Human Stakeholders and the Use of Animals in Drug Development

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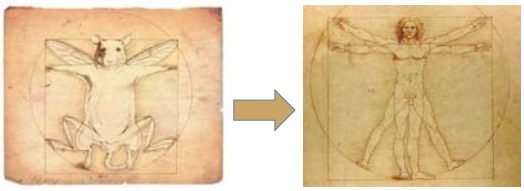
This work is a collaboration with Ray Greek

Image source: Mark Kamstra



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The Use of Animal Models from a Business Ethics Perspective

- We leave aside the question of animal ethics and focus instead on the validity of using animals based on scientific and human ethics considerations.
- Primary findings:
  - Constrained by existing standards that date back many decades, the industry is effectively required to employ animal models in early stages of the drug development process.
  - The reliance on animal models is unable to prevent the development of harmful drugs.
  - The reliance on animal models hinders the development of useful drugs.
  - Careful elimination of policies and regulations that require the use of animal models will greatly benefit stakeholders of the pharmaceutical industry.
  - Even in absence of more effective methods, there would be no reason to continue using animal models. Fortunately, more effective methods are available.

The Use of Non-Human Animal Models in Biomedical Research: Historical Perspective

- Following the end of WWII and the Doctors' trial at Nuremburg, non-human animal modeling was institutionalized in the moral codes of research:
  - Principle 3 of the Nuremburg Code and Principle 12 of the Declaration of Helsinki
- These principles aren't binding but they have been codified into various countries' laws, including those of the United States.
  - 1962 Drug Efficacy Amendment to the Federal Food, Drug, and Cosmetic Act (aka the Kefauver Harris Amendment) – driven by emotional reaction to events including the thalidomide disaster, not science.
  - Note that this revision doesn't necessarily *require* non-human animal modeling in the development of new drugs, but the interpretation of the law is such that it might as well.
- Paradigm-shifting advances have occurred in the meantime, and so these laws are grossly outdated.

Scientific Underpinnings I: Predictive Value

The mathematics of predictive value:

- Gold standard
- True positive vs false positive
- True negative vs false negative

Predictive values for responses to drugs in development are less than 50% overall, rendering them less predictive than a coin toss.

➢ *We would be better off tossing coins to pick which drugs should be marketed than basing the decision on results from non-human animal models*

Scientific Underpinnings II: Complex Systems Science

Complex systems:

- Comprised of many parts; hierarchical levels of organization
- Whole is greater than sum of parts
- Feedback loops; self-organization; dynamic with respect to environment; adaptation
- Respond to perturbations in a non-linear way
- Dependent on initial conditions

Trans-species extrapolation is generally feasible when perturbations concern low levels of organization or when studying morphology and function at the gross level.

When working with perturbations that affect high levels of organization, such as drugs, it's not good science to use one complex system in expectation of it having predictive value for another.

Image Source: NASA Hubble / Public Domain

Scientific Underpinnings III: Evolutionary Biology

Evolutionary biology:

- Small changes in genes, over long periods of time, result in new species.
- Humans & non-human animals are examples of complex systems that have evolved over time.
- Even though different species may share many common genes, there can still be vast differences in the way each species responds to perturbations.
  - Progression from HIV to AIDS, common in humans, is rarely seen in chimpanzees although we share most of our DNA.

Different species may or may not have common reactions to drugs and disease; we can't predict when the reactions will be common across species due to complex system science and evolutionary biology.

Some of the Key Stakeholders of the Drug Development Enterprise

- Patients
- Clinical trial participants
- Researchers at non-profit organizations
- Medical professionals
- New generations of scientists
- Donors to non-profit organizations
- Taxpayers
- Investors in pharmaceutical companies

Patients

Lack of safety

- Many memorable examples (e.g., fen-phen, thalidomide, vioxx)
- Note: citing examples is not intended as proof; see Greek and Kramer (2019) for formal arguments regarding overall lack of safety based on the mathematics of predictive value

"It is impossible to give reliable general rules for the validity of extrapolation from one species to another. This has to be assessed individually for each experiment and can often only be verified after first trials in the target species [humans]…

"Extrapolation from animal models, like medical art itself, will always remain a matter of hindsight…"

- Salén 1994, p. 6; *Handbook of Laboratory Science Volume II. Animal Models.* parenthetic text added.

Patients (II)

Lack of efficacy

- ~37% of drugs that make it to human trials fail in Phase I, ~55% fail after making it to Phase II, ~13% fail after making it to Phase III
- Primary reason for these failures is efficacy; secondary reason is safety.
- *"The history of cancer research has been a history of curing cancer in the mouse. We have cured mice of cancer for decades—and it simply didn't work in humans."*
  - Dr. Richard Klausner, former director of the NCI (Cimons et al. 1998).
- 100+ vaccines are effective against HIV-like disease in animal models; none are effective in humans
- ~1000 drugs protect against nervous-system damage in animal models of stroke; none are effective in humans
- Lou Gherig's disease, spinal chord injury, sepsis, …

Patients (III)

Opportunity costs: failure to identify new drugs

- Many drugs that were ruled out based on misleading results from animal models would have been lost forever if not for accidental later discovery (for instance based on "last-ditch" attempts by doctors with near-death patients)
- The number of *effective and safe* new drugs reaching market has slowed to a crawl:

"the number of new drugs that are approved annually is no greater now than it was 50 years ago."
– Munos (2009, p. 959, *Nature Reviews Drug Discovery)*

Patients (IV)

Financial costs

- Sepsis, for which animal models have yielded no effective treatments, costs U.S. hospital inpatients at least $14 billion per year. (Mayr and Yende, 2014)
- Cancer, coronary artery disease, congestive heart failure, stroke, lung disease, and other afflictions that have been extensively explored with animal models also continue to be extremely costly to treat, with treatment outcomes nevertheless still extremely risky.
- The costs of existing successful treatments are significantly inflated in order to underwrite the high costs of animal modeling, most of which fails.

Other Stakeholders

To examine the harms to other stakeholders, it is useful to consider the drug development industry's costs relative to revenues.

- The pharmaceutical industry spends more money on R&D than any other industrial sector. (Pham, 2010)
- The majority of the cost to industry of developing new drugs comes from human clinical trials.
- The top reason for failure of human clinical trials are safety and efficacy (the very properties animal models are intended to assess).
- Drug companies would prefer that harmful/ineffective new chemical entities fail early in the development process, prior to costly human trials, but the unreliability of animal data gets in the way.
- Consequently, industry (and academia) devotes vast resources to likely-to-fail drugs, representing a massive investment on the part of society.

Other Stakeholders (II)

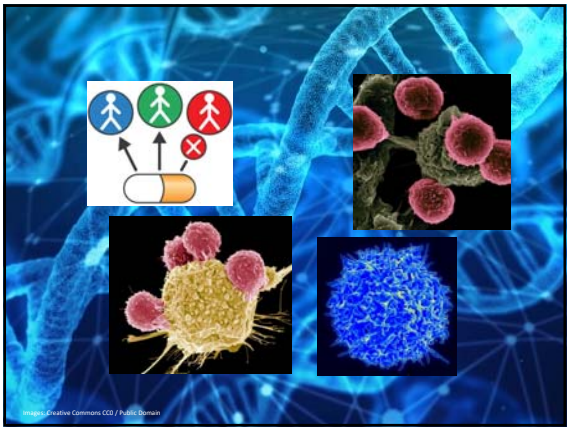
- The continued use of animal models causes harm to several groups, including:
  - Clinical trial participants
    These are among the first humans exposed to compounds that perhaps appeared safe in animal models, and they often aren't informed of the significant physical risks they face based on the methodological problems with animal models.
  - New generations of scientists
    Those who are being trained to continue employ animal models are missing the opportunity to advance scientific progress through use of better methods
  - Taxpayers and donors
    Lower bound on annual cost to society: $10-12 billion of the annual NIH budget directly funds animal-based research at universities.
  - Investors
    Constraining drug development firms to employ animal models prevents them from putting investor capital to its best use and arbitrarily limits the firms' financial returns.

In Light of All These Harms, Why Does Animal-Based Research Continue?

- Laws continue to codify the use of animal models prior to human clinical trials.
- The FDA (and counterparts around the world) likely has the power to revise their interpretation of these laws, but they are unlikely to do so without action from legislative bodies.
- Other obstacles include conflicts of interest, status quo bias and various other behavioural tendencies on the part of reseearchers, politicians, and the public.
- Additionally, often it takes a (better) model to replace a model: in this case, that effectively means 100% predictive value.

Better Options

Image Source: Peer Morville / flickr



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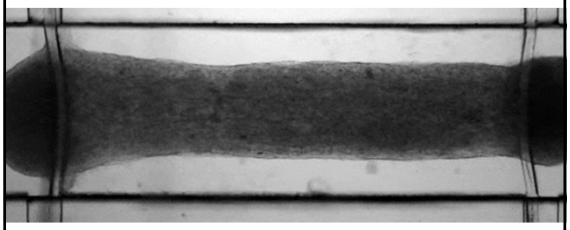

https://uoft.me/Cell

Conclusions

- Constrained by outdated standards, the pharmaceutical industry is effectively required to employ animal models in early stages of the drug development process.
- The reliance on animal models is unable to prevent the development of harmful drugs and is hindering the development of useful drugs.
- Humans are significantly harmed, including patients, clinical trial participants, researchers, taxpayers, and many others.
- Elimination of policies and regulations that require the use of animal models will greatly benefit stakeholders of the pharmaceutical industry.

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Image Source: Ashashyou / wikimedia