  - From *American National Research Council Committee on Animal Models for Research and Aging*
- An animal model allows to study
  - Basal biological / behavioral data
  - A spontaneous or induced pathological process, with one (or more) common features with a human (or another specie) pathology
    - Physiological mechanisms
    - Physio-pathologic process
    - Treatments tolerance/efficiency

Model quality

- The perfect model does not exist !
- The experiments have to demonstrate the model relevance which includes its analogy with the human pathology
- Necessity of validation according to well defined criteria
- The model has to be adapted across the time

Limits of a model

- The knowledge of the compared biology as well as compared pathology between the several laboratory animal models is mandatory
  - Anatomy
  - Physiology
  - Technics of breeding
  - Hosting
  - Anesthesia



An animal model should modelize the human psychiatric illness considering:

- 1. Induced behavioral states : similarity with the human pathology
  - ♦ *i.e.* **CREATIVE VALIDITY**
    - *The animal model has to have the same symptoms as the ones of the human illness, despites of anatomical, physiological… differences*
- 2. Involved neurochemical mechanisms
  - ♦ *i.e.* **THEORETICAL VALIDITE**
    - *The understanding of the mechanisms involved in the model and in the pathology allows an extensive comparison between the model and the human pathology.*
- 3. Treatment's answer,
  - ♦ *i.e.* **PREDICTIVE VALIDITY**
    - *The Treatment's answer of the model should be similar to the one observed in the human illness*

Conclusion

- As animal welfare is a prerequisite for reliable experimental results,
- it is essential to seek for methods and procedures that will improve the well-being of the animals.
- Animal welfare and good science are inextricably connected.

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Genetically modified animal

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Master 1 D2HP, Development of Drugs and Health Products

Making Transgenic Animals

- Why?
  - Study gene function and regulation
  - Generate new organismic tools for other fields of research.
  - Cure genetic diseases.
  - Improve agriculture and related raw materials.
  - Generate new systems or sources for bioengineered drugs (e.g., use plants instead of animals or bacteria).

Transgenic mouse model

- The organism of choice for mammalian genetic engineers.
  - small
  - hardy
  - short life cycle
  - genetics possible
  - many useful strains and tools

Credit: Ingrid Moen et alet al., *BMC Cancer,* 12/21 (2012), 1-10.

1982: the 1st transgenic mice with a phenotype

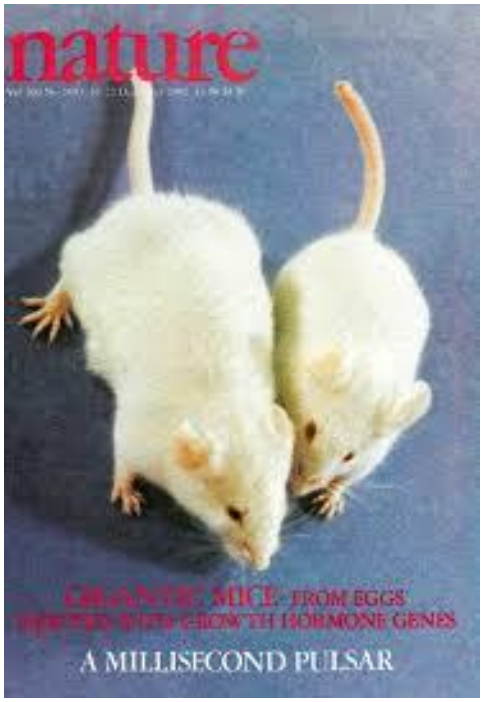
- Richard Palmiter and Ralph Brinster
  - made a construct in which the rat growth-hormone gene was placed under the control of zinc-inducible metallothionin promoter.

Published: 16 December 1982

Dramatic growth of mice that develop from eggs microinjected with metallothionein–growth hormone fusion genes

Richard D. Palmiter, Ralph L. Brinster, Robert E. Hammer, Myrna E. Trumbauer, Michael G. Rosenfeld, Neal C. Birnberg & Ronald M. Evans

Nature **300**, 611–615(1982) | Cite this article



Transgenic animals in research

- Genetically engineered or modified mice are induced mutations:
  - including mice with transgenes, with targeted mutations (knockouts) and with retroviral, proviral or chemically induced mutations

Characteristic	Trasngenic Mice	Knockout Mice
Cell receiving DNA	Zygote	Embryonic stem (ES) cells
Means of delivery	Microinjection into zygote and implantation into foster mother	Transfer of ES cells to blastocyst and implantation into foster mother
Outcome	Gain of e gene	Loss of gene

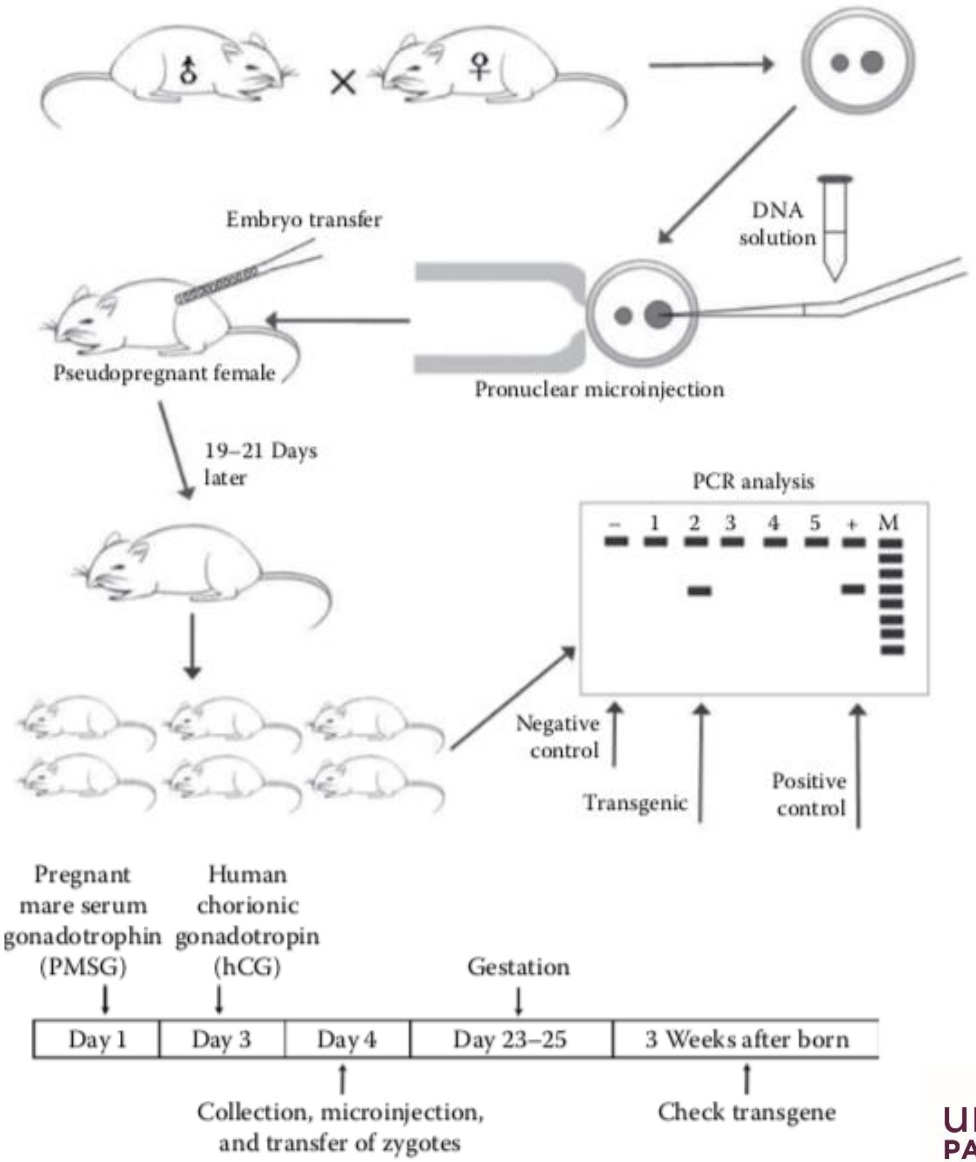
Transgenic animal technology

- An advances gene expression approach
- Preparation of the construct
  - Genetic modification and vector contruction
- Gene and embryo transfer
  - recipient cells are transplanted into the oviducts or uterus of the recipient animals,
- Validation and contruction of an animal model
  - detection of gene integration and expression

The microinjection method.

- The most widely used and effective method.
- An acceptable rate of gene transfer
- Ability to directly transfer exogenous genes
- Unrestricted length of the exogenous genes
- But:
  - requires expensive and sophisticated equipment,
  - a complicated operational procedure and specialized technical personnel

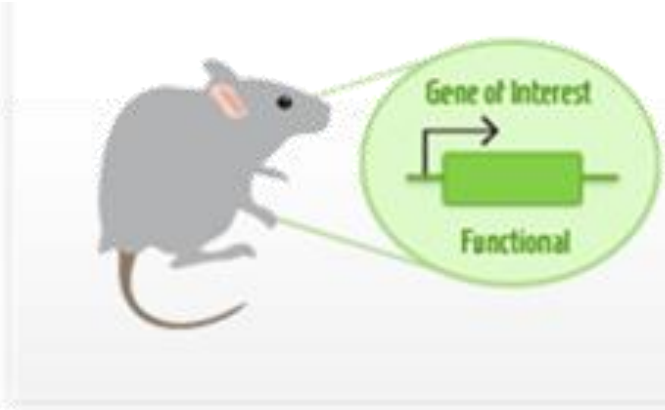
The production of transgenic mice by the microinjection method.



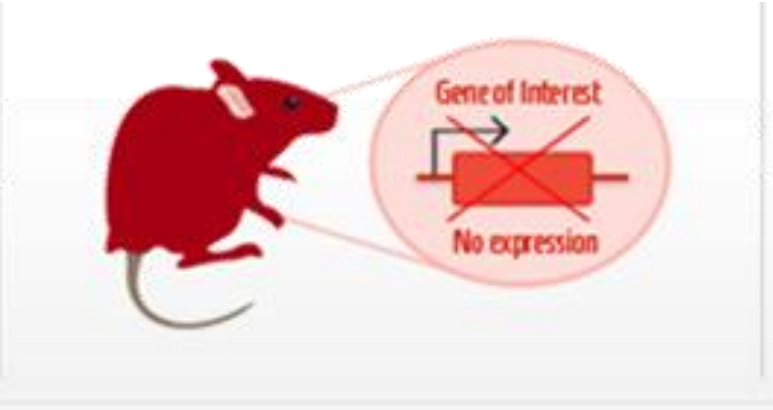
Knockout: A Special Case of Transgenics

- Gene Knockout
  - homologous recombination between DNA molecules, a specific endogenous gene of ES cells is destroyed,
    - resulting in loss of function of the specific gene.

Wild-type



Constitutive KO mice



1977–1980: homologous recombination

- 1974: Jaenisch and Mintz microinjected simian virus 40 (SV40) DNA into the blastocoel cavity of mouse embryos using a microinjection technique
  - detected SV40 DNA in the offspring

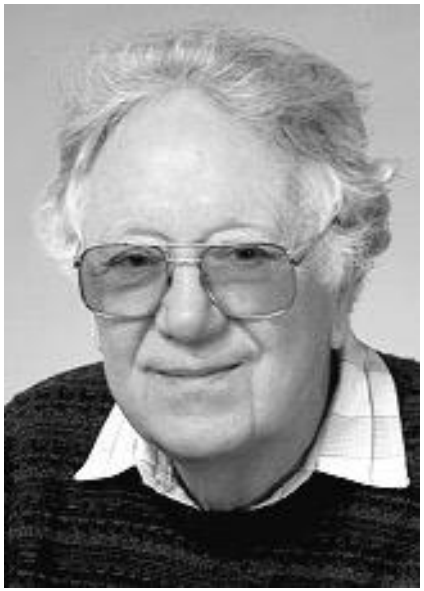
- 1982: Palmiter et al. created the ground-breaking “super mouse”
  - by injecting a rat growth hormone gene into the pronuclei of mouse zygotes.

The Nobel Prize in Physiology or Medicine, 2007

Mario R. Capecchi, Martin J. Evans and Oliver Smithies for their discoveries of "principles for introducing specific gene modifications in mice by the use of embryonic stem cells"

M. Capecchi
Univ. of Utah

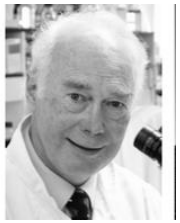
Sir M. Evans
Cardiff Univ., UK



O. Smithies
UNC Chapel Hill

Gene targeting in mice: functional analysis of the mammalian genome for the twenty-first century

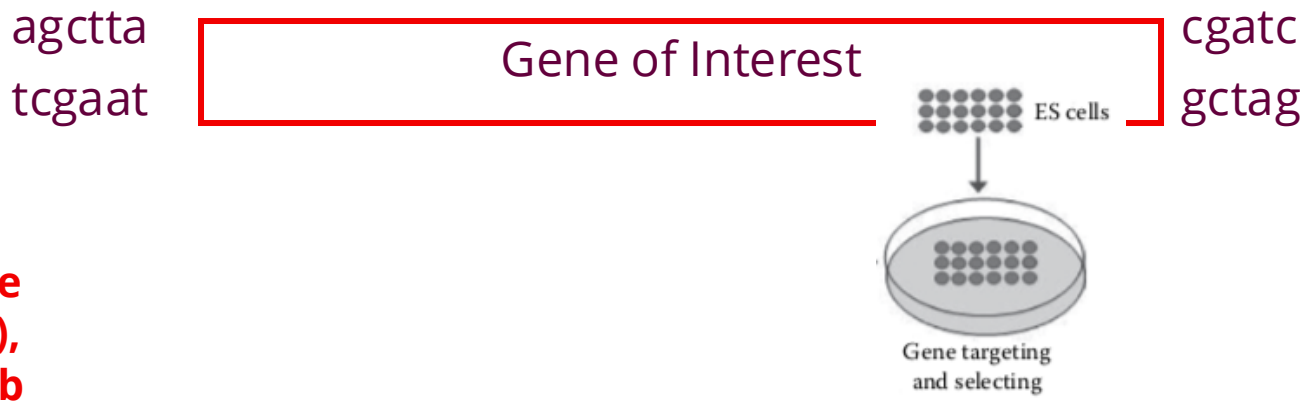
- Martin Evans
  - Identified and isolated the embryonic stem cell of the early embryo, the cell from which all cells of the adult organism are derived.
    - established it in cell culture,
    - modified it genetically,
    - reintroduced it into foster mothers in order to generate a genetically modified offspring.



- Mario Capecchi and Oliver Smithies
  - Discovered how homologous recombination between segments of DNA molecules can be used to target genes in the mammalian genome
    - developed methods to generate genetically modified mice.

Preparation of the construct

- (1) Get the nucleotide sequence of the gene of interest.



Upstream DNA (unique to the gene), usually > 1kb

Downstream DNA (unique) to the gene, usually > 1 kb

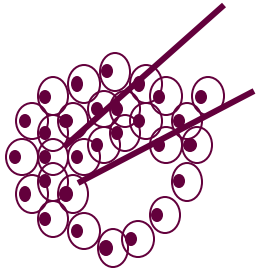
--->The Problem with trying to make KOs: random DNA Integration

Preparation of the construct

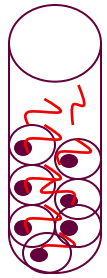
- (2) Construct the desired DNA sequence (i.e., the transgene),

Preparation of the construct

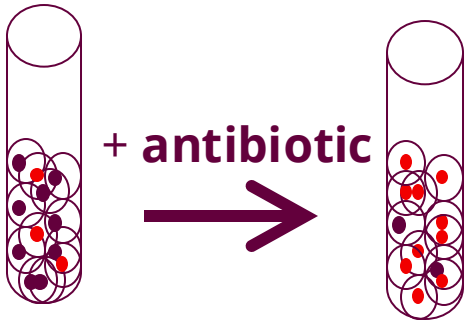
- (3) Micropipette embryonic stem cells



- (4) Culture the cells

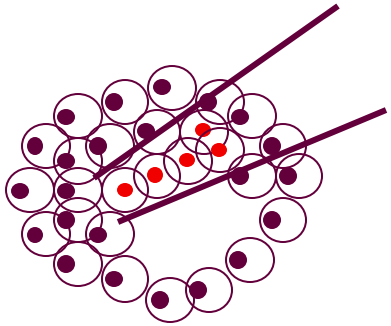


- (5) Transgenic DNA incorporation

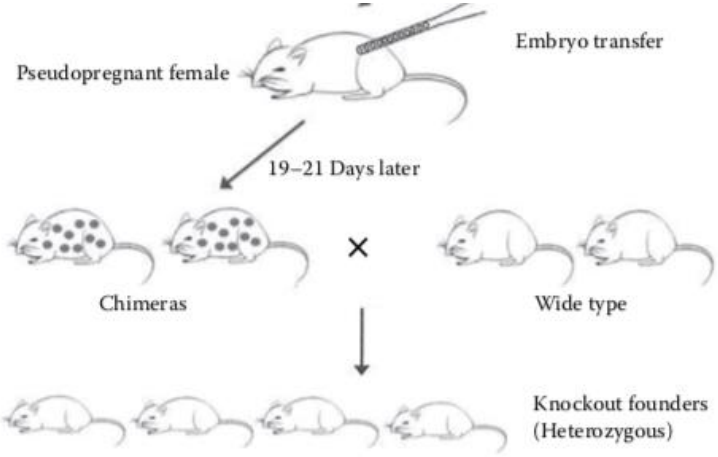


Introduction of the targeting vector into ES cells:

- (6) Insert the stem cells into the blatocyst
  - a different genetic background trait



- (7) Implant the new blastocysts into a pseudopregnant female
- (8) Offspring that have pigmented sections are chimeras
- (9) Keep breeding the offspring of the chimeras until some fully pigmented n are born



Limitation of KO mice

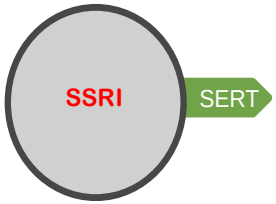
- 15% of gene KO are developmentally lethal
- The lack of adult mice limits studies to embryonic development
- The gene may serve a different function in adults than in developing embryos
- Knocking out a gene also may fail to produce an observable change in a mouse

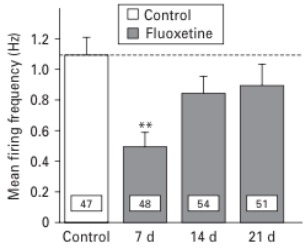
Tissue-Specific Gene Knockout

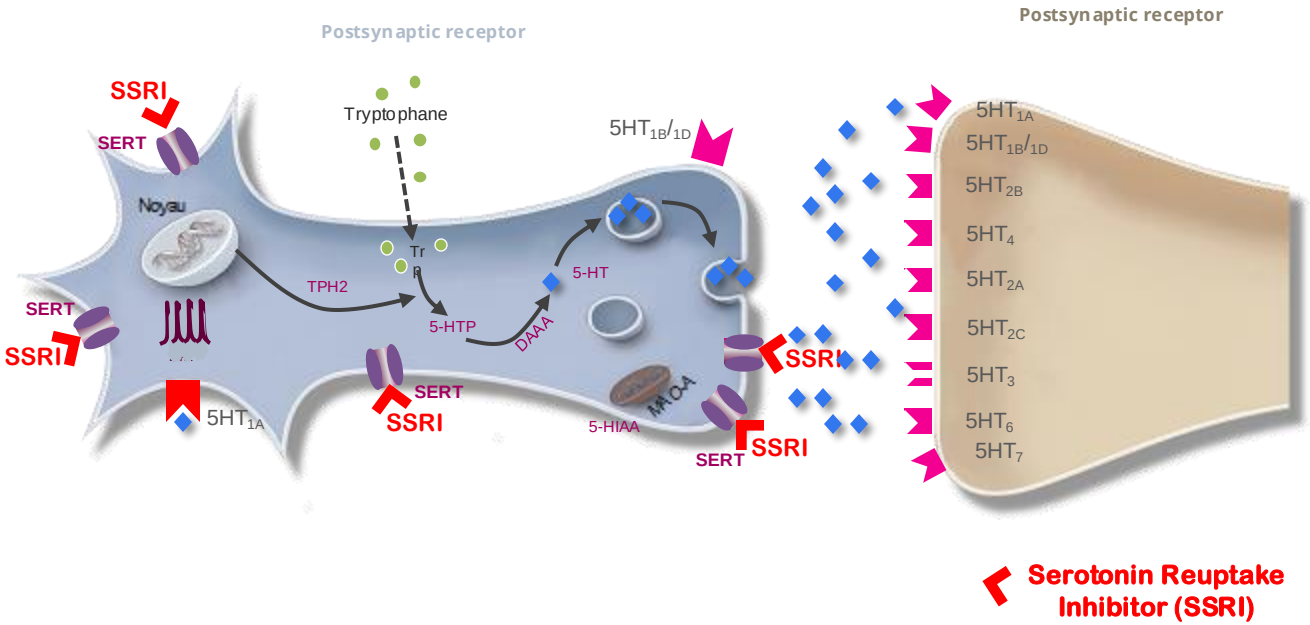
- Gene knockouts at an early embryonic stage may lead to death of the embryo
  - Conditional gene knockout techniques,
    - such as the Cre–loxP
    - flippase (FLP)-flippase recognition target (FRT) systems.

Tissue specific KO mice

Ex: The 5-HT1A KO mice







David DJ, Gardier AM. 2016, The pharmacological basis of the serotonin system: Application to antidepressant response]. Encephale. 2016 Jun;42(3):255-63. Bétry et al., 2013, The rapid recovery of 5-HT cell firing induced by the antidepressant vortioxetine involves 5-HT3 receptor antagonism. International Journal of Neuropsychopharmacology, 16, 1115–1127

Ex: The 5-HT1A KO mice

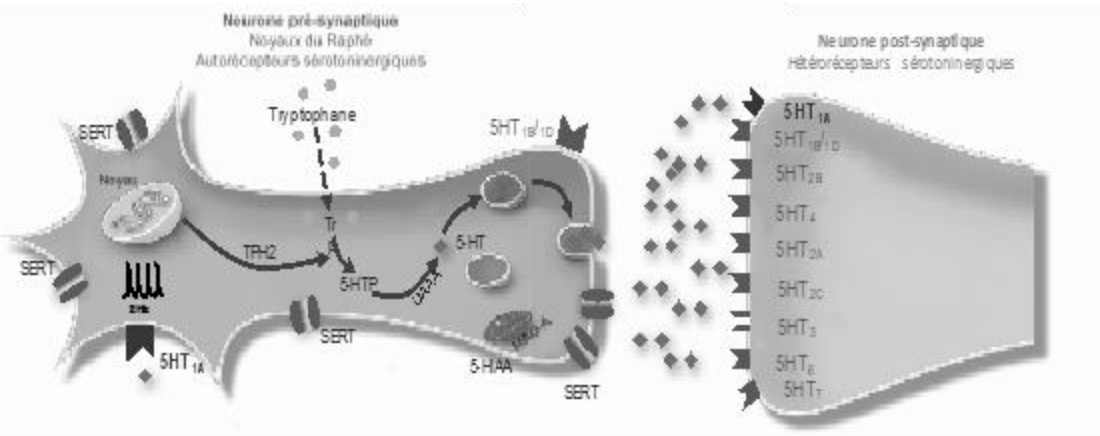
Neuropsychopharmacology (2004), 1–11
© 2004 Nature Publishing Group All rights reserved 0893–133X/04 $30.00
www.neuropsychopharmacology.org

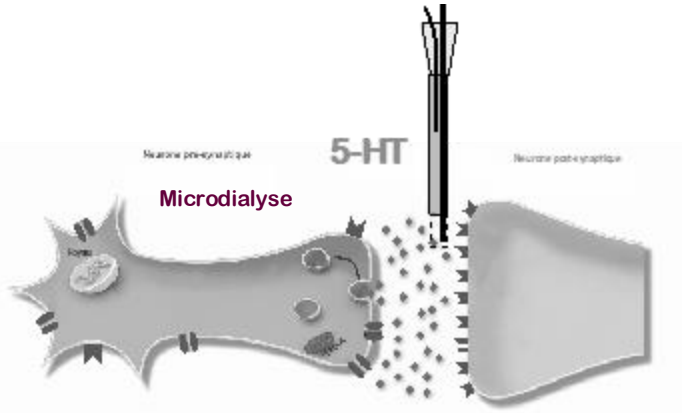
Blockade of 5-HT_{1A} Receptors by (±)-Pindolol Potentiates Cortical 5-HT Outflow, but not Antidepressant-Like Activity of Paroxetine: Microdialysis and Behavioral Approaches in 5-HT_{1A} Receptor Knockout Mice

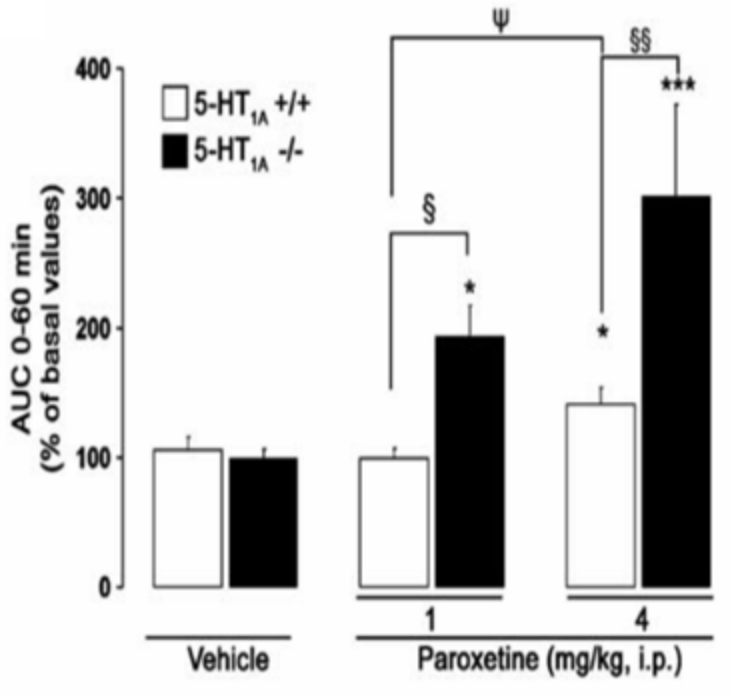
Jean-Philippe Guilloux[1], Denis JP David[1], Bruno P Guiard[1], Franck Chenu[2], Christelle Repérant[1], Miklos Toth[3], Michel Bourin[2] and Alain M Gardier[*,1]

WT

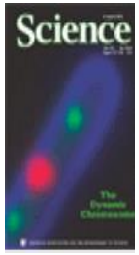
KO





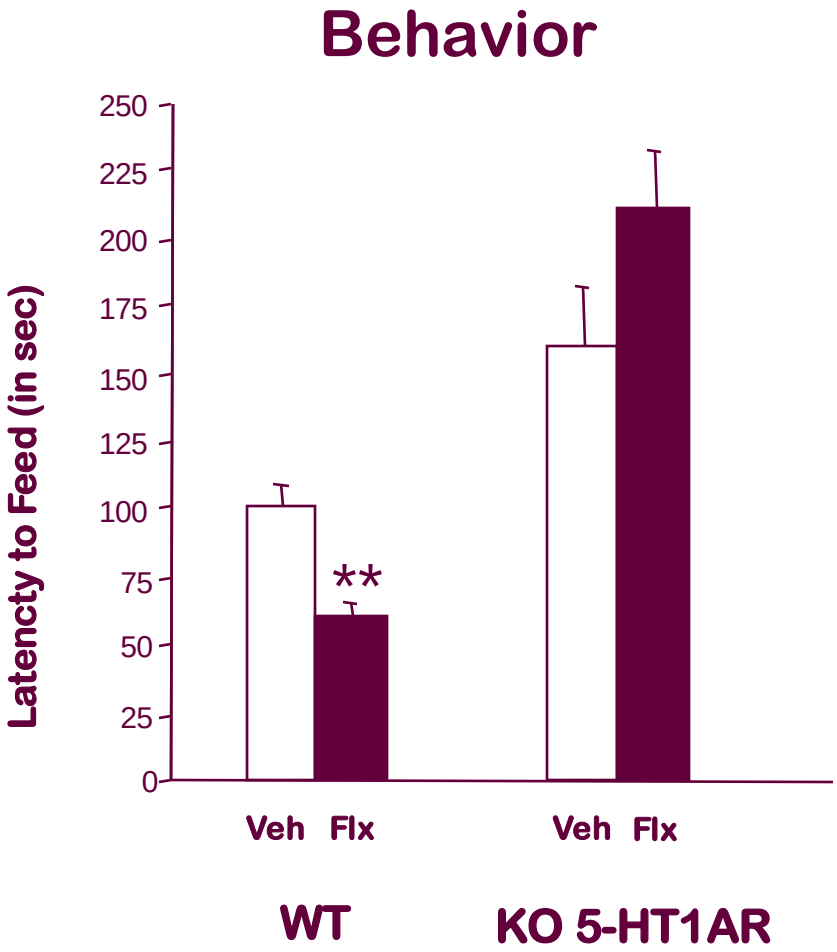


Ex: The 5-HT1A KO mice



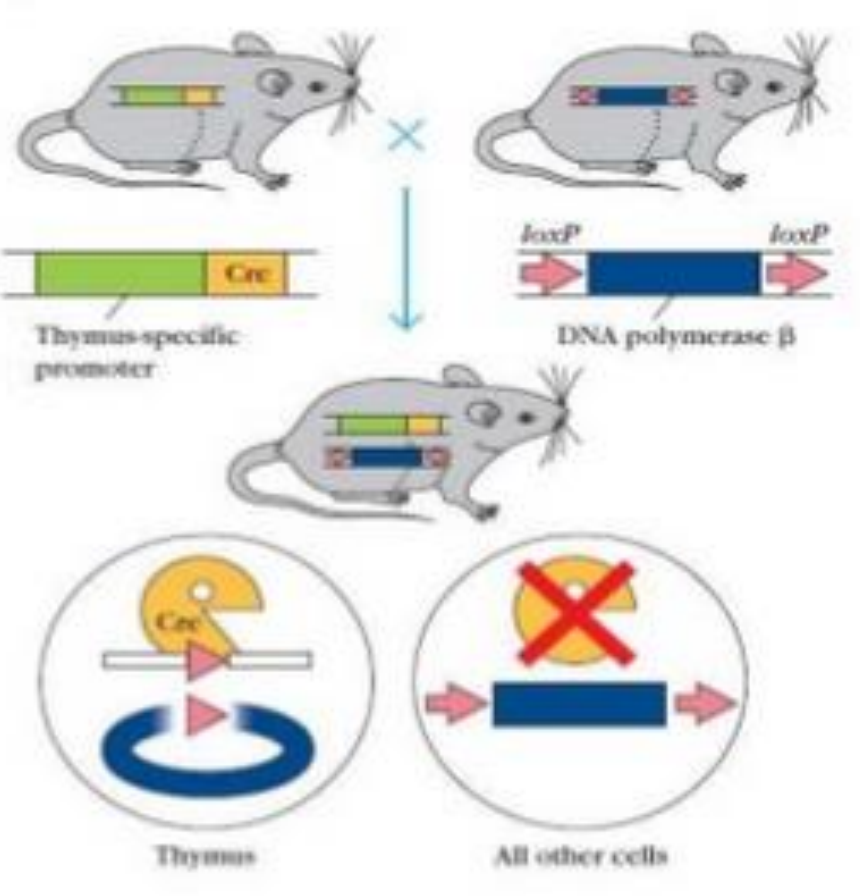
Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants

Luca Santarelli,[1]* Michael Saxe,[1]* Cornelius Gross,[1] Alexandre Surget,[2] Fortunato Battaglia,[3] Stephanie Dulawa,[1] Noelia Weisstaub,[1] James Lee,[1] Ronald Duman,[4] Ottavio Arancio,[3] Catherine Belzung,[2] René Hen[1]†



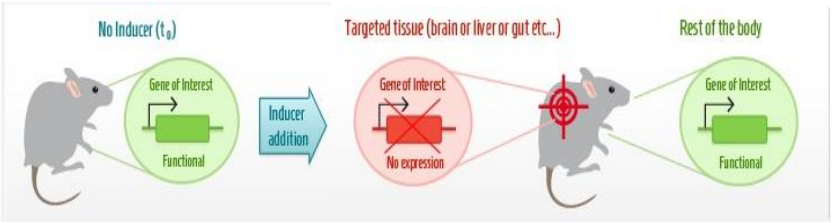
Tissue-specific gene knockout

- The Targeted DNA polymerase gene is modifiend by flanking the gene with loxP.
- Mice are generated from ES cells
- Mating of the loxP modified mice with a Cre transgenc mice
- Generation of a double transgenic mice in which the loxP flanked DNA polymerase gene is deleted in the tissue where Cre is expressed
  - Ex: Cre is expressed in thymus tissue: deletion of the loxP-flanked gene in thymus

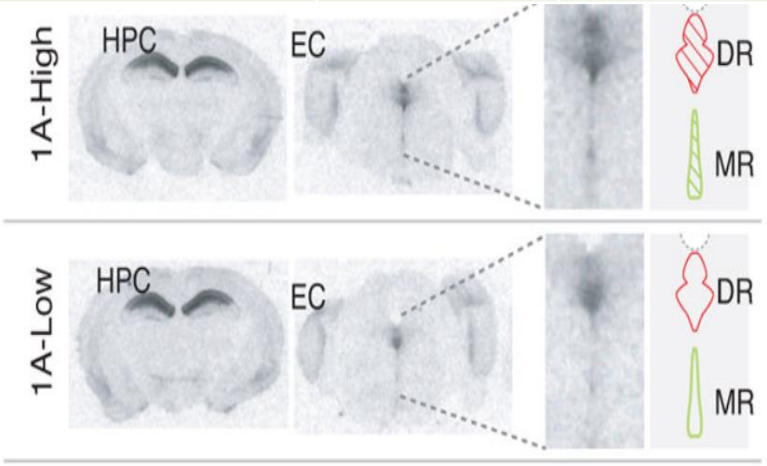


Tissue-specific 5HT1A KO Mice

Tissue Specific 5HT1A KO mice

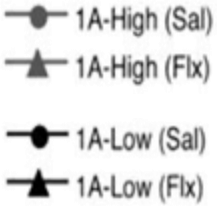


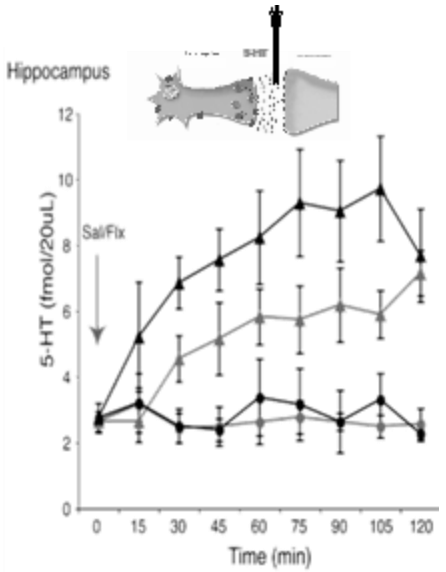
5-HT1AR expression	1A-High Line	1A-Low Line
Anterior brain (Hippocampus)	++	++
Forebrain (Dorsal Raphe Nucleus)	++	-



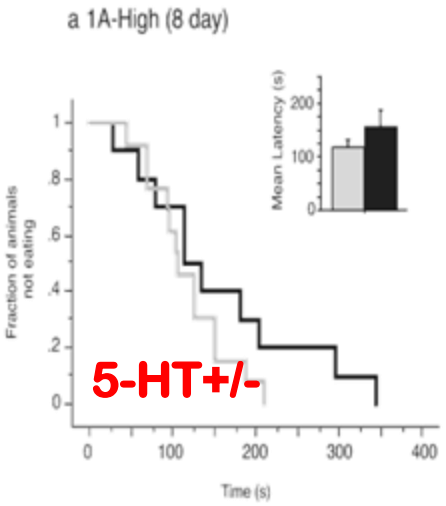
Microdialysis

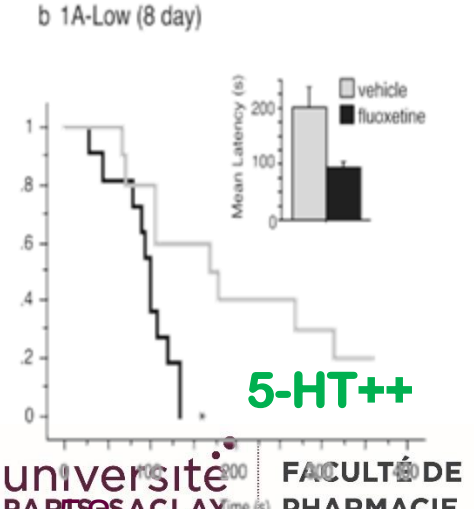
5-HT_{1A} Autoreceptor Levels Determine Vulnerability to Stress and Response to Antidepressants





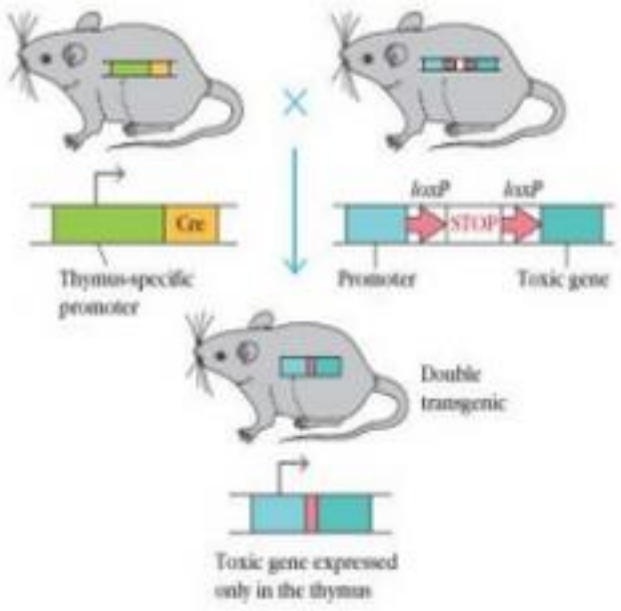
Behavior



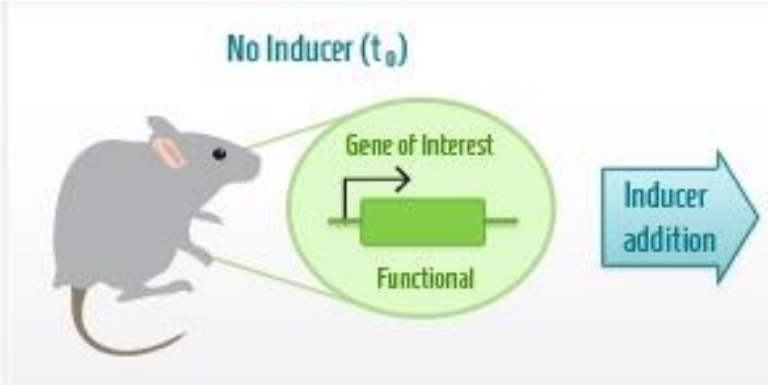


Activation of gene expression using Cre/lox

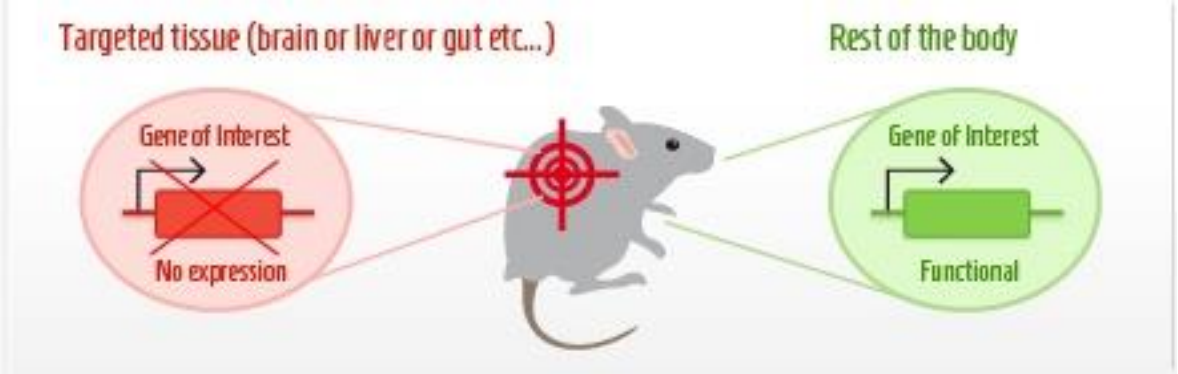
- A loxP-flanked translational STOP cassette is inserted between the promoter and the »toxic » gene



Inducible Tissue-specific gene knockout



Inducible Tissue specific KO mice



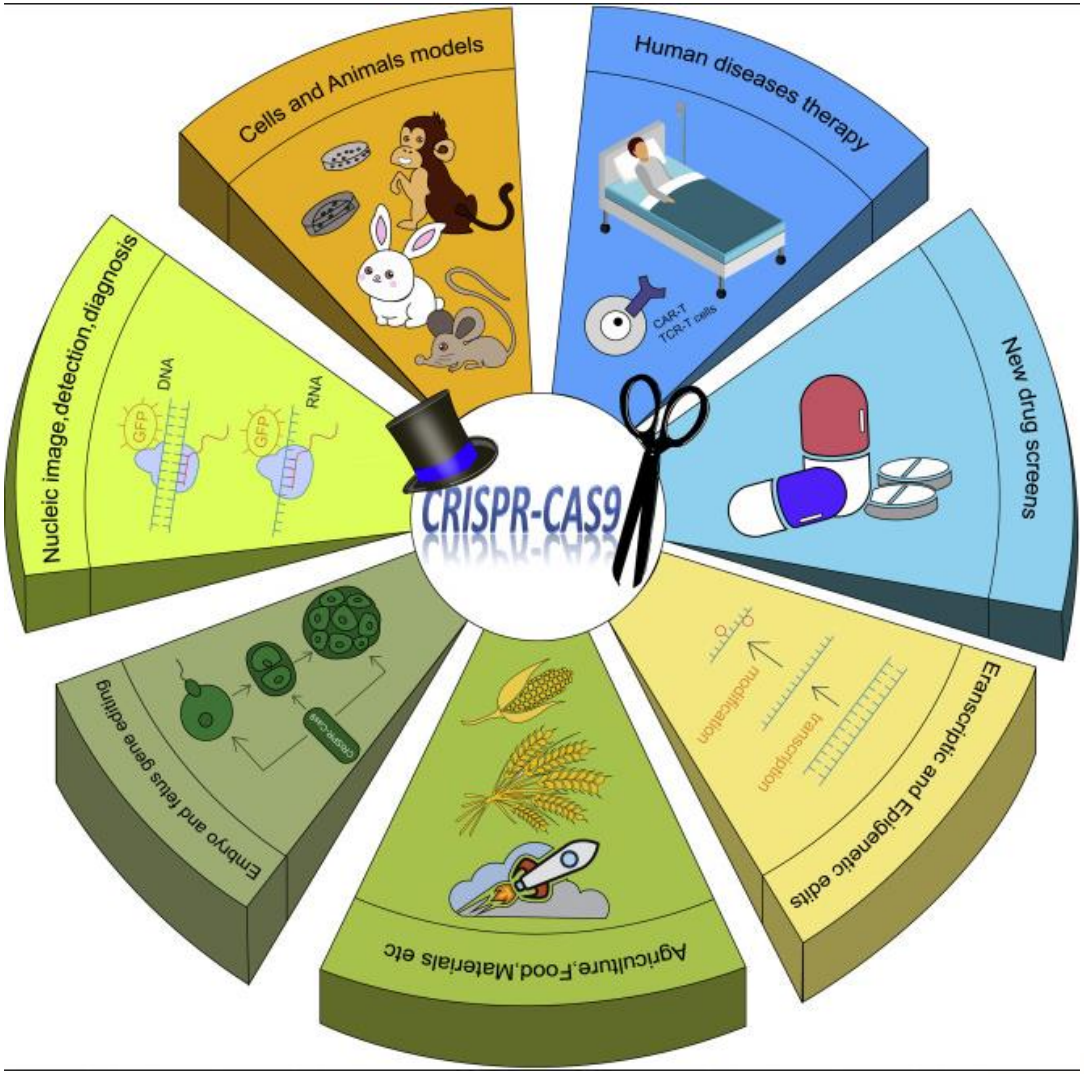
CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)/Cas9 (CRISPR associated protein 9)

Emmanuelle Charpentier and **Jennifer Doudna**

- The Nobel Prize in Chemistry 2020 for discovering one of gene technology's sharpest tools:
  - the CRISPR/Cas9 genetic scissors.

- This technology has enabled scientists to modify DNA sequences in a wide range of cells and organisms.

Applications of CRISPR-Cas9 Genomic Engineering



You et al, 2019

Conclusion

Date	Event	People	Places
June 1925	Oliver Smithies was born in Halifax, United Kingdom	Smithes	University of Washington, University of North Carolina
1929	Jackson Memorial Laboratories established to develop inbred strains of mice to study the genetics of cancer and other diseases		Jackson Memorial Laboratoroies
1974	First publication on inserting foreign DNA into mice	Jaenisch, Mintz	Salk Institute, Fox Chase Institute for Cancer Research
September 1980	Scientists reported the first successful development of transgenic mice	Barbosa, Gordon, Plotkin, Ruddle, Scangos	Yale University
November 1980	Technique published using fine glass micropipettes to inject DNA directly into the nuclei of cultured mammalian cells. High efficiency of the method enables investigators to generate transgenic mice containing random insertions of exogenous DNA.	Capecchi	University of Utah
05-nov-81	First successful transmission of foreign DNA into laboratory mice	Constantini, Lacy	Oxford University, Yale University
December 1982	Giant mice made with the injection of rat growth hormone	Brinster, Palmiter	University of Pennsylvania, University of Washington Seattle
1983	Course started in the molecular embyology of mice	Costantini, Hogan, Lacy	Cold Spring Harbour Laboratory, NIMR, Sloan Kettering Cancer Research Center, Columbia University
1985	First transgenic mice created with with genes coding for both the heavy and light chain domains in an antibody.	Kohler, Rusconi	Max-Planck Institute
November 1987	Publication of gene targeting technique for targetting mutations in any gene	Thomas, Capecchi	University of Utah
1988	Patent application filed for a method to create transgenic mice for the production of human antibodies	Bruggeman, Caskey, Neuberger, Surani, Teale, Waldmann, Williams	Laboratory of Molecular Biology, Babraham Institute, Cambridge University
April 1988	OncoMouse patent granted	Leder, Stewart	Harvard University
June 1992	First transgenic mouse model created for studying link between DNA methylation and disease	Li, Bestor, Jaenisch	Whitehead Institute for Biomedical Research
1994	First transgenic mice strains reported for producing human monoclonal antibodies	Bruggemann, S.Green, Lonsberg, Neuberger	Cell Genesys, GenPharm, Laboratory of Molecular Biology
July 1996	Dolly the sheep, the first cloned mammal, was born	Wilmut, Campbell	Roslin Institute
July 1997	Birth of first sheep cloned with human genes	Schnieke, Kind, Ritchie, Mycock, Scott, Wilmutt, Colman, Campbell	PPL Therapeutics, Roslin Institute
February 2003	Dolly the sheep, the first cloned mammal, died	Wilmut	Roslin Institute
September 2006	First fully human monoclonal antibody drug approved		Agensys, Amgen
2007	Nobel Prize for Physiology for Medicine awarded for discoveries enabling germline gene modification in mice using embryonic stem cells	Capecchi, Evans, Smithies	University of North Carolina, University of Utah
September 2015	Beijing Genomics Institute announced the sale of the first micropigs created with the help of the TALENs gene-editing technique		Beijing Genomics Institute
October 2015	CRISPR/Cas9 modified 60 genes in pig embryos in first step to create organs suitable for human transplants	Church	Harvard University
April 2017	Diabetes research using transgenic mice shows the protein P2X7R plays important role in inflammation and immune system offering new avenue for treating kidney disease	Menzies	University of Edinburgh, University College London, Imperial College
January 2019	CRISPR-Cas9 used to control genetic inheritance in mice	Grunwald, Gntz, Poplawski, Xu, Bier, Cooper	University of California San Diego