In Vivo Disease Modeling

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Outline

● What is *in vivo* disease modeling?
● Utility of *in vivo* disease models
● What makes a good *in vivo* disease model?
● Examples of disease models (🐭, 🐶, 🐟, 🙏...)
  ○ What made it a good model;
  ○ What methods were used;
  ○ Implication of the results.
● Ethics
● References
What is *in vivo* disease modeling?

Use live animals to study disease

- *in vivo*
  - (Latin for "within the living") complex biological system

- Modeling
  - devise a simplified description, especially a mathematical one, (of a system or process) to assist calculations and predictions. Definitions from [Oxford Languages](https://www.oxforddictionaries.com/)

*in vitro* (Latin for "within the glass") In vitro models are defined as synthetic experimental systems that contain living human cells, mimic tissue, and organ-level physiology in vitro by taking advantage of recent advances in tissue engineering and microfabrication.
Utility of *in vivo* disease models

- Understand disease transmission (infectious disease);
- Understand disease progression;
- Understand disease mechanism;
  - Identify disease causing genes/mutations;
  - Study the signaling pathway or gene regulatory networks that underlie the disease;
  - Identify genetic modifiers of disease phenotype and potential treatment
- Drug and vaccine development;
What makes a good *in vivo* disease model?

- Genetic diversity with well curated resources;
- Produce large amount of offsprings;
- Short life span;
- Tractable experimental systems;
- Cheap and easy to maintain;
- Resemble human physiology or disease symptoms
What makes 🐭 a good *in vivo* disease model?

- Genetic diversity with well curated resources;
- Produce large amount of offsprings; (3-14 per litter. 5-10 litters per year)
- Short life span; (26-30 months)
- Tractable experimental systems;
- Cheap and easy to maintain;
- Resemble human physiology or disease symptoms (in some cases…)
Hutchinson-Gilford Progeria Syndrome/accelerated aging

LMNA

Mutation
C1824T
Aberrant pre-mRNA splicing

PROGERIN
Farnesyl
Lamina assembly

Nuclear defects
Elevated DNA damage
Epigenetic alterations
Loss of protein homeostasis
Chromatin disorganization

Lamina defects

Cell and tissue defects
Chronic p53 signaling
Inflammatory response
Metabolic alterations
Autophagy deregulation
Stem cell dysfunction

Symptoms
Growth impairment
Cardiovascular disease
Skeletal dysplasia
Lipodystrophy
Alopecia
Skin and nail defects
Joint contractures

PHOTO BY LEAH FASTEN
Mouse model for Hutchinson-Gilford Progeria Syndrome
In vivo base editing rescues Hutchinson-Gilford progeria syndrome in mice

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In vivo base editing rescues Hutchinson–Gilford progeria syndrome in mice

Going forward

- Best result to date in the mouse model;
- A number of the longest-living treated mice developed liver tumors — a known long-term complication when using adeno-associated viruses (AAV) to deliver genes into mice;
- Base editors may be less effective in primates (61% in vivo gene editing efficacy in the liver of mice compared to 26% in primates).

🐭 offers the most comprehensive set of tools for preclinical research (if the disease pathology mimics human disease well).
Duchenne Muscular Dystrophy (DMD)
Animal models for DMD

DMD is caused by loss-of-function mutations in the Dystrophin gene

Merck Manual for the Professional/Duchenne and Becker Muscular Dystrophy
DMD is a x-linked recessive disease

Merck Manual for the Professional/Duchenne and Becker Muscular Dystrophy
DMD is a x-linked recessive disease
Dog breeds around the world provide genetic diversity

Today’s dogs can trace their ancestry to canines that lived up to 11,000 years ago. (Bergstrom et al. / Science)
There are over 340 dog breeds known throughout the world. The American Kennel Club recognizes 200 breeds.
Dog breeds are genetically isolated populations within the same species
Canine Hereditary Multifocal Renal Cystadenocarcinoma and Nodular Dermatofibrosis (RCND)

German Shepherds

- Autosomal dominant form of kidney cancer
- Early diagnosis by observation of microscopic renal cysts
- Skin-fibrofolliculomas or trichodiscomas
- Lung-cysts and pneumothorax
- Kidney -7 fold increase in risk for renal cell carcinoma tumors

Jonasdottir et al., 2000 PNAS; Lingaas et al., 2003 Hum Mol Genet

Renal cortical cyst in 8 week puppy
Conclusions

- Disease caused by germline mutations in the *folliculin* gene, which encodes a tumor suppressor.
- Signaling link between folliculin, mTOR pathway and cancer susceptibility.
- The locus found first in canine genetic study (not human), but the gene causes the human disorder Birt-Hogg Dube Syndrome.
- Such pedigrees are unusual in canine studies, impossible to find in human genetic studies, especially in cancer.
offers powerful disease pedigree and population genetic resources

Further readings related to the journal club paper

Duchenne Muscular Dystrophy: Advancements Research in the Pipeline

FDA Approves First Gene Therapy for Treatment of Certain Patients with Duchenne Muscular Dystrophy

Sarepta Therapeutics/Duchenne: A Rare Genetic Neuromuscular Disease


Understanding QQ Plots

LOD SCORE


Dog Genes Tell Surprising Tales - Dr. Elaine Ostrander
Zebrafish 🐠, a transparent model

The zebrafish is a member of the minnow family of fish.

The zebrafish embryo is transparent, it develops outside of its mother, and its development from eggs to larvae happens in just three days.

Easy to maintain. Not very susceptible to disease;

20 - 200 offspring in a single breeding;

Good model for chemical genetics approaches for drug screen.

Zebrafish model for bone marrow transplantation

Chemical Screen For Enhancers of Engraftment

Nature 2015

Tg(β-actin:GFP) → Marrow → Incubate with chemicals → Mix = Green:Red 20k/80k → 4wpt → 220 transplants/day → Increased green to red ratio

Red GloFish® → Marrow → No treatment
Zebrafish model for cancer metastasis

Mouse lemur 🦰

-Origin: Mouse lemurs are the smallest primates that are about twice the size of a mouse and live exclusively on Madagascar;
-Genetic diversity in wild populations;
-Closely resemble human physiology.

The Mouse Lemur, a Genetic Model Organism for Primate Biology, Behavior, and Health

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The Mouse Lemur, a Genetic Model Organism for Primate Biology, Behavior, and Health
Ethics

- Diseased animals breed for research purposes;
- Protocols and guidelines to manage pain and suffering of animals;
- Improve veterinary medicine;
- The most used animal models are what we feel comfortable killing in mass.
The best model that checks all the boxes @%#^$&* ......
Summary

- Different animal models offer different things;
- Understand the model systems;
- Clarify your question and pick a model that would help you address the clinical need;
- Plan your experiments well.
References


