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Clinical pharmacology at the core of translational science

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Abstract

"Convergence of national interests in advancing molecular therapeutics into practice with core competencies in clinical pharmacology represents a unique opportunity to elevate the visibility of this pioneering discipline as part of the foundation of clinical and translational science."

Keywords

clinical and translational science; enabling technologies; National Center for Advancing Translational Sciences; National Center for Clinical Research Resources

Technological advances have enabled unprecedented insight into molecular mechanisms underlying pathophysiology; however, this has surpassed the current capacity for their translation into healthcare paradigms [1,2]. Indeed, federally funded discovery programs have produced a myriad of potential diagnostic and therapeutic targets that could individualize disease management [3]. Paradoxically, these discoveries languish, reflecting limitations in facilities, resources and the skilled knowledge-based workforce required for their translation into new patient management algorithms [4]. Compounding these challenges is the reality that 95% of promising therapies brought into clinical development in the private sector ultimately fail because of limitations in efficacy or unacceptable toxicities [4,5]. To rebalance the equation and bring translational closer to discovery science, a new National Center for Advancing Translational Sciences is being created at the NIH. This center will advance novel molecular discoveries into technologies with a tractable risk–benefit ratio that appeals to private sector investment [6]. It embraces a contemporary vision of the investigational continuum from molecules to patients and populations [4], shifting translation from a focus on therapeutics that palliate, to risk stratification that prevents, disease [7,8]. This national initiative also aims to nucleate a public–private partnership in

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which science drives translation and clinical development to amplify efficiencies and reduce risks associated with improving patient care [4].

Beyond crystallizing activities along the translational continuum, the new center will develop the next generation of clinical and translational investigators. Rebalancing the equation to equilibrate discovery and translation requires a cadre of investigators fluent in the vocabulary, concepts and strategies of the laboratory and clinic, enabling the integration of new, often disparate, domains [9]. Furthermore, it requires a shift in professional culture that incents scientific teams, rather than rewarding individual achievements [1]. This vision recognizes the need to create a brand for clinical and translational science that attracts the best and brightest minds into training programs, to produce a multidisciplinary, complementary workforce ensuring the equipoise between discovery and translation [9–11].

> "…95% of promising therapies brought into clinical development in the private sector ultimately fail because of limitations in efficacy or unacceptable toxicities."

The new center will embrace the discipline of clinical pharmacology as one key element in creating this professional identity [101,102]. This recognition underscores the position of clinical pharmacology as a discipline at the core of the emerging field of clinical and translational science [4,12,13]. A central role for clinical pharmacology in this scientific revolution reflects its pioneering position as the original discipline bridging the laboratory bench and patient bedside. Rooted in the earliest inquiries into the mechanism of drug action, the discipline focuses on two fundamental questions [14]: What do drugs do to the body? And what does the body do to drugs? This focus on drug action and disposition established the earliest concepts and approaches underlying individualized medicine in which the right drug is used in the right patient at the right dose [2,8]. Furthermore, evolution and expansion of knowledge domains and analytical approaches anchored in the dynamic fields of pharmacokinetics and pharmacodynamics firmly position clinical pharmacologists as subject matter experts at every step along the continuum of drug discovery, development, regulation and utilization [15]. Clinical pharmacologists pioneered integration of molecular mechanisms in studies establishing drug actions in patients. They are involved in designing and implementing early- and late-stage clinical trials, including the use of placebos, elucidating molecular mechanisms underlying variability in drug responses and in the science of drug safety [14]. This primacy in translational science is evidenced by their leadership roles in international initiatives bridging the laboratory and clinic, including the Pharmacogenomics Research Network [16], the US FDA's Critical Path Initiative [17] and the Institute of Medicine's Committee on Qualification of Biomarkers and Surrogate Endpoints in Chronic Disease [103].

> "The mandate for the new national center is to secure early adoption of the integration of discovery innovation into clinical practice in response to patients and society who seek new products and services to address unmet needs in healthcare."

While the principles of clinical pharmacology are fundamental to translating molecular discoveries into patient-centered healthcare algorithms, the discipline has maintained a modest profile in scientific and medical communities. The practice of clinical pharmacology is primarily an academic medicine-based specialty, and its focus on cognitive, compared with procedural, activities reduces its economic imperative in the healthcare industry [18].

Furthermore, while clinical pharmacologists produce the tools underlying modern drug development, they are often wielded by subspecialty investigators outside the field, producing disciplinary anonymity [18]. Moreover, most practitioners prescribe drugs to their patients and, in that context, all identify themselves as practitioners of clinical pharmacology, diluting more fundamental contributions by the discipline [18]. This equivocation for the discipline is exemplified by the paradox of the near absence of formal didactic training in therapeutics for graduates of medical schools in the USA, in the context of the epidemic of medication errors and their impact on the healthcare system [5]. Convergence of national interests in advancing molecular therapeutics into practice with core competencies in clinical pharmacology represents a unique opportunity to elevate the visibility of this pioneering discipline as part of the foundation of clinical and translational science [101,102].

Although the new center presents an opportunity for discipline invigoration [101,102], it is essential to resist temptations to rebrand clinical pharmacology as the emerging field of clinical and translational science [9–11]. While much of translation will be served by clinical pharmacology, particularly across the discovery–application continuum, these disciplines are overlapping but not co-extensive. The core competencies of clinical pharmacology, including pharmacogenomics, pharmacokinetics, pharmacodynamics, pharmacoepidemiology, pharmacovigilence and pharmacometrics, to name but a few, are tools important to realizing the vision of translation. However, those tools are also important outside the context of clinical and translational science. They will often be applied by practitioners who identify themselves as clinical pharmacologists, but not translational investigators. Conversely, there are essential elements of clinical and translational science that go beyond the knowledge domain of clinical pharmacologists. Furthermore, clinical and translational investigators may not embrace the core competencies of clinical pharmacology as their own. In that context, the risk in rebranding and subsuming clinical pharmacology into clinical and translational science carries the potential for dilution, attrition and, ultimately, loss of those core competencies that uniquely distinguish clinical pharmacologists as subspecialists.

The National Center for Advancing Translational Sciences represents a critical next step in the evolution of the science of translation [4,104,19]. It centralizes national resources that will facilitate discovery and application across the T0–T5 translational continuum [13]. It will create a career path in translational science and medicine that will prepare the next generation of skilled investigators invested in the culture of team science. The mandate for the new national center is to secure early adoption of the integration of discovery innovation into clinical practice in response to patients and society who seek new products and services to address unmet needs in healthcare. The critical path to achieving this mandate embraces the unique knowledge domains, intellectual resources and human capital comprising clinical pharmacology as one core discipline forming the foundation for the emerging field of clinical and translational science.

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Biography

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