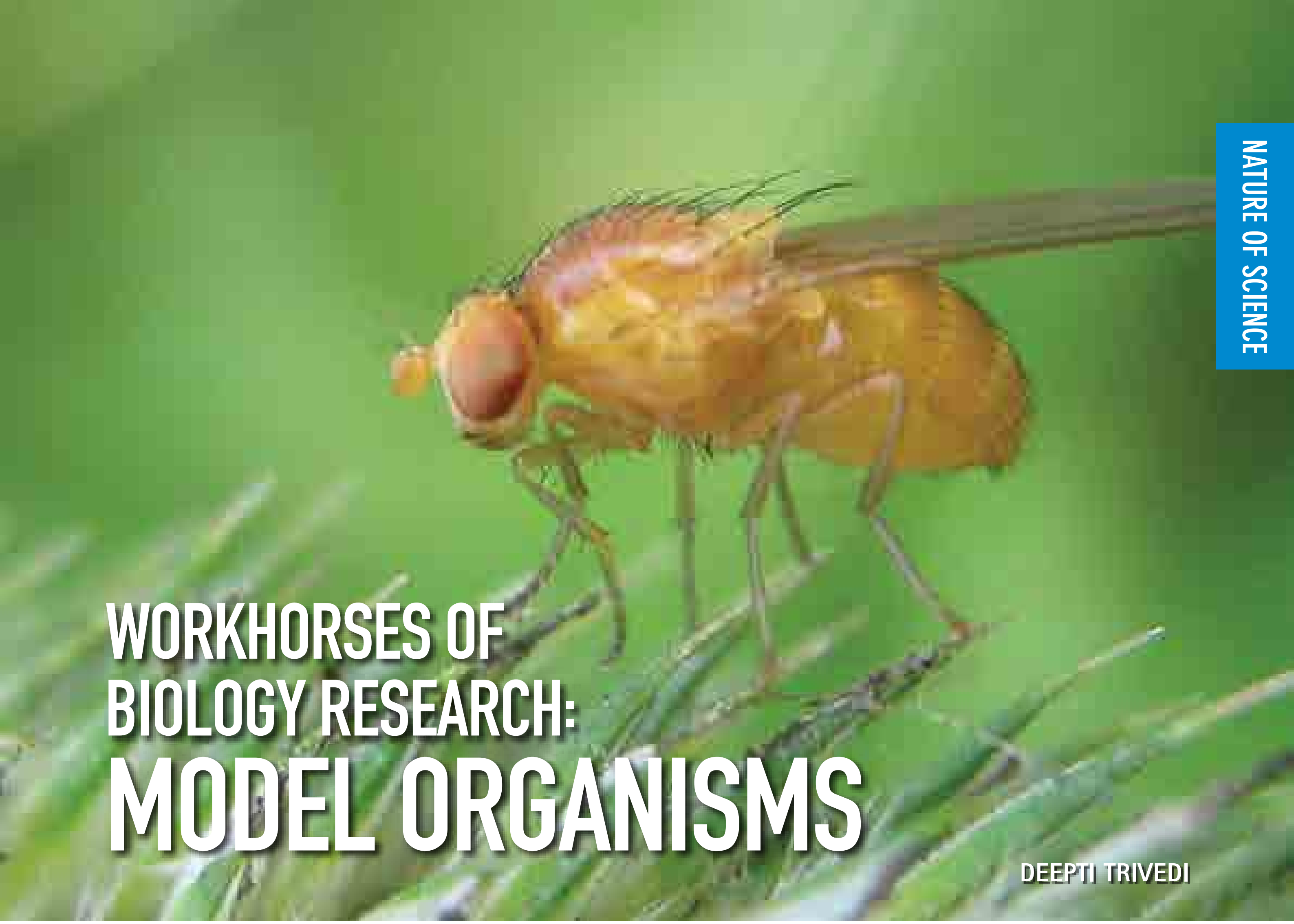

WORKHORSES OF BIOLOGY RESEARCH: MODEL ORGANISMS

DEEPTI TRIVEDI

In two centuries of modern scientific history, model organisms have contributed to our understanding of human physiology, cell biology, and diseases. But what are model organisms? What discoveries have they contributed to? What are some limitations and ethical dimensions associated with them?

Living organisms vary widely in their shape, size, habitat, and the nature of their interactions with their environment. Despite this great diversity, all living organisms share some common features. The use of model organisms began, more or less, with the knowledge that all organisms had evolved from a common ancestor. The theory of evolution put forth by Charles Darwin and others in the late 19th century suggested that all organisms had branched out from a temporal evolutionary tree (see **Fig. 1**). This meant that these organisms would share a lot of biology. Data accumulated from different model organisms in the 20th century proved this — we know that all organisms are quite the same in the way they inherit genetic material, use energy, and make their own building blocks. Their shared origins also mean that more closely related species are likely to share greater similarity than more distantly related species. Therefore, investigating the biology of organisms from one species can be a proxy to understanding organisms from other, evolutionarily close, species. The specific organisms selected by researchers (based on their amenability to experimental studies) for this purpose are called **model** or **reference organisms.**

Many bacteria, fungi, insects, worms, fishes, plants, and mammals are used as model organisms worldwide. These organisms not only help us gain in-depth knowledge of their own species, but also of closely related species, genera, and kingdoms. Many scientific advances in terms of our understanding of human anatomy, biochemistry, physiology, development and genetics would not have been possible without their use. In fact, if all research on human biology had to be done in humans, and not in model organisms, biological research would have lagged, and been a lot more expensive.

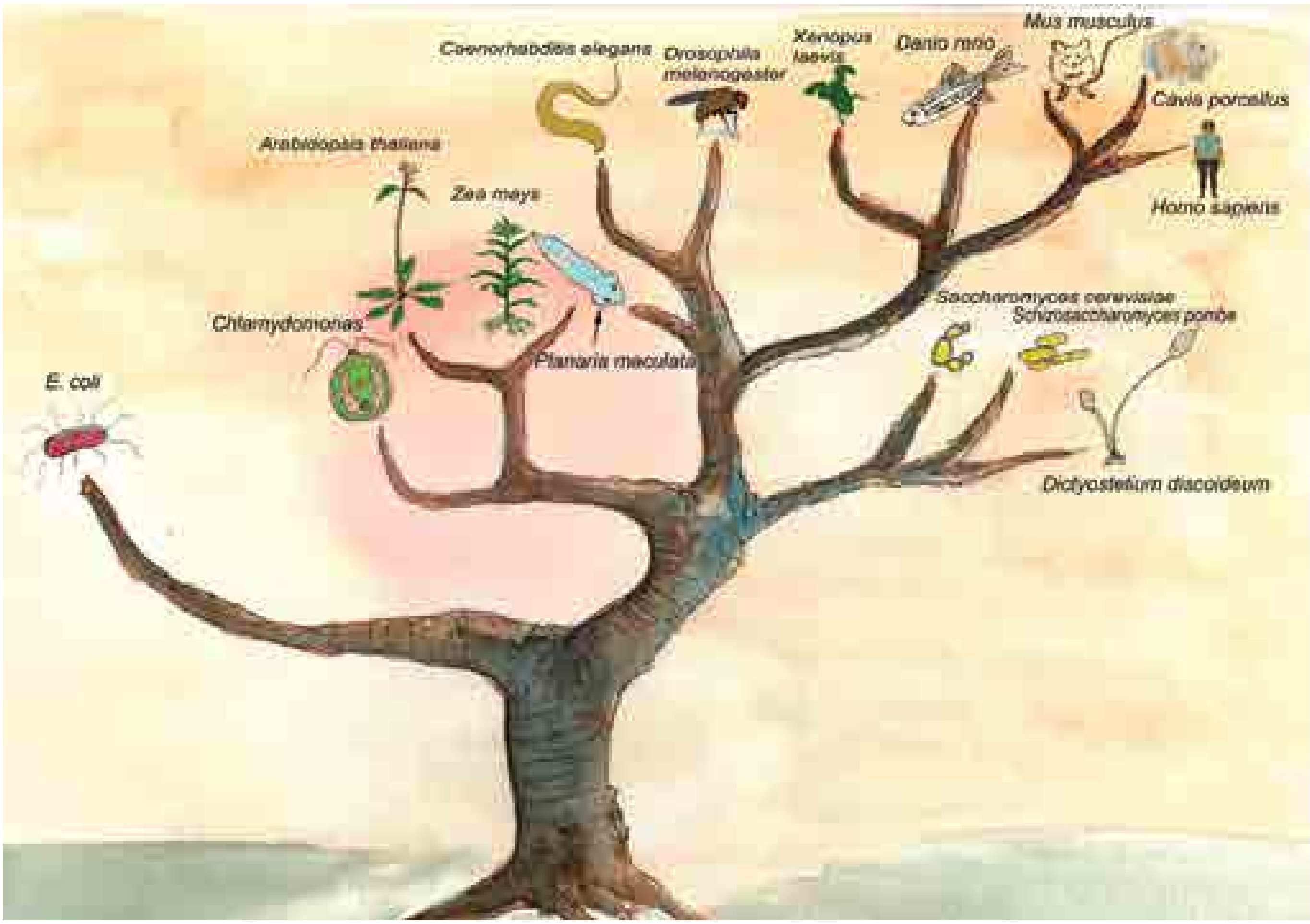

Fig. 1. **An evolutionary tree depicting the relationships between different model organisms with each other and to us humans.** The closer two species are to each other in terms of their evolutionary history, the more similarities they share with respect to their biochemistry, physiology, anatomy, and genetics.

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Choosing a model organism

These are some of the things a scientist considers before choosing a model organism for her research:

1. **The research question:** It should be possible to address one's research question in the model organism of choice. For example, mechanisms of photosynthesis can be studied in algae or plants, but not in animals.
2. **Practicality:** It should be practical to do a certain kind of research in the organism selected. For example, one may not want to study evolution or population dynamics in organisms that take years to grow and reproduce. At the same time, one would prefer that the lessons learnt from their studies be as widely applicable as possible. Other practical considerations include availability of funds, logistics and space, and ease in growing and maintaining the model organism. For example, a project using penguins as models may require huge infrastructure and maintenance costs if done in India.
3. **Methods:** The experiments that one designs should be doable in the organism of choice. Some experiments may simply be too difficult to perform in a certain model organism with currently available methods. For example, to study effects of certain mutations that do not already exist in the model organism, one first needs to create these mutations. Certain model organisms are more amenable to this requirement as the resources and methods to create mutations in them are already available.
4. **Evolutionary conservation:** Some specific phenomena may not be conserved across species. Hence, one may need to study closely related species to understand those phenomena better. For example, although breast development and cancer cannot be studied in insects, the molecular pathways that play an essential role in these phenomena are conserved in insects. Insect models can, therefore, offer insights into molecular interactions that form their genetic basis.

Box 1. Why did Morgan choose the humble fruit fly as a model organism?

Morgan was looking for a model organism that would provide an example of evolution that he could see occurring in front of his eyes. He was not completely convinced about Darwin's theory and wanted to study how organisms evolve (or if they even really evolve). This meant that Morgan's model organism had to have these specific attributes:

1. A short generation time: This would allow him to track the transmission of traits over many generations in a comparatively short amount of time.
2. The ability to grow *in vitro*: Darwin's work was based on observations in the wild that spanned millions of years, but Morgan wondered if evolution could be recaptured in a laboratory setup. Also, since Morgan expected evolutionary changes to happen at a very low frequency, the model organism had to be easy and relatively inexpensive to grow in comparatively larger numbers within the confines of a small lab space.
3. The ability to study it with available methods: Morgan wanted to be able to see evolutionary changes, if any, with the equipment available to him. Remember, in the early 20th century, many of the sophisticated methods that we know today were unavailable. All that Morgan had were some simple microscopes.

After much thought and discussion, he chose *Drosophila melanogaster* as his model organism. This tiny fruit fly was easy to grow in large numbers and developed from egg to adult in just 10 days. The genetic studies that Morgan was able to do in months in fruit flies would have taken hundreds of years in humans, been a lot more expensive, and required the participation of an entire country's population! The data it yielded would have been far more complex to interpret. And, even if it were actually possible to do so, such a study would have given the exact same result.

Examples of model organisms

(a) Drosophila as a model organism to study genetics: Thomas Morgan, an American evolutionary biologist, was the first to choose a fruit fly, *Drosophila melanogaster*, as a model organism (see **Box 1**). Thanks to Morgan and his colleagues, and later work by many other scientists, these insects that hover around in the kitchen on ripe fruit, especially bananas, are now very well-established model organisms.

Interestingly enough, Morgan's studies with the fruit fly had little to do with evolution. Yet he and his colleagues ended up providing incontrovertible evidence for the highly debated chromosomal theory of inheritance — knowledge that is pertinent across kingdoms. They showed that genes reside on chromosomes in a linear fashion, the distance between genes could be calculated based on genetic markers, and mutations in genes lead to changes in phenotypes.

Given the many similarities fruit flies share with us, Drosophila biologists have been using these insect models to understand the genetic basis of body patterning and development, circadian rhythms, immunity, and olfaction (see **Fig. 2**). All these discoveries have led to Nobel Prizes.

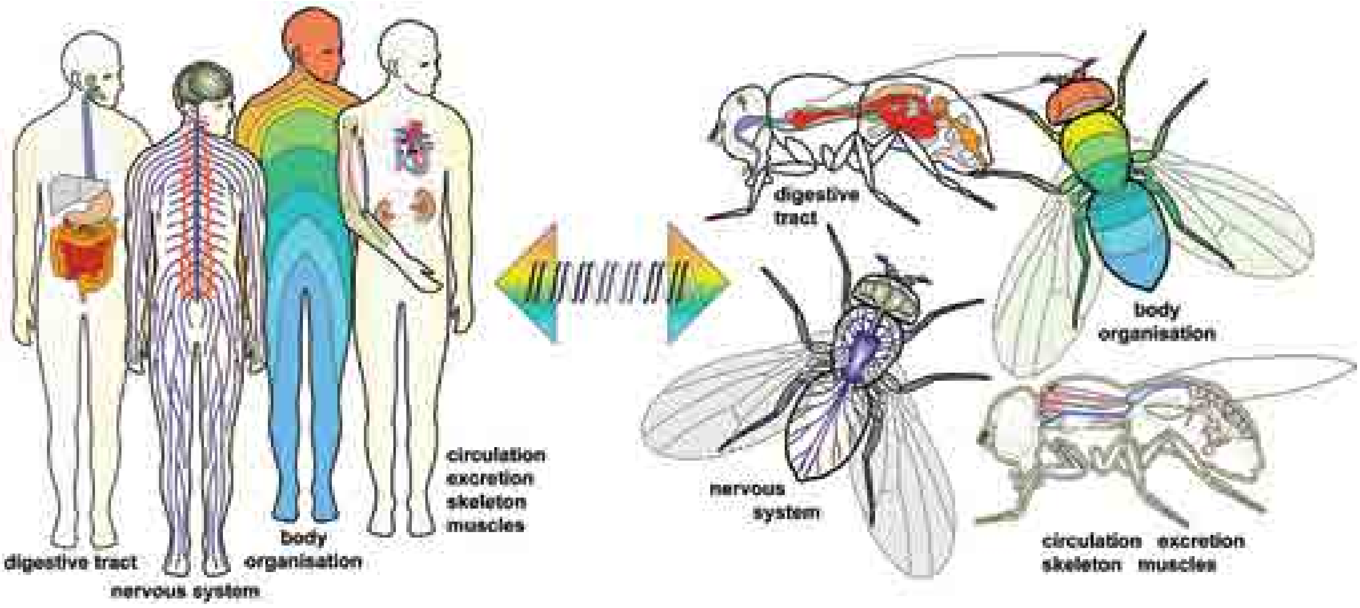

Fig. 2. Drosophila shares many similarities with humans.

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Box 2. Bringing biology from one system to another for genetic engineering:

Basic research to study the same process in different organisms not only helps bridge gaps in our understanding, it may also help in the development of technologies that use this process to manipulate other organisms. One example is the use of bacterial biology for genetic engineering.

Like humans, bacteria also get infected by viruses. Infected bacteria may either die, or survive by fighting the infecting virus. Those that survive, develop immunity against the infecting virus by 'remembering' their DNA sequences – pieces of these viral sequences get written into the bacterial genome. The next time the same virus infects them, they recognize and chop the viral DNA sequences much faster. This process helps the bacteria fight the virus more effectively than the first time.

The ability of bacterial cells to recognize and chop a foreign DNA sequence has been studied in great detail. The specific bacterial genes and proteins (called **Cas9 proteins**) responsible for performing these functions have been isolated. These proteins can be used to chop specific DNA sequences in any organism. As part of a technological application, called **CRISPR-Cas9 technology** (see **Fig. 3**), they are used to generate specific mutations in different organisms, and have great potential in treating genetic diseases.

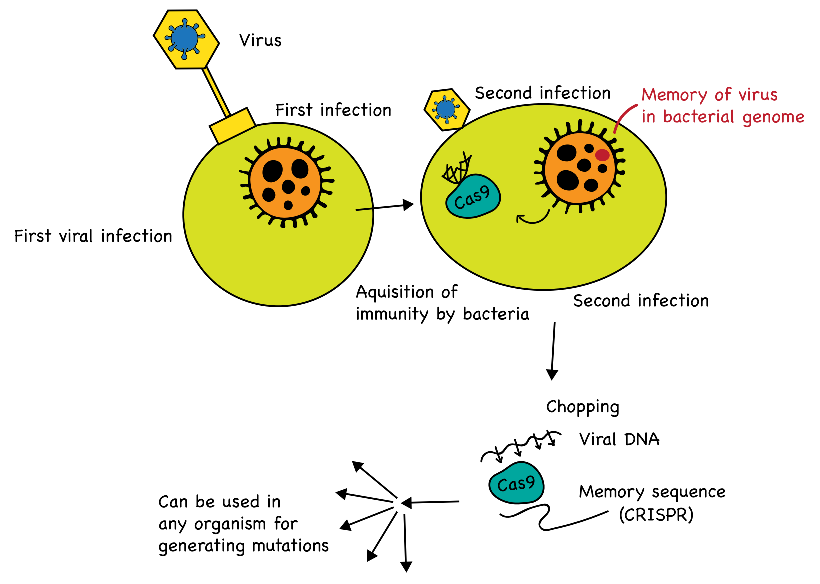

Fig. 3. CRISPR Cas9 technology.

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(b) Bacteria as model organisms: There are many compelling practical and technical reasons to study bacteria for their own sake.

First, and perhaps most importantly, bacteria cause many human, animal, and plant diseases. Therefore, we study bacteria in the hope of finding better ways, including more effective antibiotics and vaccines, to control diseases caused by them. Secondly, bacteria have been used as models in many key studies and contributed to our understanding of the general principles of growth, replication, transcription, and translation in living organisms. In addition, bacterial phenomena have been used in eukaryotes for genetic engineering (see **Box 2**).

(c) Planarians as a special model to understand regeneration and aging: What happens when you get bruised from a fall? The bruise heals in a few days, with new skin cells replacing the older, injured tissue. Soon, you may not even remember where the bruise was. But what if you were to lose a finger, or a complete arm, in an accident? Is it likely that these body parts would grow back?

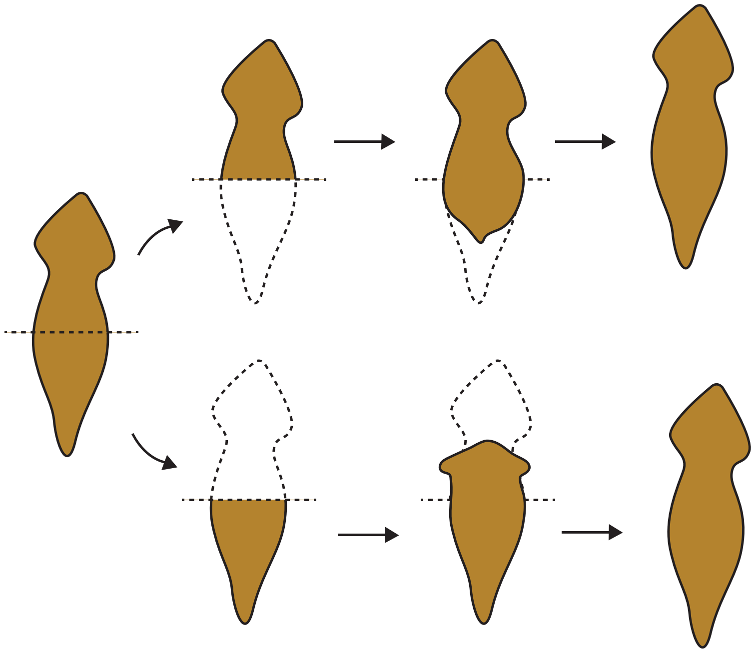

Fig. 4. Planarians are studied for their regenerative potential.

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Compare this with planarians — these flatworms exhibit the extraordinary ability to regenerate lost body parts. For example, a planarian split lengthwise or crosswise will regenerate into two separate individuals. If given sufficient time, even a hundredth piece of a planarian will develop into a fully-grown organism (see **Fig. 4**)!

Their regenerative potential makes planarians a model system for investigating a number of biological processes, many of which have important implications for human health and disease. For example, planarians are used in the identification of genes responsible for regenerating body parts. With their apparently limitless regenerative capacity, these 'effectively immortal' worms also make a great model for aging studies. For example, studies showing that the chromosomal ends of these worms are protected suggest that this protection may be important to prevent aging.

Use of model organisms in drug discovery

Often, when we fall sick, medicines or drugs are prescribed to help us get better. But have you ever wondered how drugs specific to a disease are made?

Drug discovery is a tedious process. Every disease has some physiological basis — it is either an infection, a genetic disorder, an allergy, or an injury that causes a disturbance in our body function at the cellular and molecular level. Often, this leads to over-activation or suppression of molecular pathways in our body. These molecular pathways are the targets of drugs that help restore them to normal function by blocking or activating specific enzymes. Since many cellular and molecular pathways are conserved across species, model organisms are used to screen millions of compounds for their ability to block or activate these specific enzymes. The compounds identified by these screening methods (as potential drugs) are tested in higher organisms (lower mammals, primates, and humans in that order) to study their efficacy and toxicity before they come into the market (see **Fig. 5**).

Ethics

Historically, human beings have used other living beings, including animals and plants, for their own benefit, without much consideration to these organisms. In fact, the use of animals in research dates back to ancient Greece, with Aristotle (384-322 BCE) and Erasistratus (304-258 BCE) being among the first to perform experiments on living animals. However, in the recent past, many questions have been raised regarding the ethics of using other organisms for research that benefits humans.

The use of model organisms is based on the premise that all organisms (including humans) are distant cousins of each other and, therefore, share similarities in their cellular and molecular architecture. By the same logic, there is a high probability that our animal models experience pain and suffering just like we do.

All research is focused on at least one of two outcomes — medical innovations or increased knowledge. Increased knowledge improves our understanding of the human mind and body, and can lead to medical innovations in the long run. However, the benefits of research for the sake of increasing knowledge may not always justify the costs of the suffering inflicted on the animals used for it. How well justified this kind of research is will vary depending on the extent of suffering a certain research project inflicts on its model organisms, and their psychological complexity.

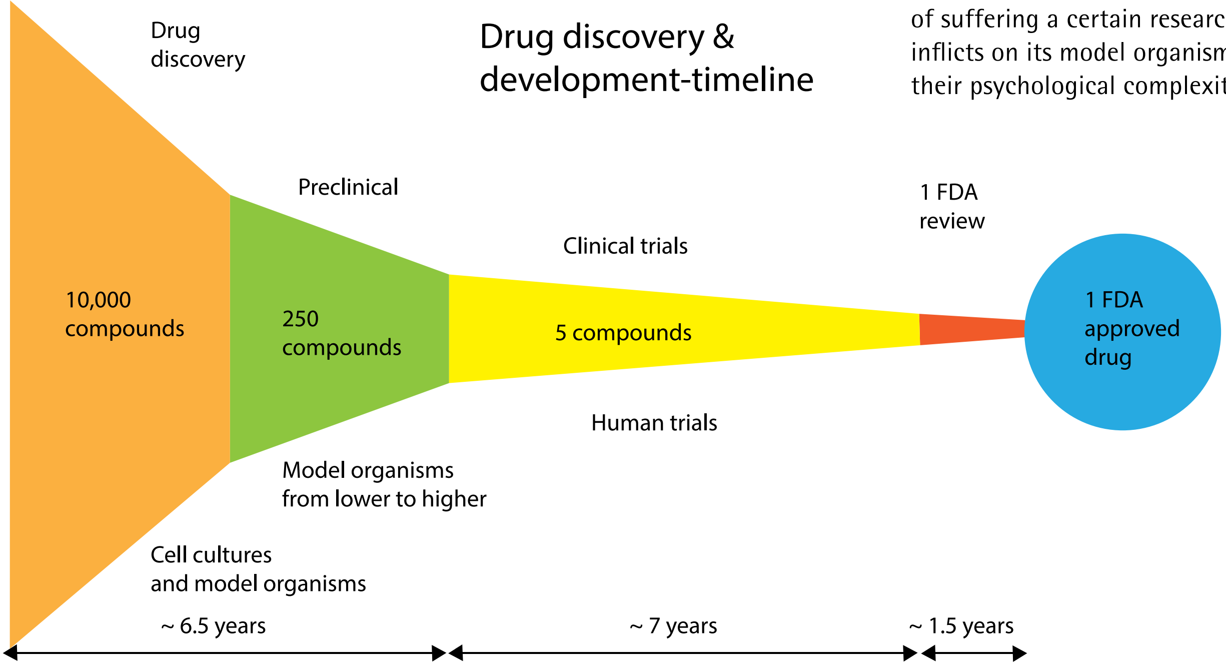

Fig. 5. A schematic of drug discovery.

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To address these ethical issues, most scientific research on model organisms is governed and regulated by ethical committees at the institutional level. These committees review the justification for a research project, among other considerations. They also attempt to ensure that Russell and Burch's (scientists appointed for the systematic study of laboratory techniques in their ethical aspects by Universities Federation of Animal Welfare in USA) three R's are followed in each project:

- **Refinement:** research methods should focus on minimizing pain and suffering.
- **Reduction:** using fewer animals in each experiment without compromising scientific output, quality of research, and animal welfare. This means that the research project should, for example, follow optimal colony management strategies.
- **Replacement:** using non-sentient materials to replace the use of conscious living vertebrate animals completely, partially, or relatively.

The use of most lower organisms, including bacteria, yeast and insects, does not currently require clearance from ethical committees.

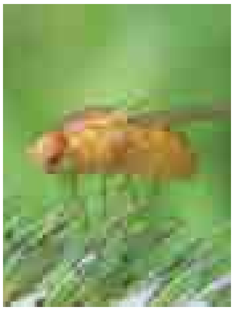
Limitations

Although fundamental discoveries can be made in model organisms, not all them hold true for humans. For example, many drugs that are successfully tested in model organisms may not work in humans. This is because many processes either do not exist or function differently in model organisms as compared to humans. In such cases, evolutionarily closer model organisms are used for a final round of testing before they are approved for use in humans.

Parting thoughts

Model organisms have been used to understand basic biology that has, in turn, led to many important discoveries. These have revolutionized core practices in diverse disciplines, such as medicine, surgery, psychiatry, and ecology. Today, the use of model organisms needs to be justified before regulatory bodies, which also attempt to ensure practices that minimize the number, suffering, and use of more psychologically complex organisms for research.

Key takeaways



- Model organisms are organisms that scientists use for research to understand general principles of biology.
- Model organisms have been used in many different fields of science, including genetics, development, physiology, neuroscience, biomedical research, and drug discovery.
- The choice of model organisms for a project is based on the research question, the specific methods of research, practical considerations, and the extent of similarity between model organisms and the organisms of interest.
- Ethical committees ensure that the intended outcomes of a research project justify the use of model organisms, and the 3R's of Refinement, Reduction and Replacement are followed.
- Model organisms enhance our knowledge, and contribute to our understanding of our environment and ourselves. However, every model organism has its own limitations.

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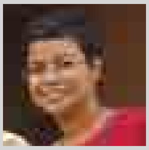

Deepti Trivedi is in charge of the Fly Facility at the Bangalore Life Science Cluster, where she works on tiny fruit flies that have revolutionized biology research. If you'd like to know more about using Drosophila in school- and college-level experiments and research, Deepti can be contacted at fly@ncbs.res.in.