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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
Pachyonychia Congenita: Cast in Translation

Asembling a keratin network is no mean feat. The process of combining acidic and basic keratin monomers, stacking them in an orderly fashion, and then polymerizing the bundles into rope-like intermediate filaments is an intricate operation, and one that relies on numerous cellular and subcellular processes. In many ways, the same organizational complexity is reflected in the International Consortium that over the past eight years has been assembled to decode the mysteries of the autosomal dominant keratin disorder pachyonychia congenita (PC). In this issue of JID, we present a collection of eight papers that detail the major clinical, diagnostic, mechanistic, and therapeutic advances that have emerged in recent years that were presented at the annual meeting of the International PC Consortium (IPCC) in May 2010.

The earliest clinical descriptions of PC appeared more than 100 years ago, and the first causative mutations were reported in the mid 1990s. Subsequently, PC has been shown to involve heterozygous mutations in the KRT6A, KRT6B, KRT16, and KRT17 genes that encode keratins K6a, K6b, K16, and K17, respectively. Of course, a similar tale of careful clinical definition followed by rigorous molecular dissection has emerged for several other Mendelian skin diseases. But where the story of PC differs from that of most other genodermatoses is in what happened next.

Establishing the molecular basis of disease provides a platform for creating in vitro and in vivo disease models, as well as translational benefits in terms of improved diagnostics and genetic counseling, but often pushing the translational envelope fails to overcome many of the obstacles blocking major benefits for patients, particularly toward the development of novel therapies. Thankfully for PC investigators and patients, however, substantial progress has been made, and key to this success has been the assembly of a multifunctional professional cast, each with subspecialist skills sufficient to overcome therapeutic inertia or stalling.

Fundamental to the translational push has been the activity of the patient advocacy group PC Project (http://www.pachyonychia.org), which helped establish the IPCC in 2004. Working together, the consortium subsequently assembled a network of clinicians, clinician–scientists, and scientists from a range of molecular biology, cell biology, imaging, chemistry, physics, and pharmacological backgrounds, collectively tasked with improving understanding of the pathophysiology of PC and driving forward new therapies that can be delivered to patients.

Central to all activities, however, has been the PC patient. The IPCC has formulated a registry for patients with PC and facilitated molecular screening. This has led to a significant expansion in the database of PC gene mutations, refinements in genotype–phenotype correlation, a new classification for PC, and a greater understanding of the impact of PC on patient quality-of-life issues, such as severity of plantar pain. But what perhaps was needed most was a clear strategy of how to develop therapies.

Modeling of PC established that mutant allele-specific silencing using RNAi approaches might be a suitable method for treating PC, and in 2010 the first human trial of siRNA for an inherited skin disease was carried out with clear clinical benefits in the treated area. Evidence was also established for some functional redundancy among certain keratins, indicating that a more generic approach in completely silencing a defective keratin was also likely to be a rational therapeutic endeavor in some other PC cases. Overhanging much of the molecular targeting, however, has been the major obstacle of effective delivery to target keratinocytes. This is a current priority for the IPCC and a focus for its assembled crew of “delivery” experts.

As a model for how to perform translational research, the PC work has established a new paradigm for progress. Germane to all advances, however, has been the close engagement with the patient advocacy group PC Project, as well as the PC patients themselves, and the multidisciplinary group of clinicians and scientists. Assembling an impressive cast of capable performers has been a considerable achievement, and now the stage is set. An expectant audience of patients and investigators eagerly awaits the next act.

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