

Preface to Pachyonychia Congenita Symposium Proceedings

Sancy A. Leachman,* W. H. Irwin McLean,† Janice N. Schwartz,‡ and Mary E. Schwartz‡

*Department of Dermatology, University of Utah Health Sciences Center, Salt Lake City, Utah, USA; †Human Genetics Unit, Ninewells Hospital and Medical School, University of Dundee, Dundee, UK; ‡Pachyonychia Congenita Project (PC Project), Salt Lake City, Utah, USA

These *Symposium Proceedings* summarize current clinical, therapeutic, and scientific challenges associated with developing effective treatments for pachyonychia congenita (PC). The impetus for these papers was the First International Pachyonychia Congenita Symposium, held on February 12–16, 2004, at the Yarrow Hotel in Park City, Utah. This symposium was sponsored by The Pachyonychia Congenita Fund (Pachyonychia Congenita Project/PC Project), a USA public charity founded in November 2003, which supports clinical and research activities related to the treatment of pachyonychia congenita. The goal of this symposium was to gather thought leaders, expert clinicians and scientists to explore approaches to the treatment and eventual cure for the disorder. As reflected in these *Symposium Proceedings*, the major topics of presentations included our most current understanding of the clinical and histologic features, therapeutic approaches, and the molecular genetics of the disease. In addition, “special topics” sessions focused on the most practical and efficient approaches to developing an eventual cure for PC, including discussions of the most useful model systems and genetic and pharmacologic approaches. Finally, the difficulty of initiating clinical trials and developing therapeutics for rare disorders of the skin was discussed at considerable length, with an emphasis on maximizing the relationship between academia and industry in this effort. All participants in this symposium were encouraged to critically evaluate options, and the roundtable discussion format permitted a productive and frequently lively exchange of ideas and information.

Sancy Leachman, Patti Champine, Mary Schwartz, and Jan Schwartz organized the symposium, which opened with a series of lectures by Irwin McLean, Leonard Milstone, Alfred Lewin, Markus Landthaler, Mario Capecchi, Olga Igoucheva, and Roger Kaspar. These lectures focused on potential gene therapy technologies that could be applied to PC. The technologies that were considered included siRNA, ribozymes, triplex oligonucleotides, homologous recombination techniques, RNA lassos, and other oligonucleotide-mediated gene repair techniques. The RNA-mediated technologies would aim to decrease the intracellular levels of the affected keratin and would have the potential advantages of being highly specific for the mutated RNA. These techniques would also have a transient, and thus reversible, character. The primary disadvantage to the RNA-based approach is that it would likely require ongoing repetitive administration in order to be effective. The gene correction therapies utilizing homologous recombination, triplex-forming oligonucleotides, or other oligonucleotide-mediated

repair techniques have the advantage of offering a more permanent correction of the mutated keratin, but are also less feasible in the short-term because of the difficulty in getting an adequate number of cells corrected *in vivo*. The problem of delivering these types of gene therapy agents to the nails and hyperkeratotic skin of PC patients was discussed in a lecture by Bhaskar Thyagarajan. It was concluded by the conference attendees that delivery will be one of the major obstacles to overcome in the treatment of PC.

The next session included a thorough examination of the clinical, histologic, and molecular genetic features of PC led by Philip Fleckman, Frances Smith, and Maurice van Steensel. It has now become clear through mutation screening of PC patients that the clinical phenotype of PC is somewhat variable and that the two major categories, PC-1 and PC-2, can be discriminated by mutations in K6a or K16 for PC-1 and K6b or K17 for PC-2. The clinical and genetic discussions ultimately led to the development of a questionnaire designed to facilitate further elucidation of genotype-phenotype relationships in PC. This questionnaire has now been completed by 57 participants in the newly formed PC Registry, and data from these questionnaires are reported in Leachman *et al* in this issue.

The final session of the conference focused on the potential model systems available to advance our understanding of the pathogenesis of PC as well as serve as pre-clinical models for therapeutic agents. Dennis Roop and Pauline Wong described the currently available cellular and mouse models. Consensus was reached by the group that a PC mouse model would be an extremely valuable tool for both basic and pre-clinical investigation. Various approaches to the development of this model were discussed, and it was felt that one of the best strategies would be to create a mutant K6a knock-in to try to replicate the dominant-negative effect of the mutation. It was also decided that models containing only a minor modification of the mouse gene as well as a “humanized” model containing human regulatory regions should be attempted.

An important outcome of the meeting was the development of the International Pachyonychia Congenita Consortium (IPCC), a collaborative team of clinicians and scientists interested in pursuing PC care and research. A major accomplishment of the IPCC has been the development of a collaborative research strategy in which PC research projects are integrated to maximize efficiency and minimize cost by sharing key resources and reagents. The IPCC has identified several important gaps in our understanding of PC and in the approaches that have been taken toward devel-

oping treatments for the disorder. These major deficiencies include the lack of good *in vitro* and *in vivo* model systems, the lack of therapeutic agents, our inability to deliver therapeutic agents to hyperkeratotic skin, and the lack of a registry to organize PC patients and facilitate clinical trials. Each of these deficiencies will need to be eliminated before the goal of a treatment for PC may be realized.

In summary, the goal of these *Symposium Proceedings* is to create a “PC Handbook” to summarize current knowledge and discuss state-of-the-art options for therapeutics in the future. Perhaps the most promising result of the IPCC is the collaborative network that has developed and is actively working to better understand PC to help these patients. PC patients have commented online that, “Having

PC has taught me to count my blessings. My feet hurt, but I do have feet. I enjoy sure knowledge that the people in my life are solid individuals, who have demonstrated by their actions that they are not superficial people who care about looks or what others might say. It’s a big positive to know my closest friends are not shallow, but terrific people with strong character, who look at my heart and not at my beautiful nails and feet.” It is our sincere hope that our combined efforts will culminate in an improved lifestyle for all PC patients.

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