Experimental Therapeutics: A Paradigm for Personalized Medicine

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Personalized medicine has emerged as a compelling strategy to actualize the medical value of scientific innovation, evolving the most effective evidence-based clinical decision systems into tailored patient care.[1] Scientific advances offer enabling technologies to individualize clinical algorithms, and thereby optimize prediction, prevention, diagnosis, and ultimately ameliorate disease outcome going beyond the parochial "one-size-fits-all" paradigm of current practice. The magnitude of the challenge is impressive, and can be appreciated by considering that there are approximately 25,000 protein coding genes in humans, whose complexity is exponentiated by >100,000 splice variants of messenger RNA. Moreover, 15 million loci along the genome where a single base can differ between individuals or populations further magnify the polygenic origins of disease. This complexity, amplified by epigenetic and posttranslational modifications, highlights the challenge of personalized medicine. The development of personalized medicine as the central path for optimizing health care underscores the requirement of an integrative paradigm that spans across the continuum from discovery science to applied therapeutics. Unison of basic and clinical sciences is vital in the fulfillment of individualized therapy, ensuring the most effective and safe approach in patient care delivery.

Experimental therapeutics has emerged as a key field at the intersection of molecular discovery and patient care, deploying translational medicine to advance disease treatment and promote patient wellness. The evolution in experimental therapeutics highlights the critical role of applied, or clinical, pharmacology in defining optimized patient care. Clinical pharmacology has advanced from ancient therapeutics exemplified by herbal remedies, animal extracts, and minerals.[2] Galen, an innovator in clinical pharmacology as early as 150 AD, recognized experimentation and theory as a fundamental principle supporting the rational use of medicines. Paracelsus in the 16th century provided a scaffold for experimental therapeutics by exploring active moieties in therapeutic preparations, articulating for the first time that dose defines the dynamic tension between therapy and toxicity for drugs.[3] In the 19th century, Oswald Schmiedeberg applied investigative principles to therapeutics initiating the science of drug development. Experimental therapeutics developed rapidly in the 20th century, reflecting the evolving understanding of pathology and physiology, associated with the identification of drug targets. Today, experimental therapeutics is the center of patient care, extending across the continuum of drug discovery, development, regulatory oversight, and utilization (DDRU) in practice.[4] From this revolution in experimental and translational medicine has emerged a critical concept for the future of personalized medicine—the "right drug for the right target in the right patient and delivered at the right dose."[5] In the last century, personalized drug dosing focused on sources of variability in responses including weight, surface area, and renal function. More recently, experimental therapeutics is positioned to extend personalized therapy deploying individual genetic and molecular profiles to target prognosis, prediction, cure, and prevention based on human variation.[6]

Uncovering key pathophysiological mechanisms has transformed the therapeutic toolbox, exemplified by the emerging importance of biomarker-based treatment algorithms; evolution of therapeutics to targeted biologics focused on re-establishing homeostatic processes; and therapeutics exploiting the inherent capability of self-healing and -repair that underscores the importance of the discovery–translation–application paradigm to innovations across the disease spectrum.[7] The exponential expansion of modern science has evolved the concepts of human health and provided technological platforms that refine experimental therapeutics within the paradigms of discovery and translation. These inevitable transformations reflecting the integration of basic, translational, and clinical sciences position the practice of clinical pharmacology at the intersection of the laboratory, patient, and population.[8,9] Integration of concepts from discovery sciences that drive therapeutic efficacy has directed clinical pharmacologists to evolve the new approaches for prognosis, prediction, and cure.[10] In turn, advances in applied pharmacology increasingly translate into strategies for patient-centric models of individualized medical management, emphasizing wellness across the continuum of age. The value of experimental therapeutics and its position in the future of patient care, in the context of the emerging importance of pharmacogenomics, targeted therapeutics, and individualized pluripotent stem cell-based regeneration, extends beyond individual patients to populations.[11–13] Ultimately, the potential of clinical pharmacology and experimental therapeutics will be maximized in the context of world health.[14]

Modern experimental therapeutics reflects the pharmacotherapeutic intersection of drug discovery, development, regulation, and utilization. Discovery has been advanced by the "omic" revolution, targeted imaging, and applied systems biology, incorporating progress in the informational sciences, including bioinformatics, medical informatics, and biorepositories to reveal the molecular foundations of disease.[15,16] Integration of these synergistic technologies provides the approaches for optimal resolution of molecular events underlying signaling essential to physiology which are disrupted in disease.[17] Definition of molecules and their interactions offer previously unachievable perspectives producing targeted diagnostics and therapeutics, prognostic biomarkers of disease variability, and predictive markers for treatment response stratification, refining therapeutic paradigms for individuals and populations. Continued deconvolution of biological networks and the molecular interactome in pathobiology will align drugable targets and diagnostic technologies to provide curative patient-specific clinical solutions.[18]

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Drug	Disease	Biomarker	Application
Biomarkers predicting adverse events			
Warfarin	Thrombosis	CYP2C9 and VKORC1	Testing recommended to identify patients at risk for increased bleeding.
Carbamazepine	Epilepsy	HLA-B*1502	Testing recommended to identify patients at risk of toxic skin reactions.
Abacavir	HIV infection	HLA-B*5701	Testing recommended to identify those at risk for potentially life-threatening hypersensitivity.
Celecoxib	Pain and arthritis	CYP2C9	Testing may identify patients at risk for accumulating toxic levels of drug.
Irinotecan	Colon cancer	UGT1A1*28	Testing recommended to identify patients at risk of myelosuppression.
Biomarkers predicting responses			
Tamoxifen	Breast cancer	CYP2D6	Testing may identify patients resistant to treatment with tamoxifen.
Cetuximab Panitumumab	Colon cancer	KRAS	Testing may identify patients resistant to therapy with monoclonal antibodies to EGF receptors.
Trastuzumab	Breast cancer	HER2	Testing required to identify patients suitable for Herceptin therapy.

Table 1. Biomarkers for personalized medicine.

In turn, translation of new discoveries into personalized therapies for individuals and populations is grounded in extending observations from clinical trials to therapeutic guidelines for practice management. The evidence base has become the benchmark for integrating clinical management solutions into practice guidelines. Advances in the science of therapeutic platforms are only beginning to approach the challenges of modern experimental therapeutics, including absence of specificity, interpatient variability, and adverse effects.[19] However, translational medicine offers a novel focus on the integration of diagnostic and therapeutic platforms tailored to the genetic and molecular profile of each patient to improve specificity, identify therapeutic responsiveness, minimize interpatient variability, and reduce adverse events (*Table 1*).[20] Advances in experimental therapeutics has transformed the contemporary clinical pharmacology continuum—discovery sciences through the definition of therapeutic targets; drug development through stratification of patients and diseases; regulatory sciences through the definition of mechanisms underlying adverse events; and therapeutic application through harmonization of optimal drug identification and dosing regimens.[21]

Beyond the synergy of novel diagnostic and therapeutic paradigms, transformative technologies provide new modalities to detect evolving pathophysiological states, revealing molecular targets for intervention to prevent and abrogate disease. Personalized medicine has provided quantitative predictors of disease progression, pharmacotherapeutic susceptibility, and sensitivity to adverse events. These modalities have unlocked insights to the mechanistic ontogeny of pathobiology, defining the sequence of alterations of cell biology and homeostasis across the advancing continuum time and space, which are integrated into networked systems to form the functional foundation spanning the spectrum from disease risk to overt illness.[22] Defining the molecular basis of diseases offers a previously unanticipated opportunity to intercede in the earliest stages of pathophysiology, prior to irreversible tissue damage and organ failure. By repairing essential homeostatic circuits that provide the biological and pathophysiological scaffold for drug action, personalized medicine transforms reciprocating feedback mechanisms, achieving systems integration across the pharmacotherapeutic continuum of practice.

Stratification of patients into classes based on disease mechanisms provides markers of prognosis, reduces interindividual variability in therapeutic responses, and improves patient identification to increase the success in critical-stage clinical trials. Conversely, metabolic stratification by genotype and phenotype identifies patients with the greatest risk for adverse drug events, who could derive the most benefit from adjustments in dosing regimens to maximize therapeutic safety.[23] Together, these approaches to optimizing pharmacotherapy applied to individual patients and populations with inherent genetic and environmental variabilities improve drug development success rates, return on research and development investment, and therapeutic efficacy, while reducing adverse drug reactions and interactions, improving drug safety for all patients.

Exploring disease pathophysiology produces insights into target and biomarker identification, prognostic, and predictive patient stratification, metabolic profiling, and target-based drug development and regulation. The resultant concepts that emerge from experimental therapeutics are evolving treatments in clinical practice. Networks by which receptors for epidermal growth factor (EGF) regulate the growth and survival of cells and their disruption in transformation established them as central mechanism-based therapeutic targets in breast and lung cancer. Heterogeneous expression motivated integration of EGF receptor testing as a prerequisite to stratifying patients with breast cancer to establish eligibility for anti-EGF receptor monoclonal antibody therapy (*Table 1*). Similarly, heterogeneity in mutations in tumors revealed the importance of profiling patients with breast cancer, to establish eligibility to receive monoclonal antibody inhibitors of EGF receptors (*Table 1*). Conversely, metabolic profiling revealed the importance of polymorphisms in drug metabolizing enzymes in adverse drug responses in patients with solid tumors receiving irinotecan (*Table 1*).

While personalized medicine has transformed each intersect along the pharmacotherapeutic continuum to optimize discovery, development, and utilization of therapeutic advances, challenges persist to realizing the full potential of individualized patient management. Principle obstacles include the lack of validation in prospective trials that provide evidence for integration into practice guidelines; unsolved concerns of costs and coverage criteria; uncertainty of federal regulatory mechanisms for products of personalized medicine; and limitations in specialized workforces and the science of health care delivery to integrate "omic"-based technologies into institutionalized patient management.[24] Moreover, there are unappreciated barriers comprising medicolegal liability and ethical obstacles pertaining to applying the emerging experimental therapeutic toolkit to routine patient management, ultimately requiring solutions to facilitate clinical adoption.[25] These obstacles are structurally interrelated, where regulatory approval, reimbursement, and clinical adoption are predicated on the evidence basis for clinical efficacy and value. Finally, tools for personalization of therapy will undergo scrutiny for cost-effectiveness. For example, use of genotype-driven dosing of warfarin sensitivity in atrial fibrillation patients has a quality-adjusted life-year cost of >$170,000, making widespread application unlikely, and from a societal perspective, possibly an unwise allocation of resources.[26]

The revolution in experimental therapeutics has revealed an unanticipated avenue to the development and integration of novel diagnostic and therapeutic elements.[27] Variability in response to therapy remains one of the greatest challenges of the health care provider when caring for individual patients, as well as society, when allocating resources for population health care. The central role of experimental therapeutics and the clinical pharmacologist, as the practitioner at the bench-to-bedside interface deploying the emerging therapeutic armamentarium, and the unprecedented impact of individualized medicine at each node along this continuum, places these paradigms at the nexus of contemporary health care practice. The imminent revolution in clinical practice emanating from this model is the evolution of diagnostic and therapeutic modalities that ultimately achieve disease prediction and prevention, contributing to personalized pharmacotherapy to optimize patient management and transform the practice of medicine.

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