PERSPECTIVE

What's Past Is Prologue: Clinical Pharmacology at the Intersection of Science, Policy, and Patients

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It has been nearly 80 years since the birth of what is often recognizable as modern clinical pharmacology.[1] The start of a new decade brings opportunity for reflection and with it an imperative for bold vision and integration of all facets of clinical pharmacology for the benefit of patients and society. Herein, we describe our vision for the discipline—one in which scientific leadership, innovation, and focus on patients intersect to transform health worldwide.

MOTIVATION FOR A UNIFIED VISION

Clinical pharmacology is a multidisciplinary translational science that can be applied to address a variety of challenges. There are urgent challenges in three specific opportunity areas that clinical pharmacology can (arguably must) be at the forefront in addressing: drug development and regulation, pharmacotherapy, and global public health. The adverse outcomes associated with inefficient drug development, inadequate medication therapy management, and insufficient patient access to appropriate and affordable medications can be attenuated by applied clinical pharmacology.

The disconnect between outsized research and development expenditure and the number of innovative new therapies reaching patients is well documented.[2] There are several orders of magnitude difference between the number of new compounds identified during drug discovery and the number that reach clinical testing. Of these, very few demonstrate adequate efficacy and/or safety to be approved by regulatory authorities, often after years of patient participation in clinical trials. When including the cost of failed drug development, bringing a new drug to patients is estimated at nearly US $3 billion.[3] Clinical pharmacology approaches must be leveraged to increase innovation and drug development efficiency and continue to shift regulatory decision making to include a more mechanistically informed orientation.

With respect to pharmacotherapy, pharmacological intervention has enabled us to address both chronic and acute diseases; however, predicting who will respond to many treatments has historically been a game of chance, with empirical trial-and-error being our predominant clinical practice paradigm. "Bedside" application of clinical pharmacology (i.e., pharmacy practice) must take a front-and-center role in comprehensive medication management in all practice settings.

The issue of access to much needed innovator products and quality-assured generics in developing countries is at crisis level. This multidimensional problem is compounded by underdeveloped regulatory systems, lack of low-cost manufacturing infrastructure, paucity of novel age-appropriate and region-appropriate formulations, proliferation of substandard and falsified products, and limited economic incentives to develop therapeutic products in these regions. Additionally, funding agencies have not traditionally contemplated investments that would lead to products, services, processes, technologies, or innovations that could rapidly and inexpensively be disseminated to underserved communities and countries. When they have, these programs have been typically resource-limited compared with the magnitude of the issue. Global health organizations can transform the human condition through holistic programs that leverage advances in clinical pharmacology, formulation science, and regulatory science.

There is reason to be optimistic about the impact of clinical pharmacology on addressing these challenges. For example, there has been a gradual increase in the rate of later phase clinical trial success in drug development, with an increasing proportion of compounds failing in phase I.[4] This suggests drug development is being informed by clinical pharmacology insights derived from early phase trials. There is also increasing evidence that the success of drug development programs is highly dependent

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on pharmacological and pharmacokinetic first principles.[5] On the pharmacotherapy front, we have seen record numbers of approvals of personalized medicines and novel platforms (e.g., siRNA, CAR T-cell therapy). An unprecedented number of products have been authorized for children, with much of the supporting data coming from pharmacologically informed extrapolation from adults. In addition, extensive study of the role of intrinsic and extrinsic factors on drug response variability, coupled with clinical decision support, has greatly enhanced therapeutic individualization. From the global health standpoint, the last 15–20 years have seen dramatic reductions in the under-5 mortality rate and increased overall longevity in low and middle-income countries. A groundswell effort to bring the full suite of clinical pharmacology tools to global health has also accelerated over the last decade and is now approaching critical mass.

The past is only prologue to the impact clinical pharmacology can have if its adherents in drug development, drug regulation, pharmacy practice, and global health policy and procurement join efforts in a strategically coordinated way. The inter-relatedness of these sectors may not be fully obvious, but we submit they are undeniable (**Figure 1**). Scientific, infrastructural, and policy advances have created touchpoints for clinical pharmacologists across the drug discovery, development, regulation, and utilization spectrum. Additionally, technologies once considered futuristic (e.g., learning health systems, modeling, and simulation) are reality today with more advances at our doorstep. These developments, coupled with our unprecedented potential to communicate across functional areas, organizational boundaries, and continental barriers, make now the time to connect clinical pharmacologists from across the planet to work together and augment health systems to save lives by delivering the latest in science and technology to those with the greatest needs.

CLINICAL PHARMACOLOGY AS A FORCE FOR GLOBAL GOOD—ADVANCING NEW THERAPIES FOR UNMET MEDICAL NEED

Clinical pharmacology innovation in drug development and regulation has been transformative. For example, we now take for granted many innovations in clinical pharmacology and biopharmaceutics that were once considered disruptive innovations.[6] Time and again, the discipline has advanced and ultimately incorporated new science into regulatory advice and decision

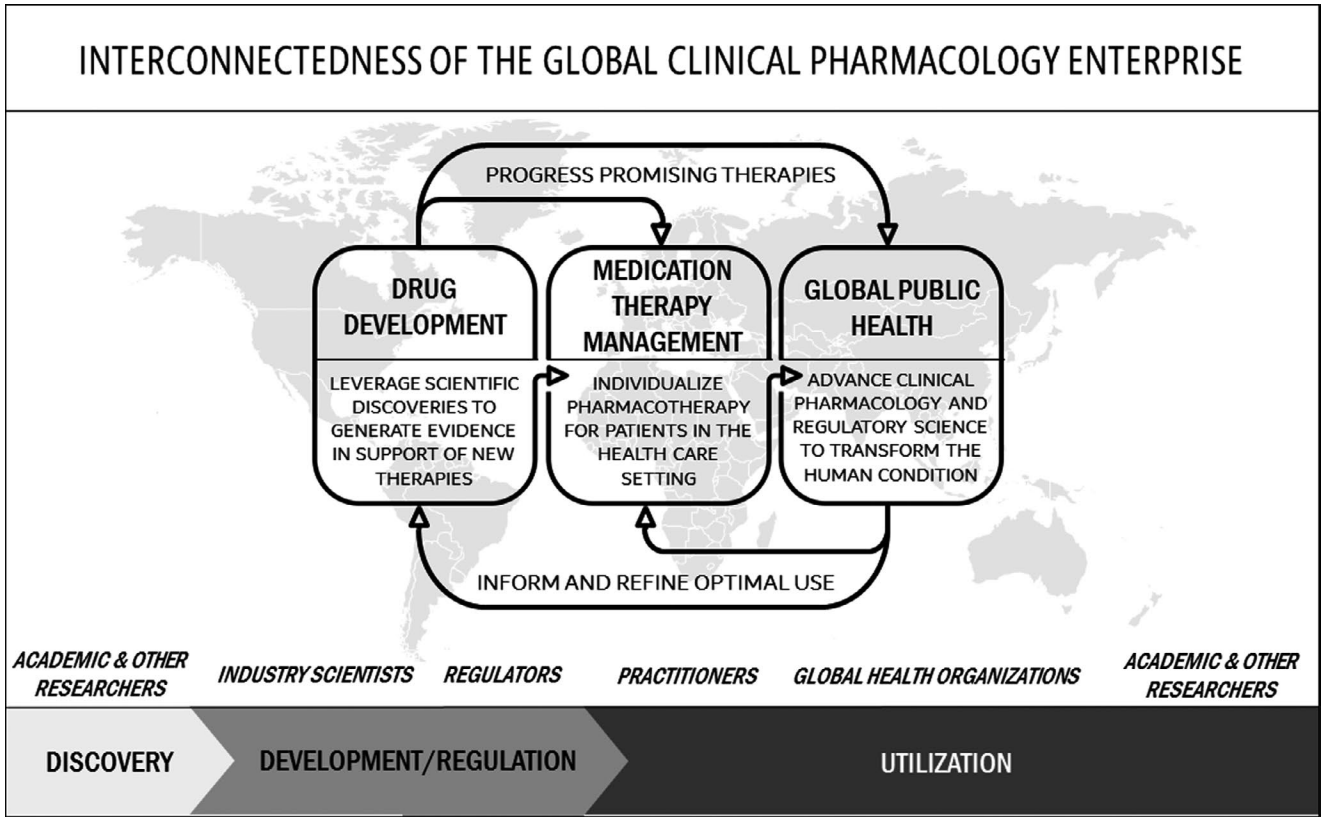

Figure 1 Clinical pharmacology on a global scale. Interconnectedness of clinical pharmacology across the drug discovery, development, regulation, and utilization continuum. Building on advances in science largely driven by academic and pharmaceutical research, industry and regulatory scientists advance promising therapies for use in patients. Clinical practitioners and global health organizations facilitate optimal pharmacotherapy and patient access, respectively. After approval, affordability, usage policies, and clinical practice inform real-world uptake, product performance, and determinants of response variability, allowing for refinement of our understanding of the drug's optimal use throughout its lifecycle. Insights derived from clinical practice, broader access, and additional research further inform optimal use and provide insights that stimulate additional drug development and regulatory science. We endorse an approach that connects clinical pharmacologists and translational scientists across all these sectors to advance public health. This unified approach would engage stakeholders on a global scale and include both low-income and middle-income countries as well as more economically advanced countries.

making. Examples include what were once the nascent knowledge topics of CYP-mediated drug metabolism, *in vitro–in vivo* correlation, pharmacokinetic/pharmacodynamic and disease modeling, physiologically-based pharmacokinetic modeling, pharmacogenomics, and pediatric clinical pharmacology, to name a few. These are now considered mainstream scientific approaches in the assessment of drug efficacy and safety, dose optimization, and therapeutic individualization. Ultimately, the aspiration of getting the right drug at the right dose to the right people at the right time is becoming increasingly viable.

We see two major ways in which clinical pharmacology can enable new therapies (both innovative and generic) for unmet medical needs on a global scale: (i) advancement and harmonization of regulatory science innovation and policy across global regulatory authorities and (ii) incorporation of clinical pharmacology innovations in the program and product portfolios of philanthropic organizations. In terms of harmonization, the science of clinical pharmacology can be brought to bear in forums like the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use (https://www.ich.org/home.html) and programs like the World Health Organization Prequalification (WHO PQ) program to promote innovation and create consistency in application of policy. We also encourage clinical pharmacology professional societies to create policy task forces to serve as incubators for development of policies that could subsequently be applied in regulatory and public health settings. With respect to clinical pharmacology as a pillar of global public health organizational portfolios, an increasing number of examples exist.

The US Food and Drug Administration has been active in both policy harmonization and collaboration with philanthropic global health organizations. The Bill and Melinda Gates Foundation, in coordination with many partners around the globe, has also been advancing these approaches to low-income and middle-income countries with increasing success.[7] Standardization and efficiency of clinical trial authorizations and assessments, product registration, and regulatory harmonization are being advanced through programs including WHO's African Vaccine Regulatory Forum, WHO PQ, and the African Union's African Medicines Regulatory Harmonization initiative, respectively. These examples illustrate the power of focusing clinical pharmacology efforts in a concerted way to address unmet medical needs.

FOSTERING COMMUNITY

There is an African proverb that reads: "If you want to go fast, go alone. If you want to go far, go together." The vision we have laid out necessarily requires interconnectedness on the part of individuals and organizations.

First, we emphasize the need for strengthening the bonds among clinical pharmacologists in academia, government, industry, and the nonprofit sector. This can be accomplished in several ways, including through coordinated efforts on the part of umbrella organizations (e.g., the American Society for Clinical Pharmacology and Therapeutics and others), memoranda of understanding between academic, regulatory, nonprofit, and other entities (ref. 8 for example), and other as-yet underexplored mechanisms of collaboration.[8]

Second, because these communities and networks will likely represent either a motivated minority or critical mass of the membership of professional organizations, we envision a strategic alliance among various clinical pharmacology organizations (of which we consider clinical pharmacy to be a part) that can help realize the singular goal of thinking globally and acting locally to transform the health of patients and societies. Whether this is accomplished through opportunistic collaborations or more formal organization (e.g., a joint commission of international clinical pharmacology organizations) should be deliberated. We also advocate for the establishment of clinical pharmacology professional societies in countries and regions where the organized presence of the discipline is needed.

Third, the establishment of a relationship with allies and those we serve is critical. To that end, we suggest the establishment of more formal collaborations between clinical pharmacology organizations and both medical societies and patient advocacy groups. Further, clinical pharmacology can maximize its impact through synergizing within its own "subspecialties." For example, in the global health context, there is significant scope for clinical pharmacology to impact health economics and outcomes research. In fact, several of the top trends in health economics and outcomes research (e.g., real-world evidence, the aging population, big data, value assessment frameworks, and precision medicine) are amenable to multidisciplinary clinical pharmacology input.[9] We believe these synergies will be mutually beneficial from an educational perspective, inform us what is most important to patients, advance the dialogue on value and access, and facilitate the use of clinical pharmacology in patient care through direct means or new technologies.

CREATING VISIONARY LEADERS

Our vision cannot be accomplished without dedicated leadership in the field. Emergent leaders should be purposely fostered, and established leaders should be supported in their continued growth. To that end, we support the launch of a task force to determine the need for and feasibility of establishing universal leadership competencies for clinical pharmacology. In our view, a well-rounded approach to leadership development includes didactic, coaching, and experiential components. Competency models exist that emphasize fundamental skills and abilities (e.g., interpersonal, communication, public service motivation, and continual learning) that can be augmented with incrementally developed executive competencies (e.g., leading change, leading people, business acumen, and building coalitions) relevant for leadership in the field.[10]

There is an imperative to train and support leadership growth of scientists in the field in an intentional way. This need includes and transcends the scientific training of students, post-graduates, and working professionals. We recommend the establishment of a Clinical Pharmacology Leadership Institute to ensure a pipeline of bold, creative leadership for generations to come.

SUMMARY

We are entering an exciting time for clinical pharmacology. Scientific and regulatory innovations, evolving interdisciplinary practice models, and increasing collaboration

among clinical pharmacologists across sectors are positive developments. A strategic approach to advancing clinical pharmacology/translational medicine principles in drug development and regulation, healthcare and pharmacy practice, and global public health could transform the health landscape. Investment in leadership development and refinement will be critical to ensure continued intergenerational momentum toward this vision.

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