



Meeting Report

Enabling a Shift Towards a Human-Relevant and Predictive Paradigm for Biomedical Research and Drug Discovery in India

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In the past decade, there has been a global rise in funding, research, and regulatory initiatives to promote alternatives to animal experimentation and make life science research more relevant to humans. With the rise in cutting-edge technologies, such as omics, high-content imaging, 3D organoids, organ-on-chip, bioinformatics and other computational tools, it is now possible to envision the shift from primarily animal model-based research to human-relevant *in vitro* and *in silico* methods.

While global research in human-relevant technologies has increased exponentially during the last decade, it is still in its infancy in India (Akbarsha et al., 2019; Palahe et al., 2020; Parvatam et al., 2020). In 2012, for the first time, a plenary session on alternative methods entitled “Animal Alternatives in Teaching and Testing” was held at the Indian Science Congress (Akbarsha et al., 2012). In 2019, the Indian Council for Medical Research, the apex body in India for the formulation, coordination and promotion of biomedical research, published a perspective paper stating the need to promote alternatives to animal research in India (Swaminathan et al., 2019). The paper emphasized the need for top-down funding decisions towards human-based methods instead of new animal models and encouraged collaborations to create a knowledgebase of these alternative methods. The paper also recognized the need to create “Centres of Excellence” to conduct research on alternatives to animal experiments in India.

The Centre for Predictive Human Model Systems (CPHMS) was established in 2019 at Atal Incubation Centre-Centre for Cellular and Molecular Biology (AIC-CCMB, Hyderabad, India) in collaboration with Humane Society International (India) to advance and enable human-relevant methodologies in India. The Centre has conducted extensive studies to document the research, funding, and challenges in conducting human-relevant research in India (Parvatam et al., 2020). The Centre has focused on three areas to achieve this: enabling human-relevant technologies; promoting frameworks that assist integration of existing biological information such as the OECD Adverse Outcome Pathways (AOP); and advancing the use of systems and computational tools that could feed on the structured information in these frameworks to build predictive models of human biology (Fig. 1). In parallel with the establishment of CPHMS, the So-

ciety for Alternatives to Animal Experiments in India was also started, as the culmination of the Mahatma Gandhi-Doerenkamp Center (MGDC) for Alternatives to Animal Use in Life Science Education (Akbarsha et al., 2020).

Nearly 25 government labs and start-ups are currently developing or using alternative model systems in India. However, lack of communication between industry and academia and multi-disciplinary cross-talk within various fractions of academia, such as molecular biologists, bio-engineering and computational scientists showed up to be a significant deterrent. Funding is also a major challenge, as organoid/organ-on-chip research receives only around 0.2% of total Department of Biotechnology (DBT), Ministry of Science and Technology (Government of India) funding, and private investment in these areas is almost non-existent (Parvatam et al., 2020).

To address these issues, CPHMS organized a virtual roundtable meeting with 25 participants from academia, industry, government and private funding bodies titled “Enabling a Shift Towards Human-Relevant and Predictive Paradigm for Biomedical Research and Drug Discovery” in December 2020 to stimulate multi-stakeholder discussion around challenges and opportunities in India.

The meeting began with a welcome address by Dr Rakesh Mishra, Director of CSIR-Centre for Cellular and Molecular Biology, Hyderabad, India, who stated that emerging non-animal methodologies are no longer ideas of the future and have to be brought to the forefront and into practice. He stressed the need for efforts to be made to create awareness about these technologies and methodologies among the public and policymakers.

With the rise of omics, high-content imaging, big data and other contemporary technologies, there has been an exponential rise in the amount of data being generated every year, and there is a concomitant need to develop frameworks that can assist in integrating these data into knowledge management frameworks. The concept of AOPs, as promoted by the OECD, is an approach to link molecular information to an adverse health or disease outcome. The Department of Biotechnology (DBT) under the Ministry of Science and Technology in India launched a crowd-sourced citizen science project titled “MANAV” in 2019 that aims to collate the human biological data that exists on pub-

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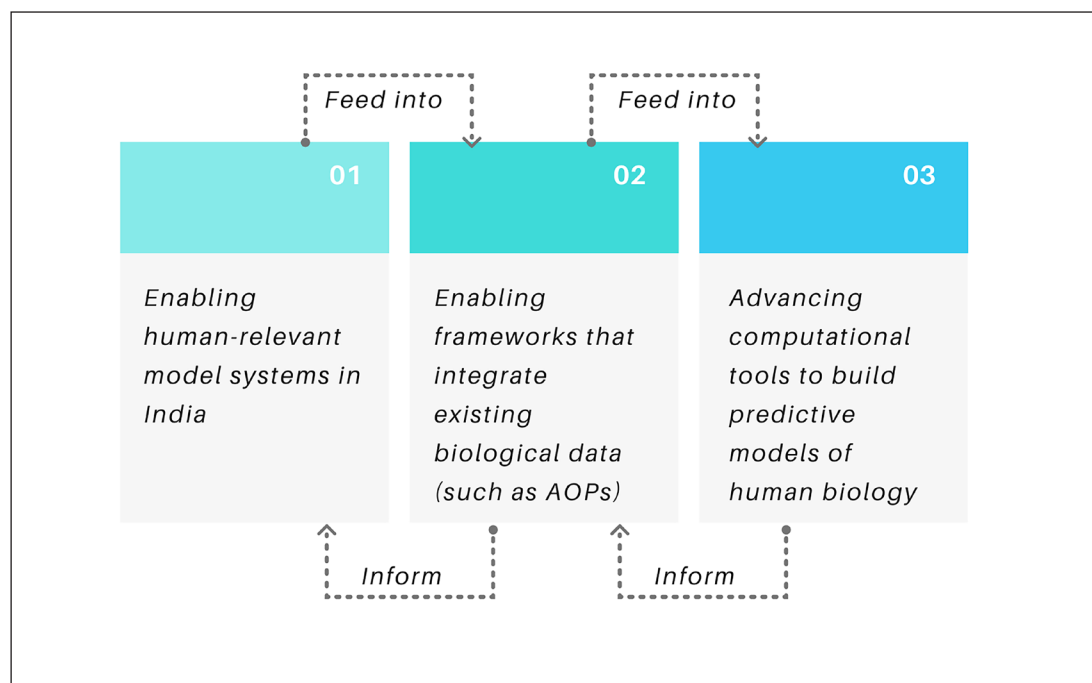


Fig. 1: Focus areas to shift towards a human-relevant and predictive paradigm of biomedical research and drug discovery

lic databases and map how changes at the molecular level affect organs and the human body. The first session thus began with a discussion on mechanisms to effectively promote the use of such powerful frameworks amongst various stakeholders. The lack of context-based searching algorithms, guidelines on how to collect data, and establishment of selection criteria for such frameworks were highlighted. It was suggested that publications that contribute to such frameworks could incentivize participation. The role of industry for maintaining and storing such databases for both long-term investments and as consultants was emphasized. Additionally, end users such as pharma companies and clinicians are critical stakeholders who need to be involved in the development of such frameworks.

The availability of three aspects – raw material (biomaterials for harvesting the cell or tissue components), technology, and user markets – is essential in India to enable human-relevant original research and development. It was suggested that India could create central facilities for manufacturing raw materials, such as chips (for organs-on-chip) to counter the current lack of indigenous tools. As there is a dearth of Indian vendors for molecular-grade reagents, it was suggested that supply chain improvement could assist in cost reduction of microphysiological systems-based experiments. It was further emphasized that computational science and bioinformatics, which are India's strengths, could contribute to improving experimental analysis aspects.

Owing to the interdisciplinary nature of human-relevant technologies, collaborations must be augmented to advance the field in India. It was felt that building a dedicated organization where engineers, material scientists, cell biologists and others could

work together would aid collaboration. Government funding could be provided to create dedicated Centres of Excellence; however, additional industry or philanthropic bodies would be required to provide longstanding support. Initially, regional Centres of Excellence could be established in collaboration with industry, which could be expanded at the national level once the proof-of-concept is established.

Several overseas initiatives that support the development of human-based predictive models include the \$35.5 million “US Federal Tissue Chip for Drug Screening Program” and the €30 million EU-ToxRisk Horizon 2020 program “Mechanism-based Toxicity Testing and Risk Assessment for the 21st Century”. Equivalent initiatives are still lacking in India, and government and/or private funding in this area is severely limited. The panel discussion focused on the concerns of the funding bodies to invest in such new and emerging technologies and how they could be addressed. The panel members stressed the importance of integration of these technologies into a translational program or industry that will apply them. Various business models were discussed that could reduce risk and improve investor confidence. The importance of identifying the end-user and market size was stressed. Lack of awareness of organoids/organ-on-chip technologies and bioinformatics technologies that analyze existing data was identified as a key barrier.

Dr Madhusudhana Rao, CEO, AIC-CCMB, closed the meeting with the observation that while there is sufficient traction for such emerging and human-relevant methodologies in India, current activities remain highly fragmented and small-scale. However, recommendations emerging from discussions, such as this

RECOMMENDATIONS	THEME A: DEVELOPING INTEGRATIVE FRAMEWORKS	<ul style="list-style-type: none"> Develop a set of guidelines and best practices for collecting and selecting data for integrating frameworks Create publications out of integrating data as an incentive Include end users, such as big pharma for consultation and long-term investments for such frameworks
	THEME B, C: ON INFRASTRUCTURAL CAPABILITIES AND INCREASING THE COLLABORATION	<ul style="list-style-type: none"> Improve the supply chain for molecular grade reagents - a huge market opportunity for India Create Regional and National Centres of Excellence for developing "proof-of-concept" and validation for human-relevant technologies Setting core facilities for raw materials, such as primary cell lines (via stable collaborations with hospitals), chips (for organ-on-chip), etc Support webinars/courses/workshops to increase awareness for organoids/organ-on-chip technologies and bioinformatics technologies that analyze existing data.
	FUNDING OF HUMAN-RELEVANT AND PREDICTIVE METHODOLOGIES	<ul style="list-style-type: none"> Develop co-funding models involving joint investments by government, pharma companies, philanthropic bodies, and venture funds Develop "exit strategy" in collaboration with industry to understand how these technologies can be adopted by industry and translational programs Encourage cross-border collaboration to bring in both global expertise and international funding

Fig. 2: Summary of recommendations to develop the human-relevant research in India

meeting, could assist in bringing stakeholders together and lead to actionable outcomes to advance this field.

Several recommendations emerged from this meeting (Fig. 2) in the areas of promoting further use of data integrating frameworks, indigenous development, and investment into human-specific methodologies in India.

These recommendations will guide further discussions in this area; provide insights for academia, industry, regulatory and funding bodies; and assist in shaping a paradigm change in biomedical and drug discovery research in India.

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