# The Applications of Microphysiological Systems in Biomedicine: Impact on Urologic and Orthopaedic Research

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Microphysiological systems (MPSs) are in vitro models that can incorporate dynamic stimuli such as flow, pressure and contraction in cell culture, enabling the formation of cellular architectures and retrieving physiological function often absent in conventional 2D-cell culture. MPS applications saw a substantial growth in recent years, drawing attention from industry as a strategy to optimize pre-clinical drug-development purposes, as well as from biomedical research, to fill a gap between in vivo and in vitro models. Several MPS platforms are now available and are employed in the development of bone and kidney complex systems for urologic and orthopaedic research. These advances have enabled, for example, the in vitro modelling of bone regeneration and renal drug secretion, and have dramatic potential to improve research into both orthopaedic and urology cancers.

Keywords: microphysiological systems ; advanced cell culture ; kidney-on-a-chip ; bone-on-a-chip

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The pursuit of improved and ever more physiologically representative in vitro models began with the development and implementation of mammalian cell culture in the second half of the 20th century. Cell lines enabled major breakthroughs in biomedical research, introducing standardized study models that can be transferred and scaled-up with ease. The development of appropriate culture solutions that could feed and maintain cells ex vivo were crucial in the early days of cell culture [1][2]. Cancer cells, given their resilience and high turnover, were key to the successful generation of the first cell lines, which are still extensively used today, with HeLa cells as the prototypical example [3]. Nowadays, virtually every cell type from any organ system can be available for in vitro testing. Advances in culture media formulations enable the growth and expansion of viable and high-quality primary cell cultures [4]. Genetically manipulated cells can be made to overexpress or suppress genes of interest, which are invaluable tools to investigate the function of individual proteins and their overall physiological impact. Stem cells and reprogramed somatic cells, widely referred to as induced pluripotent stem cells (iPSCs), can be used to generate different adult cell lines from a single donor, maintaining the genetic background [5]. However, immortalized cell lines, characterized by their distinct stability, are still extensively used for highly reproducible models representative of healthy tissues or disease conditions.

Despite their widespread use, with thousands of cell lines catalogued, and invaluable contributions to molecular biology, biomedicine and life sciences in general, cell lines have significant limitations. The artificial culture conditions that isolated cells are subject to is dramatically different from their native environment [6]. Ex vivo, cells adapt their physiology to the culture conditions. Extensive characterization studies have shown the transformations that cells undergo in vitro. Among the many phenotypic changes, noteworthy are the rewriting of regulatory pathways, loss of polarization, reduced protein expression and altered metabolic activity [7][8][9]. In traditional in vitro culture systems, such as flasks and microplates, cells grow in an adherent surface and are covered by culture media. In this format, cells have one surface attached to a rigid substrate and the other exposed to the aqueous environment of the growth media. Cells are usually maintained at 37 °C in a humidified chamber at atmospheric pressure. Arguably, these conditions are dramatically different from the physiological milieu where cells thrive and fulfil their functions. Nonetheless, these set-ups can successfully sustain cells and are very powerful and cost-effective research tools [10].

Three-dimensional (3D) cell culture formats can introduce additional levels of cellular complexity. Hydrogels consist of biological (e.g., collagens) or synthetic (e.g., polyethylene glycol) polymers that form a matrix where cells can be embedded and experience a bespoke microenvironment [11]. Cell culture media easily diffuses through the gels, reaching the embedded cells and providing an aqueous environment. Gel properties, such as stiffness, pore size and adhesion can be designed to meet the needs of specific cells in order to optimize growth, viability and differentiation, therefore improving the phenotype by mimicking an extracellular matrix (ECM) [12]. Three-dimensional cultures enable better cell polarization, and cells can also shape the gel microenvironment by secreting their own matrix proteins. Not all cell lines

are suitable for 3D culture, and usually cells that retain the ability to form structures such as epitheliums are best suited for hydrogel cultures. Certain cells can also spontaneously generate 3D structure, such as spheroids, in conventional culture, without the need for an ECM [13]. Conventional and 3D cell cultures are static, another stark difference relative to native physiology where cells experience a multitude of stimuli, to which they react. Allegedly, these static cell culture technologies have reached the limit of the physiology they can extract from cells. The next generation of in vitro culture systems is set to introduce further cellular complexity by incorporating external dynamic stimulus [14].

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