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Pachyonychia congenita cornered: report on the 11th Annual International Pachyonychia Congenita Consortium Meeting

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Summary

This is a report of the research presented at the 11th Annual Meeting of the International Pachyonychia Congenita Consortium, held on 6 May 2014 in Albuquerque, NM, U.S.A. This year's meeting was divided into five corners concerning pachyonychia congenita (PC) research: (i) 'PC Pathogenesis Cornered', an overview of recent keratin research, for PC and other skin disorders; (ii) 'From All Corners of . . .', an outline of other genetic disorders that we can learn from; (iii) 'Fighting For Our Corner', an outline of National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases programmes and U.S. funding opportunities applicable to rare skin disorders; (iv) 'The PC Corner', focusing on recent clinical studies related to PC; and (v) 'Clinical Corners: Turning the Corner?', an update on ongoing PC clinical trials.

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Conflicts of interest
R.L.K. is an employee of TransDerm Inc., with intellectual property on pachyonychia congenita.

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The 11th Annual Meeting of the International Pachyonychia Congenita Consortium (IPCC) was held on 6 May 2014 in Albuquerque, NM, U.S.A. The presentations are listed in Table S1 (see Supporting Information). The consortium regroups physicians and scientists who contribute their expertise and time to developing therapeutics for the rare orphan disease pachyonychia congenita (PC), an autosomal dominant genodermatosis caused by mutations in keratins K6a, K6b, K6c, K16 or K17.[1] The main clinical features of PC include highly debilitating pain accompanying plantar keratoderma, hypertrophic nail dystrophy, oral leucokeratosis and epidermal cysts.[2] Each year's IPCC meeting is devoted to discussing recent progress and to prioritizing future directions for PC research.

International Pachyonychia Congenita Consortium contributions of the past 10 years include building a patient registry; delineating the clinical manifestations of PC based on detailed analysis of symptoms affecting patients with genetically confirmed PC;[3] advocating for abandoning the now obsolete descriptions Jadassohn–Lewandowsky (formerly PC type 1) and Jackson–Lawler (formerly PC type 2) and using the new, more rational gene-based nomenclature based on the mutated keratin in a given patient (PC-K6a, PC-K6b, PC-K6c, PC-K16 and PC-K17);[4] conducting a phase Ib clinical trial using the mutation-specific small interfering (si)RNA TD101;[5] identifying sirolimus (rapamycin) as a modulator of keratin expression;[6] and initiating a subsequent topical sirolimus clinical trial for PC (update below), and publishing best practice guidelines for PC.[7]

Shedding light on pachyonychia congenita pathogenesis

Jiang Chen (Stony Brook University, NY, U.S.A.) opened the 'PC Pathogenesis Cornered' section with his work on the N159Del mutation of K75 (formerly known as K6hf), which triggers hair and nail defects in mice.[8] Chen's group employed an siRNA 'sequence walk' strategy to target the mutated Krt75 allele, and delivered the selected candidate to mice via a short hairpin RNA-carrying lentivirus. Their data

demonstrate that partial interference of mutated RNA is sufficient to restore the structural defects caused by a heterozygous keratin mutation. These observations further strengthen previous work with K6a,[5] suggesting that a personalized therapeutic approach to keratin disorders is clinically relevant.

Robert Rice (University of California, Davis, CA, U.S.A.) analysed global protein expression in tape circles from involved and uninvolved plantar areas of patients with PC-K6a using established techniques.[9] He showed that PC skin differs from control skin in expressing reduced levels of K9, and relatively high levels of other keratins (K5, K6 and K14) and epidermal differentiation markers (transglutaminases and S100A9). A similar gene expression signature was found in callous skin from patients with PC (collaboration with TransDerm Inc., Santa Cruz, CA, U.S.A.).

Laure Rittié (University of Michigan, Ann Arbor, MI, U.S.A.) studied the microanatomy of a PC-K16 skin biopsy using a computer-assisted three-dimensional reconstruction approach.[10] Rittié's group identified four defects in PC callous skin compared with control plantar skin: epidermal blisters and engorged blood vessels, as previously reported,[11] defects in sweat gland morphology, and fibrosis of the extracellular matrix. An interesting group exchange followed to discuss what sequence of events would best explain PC plantar pain pathogenesis, and what target should be focused on for strategic therapy.

Learning from other diseases

In the 'From All Corners of. . .' session, Paul Goldberg (Xenon Pharmaceuticals Inc., Burnaby, Canada) presented his work related to $Na_v1.7$, a voltage-gated sodium channel, which when deficient causes congenital indifference to pain. Goldberg reviewed his results on XEN402, an analgesic developed to inhibit $Na_v1.7$ that effectively alleviates peripheral neuropathic pain and erythromelalgia.[12,13]

Eli Sprecher (Sourasky Medical Center, Tel Aviv, Israel) discussed inflammatory peeling skin syndromes including Netherton syndrome (*SPINK5* mutations), peeling skin syndrome (corneodesmosin mutations) and the newly described SAM syndrome, characterized by severe dermatitis, multiple allergies and metabolic wasting [desmoglein 1 (*DSG1*) mutation].[14] Sprecher reviewed similarities and differences in the clinical and histological manifestations of these syndromes, all characterized by epidermal barrier dysfunction.

Yong Yang (Peking University First Hospital, Beijing, China) presented his work on Olmsted syndrome, a palmoplantar keratoderma accompanied by periorificial keratosis, alopecia and severe itching, recently attributed to mutations of transient receptor potential cation channel, subfamily V, member 3 (TRPV3).[15] Yang presented genotype–phenotype correlation studies and proposed a biological rationale for the severity of mild vs. mutilating forms of Olmsted syndrome.

Hans Van Bokhoven (Radboud University Medical Center, Nijmegen, the Netherlands) closed the session by presenting his work on p63 syndromes. Mutation of the *TP63* gene causes at least seven syndromes, triggering ectodermal dysplasia, limb defects, orofacial clefting, or a combination of these. Van Bokhoven showed that the ectrodactyly ectodermal dysplasia clefting syndrome is caused by mutations affecting the DNA-binding domain of p63. Taking advantage of the high homology between the p63 and p53 binding domains, Van Bokhoven's group tested the interesting idea that the binding function of p63 DNA could be restored utilizing a mutant p53-targeting compound developed for cancer therapy. By demonstrating that this was the case at least *in vitro*,[16] these results support the idea that a better understanding of the pathogenesis of a genetic disease can lead to (unexpected) therapeutic options.

Funding pachyonychia congenita research

In the last morning session, Carl Baker [National Institutes of Health (NIH)/National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), Bethesda, MD, U.S.A.] reviewed the specifics of NIH/NIAMS funding mechanisms relevant to PC, and reiterated the commitment of NIAMS to funding research on rare skin disorders such as PC.

Better delineating pachyonychia congenita symptoms

'The PC Corner' early afternoon session summarized some major clinical issues for patients with PC and new data from the International PC Research Registry (IPCRR). Ilan Goldberg (Sourasky Medical Centre, Tel Aviv, Israel) spoke about mucosal and laryngeal leucokeratosis, which if extensive can lead to poor feeding and, rarely, laryngeal obstruction.[17] Infants and children with PC-K6a sometimes have 'first bite syndrome', a severe pain anterior to the ear (probably localized to the parotid gland) on first sucking or eating that lasts about 25 s.

C. David Hansen (University of Utah, Salt Lake City, UT, U.S.A.) discussed clinical findings of 549 individuals from 296 families with a confirmed PC genotype. Details of these findings are updated regularly on the IPCC website (http://www.pachyonychia.org/pc_data.php). The clinical data support a diagnostic triad of plantar pain, plantar keratoderma and toenail dystrophy as identifying 92% of patients with PC (excluding children aged < 3 years). The most commonly mutated gene is *KRT6A* (41%), followed by *KRT16* (30%), *KRT17* (17%), *KRT6B* (9%) and *KRT6C* (3%).

Barbara Hoggart (Heart of England NHS Trust, Birmingham, U.K.) spoke about pain and PC. The differences between neuropathic and nociceptive pain were discussed.[18] Hoggart reviewed preliminary data demonstrating that neuropathic pain comprises a significant component of PC pain and varies with genotype. The outcome of this and other studies will be important because patients with neuropathic pain will require a different analgesic strategy.

Answering specifics with clinical trials

The second afternoon session, entitled 'Clinical Trials: Turning the Corner?', provided an update on strategies for treatment of the plantar pain of PC. Alain Hovnanian (Imagine Institute and Necker Hospital, Paris, France) discussed off-label use of capsaicin patches for plantar pain in one patient with PC. Capsaicin is a TRPV1 agonist that excites and then desensitizes sensory nerves.[19] Application of capsaicin patches for 30 min produced a small-to-moderate improvement in pain, which lasted for a few months. It was agreed that studying TRPV1 expression in PC skin would be useful.

The last three presentations were on topical sirolimus, a mammalian target of rapamycin (mTOR) inhibitor. Sirolimus selectively blocks translation of mRNAs with terminal oligopyrimidine tracts, including *KRT6* mRNA.[6] Oral sirolimus showed some promise for PC plantar pain, but use was limited by side-effects including gastrointestinal symptoms.[6]

Steven L. Roberds (Tuberous Sclerosis Alliance, Silver Spring, MD, U.S.A.) spoke about the use of oral and topical sirolimus in tuberous sclerosis complex (TSC) and the excellent response of TSC facial angiofibromas to treatment. Current challenges include a large variety of topical formulations without head-to-head comparisons and issues with insurance reimbursement.

Freddie Bartholomew and Viraat Patel (Stanford University, Palo Alto, CA, U.S.A.) discussed a phase Ib randomized controlled clinical trial, which has just started at Stanford, comparing topical sirolimus with placebo in 15 patients with PC. The trial consists of three phases including 6 months of treatment and 3 months of washout. A preliminary off-label study in three patients showed promising results.

Roger Kaspar and Tycho Speaker (Transderm Inc., Santa Cruz, CA, U.S.A.) discussed the good manufacturing process formulation of topical sirolimus into a cream with an aqueous base, which is being used in the Stanford trial. They showed that this formulation demonstrates satisfactory stability and an inhibitory effect on phosphorylated ribosomal protein S6, a marker of mTOR pathway activity, in both HaCaT keratinocytes and mouse skin.

Conclusions

Major progress has been made in our understanding of PC genetics and genotype–phenotype correlation, assisted greatly by data from the IPCRR. This year's meeting delineated promising advances in the pathophysiology of PC, including previously unknown aberrant eccrine sweat glands and blood vessel formation, dramatic alterations of the skin proteome, and identification of different types of pain among PC genotypes. The intense study of many patients with focal keratoderma is also yielding insights into those who do not have PC. The combined efforts of the IPCC have led to a number of clinical trials; we await with anticipation the first results of the randomized controlled clinical trial of topical sirolimus. Meanwhile, further planned projects were decided on, including examining the proteome in different PC genotypes, developing patient cell lines for collaborative studies, further delineating neural structures and pain receptors in PC skin, and broadening studies of both imaging and clinical pain and sweating. All these studies were prioritized with the same aim in mind: developing therapeutics for PC.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1. Presenters and presentation titles at the 11th Annual Meeting of the International Pachyonychia Congenita Consortium, 6 May 2014, Albuquerque, NM, U.S.A.