EJMR
ERA'S JOURNAL OF MEDICAL RESEARCH
p-ISSN: 2348-9839, e-ISSN: 2394-5222 | www.ejmr.org

Volume 12 Issue 3
REVIEW ARTICLE

Microscale Marvels: Developing Single Cell Genomics and Organ Modelling on Microfluidic Systems

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Received on: 10-10-2025 Published on: 31-12-2025

ABSTRACT

Microfluidic technologies have become a paradigm shift in the field of biological and biomedical research, enabling the specific control of fluids at the nano and picoliter levels. This review identifies the key role microfluidics serves in two fast-growing fields Single-Cell Genomics (SCG) and Organ-on-a-Chip (OOC) modelling. To achieve high-throughput isolation and barcoding of single cells, SCG uses microfluidic systems, including droplet microfluidics, to overcome cellular heterogeneity, hidden by bulk assays. At the same time, OOC systems use microfluidics to reproduce physical and biochemical microenvironments that are fundamental to human organs and which offer improved models of drug discovery and tailored medicine compared to traditional two-dimensional culture. We speak of fundamental technological developments such as the essential bonding of SCG analysis directly on OOC systems to become high-resolution readouts. More specifically, we share a new research horizon in India, complemented by efforts that seek to establish microfluidics-based, cost-effective and region-differentiated solutions to local health issues. Nevertheless, even with the difficulties in standardisation and resource allocation, the merging of microfluidics, SCG and OOC will enable faster scientific discovery and clinical translation on an international scale.

KEYWORDS: *Artificial Intelligence, Microwell arrays, Organ-on-a-Chip, Single-Cell Genomics, Technologies*

Era's Journal of Medical Research. 12(3);2025 [doi: 10.24041/ejmr.2025.40]

INTRODUCTION

Engineering innovations have continued to spur the fast development of biological research. Microfluidics or "lab-on-a-chip technology has been among the most radical technologies to coordinate fluid manipulation at sub-millimetre scales.[1] This highly controlled fluid dynamics chemical milieu and mechanical force in micro channels (tens to hundreds of micrometres) is now the basis of two new revolutionary studies: single-cell genomics (SCG) and Organ-on-a-Chip (OOC).[2,3] Traditional bulk assays are an average of cellular responses thus concealing the underlying heterogeneity required to clarify disease progression, drug resistance and developmental biology[4]. Microfluidics can address this weakness because it allows the high throughput isolation, manipulation and study of individual cells and reduces the amount of reagents used and improves the sensitivity of assays at the same time.[5] Similarly OOC systems, tiny (micro)-engineered devices that recapitulate the morphology and biology of the architecture and function of human organs, provide a more physiologically relevant approach as opposed to the two-dimensional (2D) standard culture and expensive animal models.[6] This review not only explains the technological convergence between microfluidics and SCG and OOC but also outlines the fundamental microfluidic modalities that have enhanced these fields, and their applications that are transformative globally and provides a narrowed insight into emerging biases on the research front and the challenges in India scientific arena.

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How to cite: Morad RH, Srivastav P, Anwar S. Microscale Marvels: Developing Single Cell Genomics and Organ Modelling on Microfluidic Systems. Era J Med Res. 2025;12(3):117-121.

High-throughput Single-Cell Genomics Microfluidics

Single-cell genomics is essential to unravel the diversity of the cell world, reveal the existence of populations of rare cells and rebuild the cell lineage pathways.[7] Microfluidic platforms have played a key role in scaling SCG out of manual protocols based on labour-intensive limits to high-throughput, automated processes to profile tens of thousands of cells simultaneously in a single experiment.[8]

Core Single-Cell Isolation Techniques

Microfluidic systems have mainly three approaches of isolating a single cell before omics analysis:

Droplet Microfluidics: This is the most common and the most throughput procedure and could perform the analysis of thousands of cells. It is the production of picoliter-quantity monodisperse water-in-oil droplets in the junctions within the chip, therefore serving as isolated reaction vessels.[9] Every droplet is designed to hold a single cell together with a micro bead that contains distinct oligonucleotide barcodes as well as unique Molecular Identifiers (UMIs). After lysis of cells in the droplet, cellular constituents including the mRNA transcripts hybridise to beads with barcodes.[10] Efforts by commercial systems such as 10x Genomics Chromium are based on this concept and allowed a number of processes to be done in parallel, namely, digital transcriptional profiling, which was evidenced by Zheng et al.[11] The frequency of droplet generation can be as high as thousands per second, hence making it easy to do ultra-high throughput analysis.[12]

Microwell Arrays and Traps: In these types of passive traps, microfabricated arrays of micro-sized wells or hydrodynamic traps are created on a substrate. Cells are packed on the chip and then diffusion into the fixed positions is caused by centrifugation or flow.[13] Though typically of lower throughput than droplet systems they also allow non-destructive real-time imaging and long-term observing cells before or during lysis and analysis that is essential in examining dynamically evolving processes like cell secretion.[14]

Valve-based Microfluidics: Systems like the Fluidigm C1 system make use of an open system of micro-valves in pneumatics to create a target number of cell capture chambers. After capturing an individual cell the valves are triggered to effect successive delivery of the reagents to lysis, reverse transcription, and DNA/cDNA amplification in highly controlled environment as is done by Luo *et al*.[15]

Multi-Omics and Automation: The subject matter is moving fast on the direction of single-cell multi-omics where microfluidics permits the co-analysis of DNA and RNA (or RNA and protein) of a single cell.[16] As an example, in some of them sequential steps of lysis on a chip can be used to collect surface proteins and then extract nucleic acid to guarantee complete data using a single input. Moreover, microfluidics-based miniaturisation also offers significant cost savings in reagents, which is a significant limitation to scalability of workflow based on next-generation sequencing (NGS).[5]

Indian Perspective in SCG: Single-cell genomics is a growing field of study in India, but the fact that established expensive commercial systems are still a constraint.[17]

This has stimulated native research into coming up with cost-effective and local sensitive microfluidic solutions. Design Teams in leading centres like the IISc Bangalore and other IITs (e.g. Bombay, Madras) are also focusing on the design and production of custom microfluidic chips often using low-cost technologies such as 3D printing and soft lithography to build systems in the high-throughput harvesting of rare cells, including circulating tumour cells (CTCs) as mentioned by Sharma *et al*.[18].

This is a strong focus on the use of SCG on endemic health problems. As an example, microfluidic platforms have been investigated in the context of single-cell profiling of pathogens or host immune cells in (e.g.) tuberculosis or dengue diseases, where early and accurate measurement of cellular state can be used to shape treatment strategy. These programs are in-line with the national goal of creating diagnostics and research tools that can be used in low-resource-setting.[19]

Microfluidic Up-on-a-Chip Organs of Disease

Organ-on-a-chip (OOC) technology uses microfluidics to create an in-vivo-like microenvironment around human cells, thus providing an alternative that is scalable and which is also ethically acceptable, as a way of screening drugs and delivering personalized medicine.[20] Microfluidic control is the main strength of the OOCs because it allows the recapitulation of physiological parameters that cannot be recapitulated in two-dimensional cultures in a stagnant condition.[21]

Clinical Engineering of the Physiological Microenvironment: Microfluidics provides a critical control over physical and chemical stimuli needed to make the functional tissue modelling:

Perfusion and Shear Stress: The laminar continuous flow of fluid in the micro-channels is necessary to supply nutrients, dispose of metabolic waste and induce physiological shear stress to the epithelial and endothelial cells as the example of an operational Kidney-on-a-Chip by Homan *et al*. shows.[22] This kind of shear stress cannot be substituted in keeping proper phenotype and functionality in place.[23]

Tissue Interfaces OOC systems are usually characterized by two parallel micro-channels divided with a porous membrane which allows the co-culture of different cell types (e.g., endothelial, epithelial cells) to recapitulate crucial interfaces.[24] The first vacua Lung-on-a-Chip of Huh *et al*. proved that the addition of vacuum x-ing channels to make mechanical stretching would be able to reproduce the breathing motion.[25]

Biochemical Gradients: Stable spatiotemporal chemical gradients are created by utilizing the microfluidic principles of mixing and diffusion. This has been essential in the expression of intricate biological conditions including the microenvironment of tumours (e.g. oxygen or drug gradients) or the gradient across the bowel wall in a Gut-on-a-Chip.[26]

Major Processes in Drug Discovery and Modelling

OOCs the development of OOC platforms is also moving quite swiftly towards becoming an industrial tool:

Drug Metabolism and Toxicity: A Liver-on-a-Chip (MPS) is the most developed OOC used in studying drug metabolism as well as predicting drug-induced liver injuries (DILI), making it a better prediction model than classical models.[27]

Multi-Organ Systems: Multi-organ Body-on-a-Chip systems where distinct OOCs (e.g., liver, heart, brain) are fluidly integrated, enable study of systemic drug toxicity and PK/PD between multiple organs, therefore mimicking the inter-organ communication with each other as has been shown by Esch *et al*.[6]

Organ Modelling the Indian Context

This is driven by the Indian requirement of the testing of drugs on animals, which is reduced, and fast-tracking them to meet locally relevant health concerns: Indian research in OOC.

Emphasize on Affordable Systems: Indian research institutions and start-up ventures deal with the issue of expensive OOC instrumentation by focusing on cheap materials and simplified fabrics, hence customizing devices to individual requirements. An example can be given of functional Heart-on-a-Chip models of groups building models based on patient-specific stem cells to assess cardiotoxicity profiles relevant to the Indian population.[28]

Disease Specific Models: The strong motivation would be to create OOC models of infectious and chronic diseases that are common in India, like Tuberculosis-on-a-Chip on granuloma formation and antibiotic-efficacy and different cancer models on combination therapy.[29] Local research of this nature is crucial towards changing the international OOC technology into successful health solutions within the region.

DISCUSSION

The above sections have highlighted the unique and interconnected nature between microfluidics in single-cell genomics (SCG) and Organ-on-a-Chip (OOC) technology. The inherent benefit of microfluidics in the two fields is that it can overcome ensemble averaging in bulk tests thus allowing the high-resolution, personalised and environmentally relevant biological measurements to be realised.[30]

Integration and Synergies in Technology: The most significant invention is the perfect amalgamation between SCG and OOC. The OOC will provide the physiologically realistic environment, including mechanical cues, shear stress and 3D architecture, whereas the SCG will provide the final readout by solving heterogeneous cellular reactions to drug treatment or disease-like treatment.[31] As an illustration, droplet microfluidic scRNA-seq can be performed immediately after a drug screening experiment on a Brain-on-a-Chip, revealing what types (specifically the neural or glial subtypes) of the brain are most perturbed by the agent, which would otherwise be unlearnable using bulk endpoint assays or animal models.[32] This combination forms the basis of the next-generation personalised medicine since it allows the profiling of patient-made iPSC-OOCs as referred to by Ingber.[33]

Standardisation and Hurdles of Regulation: Although the scientific potential is quite clear there is a great challenge in adopting microfluidic technologies to move beyond academic prototypes to regulated industrial tools. The most important thing is standardisation: differences between chip material (e.g., PDMS and glass), channel design or flow-control devices and sourcing of cells will lead to non-reproducibility between laboratories, a challenge underscored by Bhatia and Ingber.[34] The regulatory agencies still specify criteria of including OOC data in the package of drug submissions with a strong emphasis in the establishment of powerful, standardised protocols that affirm the OOC model as a predictable in-vivo response[2]. The microfluidic community has been busy trying to push towards quality metrics and reporting standards globally through programs like the Microphysiological Systems (MPS) Initiative.[35]

The Indian Dilemma of Dualism: The Indian scientific culture has a unique two-sidedness. On the one hand, the disease burden (e.g., the high death rates of certain types of cancers and infectious illnesses) is very substantial and the necessity to find an efficient treatment covers the urgent motivator to implement the new advanced tools like SCG and OOC. Conversely, large scale applications are limited by resources such as expensive imported microfluidics equipment and reliance on expensive reagents.[17]

Respondent Indian researchers are shifting towards what they call frugal innovation: using simple and quick fabrication techniques like paper-based microfluidics or easily available 3D printingWaheed *et al*. or designing OOC models directly to high-priority local diseases.[36] It is important to have a long-standing partnership between academic engineering faculties (IITs, IISc) with clinical research groups to make sure that these microscale innovations could be translated into the macro-level effect on Indian population health.

KEY CHALLENGES IN IMPLEMENTATION

Although microfluidic technologies have obvious scientific potential, their use as a transition between the academic prototypes and regulated industrial and clinical applications is ceremonially challenged, especially on the standardization and scale front:

Standardization and Reproducibility: The reproducibility between different labs is challenged by the absence of standardized chip materials (e.g., PDMS vs. glass), the design of channels and flow control structures, as well as, sourcing of cells, which is important and demonstrated by Bhatia and Ingber.[34] The differences in these parameters cause

inconsistency of data, which hinders acceptance of the regulations and commercial scale-up.[37]

Scale-up and Automation: Most assays in microfluidics environments are low throughput and labour-intensive in comparison to the traditional industry screening forms (e.g., 96 well plates). The transition to full automation and high throughput systems that can be applied in drug screening in industries cannot be done easily as a lot of engineering work and well-designed instrumentation is needed, as explained by Zhang *et al*.[35]

Regulatory Acceptance: There is still no stable regulatory definition of what to include in the package of drug submission as regards OOC data to be accepted (i.e., FDA, EMA). This poses an obstacle in which the proof-of-concept models have to be converted to validate systems, which regulate confident predictive in relation to the pharmacology and toxicology of humans *in vivo*.[2]

Resource and Cost Barriers (Indian Context): The barrier to the implementation is the high levels of capital expenditure needed to bring in imported equipment (sequencers, flow controllers) and the reliance on costly reagents in India and other low-resource settings. This increases disconnect between the state of art based research and practice.[17]

FUTURE PERSPECTIVES AND EMERGING TRENDS

The future of microfluidics is characterized by the attempts to address these obstacles via convergence of technologies, complexity and availability:

Standardization and Regulatory Acceptance: Future directions include worldwide endeavours, like the Micro physiological Systems (MPS) Initiative, to create common quality measures, standards of reporting and standardized protocols of the OOC validation to speed up regulatory acceptance.[2]

Multi-Omics and Spatial Transcriptomics: Moving beyond straightforward RNA sequencing, future microfluidic chips will allow analyzing both the gene expression, protein level and epigenetics of the same single cell (single-cell multi-omics).[16] Moreover, the application of spatial transcriptomics, performed by Rodriques *et al*., will enable the researchers to electronically map the gene expression of cells directly within the 3D format of the OOC model to give contextual information, which was not possible earlier.[12]

AI-Design and Analysis: The use of Machine Learning (ML) and Artificial Intelligence (AI) to implement is now seen as a requirement in the optimization of complex microfluidic design factors and automation of image and sequencing data analysis of large, complex datasets generated by integrated SCG-OOC platforms.[36] The optimal rates of flow and materials will be predicted better with the help of AI.

Body-on-a-Chip Complexity: It is the vision of OOC to develop fully interconnected, multi-organ systems (Body-on-a-Chip) capable of simulating all systemic processes including immune response, drug absorption, distribution, metabolism and excretion (ADME), on a decentralized scale across multiple organs at the same time.[6]

Indian Context: Future studies in the Indian setting will pay significant attention to the domain of open-source hardware and the creation of affordable fabrication techniques such as the 3D printing of microfluidic devices with locally available materials, so that the new innovations could become affordable and easy-to-use instruments in the health diagnostics of the population and the development of local drugs.[19,38]

CONCLUSION

Microfluidic systems, that allow unparalleled precision and high biological relevance, are the pillars of the tradition of modern single-cell genomics and organ models. Single cell analysis has been democratized by the creation of high-throughput droplet microfluidics and engineered OOC systems have given the physiological context that single cell models used to be abused, to be driven beyond their limits. The trend today to combine the two technologies is a great step ahead and researchers are now able to observe cell behaviour at a single cell resolution in complex and dynamic micro-organs. These microscale marvels are changing the drug discovery, toxicology and individualized medicine across the globe. In India, research population is also actively employing this technology to strategize disease burdens as well as resource limitations in the local communities by coming up with innovative and cost-effective solutions. It is only a matter of time before microfluidics, single-cell analysis and complex OOC systems are fully integrated and commercialized in the coming decade, which will bring us one step closer to a future of disease models occurring not just in reality but being personal.

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