RESEARCH PAPER

Mechanopharmacology in Drug Discovery: Translational Advances, Experimental Platforms, and Future Directions

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Abstract
Mechanopharmacology is an emerging interdisciplinary field at the intersection of mechanobiology, pharmacology, bioengineering, and translational medicine. It aims to improve the physiological relevance of drug discovery by recognizing that pharmacological responses are shaped not only by molecular signaling pathways but also by biomechanical cues such as extracellular matrix stiffness, fluid shear stress, cyclical stretch, tissue deformation, cytoskeletal tension, and microenvironmental architecture. Conventional in vitro systems, especially static two-dimensional cultures on rigid plastic substrates, fail to reproduce these biomechanical conditions and therefore often provide limited predictive value for efficacy, toxicity, and clinical translation.
The conceptual foundations of mechanopharmacology were clearly established in the landmark 2016 review by Krishnan and colleagues, which proposed that drug screening should employ biomechanically appropriate systems reflecting disease physiology. More recent work has expanded this framework by introducing advanced in vitro technologies such as organ-on-chip platforms, microfluidics, tunable biomaterials, spheroids, organoids, hydrogels, and microphysiological systems, together with increasing emphasis on pharmacokinetic-pharmacodynamic integration and precision medicine. In parallel, organ-on-chip engineering literature has further strengthened the translational argument by demonstrating that dynamic mechanical simulation, including breathing-like strain, pulsatile flow, and tissue deformation, can markedly improve physiological realism during pharmacological testing.
This review synthesizes the biological basis of mechanopharmacology, traces its scientific evolution through landmark literature, examines the principal mechanical determinants of drug response, summarizes current experimental platforms, and discusses translational relevance across cancer, fibrosis, respiratory disease, cardiovascular medicine, and selected neurological applications. It also identifies major barriers to broader adoption, including lack of standardization, limited scalability for high-throughput screening, incomplete integration of artificial intelligence, inadequate PK/PD-mechanics modeling, and insufficient understanding of patient-specific biomechanical variability. Mechanopharmacology has substantial potential to improve predictive pharmacology and reduce late-stage drug attrition, but its future impact will depend on stronger methodological rigor, disease-specific validation, integration across engineering, computational analysis, and therapeutics.

Keywords:
Mechanopharmacology; mechanobiology; drug discovery; translational medicine; organ-on-chip; microfluidics; biomechanics; pharmacodynamics; precision therapeutics; mechanotransduction.
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Introduction

Drug discovery remains a costly and failure-prone enterprise despite major advances in molecular biology, medicinal chemistry, and target-based pharmacology. Many compounds that perform well in conventional preclinical studies fail during later phases of development because the models used for early screening inadequately reflect the complexity of human physiology. One important and historically underappreciated contributor to this translational gap is tissue biomechanics. Standard in vitro systems generally rely on static monolayer cultures grown on rigid plastic or glass, conditions that differ substantially from the physical microenvironment experienced by cells in vivo. [1,2]

As a result, conventional systems often fail to capture the influence of tissue stiffness, fluid flow, cyclic strain viscoelasticity, extracellular matrix architecture, and cytoskeletal dynamics on cellular signaling and drug responsiveness. [1,2] These shortcomings weaken predictive accuracy for efficacy, toxicity, transport behaviour, and therapeutic sensitivity. Mechanopharmacology emerged as a response to this limitation. In its broadest sense, mechanopharmacology refers to the study of drug action within biomechanically relevant biological environments.[1] It integrates principles from mechanobiology and pharmacology to examine how physical stimuli modify target engagement, gene expression, intracellular signaling, cellular transport, phenotypic plasticity and therapeutic effect. [1,3,4]

This perspective is especially relevant in translational medicine because many diseases are characterized by altered tissue mechanics, including fibrosis, cancer, vascular disease, asthma, and age-related tissue stiffening. [2,5,6] If these biomechanical features are integral to disease biology, they should also be considered during therapeutic testing and drug development. The present review builds on two principal mechanopharmacology reviews together with organ-on-chip literature that strengthens the translational engineering dimension of the field. Rather than presenting these publications as isolated contributions, this article synthesizes them into a broader narrative review focused on biological basis, enabling technologies, disease applications, translational significance, current challenges and future directions.

Evolution of Mechanopharmacology

The scientific evolution of mechanopharmacology can be understood through three influential streams of literature. The first is the 2016 review *Cellular biomechanics in Drug Evaluation: Mechanopharmacology,* which formally established mechanopharmacology as a distinct conceptual framework for pharmacological testing under biomechanically appropriate conditions. [1] This work challenged the long-standing assumption that drug responses are determined mainly by biochemical signaling and receptor pharmacology, emphasizing instead that extracellular forces, tissue stiffness, traction, and mechanotransduction significantly influence therapeutic behaviour. [1]

The second major step is the modern translational review *Mechanopharmacology: in vitro techniques to advance drug discovery,* which broadened the field by describing technologies capable of recreating disease-relevant biomechanics in vitro. These platforms include engineered biomaterials, hydrogel-based constructs, three-dimensional spheroids, organoids, microfluidic technologies, organ-on-chip devices, and integrated microphysiological models. The review also emphasized the importance of integrating mechanical context with pharmacokinetics, pharmacodynamics, and translational pharmacology. [2]

A third important stream comes from organ-on-chip and dynamic bioengineering literature, including work on mechanical strain-enabled reconstruction of physiological environments in organ-on-chip systems. This literature highlights that living tissues are not mechanically static; lung tissue expands and contracts, vascular systems experience pulsatile flow, and gastrointestinal or musculoskeletal systems are shaped by repetitive deformation. Incorporating such dynamic forces into experimental models improves physiological realism and may enhance prediction of therapeutic response. [7] Together, these streams show how mechanopharmacology has progressed from conceptual insight to experimental actionable translational science.

Biological Basis of Mechanopharmacology

The central biological premise of mechanopharmacology is that cells are active mechanical sensors. Through integrins, cadherins, focal adhesions, ion channels, the actin cytoskeleton, and nucleo-cytoskeletal connections, cells detect and interpret forces generated by the extracellular matrix, neighbouring cells, flowing fluids, and tissue deformation. [1,2,5]

This process, known as mechanotransduction, converts physical inputs into biochemical signals that regulate proliferation, migration, differentiation, survival, metabolism, inflammation and transcriptional activity. [1,2]

Matrix stiffness is a particularly important determinant of pharmacological behaviour.

Changes in matrix rigidity influence focal adhesion maturation, actomyosin tension, nuclear mechanics, chromatin organization and downstream signaling pathways such as YAP/TAZ, RhoA/ROCK and integrin-mediated pathways. [1,5,8,9] In fibrosis, cancer and ageing pathological tissue stiffening may promote survival signaling, invasion, contractility and therapeutic resistance. [2,5,6] Consequently, the same drug may produce different effects depending on whether cells are cultured on rigid plastic, tissue-mimetic hydrogels, or physiologically relevant three-dimensional environments. [1,8,9]

Mechanical regulation also extends beyond stiffness. Fluid shear stress alters endothelial morphology, nitric oxide signaling, inflammation, permeability and transport behavior. [2,10] Cyclic stretch and oscillatory strain influence airway smooth muscle, vascular tissues, lung epithelium and other mechanically active systems. [2,11,12] Mechanosensitive ion channels and intracellular force transmission further contribute to how cells perceive and respond to therapies. [5,13] These principles together establish biomechanical context as a core determinant of pharmacological responsiveness rather than a minor culture variable.

Mechanical Determinants of Drug Response:

Matrix Stiffness and Viscoelasticity

Matrix stiffness is among the most extensively studied mechanical determinants of drug response. Substrate rigidity can significantly alter sensitivity towards anticancer agents and cells grown on tissue-mimetic matrices may retain drug-response profile more representative of real tumors than cells adapted to rigid laboratory surfaces. [8,9] Earlier work demonstrated that softer substrates could shift apparent therapeutic sensitivity in breast cancer models, illustrating how stiffness can alter interpretation of efficacy data. [8]

Fluid Flow and Shear Stress

Fluid flow is another major regulator of pharmacological behaviour. Endothelial, renal, pulmonary and epithelial tissues function under dynamic perfusion conditions that shape receptor signaling, inflammatory activity, barrier properties and transport. Static cultures do not adequately reproduce these conditions. Microfluidic systems that recreate vascular flow and nutrient exchange therefore provide more realistic platforms for studying drug exposure, tissue penetration and response.

Stretch, Compression and Dynamic Loading

Many tissues experience repetitive deformation. Airway smooth muscle undergoes breathing-related oscillation, vascular cells experience pulsatile stretch and musculoskeletal tissues respond to compression and strain. These forces influence contractility, inflammatory signaling and therapeutic responsiveness. In asthma-related work, mechanical perturbation and pressure oscillation have been shown to alter airway smooth muscle behaviour and interact with Rho-kinase-targeted pharmacology. [11,12]

Cytoskeleton Tension and Mechanotransduction

The internal mechanical state of a cell also shapes pharmacological behaviour. Traction forces, focal adhesion dynamics, actomyosin contractility and cytoskeletal stiffness influence receptor organization and intracellular signalling pathways. Single-cell force-sensing approaches have further shown that mechanical drug sensitivity may vary substantially across donors, supporting the idea of patient-specific mechanophenotypes relevant to precision therapeutics. [4]

Experimental Platforms in Mechanopharmacology:

Biomaterials, Hydrogels and Tunable Matrices

Engineered biomaterials allow systematic control of stiffness, viscoelasticity, ligand composition and matrix organization. Hydrogels and related platforms can be tuned to mimic healthy or diseased tissue environments and are especially useful in modeling tumor stiffness, fibrosis and aging-associated matrix remodelling. [2,5] These systems permit investigators to isolate the contribution of physical cues to drug exposure while maintaining closer physiological relevance than rigid plastic culture systems.

Three-Dimensional Cultures, Spheroids and Organoids

Three-dimensional culture systems provide more realistic tissue architecture than conventional monolayers. Spheroids and organoids reproduce cell-cell interactions, diffusion gradients, matrix remodeling and tissue heterogeneity, all of which influence pharmacological response and drug penetration. [2] Their translational value is especially notable in oncology, fibrosis and patient-derived disease modeling, where they help recreate disease-specific microenvironments.

Microfluidics

Microfluidic platforms enable precise control of flow, shear stress, nutrient gradients and drug exposure kinetics. They can reproduce vascular and tissue perfusion in ways that static cultures cannot. These systems are useful for studying how dynamic transport conditions influence pharmacokinetics, tissue penetration, barrier behaviour and pharmacodynamic outcomes. [2]

Organ-on-Chip Systems

Organ-on-chip systems represent one of the most important translational advances in mechanopharmacology. These microengineered devices combine living cells, tissue-specific architecture, controlled perfusion and dynamic mechanical stimulation within biomimetic environments. Depending on their design, they can simulate breathing-related cyclic strain, vascular pulsatility, tissue deformation, oxygen gradients and multicellular communication. [2,7] Examples include lung-on-chip, heart-on-chip, liver-on-chip and kidney-on-chip models, each capable of reproducing features of native organ physiology relevant to therapeutic evaluation. [7]

A major strength of organ-on-chip systems is their ability to integrate multiple physiological variables simultaneously. Mechanical strain, extracellular matrix interactions, biochemical signaling, fluid movement, oxygen delivery and multicellular tissue organization may all be incorporated into a single model. This substantially improves translational relevance and enhances prediction of efficacy and toxicity under realistic conditions. [2,7]

Microphysiological Systems and Integrated PK/PD Models

Microphysiological systems extend beyond isolated tissue models toward higher-order organ function and, in some settings, inter-organ communication. These platforms are particularly promising for studying PK/PD relationships under mechanically relevant conditions, because tissue architecture, fluid movement and matrix mechanics can influence exposure, diffusion, receptor engagement and downstream effect magnitude. [2,14] Such systems may eventually strengthen preclinical prediction and improve mechanistic modeling of context-dependent drug action.

Translational Relevance in Drug Discovery

The major translational promise of mechanopharmacology is improved predictive fidelity. Standard pharmacology often assumes that if a molecular target is present and the drug concentration is appropriate, the observed effect in vitro will meaningfully estimate therapeutic performance in vivo. However, when the experimental system lacks realistic stiffness, flow, strain or tissue architecture, important determinants of response may be missed. [1,2]

Mechanopharmacology narrows this gap by reproducing the physical features of disease microenvironments, thereby enabling more accurate assessment of efficacy, resistance, toxicity and context-dependent therapeutic behaviour. This may reduce late-stage attrition by identifying compounds that fail under physiologically relevant conditions before they enter expensive clinical development. Conversely, it may also rescue promising therapies whose activity becomes more apparent only when tissue mechanics are modeled appropriately. [2,14]

Mechanopharmacology also supports translational pharmacology by linking physical microenvironmental features to pharmacodynamic endpoints and systems-level modeling. Mechanistic models of drug discovery and development can be strengthened when mechanically informed experimental data are integrated with biochemical readouts. [14] In this sense, mechanopharmacology serves not only as a platform-improvement strategy but also as a systems-level framework for improving translational prediction.

Disease Applications:

Cancer and Chemoresistance

Cancer is one of the most compelling mechanopharmacological domains because tumors are mechanically abnormal tissues. Desmoplasia, matrix stiffening, elevated interstitial pressure, altered traction forces and abnormal perfusion all influence invasion, metastasis and treatment response. [6,9,15] In pancreatic ductal adenocarcinoma, mechanobiological factors have been implicated in chemoresistance, supporting the use of mechanopharmacological models to identify biomechanics-informed therapeutic strategies. [3] Tumor organoids, microfluidic cancer models and stiffness-tunable matrices increasingly permit more realistic and potentially patient-specific therapeutic testing.

Fibrosis and Tissue Stiffening

Fibrotic disease is fundamentally linked to altered extracellular matrix mechanics. Progressive matrix deposition increases tissue stiffness and reinforces pathogenic activation loops in resident cells.

Mechanopharmacological systems are therefore especially relevant for studying antifibrotic drugs in environments that reflect the rigidifying tissue context they are intended to modify. [2,5]

Respiratory Diseases

Airway and lung tissue are mechanically dynamic. Breathing-related cyclic stretch, pressure oscillation, and tissue deformation influence pharmacological response, particularly in airway smooth muscle and pulmonary epithelium. Studies of mechanopharmacology in asthma demonstrate that physical perturbation can alter contractility and interact synergistically with bronchodilator or Rho-kinase-targeted therapies. [11,12] Lung-on-chip systems further enhance translational modeling of respiratory inflammation, fibrosis, injury and inhaled therapies. [7]

Cardiovascular Medicine

Cardiovascular tissues are continuously exposed to flow, pressure gradients, pulsatility and vascular stretch. These forces shape endothelial function, thrombosis, inflammation, and vascular remodeling. Mechanopharmacological systems that reproduce hemodynamic conditions may improve prediction of cardiovascular drug efficacy and toxicity, especially in hypertension, atherosclerosis, endothelial dysfunction and cardiotoxicity assessment. [7,10]

Neurological and Blood-Brain Barrier Applications

Neurological mechanopharmacology remains comparatively underexplored, but it has substantial potential. Brain tissue has distinct extracellular matrix properties, vascular interfaces and mechanical sensitivities that influence transport and therapeutic response. Blood-brain-barrier-on-chip models and other microphysiological neurovascular systems may improve prediction of drug penetration and reduce translational failure in neurology. [7]

Current Challenges

Despite substantial progress, mechanopharmacology faces several important barriers. First, there is limited standardization. No universal agreement currently exists on the most appropriate ranges of stiffness, shear stress, strain magnitude, loading frequency, or biomechanical assay design for many disease-specific applications. This variability weakens reproducibility and complicates comparison across studies. [1,2,5]

Second, scalability remains a major concern. Many advanced mechanopharmacological systems, particularly organ-on-chip and microphysiological platforms, are technically demanding, expensive and difficult to implement in high-throughput screening pipelines. [2,7] Their fabrication, maintenance, imaging and data-analysis requirements may limit widespread pharmaceutical adoption.

Third, disease-specific validation remains incomplete. Mechanopharmacology is increasingly compelling in cancer, fibrosis, and respiratory biology, but remains less mature in infectious disease, autoimmunity, pediatrics and several neurological and cardiovascular contexts. Broader disease-tailored validation is necessary if the field is to become a routine part of translational pharmacology. [2,5]

Fourth, data integration remains challenging. Mechanopharmacology platforms generate multidimensional datasets involving morphology, flow, force, variability, gene expression, signaling and temporal dynamics. Artificial intelligence and computational modeling could help identify predictive signatures from these datasets, but validated frameworks remain limited. [2,14]

Finally, patient-specific biomechanics remain poorly understood. Inter-individual variation in matrix properties, tissue stiffness, and mechanical signaling may substantially influence therapeutic response, yet this variability is only beginning to be studied in pharmacological contexts. [4,6]

Conclusion

Mechanopharmacology has progressed from an important conceptual insight into a promising translational framework for improving drug discovery. The field recognises that pharmacological response is shaped not only by molecular target biology, but also by the biomechanical context in which cells and tissues exist. Landmark reviews established the conceptual basis of biomechanically relevant pharmacology and were followed by technology-rich literature describing biomaterials, organoids, microfluidic, organ-on-chip platforms and microphysiological systems capable of recreating disease-relevant mechanical conditions. This evolution has major implications for translational medicine. In cancer, fibrosis, respiratory diseases, cardiovascular biology and emerging neurovascular applications, altered tissue mechanics are integral to pathophysiology and may significantly influence therapeutic response. Mechanopharmacology offers a means to capture these effects more faithfully during preclinical testing, with the potential to improve predictive pharmacology, reveal resistance mechanisms, and support precision therapeutics.

However, widespread implementation will require more effective integration with computational and PK/PD frameworks, stronger methodological standardization, and broader disease-specific validation. If these challenges are addressed, mechanopharmacology may become an essential component of future translational pharmacology and a durable bridge between mechanobiology, engineering and clinical therapeutics.

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