



Pachyonychia Congenita Project

Use of Articles in the Pachyonychia Congenita Bibliography

The articles in the PC Bibliography may be restricted by copyright laws. These have been made available to you by PC Project for the exclusive use in teaching, scholarship or research regarding Pachyonychia Congenita.

To the best of our understanding, in supplying this material to you we have followed the guidelines of Sec 107 regarding fair use of copyright materials. That section reads as follows:

Sec. 107. - Limitations on exclusive rights: Fair use

Notwithstanding the provisions of sections 106 and 106A, the fair use of a copyrighted work, including such use by reproduction in copies or phonorecords or by any other means specified by that section, for purposes such as criticism, comment, news reporting, **teaching (including multiple copies for classroom use), scholarship, or research**, is not an infringement of copyright. In determining whether the use made of a work in any particular case is a fair use the factors to be considered shall include - (1) the purpose and character of the use, including whether such use is of a commercial nature or is for nonprofit educational purposes; (2) the nature of the copyrighted work; (3) the amount and substantiality of the portion used in relation to the copyrighted work as a whole; and (4) the effect of the use upon the potential market for or value of the copyrighted work. The fact that a work is unpublished shall not itself bar a finding of fair use if such finding is made upon consideration of all the above factors.

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.

These articles have been accepted for publication in the *British Journal of Dermatology* and are currently being edited and typeset. Readers should note that articles published below have been fully refereed, but have not been through the copy-editing and proof correction process. Wiley-Blackwell and the British Association of Dermatologists cannot be held responsible for errors or consequences arising from the use of information contained in these articles; nor do the views and opinions expressed necessarily reflect those of Wiley-Blackwell or the British Association of Dermatologists

This article is protected by copyright. All rights reserved.

Received Date : 21-Jul-2014

Revised Date : 01-Aug-2014

Accepted Date : 04-Aug-2014

Article type : Meeting Report

Title

Pachyonychia Congenita Cornered: Report on the 11th Annual International Pachyonychia Congenita Consortium Meeting

Authors

E.A. O'Toole¹, R.L. Kaspar², E. Sprecher³, M.E. Schwartz⁴, L. Rittié^{5,6}

Affiliations

¹ Centre for Cutaneous Research, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, UK

² TransDerm Inc., Santa Cruz, California, USA

³ Department of Dermatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

⁴ Pachyonychia Congenita Project, Salt Lake City, Utah, USA

⁵ Department of Dermatology, University of Michigan Medical School, Ann Arbor, Michigan, USA

⁶: address for correspondence: Laure Rittié, PhD, University of Michigan Medical School, Department of Dermatology, 6447 Medical Science Building I, 1301 E. Catherine St., Ann Arbor, MI 48109, USA. LRittie@umich.edu; Phone: (+1) 734-647-7957; Fax: (+1) 734-947-0076.

Funding Source(s)

LR gratefully acknowledges the US National Institute of Arthritis, Musculoskeletal, and Skin Diseases for support (grant K01AR059678).

Conflicts of Interest Disclosure

LRK is an employee of TransDerm Inc. with IP on pachyonychia congenita.

Meeting Report

Introduction

The 11th annual meeting of the International Pachyonychia Congenita Consortium (IPCC) was held on May 6th, 2014 in Albuquerque, NM, USA. 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 keratin (K)6a, K6b, K6c, K16, or K17.¹ PC's main clinical features include highly debilitating pain accompanying plantar keratoderma, hypertrophic nail dystrophy, oral leukokeratosis, and epidermal cysts.² Each year's IPCC meeting is devoted to discussing recent progress and to prioritizing future directions for PC research.

IPCC 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 from 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 RNA TD101,⁵ identifying sirolimus (rapamycin) as a modulator of keratin expression⁶ and initiating a subsequent topical sirolimus clinical trial for PC (update below), and publishing best practice guidelines for PC.⁷

This year's meeting was divided into 5 corners: (i) "PC Pathogenesis Cornered", an overview of recent keratin research, for PC and other skin disorders; (ii) "From All Corners", an outline of other genetic disorders that we can learn from; (iii) "Fighting For Our Corners", an outline of NIH/NIAMS programs and US funding opportunities applicable to rare skin disorders; (iv) "PC Corner", focusing on recent clinical studies related to PC; and (v) "Clinical Corners: Turning the Corner?", an update on ongoing PC clinical trials. Presentation titles are listed in Supplementary Table S1.

Shedding light on PC pathogenesis

Jiang Chen (Stony Brook University, NY) opened the "PC Pathogenesis Corner" with his work on the N159Del mutation of keratin 75 (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 an shRNA-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 keratin 6a,⁵ suggesting that a personalized therapeutic approach to keratin disorders is clinically relevant. Robert Rice (University of California, Davis) analyzed global protein expression in tape circles from involved and uninvolved plantar areas of PC-K6a patients using established techniques.⁹ He showed that PC skin differs from control skin by 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 callus skin from PC patients (collaboration with TransDerm Inc., Santa

This article is protected by copyright. All rights reserved.

Cruz, CA). Laure Rittié (University of Michigan, Ann Arbor) studied the microanatomy of a PC-K16 skin biopsy using a computer assisted 3D-reconstruction approach.¹⁰ Rittié's group identified four defects in PC callus skin compared to control plantar skin: epidermal blisters and engorged blood vessels as previously reported,¹¹ defects in sweat gland morphology, and fibrosis of the extracellular matrix. 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" 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 the TRPV3 cation channel.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, Nijmegen, The Netherlands) closed the session by presenting his work on p63 syndromes. Mutation of the *TP63* gene causes at least 7 syndromes, triggering ectodermal dysplasia, limb defects, orofacial clefting, or a combination of these. Van Bokhoven showed that the Ectrodactyly Ectodermal dysplasia Clefting (EEC) syndrome is caused by mutations affecting the DNA binding domain of p63. Taking advantage of the high homology between p63 and p53 binding domains, Van Bokhoven's group tested the interesting idea that the p63 DNA binding function 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 PC research

In the last morning session, Carl Baker (NIH/NIAMS, Bethesda, MD) reviewed the specifics of NIH/NIAMS funding mechanisms relevant to PC, and reiterated NIAMS' commitment to funding research on rare skin disorders such as PC.

This article is protected by copyright. All rights reserved.

Better delineating PC symptoms

The “PC Corner” early afternoon session summarized some major clinical issues for PC patients and new data from the International PC Research Registry (IPCRR). Ilan Goldberg (Sourasky Medical Centre, Tel-Aviv, Israel) spoke about mucosal and laryngeal leukokeratosis, 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 seconds. C. David Hansen (University of Utah, Salt Lake City) 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 toe-nail dystrophy as identifying 92% of PC patients (excluding children under 3). The most common mutated gene is *KRT6A* (41%), followed by *KRT16* (30%), *KRT17* (17%), *KRT6B* (9%) and *KRT6C* (3%). Barbara Hoggart (Heart of England NHS Trust, Birmingham, UK) 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 the plantar pain in one PC patient. Capsaicin is a TRPV1 agonist which excites and then desensitizes sensory nerves.¹⁹ Application of capsaicin patches for 30 minutes 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, an mTOR (mammalian Target of Rapamycin) inhibitor. Sirolimus selectively blocks translation of mRNAs with terminal oligopyrimidine tracts including *KRT6*.⁶ Oral sirolimus showed some promise for PC plantar pain, but use was limited by side effects including gastrointestinal symptoms.⁶ Steven L. Roberds (Chief Scientific Officer, Tuberous Sclerosis Alliance) spoke about 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) discussed a phase 1B randomized controlled clinical trial, which has just started at Stanford, comparing topical sirolimus with placebo in 15 PC patients. The trial consists of three phases including six months of treatment and three months wash-out. A preliminary off-label study in three patients had promising results. Roger Kaspar and Tycho Speaker (Transderm Inc., Santa Cruz, CA) discussed the GMP formulation of topical sirolimus into a cream with an aqueous base, which is being used in the Stanford trial, demonstration of satisfactory stability, and an inhibitory effect on phosphorylated ribosomal

This article is protected by copyright. All rights reserved.

protein S6, a marker of mTOR pathway activity, in both HaCaT keratinocytes and mouse skin.

Conclusion

Major progress has been made in our understanding of PC genetics and PC 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 amongst 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 and included 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 clinical pain as well as sweating and imaging studies. All these studies were prioritized with the same aim in mind: developing therapeutics for PC.

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, May 6th, 2014, Albuquerque, NM, USA.

References

- 1 Wilson NJ, O'Toole E, Milstone LM *et al.* The molecular genetic analysis of the expanding pachyonychia congenita case collection. *Br J Dermatol* 2014.
- 2 Eliason MJ, Leachman SA, Feng BJ *et al.* A review of the clinical phenotype of 254 patients with genetically confirmed pachyonychia congenita. *J Am Acad Dermatol* 2012; **67**: 680-6.
- 3 Schwartz ME, Hansen CD, Paller AS *et al.* Pachyonychia congenita overview. *The Dermatologist* 2014; **22**: 36-8.
- 4 McLean WH, Hansen CD, Eliason MJ *et al.* The phenotypic and molecular genetic features of pachyonychia congenita. *J Invest Dermatol* 2011; **131**: 1015-7.
- 5 Leachman SA, Hickerson RP, Schwartz ME *et al.* First-in-human mutation-targeted siRNA phase Ib trial of an inherited skin disorder. *Molecular Therapy* 2010; **18**: 442-6.
- 6 Hickerson RP, Leake D, Pho LN *et al.* Rapamycin selectively inhibits expression of an inducible keratin (K6a) in human keratinocytes and improves symptoms in pachyonychia congenita patients. *J Dermatol Sci* 2009; **56**: 82-8.

- 7 Goldberg I, Fruchter D, Meilick A *et al.* Best treatment practices for pachyonychia congenita. *J Eur Acad Dermatol Venereol* 2014; **28**: 279-85.
- 8 Chen J, Jaeger K, Den Z *et al.* Mice expressing a mutant Krt75 (K6hf) allele develop hair and nail defects resembling pachyonychia congenita. *J Invest Dermatol* 2008; **128**: 270-9.
- 9 Rice RH, Bradshaw KM, Durbin-Johnson BP *et al.* Distinguishing ichthyoses by protein profiling. *PLoS One* 2013; **8**: e75355.
- 10 Rittié L, Sachs DL, Orringer JS *et al.* Eccrine sweat glands are major contributors to reepithelialization of human wounds. *Am J Pathol* 2013; **182**: 163-71.
- 11 Goldberg I, Sprecher E, Schwartz ME *et al.* Comparative study of high-resolution multifrequency ultrasound of the plantar skin in patients with various types of hereditary palmoplantar keratoderma. *Dermatology* 2013; **226**: 365-70.
- 12 Goldberg YP, Cohen CJ, Namdari R *et al.* Letter to the editor. *Pain* 2014; **155**: 837-8.
- 13 Goldberg YP, Price N, Namdari R *et al.* Treatment of Na(v)1.7-mediated pain in inherited erythromelalgia using a novel sodium channel blocker. *Pain* 2012; **153**: 80-5.
- 14 Samuelov L, Sarig O, Harmon RM *et al.* Desmoglein 1 deficiency results in severe dermatitis, multiple allergies and metabolic wasting. *Nat Genet* 2013; **45**: 1244-8.
- 15 Lin Z, Chen Q, Lee M *et al.* Exome sequencing reveals mutations in TRPV3 as a cause of Olmsted syndrome. *Am J Hum Genet* 2012; **90**: 558-64.
- 16 Shen J, van den Bogaard EH, Kouwenhoven EN *et al.* APR-246/PRIMA-1(MET) rescues epidermal differentiation in skin keratinocytes derived from EEC syndrome patients with p63 mutations. *Proc Natl Acad Sci USA* 2013; **110**: 2157-62.
- 17 Haber RM, Drummond D. Pachyonychia congenita with laryngeal obstruction. *Pediatr Dermatol* 2011; **28**: 429-32.
- 18 Pergolizzi J, Ahlbeck K, Aldington D *et al.* The development of chronic pain: physiological CHANGE necessitates a multidisciplinary approach to treatment. *Curr Med Res Opin* 2013; **29**: 1127-35.
- 19 Anand P, Bley K. Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. *Br J Anaesth* 2011; **107**: 490-502.