Perspective

Mechanistic Clinical Pharmacology: Bridging PK–PD Modeling, Biomarkers, and Translational Therapeutics

Soroush Mohammadi Jouabadi[1], **Sanaz Mokhtari**[2*]

[1] Division of Vascular Diseases and Pharmacology, Department of Internal Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands.

[2] Department of Pharmacotherapy, School of Pharmacy. Mazandaran University of Medical Sciences, Iran.

***Corresponding author:** Sanaz Mokhtari, Department of Pharmacotherapy, School of Pharmacy. Mazandaran University of Medical Sciences, Iran. E-mail: Sanaz.mo1375@gmail.com

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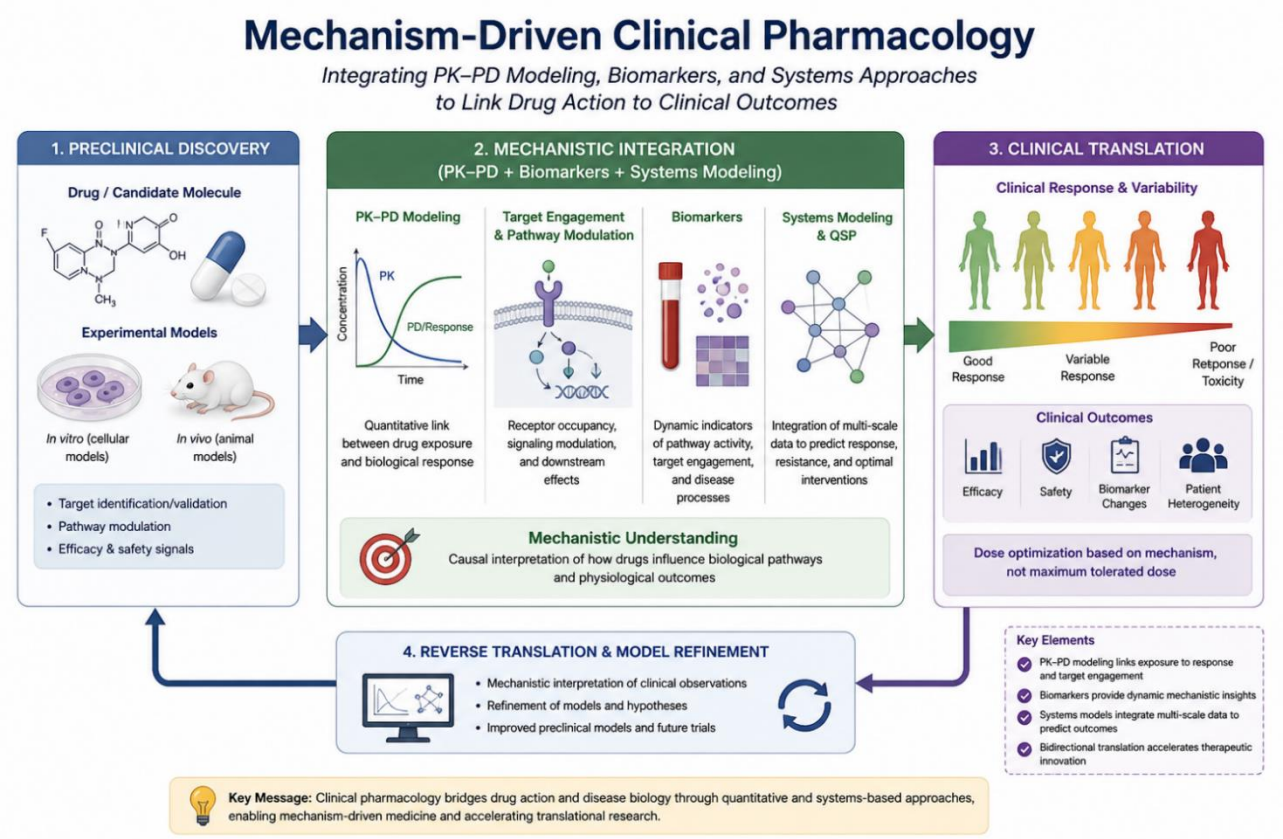
Abstract:
Biomedical research is increasingly shifting from empirical observation toward a mechanistic understanding of disease biology and therapeutic response. In this context, clinical pharmacology has evolved into an integrative discipline that links drug action to disease mechanisms across molecular, cellular, and systems levels. Central to this transformation are pharmacokinetic–pharmacodynamic (PK–PD) modeling, biomarker-based assessment, and systems pharmacology approaches, which together provide a quantitative framework for interpreting drug exposure, target engagement, and downstream biological effects. These approaches support a mechanistic understanding of dose–response relationships and facilitate more rational dose selection beyond traditional empirical strategies. The integration of dynamic biomarkers has further advanced the field by enabling real-time assessment of pathway activity and disease progression, particularly in heterogeneous disorders such as diabetes and immune-mediated metabolic diseases. For example, the clinical development of SGLT2 inhibitors such as empagliflozin illustrates how mechanistic PK–PD modeling and biomarker integration can reveal therapeutic effects extending beyond glycaemic control, including cardiovascular and renal benefits that were not predicted by glucose lowering alone. Early-phase clinical studies supported by model-informed drug development frameworks also allow earlier evaluation of mechanistic hypotheses in humans and improve the prediction of interindividual variability in therapeutic response and toxicity. In parallel, the bidirectional exchange of information between preclinical and clinical research through forward and reverse translation contributes to model refinement and strengthens predictive accuracy in drug development. Collectively, these advances position clinical pharmacology as a mechanistic framework within translational medicine, bridging experimental biology and clinical therapeutics. This evolving paradigm supports the transition toward precision and mechanism-guided drug development, where therapeutic strategies are increasingly informed by causal biological pathways rather than empirical associations.

Keywords: Clinical pharmacology, PK–PD modeling, Translational medicine, Biomarkers, Systems pharmacology.



Graphical Abstract. Clinical Pharmacology at the Interface of Mechanism and Translation. Integrates mechanistic understanding of disease biology with pharmacokinetic–pharmacodynamic modeling, biomarkers, and systems pharmacology to enable precision, mechanism-driven therapeutics, improving translational success and patient outcomes in complex disease settings.

The increasing clinical complexity of modern therapeutics has exposed a fundamental limitation in empirical, observation-driven approaches, accelerating a shift toward mechanistic understanding in biomedical science (1,2). Within this framework, clinical pharmacology is no longer merely a supportive field; it has become a central, integrative science that links drug action to disease biology across multiple levels (3). Traditionally, the discipline focused on characterizing how drugs are absorbed, distributed, metabolized, and excreted, as well as their observable effects (4). While these foundational principles remain crucial, the scope of clinical pharmacology has expanded into a far more dynamic and explanatory domain (5). Today, the field aims to address deeper questions: how and why drugs exert their effects, why individual responses differ, and how these variations can be anticipated and managed (6).

At the core of this evolution lies pharmacokinetic–pharmacodynamic (PK–PD) modeling, which provides a quantitative framework linking drug exposure to biological response (7). These models go beyond simple correlations, offering a mechanistically informed perspective on how drug concentrations influence target engagement and subsequent physiological effects (8). This includes the quantitative characterization of signaling pathway modulation, receptor occupancy, and downstream network perturbations that collectively define drug action at molecular and cellular levels. Consequently, dose selection is no longer purely empirical but increasingly guided by mechanistic insight. Equally transformative is the integration of biomarkers into clinical pharmacology. Once

validated, biomarkers play a pivotal role in monitoring treatment responses and connecting biological processes to pharmacological outcomes (9). Over time, biomarkers have evolved from static diagnostic tools into dynamic indicators of biological activity (10). When applied strategically, they function as mechanistic readouts of pathway activity, target engagement, and disease progression, a feature particularly valuable in heterogeneous conditions such as diabetes and immune-mediated metabolic disorders, where therapeutic responses can vary substantially. In clinical investigations of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), glycaemic biomarkers including HbA1c, fasting plasma glucose, and measures of insulin secretion are routinely evaluated (11). By contrast, studies of sodium-glucose cotransporter-2 (SGLT2) inhibitors additionally assess metabolic parameters that reflect shifts in energy substrate utilization, such as ketone-related markers (12). These mechanistic insights translate into tangible clinical benefits, exemplified by reductions in cardiovascular mortality and heart failure observed in patients treated with empagliflozin (13). Early-phase clinical studies increasingly use model-informed drug development approaches to quantitatively assess whether a drug engages its target and alters biological pathways, using biomarkers and functional measurements (14). Modern clinical pharmacology integrates systems biology with computational modeling to predict drug effects, anticipate disease progression, and identify optimal therapeutic combinations, all while accounting for interpatient variability (15). In the context of diabetes, clinical pharmacology studies have leveraged PK–PD modeling and biomarker analyses to dissect the mechanisms underlying disease progression and therapeutic response, with a particular focus on insulin resistance and β-cell dysfunction.

In immune-mediated metabolic disorders such as type 1 diabetes, these models are instrumental in characterizing the context-dependent heterogeneity of treatment responses. Within diabetes drug development, forward and reverse translation, which entails the mechanistic interpretation of clinical observations, establish a bidirectional framework whereby clinical findings inform laboratory research and, in turn, refine preclinical models (16).

Conclusion

Clinical pharmacology is no longer limited to describing drug behavior but has evolved into a mechanistic and translational discipline that links molecular drug action to clinical outcomes through quantitative, systems-based, and biomarker-informed approaches. This framework enables a deeper understanding of therapeutic effects by integrating biological mechanisms with clinical response, supporting a shift toward truly mechanism-driven and precision-guided medicine.

Mechanistic and Translational Relevance

This perspective highlights clinical pharmacology as a mechanistic discipline within translational medicine, where drug action is interpreted through causal biological pathways rather than empirical association. By integrating pharmacokinetics–pharmacodynamics with biomarkers and systems modeling, it links drug exposure to target engagement and physiological effects in a quantitative framework. This approach supports early biomarker-based evaluation of efficacy and safety, enables dose selection based on target activity rather than maximum tolerated dose, and helps address variability in toxicity and treatment response. Translationally, it facilitates the translation of preclinical science into the clinic and enables mechanistic integration of biological data to assess variability in treatment response.

Conflict of Interests

The author declares that there is no conflict of interest.

Author Contributions

Both authors contributed equally to the conception and design of the study, literature search, data interpretation, drafting of the manuscript, and critical revision of the article. Both authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Ethics Statement

All ethical considerations, including plagiarism, data fabrication, and duplicate publication, have been fully observed by the author.

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