TEHRAN UNIVERSITY OF MEDICAL SCIENCES

TUMS PRECLINICAL CORE FACILITY (TPCF)

ANIMAL MODELS IN PRECLINICAL RESEARCHES

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Contents

Why Preclinical Researches?

- Pharmacodynamics – what does the drug do to the body?
- Pharmacokinetics – what does the body do to the drug?
- Toxicology – it is potent, but is it safe?
- Dosing – what dosage to use? Finding optimum dosage
- From bench to bedside – the long journey from the lab into the clinic
- To launch an efficient drug formulated for the specified conditions
- Validating the beneficial effects of a drug prior to the initializing of clinical trial

Why Do Scientists Use Animals in Research?

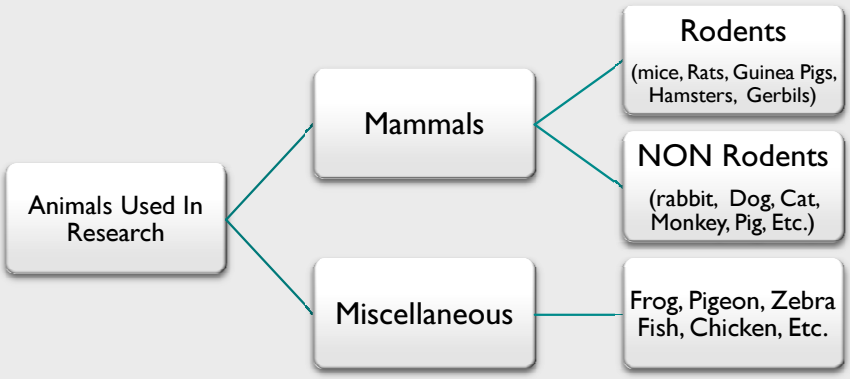
To advance scientific understanding	As models to study disease	To develop and test potential forms of treatment	To protect the safety of people and environment
• The basic cell processes are the same in all animals • Simple animals can be used to study complex biological systems such as the nervous or immune systems	• leads directly to the development of new technologies and medicines • animal models enable researchers to explore potential therapies in ways which would be impossible in humans. • Recent advances in genetic technology have allowed the development of transgenic animals, which have new genes inserted into their DNA like GFP.	• Test the potential therapies • To test data from animal studies on human patients. • To test diagnostic tools such as scanners, and implants such as pacemakers • To rely on surgical techniques	• To test new medicines to measure both the beneficial and the harmful effects of a compound on an organism. • Testing on animals also serves to protect consumers, workers and the environment from the harmful effects of chemicals.

Why Do Scientists Use Animals in Research?

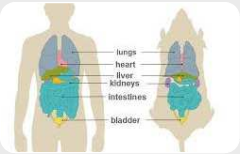
- **Are biologically similar to humans**
  - susceptible to many of the same health problems
- **Short life-cycles**
  - they can easily be studied throughout their whole life-span or across several generations
- **Control the environment around the animal**
  - which would be difficult to do with people
- **Study living whole body tissues function and the biology**
  - which would be difficult to do with people
- **Study the interaction of cells, tissues and organs within the body**
  - The interaction of cells, tissues and organs within the body is very complex, and can often only be studied in the whole animal

Why Do Scientists Use Animals in Research?

Why Do Scientists Use Animals in Research?



Why Mouse/Rat Preferred?



The closest to humans

genome has been sequenced

get many of the same diseases, for the same genetic reasons

99% of all mouse genes overlap with those of humans

The most complex

integration of systems (endocrine, immune, nervous etc.)

Short Longevity and quickly multiply

reproducing as often as every nine weeks. generation time is ~ 3 months, so genetics can be done

Why Mouse/Rat Preferred?

Easy to handle

Easy to Keep

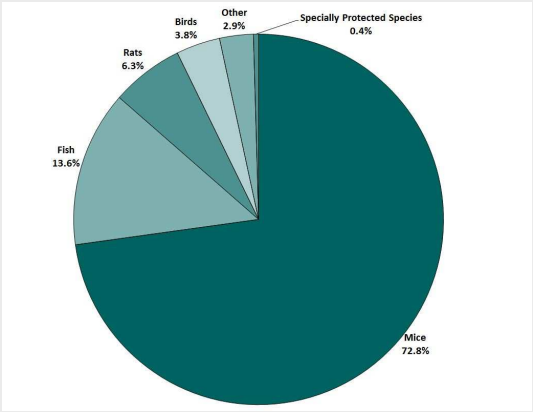
mice are ~ 3 inches long, can keep many mice in a room

highly intelligent rodents

They are natural students who excel at learning and understanding concepts

Why Mouse/Rat Preferred?

European Animal Research Association, Animal Research Statistics (2015)



http://eara.eu/en/animal-research/animal-research-statistics-europe/#eu-statistical-report

Animal Welfare and Ethics

- There are a number of federal and local laws, regulations and institutions, as well as nonprofit organizations, that ensure animals used in research & education are being treated humanely.
- These include:
  - Animal Welfare Act
  - Public Health Service
  - IACUCs
  - AAALAC

Animal Welfare and Ethics

Animal Ethics is a term used to describe human-animal relationships and how animals ought to be managed and treated.

The subject matter includes

- Animal rights
- Animal welfare
- Animal law
- Animal cognition
- Wildlife conservation
- The moral status of nonhuman animals
- And the history of animal use

Animal Welfare and Ethics: Freedoms

The five freedoms were originally developed are:

- **Freedom from hunger or thirst** by ready access to fresh water and a diet to maintain full health and vigor
- **Freedom from discomfort** by providing an appropriate environment including shelter and a comfortable resting area
- **Freedom from pain, injury or disease** by prevention or rapid diagnosis and treatment.
- **Freedom to express (most) normal behavior** by providing sufficient space, proper facilities and company of the animal's own kind
- **Freedom from fear and distress** by ensuring conditions and treatment which avoid mental suffering.

Animal Welfare and Ethics: Alternatives

- **Biological processes are complex. Understanding them requires asking a series of questions that build upon each other. At each step, researchers must decide how a particular question can best be answered.**
- Some questions can be answered using computer models or new technologies such as organs-on-a-chip—approaches based upon what is already known about a biological process.
- Other kinds of questions can be answered by sequencing genes or looking at what happens when isolated cells or tissues are exposed to certain conditions. These approaches provide a great deal of information, but they can't answer every question.
- Researchers study animals when they need to understand the stages of a normal biological process or the course of a disease. Animals are biologically similar to humans in many important ways. Studying animals provides insight into what is happening throughout the body. Whole animal studies also allow researchers to determine whether potential new treatments are effective and whether they have harmful side-effects on other parts of the body.

Animal Welfare and Ethics: 3Rs

The three Rs are encouraged to follow in order to reduce the impact of research on animals

The three Rs are:

- Replacement
- Reduction
- Refinement

Animal Welfare and Ethics: 3Rs

Replacement

Replacing experiments on animals with alternative techniques such as

- Experimenting on cell cultures (*in vitro* studies) instead of whole animals
- Using computer models
- Alternative Organisms
- Studying human volunteers
- Using epidemiological studies
- New technologies

In a system as complex as a live organism, all of the variables in physiology and pathology are not known.

Thus, any research on new biological processes must utilize a living organism at some point.

Animal Welfare and Ethics: 3Rs

Reduction

means minimizing the number of animals needed to perform an experiment or teach a concept. By examining these parameters, the IACUC can determine if thoughtful experimental design was employed to minimize overall animal use.

Reducing the number of animals used in experiments by:

- Improving experimental techniques
- Improving techniques of data analysis
- Sharing information with other researchers
- Consulting with a statistician to use only the numbers of animals required to achieve significance
- Minimizing variables such as disease, stress, diet, genetics, etc., that may affect experimental results
- Using the appropriate species of animal so that useful data is collected
- Replacement whenever possible

More than
100 million mice and rats
are killed in U.S. laboratories every year

Animal Welfare and Ethics: 3Rs

Refinement

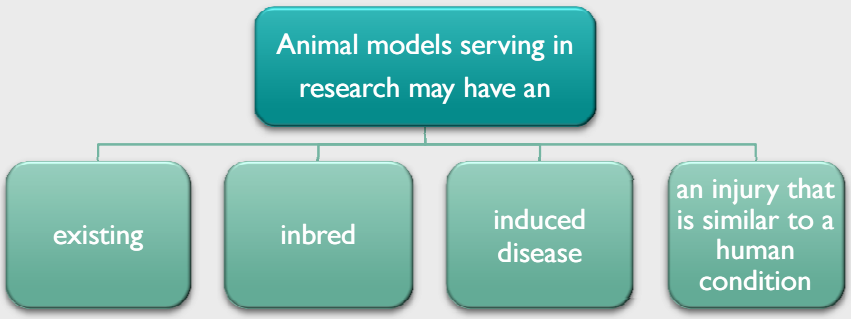
means refining experimental protocols to minimize pain or distress while achieving the most from an animal study
Examples of refinement include:

- Using less invasive techniques
- Better medical care
- Better living conditions

Animal model

- Is a living, non-human animal used during the research and investigation of human disease, for the purpose of better understanding the disease without the added risk of harming an actual human being during the process.
- The animal chosen usually meets a determined taxonomic equivalency to humans, so as to react to disease or its treatment in a way that resembles human physiology as needed.
- The use of animal models allows researchers to investigate disease states in ways which would be inaccessible in a human patient, performing procedures on the non-human animal that imply a level of harm that would not be considered ethical to inflict on a human.
- Many drugs, treatments and cures for human diseases have been developed with the use of animal models.

Animal model

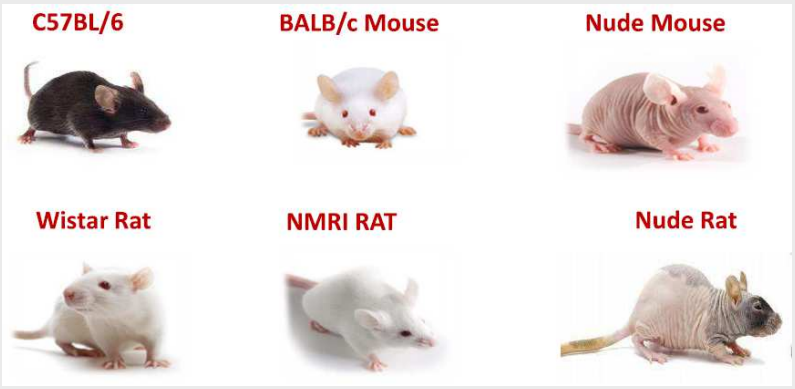


Animal model

There are three main types of animal models

Homologous animals	Isomorphic animals	Predictive Animals
• same causes, symptoms and treatment options as would humans who have the same disease	• share the same symptoms and treatments	• when animals strictly display only the treatment characteristics of a disease. This method is commonly used when researchers do not know the cause of a disease

Animal Models: Animal Strains



Animal Models

1. MI (Myocardial transplantation)
2. Orthotropic cardial infarction
3. Heart IR (Ischemia/ Reperfusion)
4. Dilated cardiomyopathy
5. Brain ischemia/reperfusion
6. Parkinson
7. Alzheimer
8. Spinal cord injury
9. Sciatic nerve injury
10. IBS (irritable bowel syndrome)
11. IBD (Inflammatory bowel disease)
12. Ulcerative colitis
13. Alloxane based diabetes model
14. STZ based diabetes model
15. Sciatic muscle pain
16. Osteomyelitis
17. Bone breaking (osteotomy)
18. Osteoporosis
19. Acute skin injures (surgical and burn)
20. Chronic skin injures (surgical and burn)
21. Full-thickness skin graft
22. Allogeneic skin transplantation
23. Liver ischemia injury
24. Ovariectomy
25. Total splenectomy
26. Subtotal splenectomy
27. Subcutaneous I transplantation
28. etc.

Animal Models

- **Animal models for preclinical cancer research**

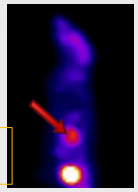
Syngeneic models

Include the spontaneous and the chemically induced tumors and in this case the inoculation of **tumor cells** in mice or rats genetically identical to those in which tumors were developed

Primer tumor and metastasis imaging:
using **^{18}F-FDG PET Imaging**

Tumor angiogenesis imaging:
using **^{68}Ga or ^{18}F-FDG ^{18}F-FDG PET Imaging**

Tumor proliferation imaging:
using **^{18}F-FDG ^{18}F-FDG PET Imaging**



Tumor

TPCF, FDG PET Scan, 2018

Animal Models

- **Animal models for preclinical cancer research**

Xenogeneic models

Xenogeneic models include immune-compromised, immunodeficient animals **transplanted with human cancers**

Tumor metabolism imaging: using **^{18}F-FDG PET Imaging**

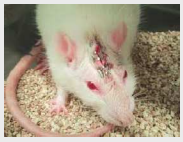
Animal Models

- **Animal models for preclinical brain research**

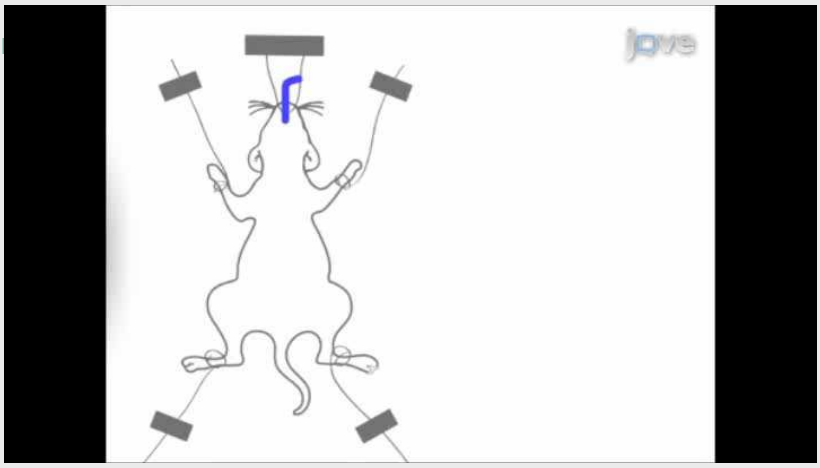
Brain models

In the research field of brain studies it is necessary to use preclinical models to predict the effects of new pharmaceuticals. Any further physiological conditions are also able to be investigated with all four tomography imaging modalities (PET, MRI, SPECT and CT).

Brain metabolism imaging: using **^{18}F-FDG PET Imaging**



Animal Models

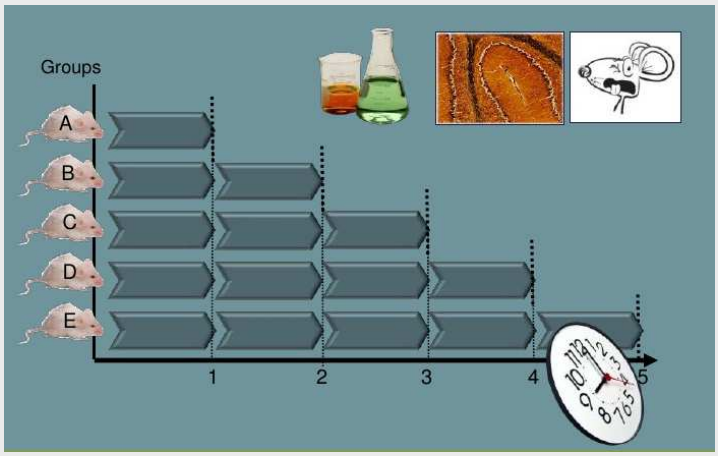


Why Preclinical imaging?

Animal Welfare Act
Public Health Service, IACUCs, AAALAC
Animal rights, Animal welfare, Animal law, Animal cognition
Freedom from pain
Reduction Refinement
whole animals, invasive techniques
New technologies
whole body, live organism, some point
Improving experimental techniques
Improving techniques of data analysis
Sharing information with others

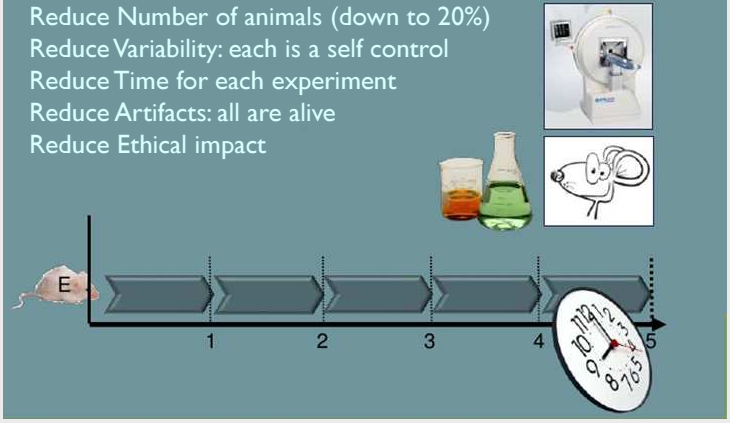
- Preclinical Imaging

Why Preclinical imaging?



Why Preclinical imaging?

Reduce Number of animals (down to 20%)
Reduce Variability: each is a self control
Reduce Time for each experiment
Reduce Artifacts: all are alive
Reduce Ethical impact

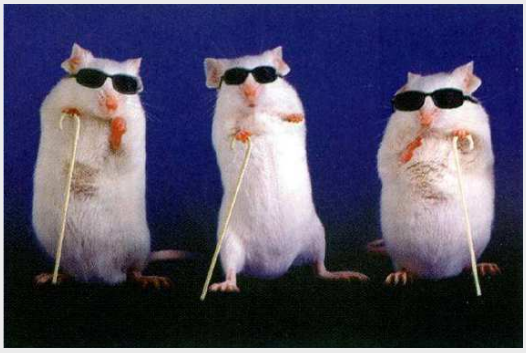


Please be more kind with us …

Try to reduce killings…!

Thanks for Your Attention

We are ready for our image to be taken by your Preclinical Imaging Systems…
So more of our relatives would be remain alive



Thanks for Your Attention