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AI-powered organoids and organ chips: Advancing human-specific models for biomedical research

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A recent in-depth report in Science on breakthrough progress in organ-on-chip technology for drug safety testing outlines a new vision for the future of biomedical research.1 The article not only details technological leaps but also reveals a profound paradigm shift: a next-generation system centered on non-animal methodologies (NAMs), integrating organoids, organ chips, and artificial intelligence (AI), pushing the construction of human health models into a new era of greater precision, efficiency, and ethics with unprecedented force (Figure 1).

AN ARTICLE REVEALING INDUSTRIAL TRANSFORMATION

The core content of the article can be summarized as follows: (1) **Validation of Technical Effectiveness**: Emulate Inc.'s liver chip demonstrated 87% accuracy in identifying compounds known to cause drug-induced liver injury (DILI) and 100% accuracy in flagging those that do not, far surpassing traditional animal models, which often fail to predict human responses, contributing to the high failure rate of drug candidates in human clinical trials. (2) **Policy Tailwinds**: Major U.S. agencies—FDA, EPA, and NIH—have sequentially introduced significant policies. FDA launched a pilot program to encourage testing new treatments without animal experiments; the EPA announced a phase-out of mammalian testing; and the NIH announced that future funding opportunities will no longer be developed exclusively for animal - model-only research, in order to promote non-animal methods. (3) **Technological Diversification and Integration**: Next-generation NAMs are not a single technology but also a matrix including organ chips, organoids (miniature 3D organ models derived from stem cells), and AI prediction tools based on big data and molecular structures. Their collective advantage lies in using *human cells* and *human data*, providing physiological models closer to humans than animals.[2] (4) **Opportunities and Challenges**: Despite the broad prospects, widespread adoption of NAMs still faces challenges like scientific validation, regulatory acceptance, cultural shift, and data sharing. Experts emphasize that this is a science-driven process requiring sustained investment and cautious advancement, instead of simply a radical replacement of all animal experiments.

This article suggests that paradigm shift from animal model priority to human model priority is quietly occurring and accelerating within global regulatory agencies and top laboratories.

GLOBAL REGULATORY AGENCIES SHAPE THE NAMS DEVELOPMENT ROADMAP

Policy shifts are the strongest catalyst for this revolution. Below are a few examples by major regulatory agencies in the world: U.S. FDA: In 2022, the U.S. Congress passed the *FDA Modernization Act 2.0*, clearing legal obstacles for using NAMs like organ chips and organoids. U.S. NIH. It emphasizes the importance of NAMs in new funding guidelines. European Union. The European Chemicals Agency (ECHA) and the European Medicines Agency (EMA) are actively evaluating the use of NAMs data in chemical and pharmaceutical regulatory decisions.[1]

THE IRREVERSIBLE PROCESS OF NAMS FROM ALTERNATIVE TO MAINSTREAM

Encouragement for non-animal experiments shows three clear trends: (1) **From Alternative to Superior**: The goal of NAMs is no longer just to replace animals but to provide a *superior* research plan. AI models can process massive data, uncovering complex correlations difficult for the human brain to discern; organ chips can monitor cell responses in real-time, non-invasively, which cannot be achieved by acute animal experiments that often involve animal sacrifice. Their combination is redefining the standard of evidence. (2) **From Single to Integrated**: The future direction is not finding a single universal chip but building a **body-on-a-chip** and integrating it with AI. Connecting liver, kidney, brain chips, etc., via fluidic systems to simulate whole-body interactions, combined with AI algorithms to predict systemic toxicity or efficacy, will provide a more comprehensive simulation of human physiology. (3) **From Back-end to Front-end**: The application of NAMs is moving dramatically from late-stage safety testing in drug development to early-stage target discovery, lead compound screening, and optimization. This allows pharmaceutical companies to identify and eliminate problematic candidate drugs earlier and more accurately before investing huge sums in clinical trials, fundamentally improving R&D efficiency.

THE ULTIMATE MISSION: HOW NAMS EMPOWER THE FUTURE OF HUMAN HEALTH

The ultimate purpose of advocating NAMs must return to empowering the value of human health itself. This transformation will have the following profound impacts: (1) Improve Quality. (2) Reduce Unnecessary Sacrifice. (3) Enhance R&D Efficiency. (4) Lower Payment Costs. (5) Promote Healthy Longevity.

THE UNLIMITED EXTENSION OF NAMS TECHNOLOGY

The combination of organoids, organ chips, and AI has applications far beyond biomedicine. NAMs also can be used for Chemicals & Cosmetics, Food Safety, Electronics Radiation, Smart Manufacturing & Semiconductors.

For instance, the rise of organoid technology has provided unprecedented opportunities for the systematic development of small-molecule marine drugs. The ocean harbors an extremely rich and structurally diverse array of small-molecule compounds, representing a largely untapped treasure trove of bioactive substances. These molecules possess unique chemical frameworks and mechanisms of action, demonstrating significant potential in areas such as antitumor therapy, antiviral activity, and neuroprotection etc. al. However, due to limitations in the predictive power of traditional screening models and interspecies differences, a vast number of candidate molecules have not been effectively evaluated or translated into applications.

Today, with NAMs, large-scale and precise evaluation of all these marine-derived small molecules is achievable.[3] Some studies have upgraded the conventional drug screening platform for marine natural products (MNPs) from the traditional 2D/animal models to 3D human organoid microfluidic chips, enabling parallel evaluation of efficacy and toxicity. For instance, the liver-islet dual-organ chip was used to test the hypoglycemic synergistic effect of macrolides derived from sponges in a co-culture system, while the anti-inflammatory targets and drug development feasibility of sea cucumber saponins was evaluated by the intestinal chip; the penetration ability of tubocurarine derivatives on glioma was assessed by the brain tumor organoid chip etc. The integration of marine natural products and organoid models are transforming the unknown treasures of marine medicine into practical medicinal resources, offering new possibilities for the treatment of human diseases and truly enabling a value leap from blue treasure trove to health treasure.

In essence, any substance that has human-application potential can be

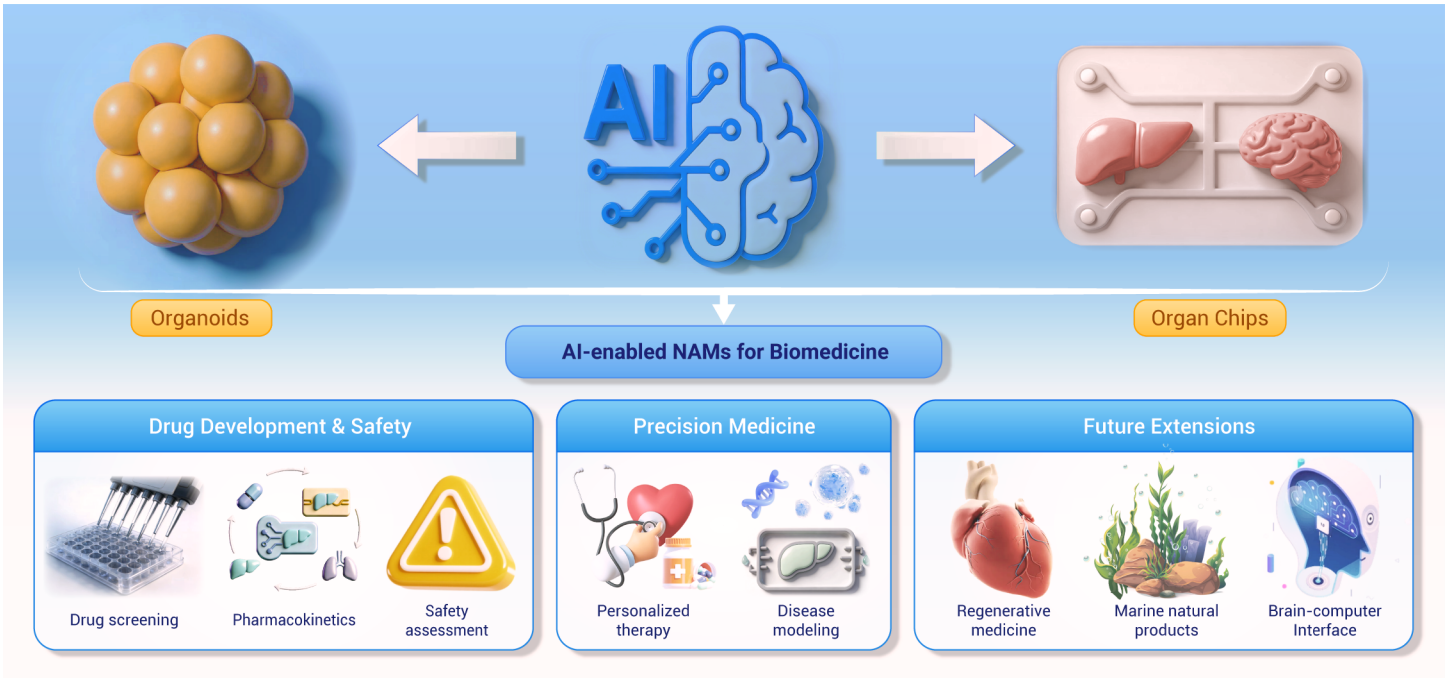

Figure 1. AI-enabled New Alternative Methods (NAMs), such as organoids and organ chips, could leverage computational intelligence to advance drug development, precision medicine, and future biomedical extensions.

prospectively or may enter the environment can be prospectively and efficiently assessed for safety using this human surrogate system.

WHEN BRAIN-ON-A-CHIP LEARN TO CONTROL A GAME

A recent study from Australian and UK teams has demonstrated a remarkable extension of this technology. By integrating human stem cell derived neuronal cultures with high-density electrode arrays, they created a brain-on-a-chip system capable of interacting with a computer game environment. Remarkably, the system exhibited learning-like behavior, improving its performance through feedback, suggesting the emergence of adaptive intelligence in vitro.[4]

WITH MODELS, THERE IS A FUTURE—FROM SURROGATE TO AVATAR

Looking ahead, the combination of organoids and organ chips as human surrogates with AI will unleash infinite potential in two cutting-edge fields. For instance: (1) Brain-Computer Interface (BCI). (2) Humanoid Robots: Future advanced humanoid robots need to process complex, unstructured environmental information in real-time. A possible paradigm is adopting a Wetware + Hardware + Software architecture.[5]

FROM MICRO SURROGATES TO MACRO RECONSTRUCTION: INDUSTRIAL INNOVATION IS HAPPENING NOW

Ultimately, industrial innovation is the fruit of technological advancement, and forward-looking policy is the spring breeze that nurtures it. The integration of organoids, organ chips, and artificial intelligence is one of the strongest technological trends of our time.

Recent technological breakthroughs are addressing key limitations. For instance, novel three-step culture systems have been developed that eliminate the need for expensive animal-derived matrices like Matrigel, and reducing steps by over 90%. The organoids can self-assemble and successfully mimic key features of the *in vivo* microenvironment: including innate immune cells (such as T cells, B cells, NK cells, macrophages, etc.) and functional vasculature. This highly biomimetic organoid model provides a more efficient, reliable, and lower-cost platform for drug screening, disease research, and personalized medicine, representing an important direction in organoid technology development. It stems from a deepening understanding of life sciences, benefits from interdisciplinary empowerment by engineering and informatics, and is ultimately driven by a shared vision centered on human health.[3]

And the future we envision extends far beyond replacing experiments. The ultimate mission of organoid technology is to move from miniature surrogates to macro reconstruction. Today's organoids and organ chips are sentinels for drug safety; tomorrow, they will be the cornerstone of regenerative medicine. By combining advanced biomaterials and AI-driven design optimization, we are gradually achieving: (1) Disease Modeling & Personalized Treatment. (2) Tissue Repair. (3) Organ Replacement.

This is a grand journey from understanding life, to simulating life, and finally to repairing and reconstructing life. We are moving beyond the limitations of the experimental cage, stepping towards a new future where life is reconstructed on a chip, health is insight in data, and well-being is ultimately reshaped through bio-fabrication. In this future, human health models will, for the first time, truly and completely belong to humans themselves, ultimately becoming a powerful cornerstone for safeguarding and continuing human health.

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AUTHOR CONTRIBUTIONS

All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.