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Review Article

Patient Derived Tumoroids and Humanized Mice: 4th International Conference on 3Rs, Hyderabad, 2024

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Abstract

As precision medicine and personalized therapies guide biomedical research, patient-derived tumoroids and humanized mice provide pioneering insights into tumor biology and drug responses. The 4th International Conference on 3Rs Research and Progress, held in Hyderabad in 2024, rooted in the principles of the 3Rs (Replacement, Reduction, and Refinement), explored innovative alternatives in biomedical research focusing on patient-derived tumoroids and humanized mice. The event featured talks across three primary sessions, with focus on invitro models, the evolution of 2D to 3D cell culture systems, patient-derived tumoroids, and the role of humanized mice in preclinical studies. Researchers highlighted the limitations of traditional 2D cell cultures and animal models, advocating for 3D cell culture systems which mimic the human tumor-microenvironment. Humanized mice with functional human immune system were discussed as a promising bridge between traditional animal models and human clinical outcomes. The conference culminated in an engaging "Us Vs Them" debate- style panel, comparing and contrasting the merits of invitro models and humanized mice, stimulating conversation on the future direction of preclinical research. The event showcased the ongoing shift towards more human- relevant models, demonstrating the global commitment to 3Rs principles in modern research, promoting ethical and scientifically robust alternatives to traditional animal experimentation.

Keywords: Tumoroids; Humanized Mice; Organoids; Tumor Microenvironment

Introduction

The landscape of cancer research is undergoing a paradigm shift with the growing integration of the 3Rs principles (Replacement, Reduction, and Refinement), which aim to enhance the translational efficacy of preclinical research to clinical settings. Over recent decades, substantial scientific, ethical, and regulatory progress has been made in minimizing animal testing through refinement and reduction practice [1]. A key part of this progress includes the development of human-derived, human-relevant models that better mimic human physiology and drug response mechanisms [2,3]. For instance, 3D disease models have shown considerable promise in improving the translation of *in vitro* findings to *in vivo* clinical applications.

As outlined by Vangala et al. [3], since the 1980s, there have been notable advancements in the application of the 3Rs principles, particularly in the clinical relevance of alternative models and improvements in ethical compliance. Preclinical models currently being introduced are focused on enhancing translational efficacy from preclinical to clinical settings with integration of 3R principles. Such models include organoid cancer models, cell line cancer modelling, Drosophila Melanogaster cancer modelling and patient derived xenografts [4]. Among these advancements, tumoroids offer valuable *in vitro* insights into the intricacies of tumor behavior by mimicking the tumor microenvironment in a controlled setting, making them particularly conducive to studying disease mechanisms and drug responses. At the same time, humanized mice—genetically engineered to carry functional human genes and immune systems—serve as an *in vivo* platform that more accurately mirrors human physiology, thus mimicking the human context. This allows for more precise predictions of how treatments will perform in human clinical trials [5]. The synergistic application of these technologies offers a holistic view of cancer progression and promises to revolutionize cancer research, advancing our understanding of tumor biology, drug development, and personalized treatments. In addition to optimizing the predictive value of pre-clinical studies, this integrated approach of 3D models and humanized mice accelerates the identification and validation of novel therapeutic strategies.

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start-ups are actively working to contribute to the progress of the Three Rs in research by using spheroid cell cultures to create 'disease in a dish' models — has been organizing a series of annual international conferences on '3Rs Research and Progress'.

This conference, Patient Derived Tumoroids and Humanized Mice: 4th International Conference on 3Rs Research and Progress, Hyderabad, 2024 is a great platform to bring together non-animal scientists/alternatives advocates, along with animal researchers, to exchange ideas and support the larger cause of replacing animal models with more effective, humane and translatable non-animal cell, tissue and computational experimental models. This article summarises the proceedings of the conference, that cover recent developments, applications, advantages of these technologies, and various challenges to address, held on 4th May 2024 at Mahindra University, Hyderabad (India). The conference was an in-person event, where speakers delivered their lectures live and in-person. The whole event was live streamed on a web platform, and a total of 9 speakers participated in the conference, in addition to a panel discussion.

Conference Sessions

The one-day conference included 9 talks which were categorised into the following two topic sessions, in addition to a special "Us Vs Them" debate style panel discussion:

- ***Patient Derived Tumoroids***
- ***Humanized mice; and***
- ***Special "Us Vs Them" debate style panel discussion***

All of the presentations are summarised under their respective topic sessions below.

Introductory Talk

The Future of Cancer Research Using Tumoroids and Humanized Mice

Ms. Nikita Naik, the Organizing Secretary, opened the conference by introducing its focus on revolutionary advancements in cancer research through the use of patient-derived tumoroids and humanized mice. These innovative models represent a significant shift from traditional methods, offering improved translational efficacy and laying the foundation for personalized cancer therapies and drug development. In a human body, when a tumor is treated with a therapy, the results we see is a cumulative effect of the interactions between the treatment, tumor and other components of the tumor microenvironment. By replicating the tumor microenvironment, tumoroids facilitate a deeper understanding of cancer progression, disease mechanism, drug sensitivity, and immune interactions [6]. These models offer a more accurate reflection of tumor biology, assisting in the development of personalized treatment strategies.

Ms. Naik highlighted key advancements in the field, including the coculturing of tumoroids with immune cells. This approach enables researchers to better predict and evaluate individual tumor responses to immunotherapy, significantly improving the potential for personalized treatment. Another major innovation is the use of patient- derived xenografts (PDX) and the creation of organoids from these xenografts, referred to as PDOX-ORG. These organoids offer a powerful method for correlating drug sensitivity between patients and preclinical models, bridging the gap between research and patient-specific therapeutic responses [7,8].

In addition to tumoroids, Ms. Naik discussed the importance of humanized mice models, which are engineered using techniques such as the CD34+ hematopoietic stem cell (HSC) model, peripheral blood mononuclear cell (PBMC) model, and bone marrow-liver-thymus (BLT) model. These models are essential for replicating the dynamics of the human immune system, making them invaluable for evaluating immunotherapies [9]. Humanized mice also provide insights into the limitations of current research methods and highlight areas for improvement in studying human immune responses.

In conclusion, Ms. Naik emphasized that the combined use of tumoroids and humanized mice offers a comprehensive view of cancer progression. Together, these models optimize the predictive value of preclinical studies, accelerating the discovery of new therapeutic strategies and enhancing the development of personalized treatments. This presentation set the stage for the conference sessions to follow, framing the discussion within the context of these transformative cancer research models.

Session 1: Patient Derived Tumoroids

The session focused on the transformative potential of patient-derived tumoroids in cancer research, particularly in drug discovery and personalized medicine. In this session, the speakers discussed why many oncology drugs fail in clinical trials and how 3D human models can enhance success rates by better replicating the tumor microenvironment. Talks also covered AIC-CCMB's engagement with human-centric science in India and the integration of Complex *In Vitro* Models (CIVMs) in drug discovery. The 3D tumoroid model was highlighted as a predictive platform for preclinical drug/nanomedicine screening and personalized treatment strategies.

Why drugs fail during clinical trials. Case examples in oncology and how can 3D human models improve success rates

This presentation by Dr. Subrahmanyam Vangala, CEO of Reagene Biosciences, discussed factors behind drug failures in clinical development, particularly in oncology, and the potential of human 3D models to reduce clinical attrition rates. Traditional preclinical models often lack human relevance, leading to poor predictability in drug safety, toxicity, and efficacy. Human 3D models, like Reagene's "disease in a dish" systems for lung cancer, diabetes, and other conditions, allow simultaneous studies of drug metabolism, efficacy, and toxicity. These models offer promise in addressing species-specific differences in drug responses and refining predictive tools for cancer therapies and nutraceuticals, such as ginger-based compounds, in cancer prevention.

How AIC-CCMB is Engaging with Human-centric Science in India

Dr. Kasturi's talk emphasized the critical need for human-centric science in India and showcased the Center for Predictive Human Model Systems (CPHMS) at AIC-CCMB's efforts in advancing human-relevant technologies for both fundamental and translational research. She highlighted the importance of adopting human-relevant

research models and stressed the need for collaboration among varied stakeholders. CPHMS's initiatives include raising awareness through webinars, newsletters, publications, and white papers; building capacity via training programs, bootcamps, and researcher databases; and facilitating dialogue in stakeholder forums, all to drive forward human-focused scientific advancements in India.

Integrating CIVMs/MPS in Drug Discovery: Applications and Industry Adoption Strategies

Dr. Viraj Mehta's presentation focused on the strategies to enhance the adoption of Microphysiological Systems (MPS) and Complex *In Vitro* Models (CIVMs) in industries. He emphasized the importance of validating MPS models aligned with the top therapeutic areas in the global biopharma market. These areas highlight the need to prioritize the validation of MPS models in oncology, cardiometabolic diseases, and autoimmune disorders. Additionally, he reviewed the recent IQ-MPS survey results [10], underscoring the importance of validating MPS organ models for ADME applications. The IQ-MPS findings offer valuable insights for emerging startups and industries looking to make strategic investments in this evolving space.

He also explored potential use cases where MPS models can be rapidly adopted, such as mechanistic studies to elucidate new targets and pathways, and efficacy assessments of highly human-specific biologics, including immunotherapies. Furthermore, he addressed the current challenges in the field, such as the lack of standardization, regulatory frameworks, data reproducibility, and low throughput, while suggesting strategies to overcome them.

In conclusion, he outlined emerging trends, including the integration of PBPK models to create digital twins of MPS systems and the use of automation, OMICS, and deep learning to facilitate high-throughput screening and enhance the understanding of new drug modalities including ADCs, peptides, oligonucleotides, and PROTACS.

The 3D Tumoroid Model as a Predictive Platform for Pre-clinical Drug/nanomedicine Screening and Personalized Medicine

Dr. Manu Smriti Singh, Associate Professor at the Center for Life Sciences, Mahindra University, discussed the use of 3D tumoroid models as a predictive platform for preclinical drug and nanomedicine screening, as well as for personalized medicine. Emphasizing the advantages of 3D models over traditional 2D models, she illustrated how they better mimic the tumor microenvironment, enhancing predictability [11]. Using an example of hyaluronic acid (HA)-coated lipid nanoparticles (LNPs), Dr. Singh demonstrated CD44-specific binding in Ovcar8 cells, achieving 1500 times the activity in 3D cell culture compared to 2D, underscoring the model's potential in discovering new targets as well as validating targeted cancer therapies [12]. Success of drugs/ nanomedicine screening in 3D tumoroid models will reflect in mice tumor models and consequently in clinical trials.

Session 2: Humanized Mice

This session focused on the critical role of humanized mice in preclinical research, particularly their application in immuno-oncology and therapeutic development. Speakers discussed how these advanced models, which carry functional human genes or immune systems, are transforming drug discovery by enabling more accurate predictions of human clinical outcomes. Talks covered insights into JAX models for various therapeutic areas, Janvier-Labs' contributions to preclinical research, the refinement of immuno-oncology mouse models, and practical strategies for selecting xenografts and models for preclinical cancer studies.

An insight into JAX models and services in advanced Therapeutic areas

Dr. Krishna Bhagavatula, Director of Business Development for The Jackson Laboratory in India, Southeast Asia, and the Pacific, provided insights into JAX's models and services for advanced therapeutic areas, particularly focusing on humanized mice. Dr. Bhagavatula discussed the role of preclinical studies in establishing safe starting doses and assessing potential toxicity before human trials, emphasizing the importance of validating therapeutic hypotheses. Key factors for success include selecting appropriate models, adopting effective strategies, and custom model generation. Additionally, Dr. Bhagavatula highlighted immuno-oncology-focused cancer models, which play a vital role in advancing cancer research and therapeutic development.

"Janvier-Labs: A New Partner for your Pre-clinical Research Studies"

Dr. Lily Aurelie Jory, Head of International Operations at Janvier Labs, outlined Janvier Labs' contributions to preclinical research by providing high-quality, professionally bred laboratory animals. Emphasizing their global support in delivering reliable animal models, Janvier Labs offers a wide array of services, including the development of custom genetically modified and immunodeficient models such as the NXG/Rj mice, which are used in immunology, oncology, and other fields. Their expertise extends to humanized models, notably FRG® liver-humanized mice, which possess human liver cells and are valuable in studies related to gene editing, liver disease, and regenerative medicine. Janvier Labs ensures strict genetic and quality control to support clients worldwide, providing models that meet rigorous research needs across various biological and therapeutic domains.

The Evolution and Refinement of Immuno-oncology Mouse Models

Dr. Mandar Kulkarni, a seasoned leader in life science strategy and business development, shared insights on the evolution and refinement of immuno-oncology mouse models, focusing on various Hu-strains and their unique characteristics. He highlighted the NBSGW mouse model, an immunodeficient strain engineered to support human hematopoietic stem cell (HSC) engraftment without requiring irradiation or conditioning treatments. Dr. Kulkarni detailed a protocol for the independently validated use of NBSGW mice in drug discovery, emphasizing their application in advancing preclinical immuno-oncology research.

'How-to Guide for Selecting Xenografts & Models for Preclinical Cancer Research'

Dr. Charu Gupta, a Technical Information Scientist specializing in mouse disease modelling, haematology, and oncology, presented

a practical guide on selecting xenografts and models for preclinical cancer research. She outlined strategies for constructing optimal preclinical models, addressing the choice between xenografts, mouse models, and immune cell humanization based on specific research needs. Dr. Gupta detailed distinctions between cell line-derived xenografts (CDX) and patient-derived xenografts (PDX), offering tailored insights for researchers and companies aiming to evaluate therapeutic mechanisms or efficacy in clinically translatable invivo models.

Special "Us Vs Them" Debate Style Panel Discussion

In this engaging "Us vs. Them" debate-style panel discussion, experts from diverse scientific fields weigh in on the strengths and limitations of animal models compared to emerging alternative models in biomedical research. Our distinguished panellists bring perspectives from oncology, biotechnology, R&D, and ethical frameworks, enriching the discourse with insights from their respective fields.

Panelists:

- Dr. Suresh Poosala, Oncoseek Bio Pvt Ltd
- Dr. Reddanna Pallu, FABA
- Dr. Jugnu Jain, Sapien Biosciences
- Dr. Ajith Kamath, Pandorum Technology
- Dr. Subrahmanyam Vangala, Reagene
- Dr. Ranjan Chakrabarti, R&D Expert
- Dr. M. A. Akbarsha, Society for Alternatives to Animal Experiments

The "Alternatives to Animal Models" panel was a unique, US vs. Them debate-style discussion moderated by Dr. Uday Saxena. He opened by asking Dr. Jugnu, advocating for alternatives, if she believed in their potential. She replied, "If used intelligently and interpreted realistically," referencing her work on cystic fibrosis using patient-derived models in the absence of animal options.

Dr. Rajan, supporting animal models, noted their use depends on the study area (e.g., small molecules, biosimilars) and the disease, requiring a case-by-case decision. Dr. Uday highlighted the success of animal studies in producing blockbuster drugs like statins, which have greatly improved human health, questioning the need to fix a proven system.

Dr. Ajith countered that drug discovery has evolved towards patient-relevant models to improve translational efficacy and reduce timelines. Dr. Jugnu added that while alternative models excel in efficacy studies, they still require progress to reliably predict human toxicity.

Dr. Uday next asked Dr. Suresh about the use of humanized mice. Dr. Suresh noted that while humanized mice are on the path to acceptance, progress has been slower than ideal. He predicted that in oncology, they could achieve FDA approval within five years, supported by the increasing volume of data generated by major labs worldwide.

Building on Dr. Suresh's comments, Dr. Akbarsha added that humanized mice have limitations and are far from being suitable models for all diseases, citing diabetes as an example. He highlighted the rising importance of New Approach Methodologies (NAMs) and expressed hope that animal experimentation might be replaced entirely by NAMs in the next few decades.

Prof. Reddanna emphasized the irreplaceable complexity of whole living systems, arguing that isolated models like cell lines, organoids, or in silico approaches cannot replicate the systemic interactions of an entire organism. Even advanced 3D models, which may mimic specific organ environments, fall short of capturing the broader physiological context.

Dr. Uday then sought Dr. Subrahmanyam's insights on whether alternative models can replicate pharmacokinetics and pharmacodynamics (PKPD). Dr. Subrahmanyam explained that while animal models remain standard for carcinogenic studies, developing mechanistic human models to replicate PKPD is a long-term endeavor.

The discussion concluded with the consensus that the future of research will involve a nuanced approach, integrating both animal and alternative models based on the specific requirements of each study.

Summary

This fourth international conference comprised two sessions, including eight talks and one introductory talk, and a spirited "Us vs. Them" debate-style panel discussion. The sessions covered various aspects of patient derived tumoroids and humanized mice. The aim of this conference, was along the same line as of the previous three conferences in the series, was to bring together global researchers with a variety of expertise and interests, and to provide a platform to share and discuss their findings to promote practices aligned with the Three Rs principles. This conference, however was focused on a sub-field of in-vitro and in-vivo disease modelling according to the 3Rs principles.

The one-day conference focused on groundbreaking advancements in cancer research through the use of patient- derived tumoroids and humanized mice models. The event commenced with an introductory talk by Ms. Nikita Naik, the organizing secretary, "The Future of Cancer Research Using Tumoroids and Humanized Mice," which highlighted the revolutionary potential of these models in facilitating personalized therapies and optimizing drug development. Ms. Naik emphasized the enhanced predictive value that these models offer by simulating the human tumor microenvironment, thereby improving the accuracy of drug efficacy assessments and immune response predictions. She outlined key innovations, such as the coculturing of tumoroids with immune cells and the development of PDOX-ORG, an advanced model using patient-derived xenografts, which bridge the gap between research and patient-specific therapeutic responses. Ms. Naik also discussed humanized mice models, including CD34+ HSC and PBMC models, which replicate the human immune system dynamics, providing valuable insights into immunotherapy responses and limitations of traditional research methods.

Session 1 focused on patient-derived tumoroids and the impact of 3D models in improving the predictability of preclinical cancer research. Presentations delved into how these models reduce

drug failure rates in clinical trials by better replicating human-specific reactions, thereby enhancing success in drug discovery. Subrahmanyam Vangala, CEO of Reagene Biosciences, discussed the shortcomings of traditional models and the promise of human 3D models in reducing clinical attrition. Dr. Kasturi highlighted AIC-CCMB's initiatives in promoting human-centric science in India, while Dr. Viraj Mehta and Dr. Manu Smriti Singh showcased innovative applications of CIVMs, MPS, and 3D tumoroid models in cancer research. These discussions underscored the potential of these models to enhance predictive accuracy, from preclinical screening to personalized medicine.

Session 2 centered on humanized mice and their growing importance in immuno-oncology and therapeutic development. Talks covered the utilization of JAX models, Janvier-Labs' high-quality animal models, and the evolution of immuno-oncology mouse models like the NBSGW strain, which supports human HSC engraftment. Presenters like Dr. Krishna Bhagavatula and Dr. Mandar Kulkarni discussed how these models, customized for cancer and immunological studies, are transforming preclinical research by mirroring human-specific responses. Dr. Charu Gupta further provided practical strategies for selecting appropriate xenografts, reinforcing the value of humanized mice in evaluating therapeutic efficacy.

The conference concluded with a spirited "Us vs. Them" debate-style panel discussion, where experts from oncology, biotechnology, R&D, and ethical organizations compared the benefits and drawbacks of traditional animal models versus alternative human-centric models. The panellists along with the moderator, offered varied insights, enriching the discourse on the future of biomedical research. The event underscored the significant strides being made in cancer research and the promise of these advanced models to revolutionize personalized cancer therapies and preclinical studies.

Conclusion

In conclusion, the shift towards human-relevant models in cancer research is gaining momentum, addressing scientific, ethical, and regulatory challenges worldwide. This conference has highlighted the availability of diverse and increasingly sophisticated human-derived models, ranging from patient-derived tumoroids and 3D cultures to humanized mice and organs-on-chips, each selected based on the specific research objectives. These models reflect the principles of the Three Rs—Replacement, Reduction, and Refinement—by reducing reliance on traditional animal models and enhancing research precision. With these advances, it is imperative to strengthen collaboration within the research community to achieve the following goals:

— reduction in the use of animal models in preclinical studies;

— refinement of remaining animal-based studies to align with ethical standards and scientific rigor; and

— an eventual transition toward a fully animal-free research environment, including the use of non-animal-based reagents.

Such concerted efforts can accelerate innovation in personalized medicine while upholding ethical commitments across scientific disciplines.

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Author Contributions

Nikita Narayan Naik and Suresh Poosala drafted the manuscript. All authors contributed to the content of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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