Clinical and Translational Sciences: At the Intersection of Molecular and Individualized Medicine

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Introduction

Advances in patient care exploit opportunities offered by discovery paradigms and their translation to therapeutic interventions.[1] Critical challenges in therapy at present include disease specificity, interpatient variability, and off-target effects.[2] Molecular medicine provides a powerful catalyst for diagnostic and therapeutic platforms tailored to the genetic and molecular profile of individual patients to improve specificity, reduce variability, and minimize adverse events.[3–6] Indeed, advances in molecular medicine have transformed the contemporary therapeutic landscape from drug discovery through identification of drugable targets, development through stratification of patients and diseases, regulation through identifying pathways mediating off-target effects, and utilization through matching patients with their optimal drug regimens.[2,7,8] This revolution in molecular therapeutics has entrained an evolution in biology and medicine. Insights achieved in molecular and genetic mechanisms directing cell, tissue, and organ function and their interface with the environment are translated to identify pathophysiological risks, define exogenous and endogenous mechanisms mediating disease susceptibility, target mechanism-based therapeutic interventions, and tailor prevention and control strategies to provide integrated patient-specific life-long disease management.[9,10] The emerging field of clinical and translational science drives the leading edge advancing discovery from the laboratory bench to evidence-based practice at the bedside, and beyond to populations, to transform the clinical enterprise and create predictive, personalized, and preemptive paradigms for customized patient-specific therapeutic strategies.[3,5,9,11]

Predictive Medicine

Medical research has ascended beyond information curation into the new, and still evolving, science of predictive medicine, which holds the promise of establishing disease risk for each individual, and ultimately preventing disease development and managing disease treatment.[9] It is increasingly understood that disease pathophysiology, in part, reflects the outcome of innate malfunction of genetic programs established at the time of conception. In other cases, disease pathogenesis is the consequence of acquired abnormalities in genetic programming. Still in others, aberrant genetic programs are revealed by permissive environmental interactions. Prediction of disease risk in individuals depends upon the decoding of abnormal genetic programming at birth and/or the identification of acquired abnormal programming longitudinally over the lifetime of the patient. Advancing the field of predictive medicine will require genome-wide assessment of populations necessary to define the association of genetic mechanisms contributing to the final common pathway manifested as overt disease. Moreover, paradigms that discriminate germline-inherited genetic predisposition to disease versus acquired alterations in genetic programming predisposing individuals to develop disease must be defined to secure optimal predictive management. The output of this approach will be the identification and application of genetic biomarkers associated with a quantifiable risk of disease. Collectively, the integration of multiple markers of risk will provide a cumulative disease risk index for individual patients.

Beyond alterations in protein coding sequences in DNA, there are mechanisms, both inherited and acquired, that modulate genetic programs. DNA and histone modification are prototypic mechanisms defining the interindividual susceptibility to disease. In disease entities, which do not exhibit typical Mendelian inheritance, epigenetic mechanisms are implied as critical elements of the pathogenetic process. In that context, the enumeration of epigenetic mechanisms underlying the development of disease, and their associated biomarkers, will remarkably contribute to defining individual disease risk. Moreover, an emerging paradigm has revealed a layer of genetic programming by which cells determine their fate, and which involves posttranscriptional regulation of gene expression by micro-RNAs.[12] This represents the most recent addition to mechanisms regulating nuclear-cytoplasmic information processing, at the interface between epigenetic and genetic mechanisms—and transcriptional, translational, and posttranslational regulation.[13] Importantly, their function continues to provide insights into the genetic circuitry whose corruption compromises homeostatic mechanisms underlying pathogenesis.[1,14] Beyond inherited genetic and epigenetic polymorphisms associated with a risk of disease, there is an interaction between the environment and the patient, which can induce changes in genetic programming ultimately leading to pathophysiology. In this context of ecogenetics, the risk of an individual to develop disease can be defined both by endogenous genetics and epigenetics and by the environmental pressures, which evolve those programs, ultimately inducing pathophysiology.

Personalized Medicine

Personalized therapeutic intervention, envisioning a shift from the current paradigm of disease palliation to cure, presumes the identification of well-defined molecular mechanisms whose disruption underlies disease and whose components serve as drugable targets.[1,5] Further, disease reflecting disordered genetic programming may be interrupted or reversed employing gene replacement therapy. Moreover, degenerative diseases associated with cell attrition and tissue disruption may be addressed employing regenerative cell-based therapies.[15] Finally, for all of these approaches, the safety of therapeutic interventions will reflect the genetic, and associated protein-based, polymorphisms underlying pharmacokinetics and therapeutic disposition, reflected as idiosyncratic individual drug reactions.[10]

In that context, signaling mechanisms defective in pathophysiology underlie the molecular substrate of the clinical manifestation of disease. Changes in components of critical signaling cascades produce a diversity of disease states, depending on the specific tissues in which they are disrupted. Moreover, changes in different components may ultimately lead to common clinical manifestations reflecting a final common pathway to disease. This diversity notwithstanding, the array of involved signaling mechanisms underlying disease manifestation and

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progression, and the specific components of these pathways that are altered in pathophysiology require definition. Once identified and their role in disease defined, the ability to disrupt their signaling function and, thereby, interrupt the molecular mechanisms underlying pathophysiology becomes a primary focus for individualized disease management.

In many cases, pathophysiology has its origins in disordered genetic programming, referable to one or a few genes, which are polymorphic or mutated, resulting in abnormal function. Genetic abnormalities may be approached employing gene replacement therapy techniques.[16] Also, some disease processes result in the loss of significant cell and tissue mass resulting in organ dysfunction. In those cases, tissue repair may be provided employing regenerative stem cell therapeutic approaches, including the use of adult and embryonic stem cells to repair irrevocably damaged tissues.[17] Moreover, all therapeutic interventions carry a risk of adverse, sometimes life-threatening, side effects. In many instances, adverse effects of therapy reflect polymorphisms in genes programming the disposition of drugs and biologicals, including transporters, drug-metabolizing, and drug-conjugating enzymes. Individual minimization of therapeutic risk will require the definition of the universe of genetic and metabolic polymorphisms that impact pharmacokinetics and drug disposition and that can be assessed employing appropriate biomarkers, to permit dose individualization to prevent adverse events.[2]

Preemptive Medicine

Ultimately, the evolution of individualized clinical care will require a paradigm shift from reactive to preemptive medicine, in which diseases are anticipated and prevented before impacting quality of life.[5] In some cases, preemptive medicine and the assessment of risk will entail longitudinal follow-up and vigilant serial screening to identify the earliest evidence of pathophysiology. In other cases, preemptive assessment can be coupled with specific targeted interventions to prevent development of disease in high-risk individuals. Similarly, in some patients who carry a disease diagnosis, risk of progression can be assessed and controlled by targeted intervention. Beyond individual patients, algorithms employing preemptive disease management, including disease screening and lifestyle alterations, will have the greatest impact on individual health within the context of populations.

Molecular Medicine and Global Health

Beyond individuals and populations, the intersection of molecular and translational medicine represents a pivotal point in the evolution of national and global healthcare reform. They are central to realizing the clinical value of advances in the new biology, driving translation of discovery to practice. In the context of a parallel evolution in the science of healthcare delivery, they are the engines that will drive the transformation of medicine.[9] Further, molecular and translational medicine represents emergent solutions to the crises in healthcare delivery nationally and globally. Indeed, pharmacotherapy, the most cost-effective management tool in the clinical armamentarium, will particularly benefit from advances in molecular and translational medicine, enhancing the cost-effectiveness proposition by prognostic and predictive subsetting of patient populations, targeting disease processes, and avoiding life-threatening adverse events. Moreover, the shift from palliation to curation with the revolution in regenerative medicine and therapeutics has the potential to transform the efficiency of disease resolution, shortening hospital stays, and decreasing healthcare expenditures.

Conclusion

Clinical and translational sciences provide a multidimensional paradigm of medicine without borders, bridging communities of practice across biological and medical specialties. The strength and uniqueness of this emerging field is rooted in its comprehensive approach incorporating research, clinical practice, and education to advance patient care. Its success depends on the evolution of discovery and development paradigms to translate molecular insights into evidence-based practice. In turn, this translation requires unprecedented cooperation and collaboration among stakeholders from different ends of the scientific and practice continuum, a directional realignment that has been anathema to these communities in the past. The products of this realignment and the resultant success of this nascent discipline will be novel diagnostic and therapeutic tools to predict, prevent, and cure disease in patients, individually and across global populations. In this context, the stakes are high and the professional rewards great. Moreover, our patients are waiting.

Acknowledgments

S.A.W. is the Samuel M.V. Hamilton Endowed Professor of Thomas Jefferson University. A.T. is the Marriott Family Professor of Cardiovascular Research of the Mayo Clinic.

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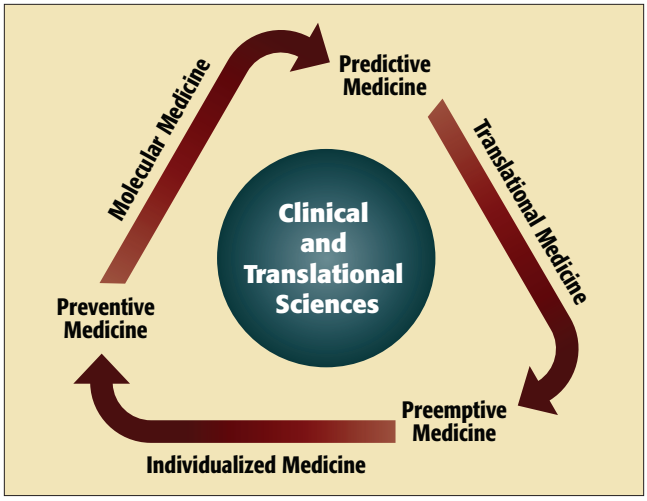

Figure 1. Clinical and translational sciences, driven by advances in molecular, translational, and individualized medicine, have evolved into a multidisciplinary platform transforming the clinical enterprise, and enabling the application of evidenced-based customized solutions in predictive, preventive, and preemptive medicine.

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