DTI
Drug Target Insights 2026; 20: 1-2
ISSN 1177-3928 | DOI: 10.33393/dti.2026.3733
EDITORIAL

Alternative model organisms: growing popularity, and the challenges

Vijay Kothari

Institute of Science, Nirma University, Ahmedabad - India

For decades, biological breakthroughs have relied heavily on a select group of "canonical" model organisms—species like *Mus musculus*, *Rattus norvegicus*, and *Arabidopsis thaliana* that have defined the boundaries of modern genetics and physiology. While these established systems have yielded transformative insights, they represent only a tiny fraction of the biological diversity found across the tree of life. As we enter the second quarter of the twenty-first century, the scientific community is increasingly recognizing that the exclusive use of these models can limit our understanding of complex biological principles that are absent or significantly different in non-traditional species. To address this gap and foster a more inclusive approach to biological inquiry, we are proud to launch a new journal section: *Alternative Model Organisms*.

Why Expand the Toolkit?

Several converging factors fuel the drive toward non-traditional models:

- **Evolutionary Insights:** Established models are often phylogenetically concentrated. Investigating organisms at key evolutionary positions—such as the basal bilaterian *Macrostomum lignano*—allows researchers to link genetic modules to the emergence of biological novelties.
- **Translational Gaps:** The "gold standard" mouse model often fails to predict human clinical outcomes, particularly in complex areas like immunology and drug toxicity. Alternative models, including emerging organ-on-a-chip technologies and 3D bioprinting, offer more human-relevant physiological simulations.
- **Specialized Traits:** Biodiversity offers models for phenomena that traditional systems cannot replicate, such as the extreme regenerative abilities of the apple snail (*Pomacea canaliculata*) or the unique social structures of eusocial insects.
- **The 3Rs Framework:** There is a growing ethical and regulatory mandate to Replace, Reduce, and Refine animal use. Using "lower" organisms like *Caenorhabditis elegans* or *Danio rerio* for high-throughput toxicity screenings facilitates adherence to these principles while reducing costs (1).

Different branches of biological, clinical, and environmental research rely heavily on the availability of a suitable model organism, which can mimic the actual application platform, while allowing the work to progress at a reasonable speed. Research on certain pathogens (e.g. certain obligate intracellular parasites, including viruses) is often hampered due to the non-availability of a compatible model organism. On the other side, there are some organisms that match the criteria of being an acceptable model so well that they have become almost indispensable for research in specific domains. For instance, *Escherichia coli* has remained the handiest model for bacteriological research for decades, and one of the most popular platforms for expressing cloned genes. *Saccharomyces cerevisiae* has been widely exploited as a model yeast and as a platform for bioprocess intensification for industrial alcohol production. *Candida albicans* serves as a model for pathogenic yeasts. *Mycobacterium smegmatis* has helped the researchers develop useful insights into the genus *Mycobacterium* without necessitating the risk of handling *M. tuberculosis.* Pre-clinical research has depended heavily on pig, mouse, rat, and primate models. However, in the face of the serious ethical concerns raised over the use of higher animals in research labs, alternative strategies are being envisaged to reduce their sacrifice. In this background scenario, three lower organisms—*Caenorhabditis elegans*, *Drosophila melanogaster*, and zebrafish—have gained increasing popularity, particularly for preliminary *in vivo* studies. Though they are not new to biology labs, their use has gained wider popularity in the last two decades, and the availability of their transgenic strains has contributed notably towards extending their utility spectrum. While use of conventional model organisms still continues, the alternative models (nematode, fly, zebrafish) are gaining entry in more and more labs, new models are being proposed, and the regulatory agencies globally are trying to reduce the animal sacrifice in biological and pharmaceutical research. "Organ on a chip" type of novel approaches are also expected to contribute towards reduced use of model animals in research. The field is slowly changing and evolving dynamically, and there is a need for researchers in the fields of biology, pharmacy, cosmetics, nutraceuticals, toxicology, and environmental sciences to keep themselves updated.

With each passing year, the scientific community is witnessing a transformative shift toward alternative model organisms, driven by a combination of ethical mandates (such

Received: January 26, 2026
Accepted: February 3, 2026
Published online: February 17, 2026

Corresponding author:
Vijay Kothari
email: vijay.kothari@nirmauni.ac.in

as the 2023 FDA Modernization Act 2.0 and new NIH 2025 policies) and the need for higher-throughput research. These "non-traditional" systems fill a critical gap between simple cell cultures and complex, expensive mammalian models like mice. Some key alternative models and their utility features are listed below:

- **Invertebrate models**:
  - ***Caenorhabditis elegans* (Roundworm)**: Remains the gold standard for high-throughput aging and neurodegenerative disease research due to its fully mapped "connectome" (302 neurons) and 40-65% genetic homology to humans.
  - ***Drosophila melanogaster* (Fruit Fly)**: Essential for nutrigenomics (2) and respiratory research; New "fly-on-a-chip" tools are being used to automate behavioral and cardiac screening.
- **Aquatic Vertebrates**:
  - **Zebrafish** (*Danio rerio*): Valued for its transparent embryos, allowing real-time visualization of organ development. Under 2026 EU regulations, embryos under 5 days post-fertilization (dpf) are prioritized as non-animal alternatives for toxicity testing.
  - **Japanese Medaka** (*Oryzias latipes*): Gaining prominence for cancer research and endocrine disruptor screening due to its smaller genome and superior transparent skin in adult mutant strains.

Emerging Technological Integration

- **Organ-on-a-Chip (OOC)**: These microfluidic "Lab-on-a-Chip" systems mimic human tissue architecture (e.g., gut-on-a-chip, placenta-on-a-chip) to provide dynamic metabolic data that static cell cultures cannot.
- **AI (Artificial Intelligence) and Orthology Databases**: Tools like OMAMO (Orthologous Matrix and Alternative Model Organism) use AI to help researchers select the best non-complex organism based on specific human gene relationships, expanding research into "obscure" species like *Volvox* or *Dictyostelium*.

Expanding the species toolkit is not just about ethical "replacement" (the 3Rs), but about uncovering "biodiversity treasures"—biological mechanisms like extreme longevity or limb regeneration that are absent in traditional models. Even in the face of increasing use of alternative models, the "Safety Gap" concern is there. Despite recent regulatory reforms, some experts hold the opinion that alternatives like AI or non-mammalian models cannot yet fully replicate human-specific unknowns. Humane animal research remains 'indispensable' for confirming product safety before human clinical trials. Example resources on selecting and using alternative models, researchers can utilize include, the NIH Office of Research Infrastructure Programs (ORIP) and specialized databases like FlyBase and the Zebrafish Information Network (ZFIN).

Expansion of this field is made possible by recent technological leaps. Advanced omics (3) and CRISPR-Cas9 genome editing are no longer restricted to traditional labs; they can now be applied to almost any species, transforming "experimental organisms" into tractable "model organisms". Proteomics, in particular, is emerging as a powerful tool to characterize niche biological mechanisms without requiring fully annotated genomes in advance.

The **Alternative Model Organisms** section will serve as a dedicated home for manuscripts dealing with:

(1) **New Model Development:** Studies establishing the genetic and experimental tools for non-traditional species.
(2) **Comparative Biology:** Research that leverages evolutionary diversity to solve fundamental questions in development, aging, and disease.
(3) **Human Health and Toxicology:** Innovative applications of "New Approach Methodologies" (NAMs) that improve the human relevance of pre-clinical research.

I, as a Section Editor, with my fruitful lab experience with the nematode *C. elegans*, as well as ambiguous experience with respect to the acceptability of alternative models among certain funding agencies' review panels with a "less flexible" mindset, remain excited to witness new developments with alternative models at the global level. We invite the global research community to submit their most innovative work to this new section. By diversifying our models, we don't just expand our toolkit—we expand our understanding of life itself.

Disclosures

Conflict of interest: The author declare no conflict of interest.

Financial support: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

AI Use Declaration: Some of the content in this article was generated in an AI-assisted manner, later modified by the author.

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