Twelfth Annual Symposium
International Pachyonychia Congenita Consortium

Tuesday, May 5 from 1pm—5pm
Tuesday Evening Dinner 7:30 pm
Wednesday Morning Breakfast 7:30 am
Wednesday, May 6 from 8:30 to 12:15

All Fees Waived with Pre-Registration—Register Now
https://www.surveymonkey.com/s/2015IPCC

We will set goals. We will meet those goals. We will empower research.

We hope that every IPCC member will be available to attend the 12th Annual IPCC Symposium. As you all know, each year we set targets at the IPCC meeting and strive to achieve those goals. We need your participation to ensure continued success.

We know there are many conflicting events this year. We have re-scheduled our meeting and hope that IPCC members will find a way to participate with the IPCC without missing other important opportunities.

Our 2015 program includes invited speakers: Rox Anderson, Carl Baker, Peter Itin as well as Bradley Bloom, Christopher Bunick, Michael J. Caterina, Roger L. Kaspar, Heidi Kong, Vinzenz Oji, Michael Polydefkis, Robert H. Rice, Sarah Tariq, Joyce M. Teng and Maurice A.M. van Steensel.

We will have a report on the clinical trial conducted at Stanford, updates on PC research at TransDerm, Johns Hopkins and UC Davis and presentations by leading researchers on related topics.

IPCC GOALS SET AND MET
2004—5 Research Grants funded
2005—Initial clinical studies
2006—move siRNA forward to clinic
2007—grow the IPCC membership
2008—siRNA Phase 1b clinical trial
2009—Delivery!Delivery!Delivery!
2010—Educational Outreach for PC
2011—14 PC articles published
2012—Best Practice Guidelines
2013—Topical sirolimus clinical trial
2014—Gather more PC data (Pain, Clinical Exam, Genetics and Histology)
The Keratin Corner

What would life without keratins look like? This is the question addressed by Thomas Magin and his colleagues in a paper published last October online in the *Journal of Investigative Dermatology*. The authors of the paper generated two models. In the first of these two models, all keratin type II genes were deleted in the skin in a mosaic pattern. These mice died at 8-12 days of age. The second model was generated by mating keratin type II negative mice with mice transgenic for K8, allowing for normal morphogenesis of internal epithelia. These mice died upon birth.

In both models, cell cytolysis was observed in basal cells. Desmosomes were fewer and smaller as compared with normal skin, suggesting that keratins are necessary to stabilize desmosomes and ensure cell-cell adhesion. In parallel, acanthosis was marked, suggesting a response to injury, possibly stimulated by intraepidermal blistering. Of interest, a marked inflammatory response with increased expression of interleukin-1beta was observed. The new data also suggest that keratins are able to mutually compensate for their malfunction as the phenotype of keratin II deleted mice was significantly more severe than that of single or double keratin knock out mice. In addition, the fact that the patchy keratin II deficient mice were able to survive after birth, suggest that regional and partial restoration of keratin function may be sufficient to mediate a clinically significant therapeutic effect in keratinopathies.


**NEWS FROM PC PROJECT GENETIC TESTING**

In 2009, recognizing from confirmed cases in the Int’l PC Research Registry, that there were no confirmed recessive cases and that PC is consistently a dominant disorder within confirmed cases, PC Project reached out to patients mentioned in a 1986 article about ‘recessive PC.’ Based on data in the IPCRR registry, we felt the patients did not have PC, but some other disorder. We wanted to confirm and the patients were eager to know what condition they have.

It has taken the geneticists six years and the cooperation of family members providing additional samples — but these patients now know their specific gene and mutation. The answer sometimes comes quickly to those with PC — but for this family and many others diagnosed with PC who have other disorders, the on-going effort by PC Project and those working with us on the Genetics Team, has been gratefully received.

We are pleased that now a correction will be published by the author of the original paper clarifying the condition and confirming PC as a dominant disorder. There are no ‘recessive’ PC cases.

At PC Project all the ‘unsolved cases’ are reviewed each month by the IPCC Genetics Team. Being involved in preparation of a paper for a new disorder caused by mutations in the CAST gene, the team noticed many similarities between the CAST cases and this case reported as ‘recessive PC.’ And, after testing, the mutation was confirmed for this family.


This is great example of the knowledge gained from the IPCRR data — and learning what is and what is not PC.

**RECENT PUBLICATIONS**

Jiráková A1, Rajská L, Rob F, Džambová M, Sečníková Z, Gopfer- 
tová D, Schwartz M, Smith F, Lotti T, Hercogová J. “First Case of 
Pachyonychia Congenita in the 
Czech Republic” Dermatology 

Knöbel M1, O'Toole EA, Smith 
FJ. “Keratins and Skin 
Disease” Cell Tissue Re-
search. 2015 Jan 27.

Lin Z, Zhao J, Nitoiu D, Scott 
CA, Plagnol V, Smith FJ, Wil-
son NJ, Cole C, Schwartz ME, 
McLean WH, Wang H, Feng 
C, Du L, Zhou YE, Ren Y, 
Dai L, Chen Y, Zhang J, Xu X, 
O'Toole EA, Kelsell DP, Yang 
Y. Loss-of-Function Mu-
tations in CAST Cause Pelle-
ting Skin, Leukonychia, 
Acral Punctate Keratoses, 
Cheilitis, and Knuckle 
Pads. American Journal Hu-
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Baurecht H, Hotze M, Brand S, 
Büning C, Cormican P, Corvin 
A, Ellinghaus D, Ellinghaus E, 
Espzarra-Gordillo J, Fölscher-
Holst R, Franke A, Gieger C, 
Hubner N, Illig T, Irvine AD, 
Kabesch M, Lee YA, Lieb W, 
Marenholz I, McLean WH, 
Morris DW, Mrowietz U, Nair 
R, Nöthen MM, Novak N, 
O'Regan GM; PAGE Consorti-
um, Schreiber S, Smith C, 
Strauch K, Stuart PE, Trem-
bath R, Tsoi LC, Weichenthal 
M, Barker J, Elder JT, 
Weidinger S, Cordell HJ, 
Brown SJ. Genome-wide 
Comparative Analysis of 
Atopic Dermatitis and 
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Mechanisms. American 
Journal Human Genetics. 2015 
Jan 8; 96(1):104-20.

Rorke EA, Adhikary G, Young CA, 
Roop DR, Eckert RL. Suppressing 
AP1 factor signaling in the su-
prabasal epidermis produces a 
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of Investigative Dermatology. 

Samuelov L, Sprecher E. Inherited 
desmosomal disorders. Cell Tis-
tue Research. 2014 Dec 9. [Epub 
ahead of print.]

<table>
<thead>
<tr>
<th>Date</th>
<th>Authors</th>
<th>Describe</th>
<th>Submission Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>Agarwala, Manoj K.</td>
<td>P17 Cases (in India and elsewhere; need for genetic testing)</td>
<td>2015</td>
</tr>
<tr>
<td>2012</td>
<td>Sirjani, Davud</td>
<td>PC and 'First Bite Syndrome and PC'</td>
<td>?</td>
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<td>5/15/2012</td>
<td>Fujimoto, Wataru</td>
<td>PC Cases - 'failure to thrive' in PC K6a babies</td>
<td>2013</td>
</tr>
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<td>Jul-05</td>
<td>Hansen, David; Goldberg, Ilan; Warshaur, Emily</td>
<td>IPCRR Data Update</td>
<td>2015</td>
</tr>
<tr>
<td></td>
<td>Hansen, David; David Hansen, David</td>
<td>PC cysts</td>
<td>2014</td>
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<td></td>
<td>Hovanian et al</td>
<td>Case report on treating PC with capsacin</td>
<td>?</td>
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<tr>
<td>2/15/2015</td>
<td>Morasso, Maria; Lessard, Julia</td>
<td>Role of Keratins in PC Teeth (follow-up to a recent publication)</td>
<td>2016</td>
</tr>
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<td>5/13/2012</td>
<td>O'Toole, Edel</td>
<td>Keratinocyte biology paper using cell lines with PC mutations</td>
<td>2012-2013</td>
</tr>
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<td>9/2014</td>
<td>Rice et al</td>
<td>Proteomics profiling of pachyonychia congenita keratoderma, data collected</td>
<td>2013</td>
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<td>2/19/2015</td>
<td>Rice et al</td>
<td>Proposed study of PC nail clippings (follow-up to a recent publication)</td>
<td>2016</td>
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<td>5/12/2012</td>
<td>Salphale, Pankaj</td>
<td>Case report of a family with pachyonychia congentia</td>
<td>2015</td>
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<td>Sep-13</td>
<td>Sprecher, Ojí, Smith, van Steensel</td>
<td>Differential Diagnosis</td>
<td>2014</td>
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<td>5/12/2012</td>
<td>Swendsen, Mathias; Tiedemann</td>
<td>Retrospective cases</td>
<td>2012</td>
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<td>11/1/2014</td>
<td>Thomas, Eapen</td>
<td>PC Cases in India</td>
<td>2015</td>
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<tr>
<td>Feb-15</td>
<td>Tariq, Sarah</td>
<td>Treatment of PC with Botulinum toxin</td>
<td>2015</td>
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INTERNATIONAL PACHYONYCHIA CONGENITA CONSORTIUM (IPCC)
Eli Sprecher, MD, PhD, IPCC Chair

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Webmeeting 1st Wednesday monthly
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Members —
Philip Gard, C. David Hansen, Leonard Milstone, Edel O’Toole, Eli Sprecher, Maurice van Steensel

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Spirit of ’76

by

Emily Warshaur

Sentiments of self-determination and individual liberty are evoked by the catchphrase “Spirit of ’76”, often associated with the morale during the American Revolution. Those times engendered a special kind of inspiration, vitality, drive and passion. That same remarkable spirit and motivation is shared at the IPCC, revolving around the keratins. Coincidentally, this “Spirit of ’76” applies now to Keratin 76 (KRT76) with new and exciting findings revealed by a skin specific phenotype screen applied to conditional targeted mutant mice generated by the Wellcome Trust Sanger Institute’s Mouse Genetics Project (Sanger-MGP).

In the October issue of PloS Genetics, DiTommaso and colleagues utilized a multi-parameter, multi-test skin screen applied to 562 mutant mice generated from knockout embryonic stem cells in order to study underappreciated genetic determinants important for proper skin development and function. Macroscopic clinical disease, hair follicle cycling, histological changes and aberrant marker expression were evaluated and the results demonstrated a correlation of 23 genes with a skin phenotype. Many of the genes revealed in the screen that were found to have an association with the skin were previously unrecognized in cutaneous biology (Mysm1, Vangl1, Trpc4ap, Nom1, Sparc, Farp2, and Prkab1) while a number of other identified genes with known epidermal phenotypes were in fact found to have novel functions in the skin (Krt76, Lrig, Myo5a, Nsun2, and Nf1). To date, this reverse genetic screen in the skin is the most comprehensive screen ever completed in any organ.

In the same issue of PloS Genetics by DiTommaso and colleagues, KRT76 was further explored as a result of the initial reverse genetic screen findings. The KRT76 null mice exhibited neonatal skin flaking, inflammation, hyperpigmentation, and impaired wound healing. Of unique interest, their investigations demonstrated a physical interaction between KRT76 and Claudin 1 (CLDN1) which is a transmembrane protein belonging to the tight junctions (TJs). KRT76 was found to be crucial for the normal composition of TJs. Specifically, KRT76 is important for the correct membrane localization of CLDN1. TJs were previously known to interact primarily with actin filaments, but this novel connection between the TJ and KRT76 may indicate a broader scope for TJs in conjunction with the keratin network.

An important physical interaction between KRT76 and CLDN1 in TJs has been established, but it is not known whether this interaction is direct or indirect. This leaves open the possibility that other players are involved such as KRT6 and KRT16. Both KRT6 and KRT16 are known to be expressed with KRT76 in the suprabasal epithelial cells of the hard palate and gingiva and are relevant to PC. In conclusion, the newly established finding linking KRT76 and CLDN1 highlight a previously unknown connection between the keratin intermediate filaments and TJs. Delving more deeply into the keratin-TJs interaction has the potential to reveal additional intricacies of the cytoskeleton network. In the "Spirit of Keratin 76" and aligned with the goals at the IPCC, the KRT76 null mice and other mutant mice models generated by Sanger-MGP will facilitate future investigation of the keratins and provide a foundation for new discovery.

References


12TH ANNUAL IPCC SYMPOSIUM
The 12th International PC Consortium Annual Symposium was held May 5–6, 2015 in Atlanta, Georgia. In this NewsBrief, we share a few short reports from some of the presentations at the IPCC meeting.

Andreas Berroth, PhD
TransDerm/Stanford University
Andreas reported on his progress identifying the influence of microRNAs (miR) on the pathogenesis of pachyonychia congenita (PC).

Differentially-expressed miRs, previously identified in involved vs. uninvolved patient biopsies, were analyzed for their influence on cell morphology, proliferation, migration and differentiation. The induced miRs identified in PC-involved skin (miR-143, miR-199a, miR-199b) increased proliferation of primary keratinocytes.

Simultaneous transfection with two miRs showed an even more pronounced effect on the keratinocyte proliferation, suggesting that multiple pathways and targets are involved. On the other hand, two of the five miRs that showed decreased expression in PC-involved skin induced keratinocyte differentiation. In future experiments, the influence of miRs on 3D epidermal skin equivalents will be evaluated and the targets of the miRs will be assessed.

Christopher G. Bunick, MD, PhD
Yale University
Christopher presented his research on the structural biology of epidermal proteins, particularly human profilaggrin and human keratins 1 and 10.

He used x-ray crystallography to determine the atomic resolution crystal structures of the N-terminus of human profilaggrin and the heterocomplex of the 2B domains of keratins 1 and 10.

He further discussed how x-ray crystallography could be utilized to correlate mutations observed in patients with pachyonychia congenita with the structural biochemistry that the mutations are causing to the keratins. He presented structural modeling of pachyonychia congenita mutations mapped onto a keratin 6/16 model, highlighting the resulting biochemical changes to the structure.

Robert H. Rice, PhD
University of California-Davis
PC Proteomics - Update
In this study, foot callus samples from the ball of the foot and the arch, collected on tape circles, were compared by shotgun proteomic profiling.

Pachyonychia congenita subjects were sampled who exhibited a mutation in keratin 6a, 6b, 6c, 16 or 17, and the proteins were digested and analyzed by mass spectrometry.

In comparison with samples from unaffected control subjects, those from subjects with keratin 6a or 16 mutations displayed the most differences in profile from normal, while those from subjects with keratin 6c or 17 mutations showed few differences from normal. The profiles from subjects with keratin 6b mutations were intermediate in protein profile differences. Degree of departure from the normal profile could be estimated by expression of several proteins that were most consistently different from normal.

Roger Kaspar, PhD
TransDerm, Inc.
The TransDerm team (Tycho Speaker, Yuan Cao and Roger Kaspar) reported on their progress on preclinical studies for a 1% topical sirolimus cream. This formulation was used in the Phase 1b clinical trial reported by Joyce Teng in this same IPCC meeting. The stability of the formulated drug product was reviewed (stable through 12 months at the 5°C label storage condition, stable through 1 month at ambient temperature).

They also discussed various next generation mTOR pathway inhibitors and reasons why these compounds may provide more effective delivery, stability and mTOR pathway inhibition (TORC2 suppression as well as TORC1; only TORC1 is inhibited well by sirolimus) as well as preliminary results in screening these formulated compounds in mouse skin models.
Inherited palmoplantar keratodermas (PPKs) form a highly heterogeneous group of disorders characterized by hyperkeratosis of palm and sole skin. Recent advances in our understanding of the pathogenesis of these conditions have revealed a wide range of PPK-causing molecular defects, significantly complicating the diagnosis of these common genodermatoses.

Given the fact that PPKs are not only associated with significant functional and psychosocial burden, but can also often predict visceral complications, accurate diagnosis is pivotal to provide affected families with prognostic information, genetic counselling and prenatal diagnosis.

We have developed a streamlined approach leading from simple physical and histopathological features to clinical and molecular diagnosis. This algorithm significantly facilitates the diagnosis of inherited PPK, which should be instrumental in guiding targeted treatment choices in the near future.

Yong Yang, MD
Peking University First Hospital
Peking, China

PLACK syndrome: a new entity may mimic PC, EB, Ichthyosis and

Keratoderma

Peeling skin syndrome is an autosomal recessive genodermatosis characterized by the shedding of the outer epidermis. PSS can be divided into two clinical forms: acral PSS and generalized PSS. By now at least 5 causative genes have been identified in the PSS patients.

Here we report 4 patients from three families, including two siblings previously diagnosed as recessive form of pachyonychia congenita was reported nearly 30 years ago. The clinical feature of these patients is characterized with peeling skin, Leukonychia, acral punctate keratoses, cheilitis and knuckle pads, we proposed this new entity to be given the acronym PLACK syndrome.

By gene sequencing, homozygous loss-of-function (LOF) mutations of CAST gene were found in the patients. CAST encodes calpastatin. It’s ubiquitously expressed, highly in skin. It is a specific endogenous inhibitor of calpains. Calpains are kinds of calcium-dependent, non-lysosomal cysteine proteases, can regulate cell apoptosis. LOF mutation of our patients mediated mRNA decay of calpastatin, immunohistochemistry shows absent calpastatin staining in the patients. TUNEL assay demonstrated increased apoptosis of keratinocytes in skin from patient. CAST knockdown revealed breakage of the intercellular connections, independent of whether been subjected to mechanical stress.

In summary, LOF mutations of CAST gene cause absence of calpastatin in epidermis, disinhibition of calpains, lead to increased apoptosis of KC, as a consequence, acantholysis, Hyperkeratosis and skin fragility are occurred in the patients.

2015-2016 IPCC Goals

Each year IPCC goals are set and achieved. The IPCC 2014-2015 goal to capture more detailed clinical information on PC through a qualified pain study, full dermatological exam, biopsy and clinical photos will be completed on 60 PC patients by the end of June.

Based on the discussion at the 2015 PC MSAB meeting held after the IPCC Symposium, this is a DRAFT of the 2015 IPCC goals.

We welcome comments, corrections, input, discussion so that we have a consensus across the MSAB and the IPCC members as we move forward.

Clinical Studies

Clinical Trials

Our major goal is therapies. To accomplish this, we want to have meaningful clinical trials and clinical studies. Because the PC patient population is very small and scattered in many locations, we must organize multi-center studies.

Here are studies we hope to move forward as quickly as possible:

Topical Rapa (TD201). The Phase 1b study is completed. If TransDerm is interested in pursuing this treatment, we would like involve MSAB members and others in the wider IPCC community to assist TransDerm in developing the next clinical trial for TD201.
More discussion on the trial is needed from IPCC members.

**Botox.** Injections of either Botox or Dysport are being tried in numerous ‘one-off’ studies. We continue to seek to develop a unified protocol and establish a meaningful study of this treatment.

**Topical Pain Formulation.** We are developing a protocol and plan involving Dr. Marco Pappagallo, Bruce Hammond (UC Davis) and Sphaera Pharma to have this tested in several centers involving two to three patients in each center.

**Pain Specialists.** We want to involve pain specialists with PC treatment. A few individual patients have been treated with Gabapentin, Cymbalta or other pain medications. However, nothing can really be gained from these individual experiments and our goal is to organize a group of pain specialists interested in PC, establish a protocol on what/how to test these products and conduct studies that can lead to results applicable to the entire PC community.

**Targeted siRNA.** We have only nine patients in the world that have the specific mutation for the targeted siRNA that is ready-to-go. TransDerm must determine where to conduct this trial. Again, if TransDerm is interested, we would like to involve MSAB members and others in the wider IPCC community to assist TransDerm in developing this clinical trial.

**Research Studies**

Nail clippings. This is being revisied for a further proteomic study with Bob Rice at UC-Davis.

Dental health. An Addendum (#6) to the IPCR has been developed by the NIH and is being collected. Over 100 patients have responded so far.

GRDR (Global Rare Disease Registry/NIH). We are adding the 25 PROMIS measures adopted by the GRDR. We are going to re-survey all of our patients to create better life history data.

Neuroanatomy. Work is being done by Michael Polydefkis at Johns Hopkins using biopsies collected by Dr. David Hansen with Roger Kaspar’s assistance.

MicroRNAs are being studied at TransDerm under the direction of Roger Kaspar and his team.

**CME.** A new goal of PC Project is to increase Educational Outreach efforts by developing a CME course with education on Pachyonychia Congenita. If you are interested in being one of the experts on this course, please let us know.

**Recent Publications**

Clinical and molecular findings of pachyonychia congenita type 2

Olmsted syndrome: clinical, molecular and therapeutic aspects.

Advances in the therapeutic use of mammalian target of rapamycin (mTOR) inhibitors in dermatology.

A case of pachyonychia congenita with unusual manifestations: an unusual type or a new syndrome?

Gene expression profiling in pachyonychia congenita skin.

Keratins and skin disease.

Mutations in GJB6 causing phenotype resembling pachyonychia congenita.
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12th International PC Consortium Annual Symposium, May 5-6, 2015 in Atlanta, Georgia

PROGRAM OVERVIEW

WEDNESDAY—May 6
7:30 am—8:30 am BREAKFAST

8:30 am  Welcome—Eli Sprecher, IPCC Chair
Soussary Medical Center, Tel Aviv, Israel

8:40-8:50  PC Project Greetings
Stephen Wittner, PC Advocate
Sulpher Springs, Texas, USA

Session Chair: Leonard M. Milstone,
Yale School of Medicine, New Haven, Connecticut, USA

8:55-9:15  Exploring neuro- and microbiology for symptom relief in PC
Maurice A.M. van Steensel
University of Dundee, Dundee, Scotland UK

9:20-9:40  Mouse models of Mal de Meleda and Prospects for Testing a Possible Therapy
Stephen Young
University of California at Los Angeles, California, USA

9:45-10:05  PPK Diagnosis Made Simple
Eli Sprecher
Soussary Medical Center, Tel Aviv, Israel

10:05-10:25  BREAK

Session Chair: C. David Hansen,
University of Utah, Salt Lake City, Utah, USA

10:30-10:50  Management of Chronic Foot Pain in a Pediatric Patient with Pachyonychia Congenita
Sarah Tariq
University of Arkansas, Little Rock, Arkansas, USA

10:55-11:15  Preclinical Studies of Topical mTOR Inhibitors
Roger L. Kaspar, Yuan Cao, Tyncho J. Speaker,
TransDerm, Inc., Santa Cruz, California, USA

11:20-11:40  Topical Sirolimus Therapy for Planar Keratoderma in Pachyonychia Congenita
Joyce M. Teng
Stanford University, Stanford, California, USA

TUESDAY—May 5
1:30 pm  Welcome—Eli Sprecher, IPCC Chair
Soussary Medical Center, Tel Aviv, Israel

Session Chair: Dennis R. Roop
University of Colorado, Denver, Aurora, Colorado, USA

KEYNOTE
1:35-1:55  Cell Culture models of Pachyonychia Congenita for drug testing
E. Birgitte Lane
Institute of Medical Biology Singapore, Singapore

2:00-2:20  The Role of MicroRNA’s in PC
Andreas Berroth
TransDerm, Inc., Santa Cruz, California, USA

2:25-2:45  PC Proteomics - Update
Robert H. Rice
University of California Davis, Davis, California, USA

2:50-3:10  Quantitative Analysis of Cutaneous Neuropathology in Patients with PC
Michael Polvedis
John Hopkins University, Baltimore, Maryland, USA

3:10-3:30  BREAK

Session Chair: Laura Bittie
University of Michigan, Ann Arbor, Michigan, USA

3:35-3:55  Using x-ray crystallography to correlate protein structure with function in human skin diseases
Christopher G. Bunick
Yale School of Medicine, New Haven, Connecticut, USA

4:00-4:20  Other Hereditary Disorders of the Nail
Amy S. Paller
Northwestern University, Chicago, Illinois, USA

4:25-4:45  PLACK Syndrome: a new entity may mimic PC, EB, Ichthyosis and Keratodermas
Yong Yang
Peking University First Hospital, Beijing, China

5:45 pm  DINNER & ATLANTA BRAVES GAME
Meet in lobby of Hilton Atlanta for bus ride to dinner and game.
Keratin 17 (KRT17) is well known to be involved in a variety of skin conditions across the spectrum from common to rare and benign to malignant. In the interest of Pachyonychia Congenita (PC) specifically, KRT17 has been on the radar since McLean and colleagues established its role in PC twenty years ago in *Nature Genetics*. Today, great progress continues towards improved understanding of the pathogenesis of disorders involving KRT17 as we elaborate on the relationship between KRT17 and the autoimmune regulator (Aire), a transcriptional regulator with an established role mediating immunologic tolerance in the medullary thymus.

Initially, the physical connection between KRT17 and Aire was described by Kumar and colleagues in the *American Journal of Pathology* in 2011 and identified in the cytoplasm via coimmunoprecipitation and *in situ* colocalization in keratinocytes. This discovery was hardly surprising given that a mutation in Aire was already known to cause Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED), a syndrome presenting commonly with alopecia, nail dystrophy, vitiligo, and enamel hypoplasia. The ectodermal anomalies exhibited in APECED syndrome considered in combination with the KRT17 mutation in PC suggested that the KRT17-Aire bond may also be of pathophysiologic relevance.

Hobbs and colleagues continued to pursue the relationship between KRT17 and Aire and recently in the July 2015 publication of *Nature Genetics*, exciting new discoveries were revealed. In both human and mouse tumor-prone keratinocyte cell lines, they identified a nucleus-localized form of KRT17, previously thought to solely localize in the cytoplasm, and recognized its role regulating gene expression at the transcriptional level. Furthermore, an extrathymic role for Aire during the acute inflammatory process and tumorigenesis was established in the skin to require a physical and functional association with KRT17.

This newfound relationship between KRT17 and AIRE confirm yet another strong thread connecting the skin and immune system, providing completely new insight relating to the pathomechanisms underlying KRT17 involvement in inflammatory processes and immune responses in affected skin. Ultimately, these new findings contribute to our knowledge relating to some of the complex mechanisms involving KRT17 so that understanding may no longer be “up in the AIRE”.

### References


INT’L PC RESEARCH Registry (IPCRR)

The IPCRR continues as one of 17 registries selected to participate in Phase 2 of the NIH/NCATS GRDR® Program. Our registry was one of 12 patient advocacy groups in the GRDR pilot project and also participated in Phase 1 of the GRDR. The pilot project involved validating and implementing Common Data Elements (CDEs) and gauging general interest from the rare diseases community. Under the direction of Yaffa Rubenstein (NIH/NCATS), the GRDR is beginning the next phase of development of this important resource for rare disease research.

For more about the NIH/NCATS GRDR® Program see https://ncats.nih.gov/grdr

Data from the IPCRR often provide the basis for publications, clinical studies and research studies. We welcome researchers and authors who wish to publish IPCRR data.

In this Newsletter, we include

1) Findings from a recent clinical study in which patients were recruited from the IPCRR
2) Graphs showing IPCRR data and statistics

To access IPCRR data, please contact info@pachyonychia.org.

RECENT PUBLICATIONS ON PACHYONYCHIA CONGENITA


### Topical Rapa (Sirolimus)
Since the trial data is now locked, and the post-trial data collected, we are pleased to be able to publicly report some findings from the study.

#### Post-trial Questionnaire
Thinking about your PC while in the study, which PC feature was your MOST bothersome feature? PAIN 11/11

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>While you were in the study, did you notice improvement in your most bothersome feature?</td>
<td>8/11</td>
<td>3/11</td>
</tr>
<tr>
<td>Did you notice improvement in any other PC feature?</td>
<td>9/11</td>
<td>2/11</td>
</tr>
<tr>
<td>After you stopped using the drug, did you notice any changes?</td>
<td>7/11</td>
<td>4/11</td>
</tr>
<tr>
<td>Did you feel that the cream on your feet was helping?</td>
<td>9/11</td>
<td>2/11</td>
</tr>
<tr>
<td>If the TD201 study drug were available to you now, would you use it?</td>
<td>11/11</td>
<td>0/11</td>
</tr>
</tbody>
</table>

The following graphs show the individual responses.
Distribution of PC genes in 641 individuals in 494 families with genetically confirmed Pachyonychia Congenita

(2) AAGAB
(1) APS Type 1
(1) CAST
(2) COL7A1
(12) Connexin 30
(5) Desmoglein1
(2) Desmplakin
(6) FZD6
(3) K1
(6) K9
(1) Kawasaki
(1) Rabson-Mendenhall
(8) TRPV3

Demographics of 641 individuals with genetically confirmed PC

<table>
<thead>
<tr>
<th></th>
<th>PC-K6a</th>
<th>PC-K6b</th>
<th>PC-K6c</th>
<th>PC-K16</th>
<th>PC-K17</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=253</td>
<td>N=58</td>
<td>N=21</td>
<td>N=197</td>
<td>N=100</td>
<td>N=641</td>
</tr>
<tr>
<td># Individuals</td>
<td>257</td>
<td>59</td>
<td>21</td>
<td>202</td>
<td>102</td>
<td>641</td>
</tr>
<tr>
<td>in # Families</td>
<td>160</td>
<td>22</td>
<td>7</td>
<td>100</td>
<td>58</td>
<td>494</td>
</tr>
<tr>
<td>Female</td>
<td>146</td>
<td>23</td>
<td>11</td>
<td>90</td>
<td>62</td>
<td>332</td>
</tr>
<tr>
<td>Male</td>
<td>111</td>
<td>36</td>
<td>10</td>
<td>112</td>
<td>40</td>
<td>309</td>
</tr>
<tr>
<td>In USA</td>
<td>108</td>
<td>20</td>
<td>11</td>
<td>98</td>
<td>48</td>
<td>285</td>
</tr>
<tr>
<td>Outside USA</td>
<td>149</td>
<td>39</td>
<td>10</td>
<td>104</td>
<td>54</td>
<td>356</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>109</td>
<td>8</td>
<td>0</td>
<td>51</td>
<td>31</td>
<td>199</td>
</tr>
<tr>
<td>Familial</td>
<td>148</td>
<td>51</td>
<td>21</td>
<td>151</td>
<td>71</td>
<td>442</td>
</tr>
</tbody>
</table>

INTERACTIVE MAP
An interactive map showing location of all genetically confirmed patients with Pachyonychia Congenita is available on the website at: www.pachyonychia.org/pc_data.php
Human hair has long been a great source of fascination across continents and people spend enormous time and effort maintaining and manipulating their hair. Not critical for our biological survival, yet critical to our psychosocial identity, hair will forever remain intriguing. Equally as fascinating is the current research focusing on the constituents of hair on a molecular level. Keratin 75 (Krt75), important in maintaining the integrity of the hair follicle and hair shaft, has come to the forefront as a promising target to reverse hair abnormalities.

In the recent September 2015 advance online publication of the Journal of Investigative Dermatology, Liu and colleagues generated specific siRNAs targeting the dominant mutant allele of Krt75 and demonstrated that silencing a mutant Krt75 in a knock-in mouse model may reverse structural hair defects by restoring the strength of the keratin filament network. Their findings revealed altered enamel structure and a significant reduction in enamel hardness associated with a Krt75 variant. Essential to the maintenance of tooth enamel, the toughest substance in the human body, Krt75 clearly makes a strong mark wherever present.

In conclusion, the findings from these two articles may have application extending much beyond hair to include the majority of keratin disorders. These are exciting times with respect to siRNA-based therapy as a valuable therapeutic approach, so let your hair down and enjoy the ride.

References


**Clinical Trial Planning**

by Frances Smith, PhD

Members of the IPCC Steering Committee met in London in September 2015 to discuss and plan future clinical trials. The first day focused on clinical trial selection. The attendees Roger Kaspar, Irwin McLean, Edel O’Toole, Mary Schwartz, Frances Smith, Eli Sprecher (Chair) and Maurice van Steensel each presented a short report on five to six clinical and research studies that PC Project has been involved with over the last 12 years. These were assigned and researched prior to the meeting so full data was available. Possible studies were from completed preliminary trials, from both patient-reported and physician-reported treatments. Phil Gard and Dave Hansen have also provided input as members of the Steering Committee.

After extensive discussion, three drugs were unanimously selected as the best options. These are:

1. Botox injections
2. Oral retinoids
3. Topical Sirolimus (TD201)

On the second day discussions were on clinical trial planning. This included points such as

(a) what centre/physicians to use
(b) how many patients to enroll
(c) what are enrolment criteria such as age, sex, mutation etc.
(d) what to measure and
(e) how to measure. All of these points may make a difference between a trial being approved or not by regulatory authorities and funders, and a trial providing necessary evidence of safety and efficacy. Some time was spent discussing assessment tools/measurement outcomes including use of a treadmill, ergometer, 6 minute walk test, PROMIS 29, pain scales, photography, ultrasound and an activity measurement such as a 'fitbit' bracelet or equivalent. It was decided that good baseline pain and quality of life data needs to be collected prior to any clinical trial.

This was followed by a discussion on running clinical trials and the need for a CRO to help design, manage, monitor and report during a clinical trial. The cost of this was briefly discussed as it will be expensive and for trials with centres in different countries, a representative will be required in each country. It was proposed to get offers from several companies.

For the remainder of the meeting the discussion focussed on setting up the three clinical trials over the next year and possible designs of these trials.

Assignments were made to DRAFT a protocol for each of the studies which will be further reviewed and discussed.

Following the meeting, the Steering Committee and PC Project staff have been in active discussions on measurement devices.

Also, initial contacts are being made with drug manufacturers to seek funding support for these clinical trials. If you are interested in helping design these trials, securing drug product or enrolling patients, please email info@pachyonychia.org.

**PC Project Collecting PC Baseline Data**

PC Project is actively gathering additional data from patients in the International PC Research Registry. Since the September 2015 Steering Committee meeting, PC Project has initiated these actions.

1. PC Natural History. In an effort to establish natural history details, patients are encouraged to update their basic registry data on a regular basis based on their age.
2. Over 100 patients responded to a survey regarding smart phone usage. A simple 0-10 pain scale app has been developed which automatically collects the data in a spreadsheet.
3. Over 80 PC patients have completed the PROMIS 29 survey on quality of life. The next step will be to evaluate whether this scale has application to PC and whether it would show changes if an effective treatment were available.
4. A wearable tracker will be evaluated which will record activity. It is felt that with an effective treatment to reduce pain, a PC patient will be more active.

A DRAFT proposal for a small study on items 3 and 4 above in a group of 12 patients and 12 controls has been circulated by PC Project to the Steering Committee. If approved, PC Project will obtain approval and move forward to test these measurement tools.

If you would like additional information on any of these measurement tools, please contact PC Project at info@pachyonychia.org.

2386 East Heritage Way, Ste B, Salt Lake City, UT 84109 · www.pachyonychia.org · Phone 877-628-7300 · Email: info@pachyonychia.org
Frances Smith Named PC Project Scientific Director
Effective October 15, 2015, Frances J. D. Smith, PhD became the Scientific Director at PC Project. Dr. Smith was one of the researchers who discovered the PC genes in the mid-1990s. She has been the director of genetic testing for PC Project at the University of Dundee and has often given presentations at scientific meetings, patient support meetings and other events.

This is a major and important step forward for PC Project and we are delighted to work closely with Dr. Smith. She will continue to supervise the genetic testing for PC, coordinating testing at the University of Dundee and other labs. She will also oversee PC Project’s scientific efforts, including clinical trials and publications and will be Principal Investigator for the IPCRR.

NORD to Feature Pachyonychia Congenita on Rare Disease Spotlight
Pachyonychia Congenita will be featured on the NORD Rare Disease Spotlight the first week of December 2015. Here is a portion of the NORD posting:

What are some of the challenges your organization has faced?
The greatest challenge is finding any effective treatment for Pachyonychia Congenita (PC). Other challenges include:

1. Although PC patients experience excruciating, constant pain from the time they begin to walk and throughout their life, PC does not cause death and, therefore, the debilitating nature of this disorder is often minimized
2. With few patients in the world (and only about 300 in the USA) we still must interest physicians and scientists, support clinical trials, provide educational outreach and other services to make a difference for patients – the same challenges as organizations with many more patients.
3. With a rare disease, misdiagnosis and misinformation is common, so a challenge is to publish correct information based on a larger patient population (not single cases).
4. An important goal is to focus attention on pain as the main disabling feature of PC (rather than thickness of nails).

What do you find your patient community values most from your organization serving the rare community?
“I am literally brought to tears at the thought of not being alone in this.”
“We have just found your site. I never fully appreciated how much a bit of information can change one’s life. You have essentially given us a voice. Thank you”

Recent Publications Related to PC


INTERNATIONAL PACHYONYCHIA CONGENITA CONSORTIUM (IPCC)

Eli Sprecher, MD, PhD, IPCC Chair

The IPCC is an open membership organization for researchers and physicians who have an interest in Pachyonychia Congenita research and who agree to work together to develop PC therapeutics.

IPCC STEERING COMMITTEE 2013—

The following have been invited to serve as the IPCC Steering Committee to assist PC Project in guiding PC Project collaborations with the IPCC and others.

Philip Gard, C. David Hansen, Roger L. Kaspar, W. H. Irwin McLean, Edel O’Toole, Frances Smith, Eli Sprecher, Maurice van Steensel

DIAGNOSTICS AND GENETICS TEAM

Webmeeting 1st Wednesday monthly
FRANCES J.D. SMITH, Chair

Members —
Philip Gard, C. David Hansen, Edel O’Toole, Frances Smith, Eli Sprecher, Maurice van Steensel

RESEARCH AND CLINICAL TRIALS TEAM

Annual IPCC Meeting, Webmeetings and Individual Collaborations
ROGER L. KASPAR, Chair

The purpose of this team is to focus specifically on clinical trial development and to assist one another in moving lab research forward for delivery to patients. The team membership fluctuates depending on specific needs and focus. Outside consultants are often involved with IPCC members where special expertise is needed. Many IPCC researchers have ongoing projects to develop therapeutics for PC. These are often featured at the annual IPCC meetings.

PHYSICIAN NETWORK

Quarterly Webmeetings, Annual IPCC Meeting

Led by the physicians on the PC Project MSAB, this network is open to all who treat or are interested in treating patients with Pachyonychia Congenita. The quarterly meetings are recorded for viewing online at any time and present current data and discussions on research and treatments for PC.