

Editor-in-Chief's Commentary: Gene Penetrance, Therapeutic Targets, and Regulatory Science

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There has been a tendency of late to add the suffix “science” to a variety of disciplines. This often is done to make the named enterprise somehow *seem* more scientific or steeped in the scientific method. However, in the case of “regulatory science” I think there is a strong, even overwhelming rationale for creating the term, and for pursuing its inherent goals. While defined somewhat differently by various individuals and groups, to me the need for an *applied, scientific* discipline to drive the wise application of basic, translational, and clinical sciences into improved practical decision making about medical product development and evaluation is compelling.

In this issue of *TIRS*, there is an article reviewing a DIA workshop on co-development of personalized medicine and in vitro companion diagnostics (see Kim et al¹). This approach to therapeutics has literally exploded in the last several years. The scientific rationale underlying much of this effort is driven heavily by advances in genomic technology, and by the growing concepts surrounding “precision medicine” (see the National Academy of Sciences report, “Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease”²). Disease definitions are rapidly changing. As we understand the molecular basis of syndromes (based on complex genomic, epigenomic, metabolic, environmental interactions), new horizons open to design interventions aimed at increasingly specific, disease-associated targets. Use of in vitro diagnostics holds great promise to select those patients most likely to respond to an intervention. The potential for transforming the drug development and regulatory process is enormous. As use of such tests expands, issues of analytic validity and of clinical validity become increasingly important areas for both drug development and regulation. As we enter this era of new biology and try and define clinical validity of a diagnostic and of a drug target, it is important to reflect on some basic concepts in genetics and the association of an individual’s phenotype (appearance, health, and illnesses) and their genetic makeup.

In traditional genetics, we have long discussed “gene penetrance,” the association between a genotype and a clinical

phenotype. So much of our understanding of genetics, from the time of Mendel, to Garrod’s descriptions of inborn errors of metabolism, to our present classification of genetic disease, has come from “high penetrance” genotypes in Mendelian inherited diseases. A relevant example today is a disease such as cystic fibrosis, now known to be caused by a variety of mutations in the CFTR, a gene coding for a membrane chloride channel. It is inherited as an autosomal recessive trait, patients with two “abnormal” genes developing the disease. While other genes and environmental factors can modify a specific patient’s clinical course, a patient with the genotype has an extremely high probability of developing the disease. The diagnostic tests for mutations in the CFTR are well established, and both analytically and clinically validated. Indeed, patients are genotyped at the time of clinical diagnosis. One of the variant genes codes for a CFTR that is transported into cell membranes but does not form an “open” chloride channel. Remarkably, a new drug has been developed, based on basic understanding of the variant CFTR, that corrects the defect, and it has been shown in clinical trials to be effective in improving many aspects of the clinical syndrome. Strikingly, the therapeutic effect size is very large and easily differentiable from placebo-treated patients, and the vast majority of patients with this specific gene defect respond to the drug. Because of the large effect size, the definitive clinical trial required only small numbers of patients; demonstration of efficacy was facilitated by clear understanding of the disease, its pathogenesis and molecular basis, and well-organized patient advocacy and international clinical trial networks. The regulatory approval process, in turn, was enhanced and made more confident by the excellence of the science, from basic through clinical. The clarity of the scientific approach further facilitated positive collaboration among patient advocates, the academic medical community, the drug’s sponsor, and regulators. The development program and regulatory approval processes have been hailed as models of transparent and efficient therapeutic innovation.

So, it can be done: translation of science from basic to clinical to regulatory into an efficient and effective process of drug

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development. And yet, can this be a model for the development of other products for other diseases? Returning to the issue of gene penetrance, for most complex human illness, multiple genes, epigenetic modification, their “microbiome,” and other environmental variables ultimately determine phenotype. A specific therapeutic target, associated with an analytically validated and even clinically associated biomarker or diagnostic test, may not be determinative of the disease phenotype, and intervention may or may not alter the phenotype (ie, demonstrate efficacy). A diagnostic test may help select patients for clinical trials, or subsequently in clinical use, who *can* respond to a targeted intervention. But for polygenic disease, it is less clear at the outset what the *extent of the response* will be. Models of drug development and approval in Mendelian genetic conditions such as cystic fibrosis with highly penetrant targets may not apply with as much ease of practical implementation as developing drugs aimed at “lower penetrance targets” in polygenic, complex disease. We should expect to see lower therapeutic effect sizes as well as a lower percentage of patients responding, based on the likely variable impact of a given target response in a complex disease within a population of patients. This does not mean that a drug so developed may not be clinically useful. However, these considerations do have implications for “expectations” for the drug, and for commitment to pursuing specific targets, planning clinical development, and regulatory planning including acceptance of “surrogate” markers. Incorporation of contrasting expectations of “high penetrance” and “lower penetrance” etiologies and drug targets into discussion of development programs and regulatory practice may help set more reasonable expectations of what will be needed to demonstrate efficacy and to be a meaningful addition to our therapeutic armamentarium.

The new approach to targeted therapeutics has driven remarkable innovation in the treatment of cancer. Targeting specific molecular drivers of cancer has resulted in multiple new drugs, many of which exhibit very large treatment effects (sometimes with fewer side effects) than older therapies. Yet, we have quickly learned about the complexity of multiple drivers of the malignant process, and of treating disease with high mutation rates. As we learned about resistance in antimicrobial therapies, cancer cells that may be driven by a highly penetrant gene product can change, making the target less “penetrant”

and thus diminishing the efficacy of a targeted therapeutic. Initial spectacular response may give way to return of the cancer. The development of resistant cells in the presence of treatment (selective pressure), change in multiple gene expression in a primary versus metastatic site, and alteration in membrane transporters all challenge our understanding of the complexity of the process we are treating. Similar to many infectious diseases including HIV with rapid mutation rates, the likely need for multiple drug therapies to truly control and cure many cancers is becoming increasingly apparent. This, in turn, will lead (and is already leading) to new paradigms for cancer drug development and regulation, foreshadowing increasing complexity of multidrug regimens determined by tumor gene expression. The informatics challenges, validation of diagnostics, and validation of responses all will evolve. Thoughtful, flexible, transparent discussion of the state of science in real time, and of evolving science by all—patients, physicians, drug developers, and drug evaluators—will be required to optimize the translation of new knowledge into validated therapeutics.

Returning to basic genetics and science, I think it is useful to consider the concept of highly penetrant genes, low penetrant genes, and changing penetrant genes, and the consequence this has for drug development and regulation. As our ability to tap genomic/gene expression/epigenetic/proteomic/metabolomic information continues to expand, implementation of that information in a regulatory science context will be increasingly complex. Placing “new” science in the context of overall biology can help set expectations and provide a sound basis for regulatory science, for enhanced wise decision making.

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References

1. Summary of DIA workshop on co-development of personalized medicine and in vitro diagnostic companion devices. *Therapeutic Innovation & Regulatory Science*. 2013;47(3):294-298.
2. National Research Council Committee on A Framework for Developing a New Taxonomy of Disease. *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*. Washington DC: National Academies Press; 2011.