JUST AROUND “THE CORNER” —
11TH INTERNATIONAL PACHYONYCHIA CONGENITA CONSORTIUM SYMPOSIUM
TUESDAY, MAY 6, 2014 (JUST PRIOR TO THE SID)
CONVENTION CENTER—ALBUQUERQUE, NEW MEXICO
401 2nd Street Northwest, Albuquerque, NM, 87102

Confirmed speakers include —
Carl Baker, Pierre Coulombe, Roger Kaspar, Thomas Magin, Robert Rice,
Frances Smith, Eli Sprecher, Hans van Bokhoven, Ying Yang
and others (both well-known researchers and new investigators.)

The meeting schedule includes breakfast, working lunch and dinner:
7:00 am to 8:30 am – continental breakfast (meet and greet other attendees)
8:30 am to 12:00 noon – sessions
12:00 noon to 1:30 pm – working lunch
1:30 pm to 4:15 pm – sessions
4:15 pm to 6:30 pm – break
6:30 pm – working dinner
(a bus will transport attendees to the dinner site at the Pueblo Indian Cultural Center)

All Interested Researchers and Physicians Are Invited
Don’t Miss This Excellent Meeting
Pre-Register and Meeting Fee is Waived

2014 IPCC Registration Link
https://www.surveymonkey.com/s/2014IPCC

Each year the IPCC reports on progress and sets new goals. Please join
with us and be a part of this unique effort in translational research
to make a difference for patients with this ultra rare disorder.
The Keratin Corner

Emily Warshauer MD
Tel Aviv Sourasky Medical Center
emwarshauer@gmail.com

The role that keratins play in maintaining the mechanical integrity of the cell is not a newly discovered phenomenon and it has become widely accepted as a primary function of keratins. Yet, as the roles of keratins are being more highly scrutinized, it raises the question whether the preservation of mechanical integrity by keratin networks indeed plays as central a role as originally recognized.

In the November 2013 issue of the Proceedings of the National Academy of Sciences (PNAS), Bernd Hoffman and his colleagues thoroughly delve into this topic by analyzing keratinocyte cell lines lacking all keratins with the use of two intriguing techniques: atomic force microscopy and magnetic tweezers. Exerting an external force via atomic force microscopy (AFM) indentation demonstrated significant cell softening in the keratin-deficient cells. Furthermore, cyclic force pulses directed at superparamagnetic beads in the magnetic tweezers experiment confirmed the AFM findings.

In a complementary article in the same issue of PNAS, Thomas Magin and his colleagues address the same question in keratin-deficient murine keratinocytes. Utilizing an automated microfluidic optical stretcher composed of a two-beam laser to trap and deform single cells, they confirmed decreased cell stiffness in the keratin-deficient cells.

Further investigation with invasion and 3D growth assays revealed a greater invasive potential associated with more pliable keratin-deficient cells. Based on these findings, they concluded that the absence of keratins is correlated with properties characteristic of tumor cells.

These current studies that “cross the t’s and dot the i’s” drive home the critical connection between keratins and mechanical integrity, underscoring the important role that keratin networks play as a mechanical buffer. In addition, these investigations may also have vast implications for the association of malignant transformation with the disruption of keratin networks.

References:


(Thanks to Eli Sprecher for recommending this Keratin Corner)

Educational Outreach: EADV Trainee Course on Genodermatoses

Features PC Patients
January 2014. Innsbruck, Austria.
At the invitation of Prof. Matthias Schmuth and Dr. Robert Gruber, PC Project participated in a special session at the EADV Training Course on Genodermatoses.

Six patients (from Austria, Germany, Sweden and Switzerland) represented four of the different PC types (PC-K6a, PC-K6b, PC-K16 and PC-K17). Dr. C. David Hansen from the University of Utah gave the formal presentation on PC. A booklet including current IPCRR data and copies of all of the relevant PC publications was provided to each attendee.

If you are interested in hosting an Educational Outreach program at your institution, please contact PC Project. PC Project recruits the patients, covers the travel costs and provides the printed materials. We have received excellent reports from those hosting these events, the attendees — and from the patients who participate and no longer feel ‘all alone’ as the only specimen on display, but have an opportunity to meet with other PC patients. By inviting a variety of PC patients, the event is both a more valuable Grand Rounds and a small patient support meeting.

Benefits of Stress: Scientists Discover a Unique Path for Cells to Become Pluripotent

Dennis Roop, PhD
University of Colorado, Denver

Recently, a team of Japanese and American scientists published two papers in Nature:
http://www.nature.com/nature/journal/v505/n7485/full/nature12968.html
http://www.nature.com/nature/journal/v505/n7485/full/nature12969.html
reporting a unique phenomenon that allows differentiated somatic cells to convert into a pluripotent
state in response to stress, such as the exposure to an acidic environment.

For years, it has been generally believed that the reversal of the differentiated state of adult somatic cells involves a complex set of nuclear or genetic manipulations, which can be accomplished only by nuclear transfer or upon the introduction of multiple reprogramming factors. Surprisingly, the new reports by Obokata and collaborators challenge this view and offer an extremely simple and fast method to reprogram mouse somatic cells into pluripotency by stressing them.

The resulting pluripotent cells are similar, yet not identical, to embryonic stem cells, and importantly can produce a viable animal, the most stringent test for pluripotency. While groundbreaking, the discovery raises several questions:

- For example, how reproducible are these findings and what are the implications for the clinic and for basic research?
- How similar are the resulting stimulus-triggered pluripotent stem cells to embryonic or induced pluripotent stem cells?
- Can human cells be reprogrammed to pluripotency by exposure to stress factors, or is this phenomenon specific to rodents? These questions, among others, need to be addressed.
- Only time will reveal the impact of this discovery on the stem cell field. However, needless to say, such an unexpected and apparently simple reprogramming method will stimulate many scientists around the world to quickly attempt to reproduce these findings.

**PC Therapy Summary**

There are no effective treatments currently available for PC patients. A few of the therapies that have or are being considered will be presented at the 2014 IPCC meeting.

The focus for patients is not simply ‘thinning callus’ or ‘thinning nails’ (which long was the focus of experts), but rather the reduction of pain. The treatments currently reviewed by the IPCC include:

- **Botox**—Approximately 11 PC patients have undergone botox injections. While at first it was thought that the mechanism of effect was due to hyperhidrosis, recent treatments where the entire foot is not treated, but injections are only into the painful callus areas, seem to indicate some other action is taking place to reduce the pain in PC.

- **Capsaicin**—We know of one patient treated with capsaicin injections who has had pain relief from the treatment.

- **Gabapantin, Topical.** A small off-label study was conducted, but no promising effects were reported after six weeks.

- **Retinoids**—Although retinoids continue to be prescribed because retinoids ‘thin skin’, our research (Gruber et al., 2012, JAAD) indicates that retinoids do nothing to alleviate the exquisite pain suffered by PC patients.

Although many PC patients have tried retinoids as a therapy, almost no patient in the IPCRR registry has chosen to continue retinoid treatment due to lack of benefits and unpleasant side-effects.

- **Salicylic acid**—this is often prescribed when a physician encounters PC for the first time or has little experience with PC patients. Based on patient reported outcomes in the IPCRR and PC Project emails, etc., salicylic acid gives some improvement when first prescribed. Eventually, the results reported are very mixed and about the same as for those patients who simply use a petroleum based moisturizers like Vaseline. Some patients reported an increase in callus when they discontinued use of salicylic acid. Most patients with the most severe callus (i.e. PC-K6a and PC-K16) do not continue using salicylic acid over long periods of time as the benefits are not sufficient.

**siRNA.** The clinical trial of the TransDerm drug TD101 (a targeted siRNA) in 2008 showed great promise and effectiveness. However, the administration by injection was unbearably painful and efforts were undertaken to (a) improve the drug for delivery and (b) develop a more ‘patient friendly’ (i.e. painless) form of delivery.

TransDerm has been successful in developing TD101sd (a self delivery form of the drug). Also, TransDerm has developed and manufactured under GMP standards for human use a dissolvable microarray pad that delivers painlessly.

TD101sd is targeted to a specific mutation and there are less than 20 patients in the world with this mutation. Since the patients live in five different countries the logistics of who/what/when/where and how for the clinical trial has been challenging. Each dermatologist, institution and country has different requirements.

We are working to move this clinical trial forward. Targeted siRNA is a real ‘individualized medicine’ treatment that targets only the mut-
tant and leaves the wild type copy of the gene. Although it may be many years before siRNA targeted drugs will be practical for each of the PC types, we feel an urgency to move this clinical trial forward. We believe this has great importance not only for PC — but for many other conditions with no current treatment option.

Sirolimus (Topical.) We strongly believe the availability of topical rapamycin will be a boon to pachyonychia congenita (PC) patients based on the results of the study that was published showing that oral rapamycin, despite all of the side effects associated with oral administration, dramatically improved PC symptoms. We look forward to the Phase 1b clinical study which will initially enroll 15 patients. If effective, we intend to make this available as quickly as possible to PC patients everywhere. This is the most promising therapy for PC we have reviewed in the last decade.

Statins—several clinical trials have been completed using statins based on basic research reported in 2011 (Zhao Y, Gartner U, Smith FJ, McLean WH. Statins downregulate K6a promoter activity: a possible therapeutic avenue for pachyonychia congenita. The Journal of Investigative Dermatology. May 2011;131(5):1045-1052.) However, the findings are not conclusive and at this time, no further clinical studies are planned.

Urea—Generic Name: Urea Cream, Gel, and Ointment 25%, 30%, 40%, and 50% Brand Name: Examples include Carmol 40, NS-8 and Keralac. Another common recommendation from those first treating PC is a 40% urea cream which is suggested for both thinning callus and thinning thickened nails. While urea is a good emollient which helps to moisturize the skin and if covered by an occlusive dressing, 40% urea preparations may be used as keratolytic agents (for debridement of nails and removal of calluses), for PC patients it does not provide any long term benefit.

Patients initially report some improvement. However, over time the majority of patients find that only mechanical removal of the callus and trimming/grinding the nails provide needed results.

OTHER POSSIBLE STUDIES
In addition to the topical sirolimus study, other studies are being considered. For example:

1) A clinical study to using a standardized protocol to measure effectiveness of the use of botox in PC patients. Initial discussions have taken place. Anna Bruckner, MD (Head of Pediatric Dermatology at the University of Colorado/Denver) is working with PC Project to coordinate efforts and organize this study which may be based in the EU where the costs may be covered.

2) PC Project is interested in a small 10-15 patient clinical study using salicylic acid and/ or urea creams. This could be organized by an interested IPCC dermatologist to fully determine and report the effect of these products for PC over a 6 month period and to determine the ‘after’ effects when the products are discontinued.

3) Nail removal data is being analyzed by Cynthia Carver DeKlotz to see if enough data has been collected.

RECENT PC PUBLICATIONS


NOTE: No genetic information is included. This may or may not be PC. Since genetic testing is provided at no cost to patients/physicians anywhere in the world, we encourage physicians to obtain genetic testing before publishing articles.


PROPOSED PUBLICATIONS
PC Project is actively interested in partnering with authors for publications that further accurate information on Pachyonychia Congenita. We continue to be disappointed in articles published without any genetic confirmation or single case studies which feature some ‘odd’ feature which does not truly relate to the understanding of PC.

We feel it would be much more
valuable to publish facts found in the majority of cases. We think this tendency to look for ‘novel’ or ‘odd’ features in a condition now with nearly 600 genetically confirmed patients is a detriment to progress not just for PC, but for other rare diseases.

The following are a few of the publications currently proposed which we hope will be prepared and published over the next year. This is a tentative list and the authors may or may not be finalized at this time. We welcome suggestions for other articles and will collaborate to provide data, images or other support.

Cao et al. “Gene Expression Profiling in Pachyonychia Congenita Skin.”

Cao et al. Micro RNA “Profiling in PC Biopsies.”

Cao, Speaker et al. “Topical rapamycin inhibition of mTOR pathway.”


Goldberg, Hansen, “IPCRR Data Update: Data on 523 PC Patients” (initial statistical evaluation is now underway at UC San Diego).

Hoggart, Barbara et al. “PC Pain” (from a 2011 study).

Hovnanian et al “Case Report: Capsaicin treatment of PC.”

Hull, Peter “PC Quality of Life Index.”

Hull, Sprecher et al “Statin treatment of PC.”

Jirakova, Anna “Case Study: K6a R164P.”

12% of those clinically diagnosed with PC actually do not have PC. Since, PC Project sponsors the testing so patients and physicians can have correct diagnosis at no cost, there is no reason to have publications without genetic testing results.


Rice, Robert et al “Proteomics profiling of Pachyonychia Congenita keratoderma.”

Smith, Frances “PC Genetics”

Smith, Frances “TRVP3 and PC.”

Oji, Smith, Sprecher, Van Steensel “Differential Diagnosis.”

Teng et al “Topical Rapamycin Treatment of PC Patients.”

(Author TBD) “PC and First Bite Syndrome.”

We welcome your suggestions for additional publications.
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.

W. H. Irwin McLean, Roger L. Kaspar, Frances Smith, Eli Sprecher

DIAGNOSTICS AND GENETICS TEAM
Webmeeting 1st Wednesday monthly
FRANCES J.D. SMITH, Chair
Members —
C. David Hansen, Leonard M. Milstone, Edel O’Toole, Eli Sprecher, Maurice van Steensel

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Annual IPCC Meeting, Webmeetings and Individual Collaborations
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The purpose of this team is to focus specifically on clinical trial development and assist one another in moving lab research forward to 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 on treatments for PC.

Prior to the IPCC meeting in May 2014, we will contact you to determine if you wish to have additional assignments in the IPCC.
2014 IPCC SYMPOSIUM
We appreciate all who participated in the recent IPCC symposium held May 5 in Albuquerque, NM. It is gratifying to note that a number of research studies have already been approved and are moving forward as a result of the presentation and discussion at the IPCC. Here are a few of the studies about to begin:

BIOPSY SKIN SAMPLES
(1) Michael Polydefkis and Michael Caterina, researchers at Johns Hopkins who specialize in pain and keratoderma, will study the effect of PC on nerves and other structures found in the skin to help identify possible targets for treatment. We will collect 10 biopsies from PC-K6a patients. These biopsies will be entirely used for this project and the research will begin as soon as we have the biopsies. Dr. C. David Hansen, MD and Roger Kaspar, PhD will assist in the collection. PC Project is funding the study and funding the patient travel costs for the biopsy collection. The researchers and physicians are not asking compensation for their time.

BIOPSY FOR 3-D IMAGING
Laure Rittie at University of Michigan will receive additional skin samples to further her research using 3-D imaging of PC cells.

PRURITIS AND PC
PC Project has permission to use the recently published “Leuven Itch Scale” to assess itch in PC. This is a known characteristic in PC described by patients not as a surface itch, but a deep itch under the skin. PC Project is obtaining IRB approval and will conduct the survey on at least 100 genetically confirmed PC patients and provide the data for publication.

PC CLINICAL STUDY
A dominant theme at the IPCC meeting was the need for more information about PC. During the IPCC meeting and in emails and meetings which followed, a plan was formulated to gather from 40 to 60 PC patients and conduct a consistent and detailed clinical exam of the patients. This will include at least the following:
1. A complete physical by a team of two or more dermatologists using consistent measurements and evaluations
2. Collection of skin cell samples as needed for studies including creating PC cell lines for use by researchers.
3. An in-depth pain study to build on the preliminary work done at the patient meeting in 2011.
4. Photography and imaging

TWO PC PATIENT SUPPORT MEETINGS NOW PLANNED
As a result of the need for this clinical information, two patient support meetings are now planned to conduct these studies.
2. Bi-Annual Patient Support Meeting to be held October 28-30 in Edinburgh co-sponsored by PC Project and University of Dundee.

We will use both of these patient meetings to gather important information for PC research. If you are interested in attending, please email www.pachyonychia.org/

2015 IPCC MEETING
As our schedules and interests overlaps, in 2015 the IPCC will hold a joint meeting with dEBra so allow speakers and attendees to participate in both meetings.

MARK YOUR CALENDAR NOW
Joint IPCC & dEBRA before SID
May 3, 4, 5—Atlanta, Georgia
IPCC probably Tuesday May 5, 2015
CLINICAL TRIAL UPDATE
We agree it would be great to be able to report how things are going. However, the clinical trial for topical rapamycin now underway will not end until there is a 3-month ‘wash out’ period following the end of treatment. The study is a Phase 1b Clinical Trial sponsored by PC Project at Stanford University (Dr. Joyce Teng) using the topical rapamycin developed by Roger Kaspar (TransDerm, Inc) with API from Pfizer. As it is a double-blind placebo controlled study, the data will not be available until the trial is completed.

RECENT PC PUBLICATIONS
We are sorry most of these patients have never been referred to PC Project where genetic testing and other support services are provided at no cost to patients/physicians.


We read with great interest the report by Guo and colleague on a patient displaying nail thickening, palmoplantar keratoderma, corneal hyperemia and alopecia, which they refer to as pachyonychia-unknown (PC-U).

As mentioned by the authors of this report, the phenotypical features displayed by their patient do not fit to the clinical manifestations usually observed in PC. Alopecia is highly unusual and corneal involvement has never been reported to date in conjunction with a mutation in any of the 5 genes known to be associated with PC.

We believe that the mere occurrence of palmoplantar keratoderma and nail thickening is not sufficient to pose a diagnosis of PC, especially in the face of highly unusual clinical features, and that it may in fact be misleading. Indeed, the constellation of signs demonstrated in their patient may possibly be due to mutations in another gene, associated with another mode of inheritance than PC, which in turn may result in ill-founded genetic counseling. As an example, the combination of signs displayed by the case under study may reflect a mild form of IFAP due to mutations in MBTPS2. IFAP is inherited as an X-linked recessive trait whereas PC is inherited in a dominant fashion which obviously carries serious implications in terms of genetic counseling. In addition, in the era of next generation sequencing, many such unusual phenotypes are in fact found to be the result of the unfortunate co-occurrence of two mutations in two genes, a possibility than cannot be excluded here either.

In conclusion, disease classification should nowadays be based whenever possible, on a combination of clinical and molecular features, which is why we would recommend thorough molecular analysis of the present case using advanced sequencing technologies prior to assigning it to a given clinical entity.
11th Annual International PC Consortium (IPCC) Symposium
“Corners”
Albuquerque, NM—May 6, 2014

7:00—7:45 BREAKFAST

Keynote Introduction—Eli Sprecher
8:00—8:20 Pierre Coulombe
An Overview of Keratin Research

PC pathogenesis cornered
Section Chair: E. Birgit Lane

8:25—8:40 Thomas M. Magin
Keratins as gatekeepers of epidermal homeostasis - novel insights from knockout mice

8:45—9:00 Jiang Chen
Correction of Hair Shaft Defects in a Mutant Mouse Model Related to PC

9:05—9:20 Robert Rice
Proteomics: PC Samples

9:25—9:40 Laure Rittie
PC Skin in 3D

9:45—10:15 BREAK

From all corners of...
Section Chair: Dennis K. Roop

10:15-10:30 Y. Paul Goldberg
From Genes to Drugs: A Novel Topical Sodium Channel Inhibitor for the Treatment of Pain

10:35—10:50 Eli Sprecher
Inflammatory Peeling Skin Syndromes

10:55—11:10 Yong Yang
Olmsted or not — Differential Diagnosis of TRPV3 Disorders

11:15—11:30 Hans Van Bokhoven
Molecular Genetics of p63 Syndromes

12:15—1:15 LUNCH

The PC Corner
Section Chair: W. H. Irwin McLean

1:30—1:45 Frances J.D. Smith
PC Genetic Findings

1:50—2:05 Ilan Goldberg
Pachyonychia Congenita Case Studies

2:10—2:25 C. David Hansen
IPCRR Registry Data Update

2:30—2:50 BREAK

Clinical trials: Turning the Corner?
Section Leader: Edel O’Toole

2:50—3:05 Alain Hovnanian
Capsaicin for PC

3:10—3:25 Steven L. Roberds
Clinical Studies of Topical Sirolimus for Angiofibromas associated with Tuberous Sclerosis Complex

3:30—3:45 Frederick B. Bartholomew and Viraat Patel
Off Label Topical Sirolimus Trial for PC

3:50—4:10 Roger L. Kaspar,
Tycho Speaker, Yuan Cao
Development of Topical Sirolimus for Pachyonychia Congenita

4:15—4:30 Discussion
Decision 2014

6:30 pm—Bus leaves DoubleTree Hotel lobby for dinner at the Indian Pueblo Cultural Center
INTERNATIONAL PACHYONYCHIA CONGENITA CONSORTIUM (IPCC)

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NIH Putting in Place Global Rare Diseases Repository

Health Data Management

http://www.healthdatamanagement.com/news/NIH-Putting-in-Place-Global-Rare-Diseases-Repository-48546-1.html

“As the world healthcare community struggles with how to contain an Ebola outbreak in Africa, the National Institutes of Health is quietly putting in place a web-based central data repository to support and accelerate research in the cause, diagnosis, and treatment of rare diseases globally.

With an estimated 30 million individuals worldwide affected by one of more than 7,000 known rare diseases, the goal is to improve drug and therapeutics development and the quality of life for those suffering from the diseases by providing researchers with the infrastructure to store, search, retrieve and analyze critical datasets. Though the data is not yet available, NIH is working towards a May 2015 launch of the repository’s public website.

Started as a pilot project that ended in September 2013, NIH’s Global Rare Diseases Patient Registry Data Repository (GRDR) program is designed to aggregate standardized, coded and de-identified patient information and clinical data to make it available to scientific investigators to conduct new biomedical studies including clinical trials. Housed at the NIH National Center for Advancing Translational Sciences (NCATS), the GRDR program collects into a single centralized resource a wide range of data types, including phenotypic, clinical, and genomic, as well as medical images, derived from individuals who participate in rare disease patient registries.

Out of the approximately 7,000 rare diseases globally, only a small portion of them have patient registries. The two-year pilot project included 12 patient advocacy group registries.*

Currently, the GRDR program—led by staff in NCATS’ Office of Rare Diseases Research—includes about 50 diseases, including 3,800 patients in 90 countries. Data is collected by registry owners, which in most cases are rare disease advocacy groups or academic-based scientific teams.

"Patient registries represent one of the best resources to collect prevalence, demographic, natural history, and comparative effectiveness data on rare diseases," says Marshall Summar, M.D., chief of genetics and metabolism and a professor of pediatrics at Children’s National Medical Center in Washington, D.C.

As the GRDR program ramps up for the May 2015 launch of its web-based repository, registry data shared for the program will be standardized to common formats and terms so that the registries are interoperable with one another and with other national databases. Mapping the data is the most difficult and challenging step in ensuring that the data is integrated in a uniform manner, say program officials. ‘A goal of the GRDR is to harmonize the way that patient registries collect the data so they can talk to each other and share data,’ says Yaffa Rubinstein, Ph.D., director of Patient Resources for Clinical and Translational Research in NCATS’ Office of Rare Diseases Research.

Data is collected and aggregated from rare disease registries in a standardized manner, linking the registry data to Common Data Elements (CDEs) using nationally accepted standards and standard terminologies.

*PC Project was one of the participating existing registries in the pilot project and has been invited to participate in phase 2 of the GRDR project.

IPCRR registry graphs and charts are updated online monthly showing mutations, location of patients, related disorders, etc. See http://www.pachyonychia.org/pc_data.php
The Keratin Corner

Emily Warshauer

It is no secret that to play their role properly in epithelial tissues, keratins function in pairs. In fact, the heterodimeric interactions between type I and type II keratins are among some of the most potent found in nature. These stable complexes feature remarkable structural and functional specificity, and are perpetually adapting to maintain a state of dynamic equilibrium. New studies continue to broaden our knowledge about the molecular mechanisms underlying the activity of these keratin heterodimers within the epidermis.

In the May issue of the Journal of Investigative Dermatology, Heinz Fischer and his colleagues utilize K2, K10 and K2/K10 knockout mice to elucidate the biological significance of K2 in terms of the degree of interdependence with its known binding partner K10. They reveal that K1 and K2, which can both bind to K10, are expressed in a mutually exclusive manner at different body sites of the mouse, with K2 being expressed preferentially in epidermis of the ear, sole, and tail skin. Not only did K2 absence result in impaired epidermal differentiation, but it also led to local inflammation and to K10 aggregate formation. Thus, K2 is a critical binding partner for K10 at distinct body sites of the mouse. The implications of these findings to the human epidermis remain to be determined.

The functional relevance of keratin heterodimer self-organization is also investigated by David Alvarado and Pierre Coulombe in the May issue of the Journal of Biological Chemistry by analyzing another equally distinct keratin pair, K5/K14. In K5 null mice, a chimeric type II keratin, K8bc, is used to replace K5 and competently bind with K14. The mice are partially rescued from severe perinatal blistering and death, yet the unique and comprehensive functions of the K5/K14 pair cannot be fully recuperated as alopecia and skin erosions eventually develop. This again highlights how the cross-linking and synchronous activity of very specific keratin heterodimers is essential for epithelial homeostasis.

In conclusion, similar to the resounding message of Yin and Yang, opposite but complementary and stronger together, keratin heterodimers also co-exist in a harmonious balance to provide strength in the epidermis as a collective pair that is far greater than the capacity of any individual keratin monomers.

References:


New PC Fellow at Stanford University

Andreas Berroth, PhD, a highly qualified young scientist, will begin in mid-August as a Pachyonychia Congenita Fellow at Stanford University. In addition to working at Stanford, Andreas will work closely with TransDerm, Inc. on projects focused on PC research goals. He will also interact and work with additional groups within the International Pachyonychia Congenita Consortium (IPCC) to facilitate PC research and progress.

In 2009, Andreas completed a degree in Biotechnological Engineering Degree (Diplom-Ingenieur (FH) at Furtwangen University in Villingen-Schwenningen, Germany and his PhD in Biology at Christian-Albrechts University in Kiel, Germany Ph.D. in December 2013.

We welcome Andreas and look forward to excellent collaborations within the IPCC to advance PC research.

2014 IPCC Meeting Review

We are pleased that the 2014 meeting review (prepared by Laure Rittié, Edel O’Toole, Eli Sprecher and others) has been accepted for publication in the British Journal of Dermatology and will be available online shortly. We appreciate this effort very much.

Research Papers Submitted

Y Cao, D Grapov, RP Hickerson, MM Gross, MR Bessette, BL Seegmiller, BS Phinney, MA Flores, TJ Speaker, A Vermeulen, D
Leake, JY Tang, AA Bravo, AL Bruckner, LM Milstone, ME Schwartz, RH Rice, RL Kaspar.  
Gene Expression Profiling in Pachyonychia Congenita Skin.

Pachyonychia congenita (PC) is a skin disorder resulting from mutations in keratin genes (KRT) 6A, KRT6B, KRT6C, KRT16, and KRT17 genes. One of the major symptoms is painful plantar keratoderma. The pathogenic sequelae resulting from the keratin mutations remain unclear.

Many differentially-expressed genes identified in PC-involved skin encode components critical for skin barrier homeostasis including keratinocyte proliferation, differentiation, cornification, and desquamation. The profiling data provide a foundation for unraveling the pathogenesis of PC and identifying targets for developing effective PC therapeutics.

Reciprocal keratin 9 and keratin 6/16 expression patterns in pachyonychia congenita plantar skin harboring the keratin 6a N171K mutation suggests an altered epidermal differentiation program.

Gene expression profiling has the potential to rapidly reveal pathogenic mechanisms and identify therapeutic targets of inherited skin disorders, including the rare skin disorder pachyonychia congenita (PC). Global mRNA expression patterns in PC plantar biopsies (involved and adjacent uninvolved regions), control plantar biopsies, abdominal skin and human keratinocyte lines were analyzed by microarray chips and selected differentially-expressed genes were confirmed by RT-qPCR and/or immunohistochemistry.

As expected, PC-related keratin genes encoding keratin (K) 6a, K6b, K6c, K16 and K17 were upregulated (greater than 5 fold) in PC-involved relative to PC-uninvolved or non-PC plantar skin.

Unexpectedly in involved tissue harboring a K6a N171K single nucleotide mutation, K9 mRNA expression was greatly reduced (30 to 120 fold) compared to controls and when compared to K6, K16 and K17 expression. To further elucidate the potential role of keratins in the PC disease process, absolute amounts of the mRNAs encoding the major plantar keratins (K1, K5, K6a, K6b, K6c, K9, K10, K14, K16 and K17) were determined. Proteomic analysis of corneocytes from K6a N171K patients confirmed that K9 protein levels were dramatically decreased in PC-involved skin.

The combined results suggest an impaired epidermal differentiation program, including reduced K9 expression. Gene expression analysis in tissue from patients with mutations in keratin genes other than KRT6A did not show this pattern, suggesting that different PC gene mutations may have distinct pathophysiologies.

UPCOMING EVENTS

CLINICAL STUDY—BIOPSIES
Fifteen PC patients will travel to Salt Lake City on August 8-9, 2014 to provide biopsies for the PC Neuroanatomy study at Johns Hopkins (Michael Polydefkis laboratory). The biopsy collection will be under the direction of C. David Hansen, MD and Roger Kaspar, PhD.

CLINICAL STUDY—BIOPSIES, CLINICAL EXAM AND PAIN STUDY. Twenty patients will visit the Imagine Clinic in Paris on October 11, 2014 for a special PC study. This study will be co-sponsored by PC Project and Le Coeur au Pied and is under the direction of Eli Sprecher and Alain Hovnanian, MDs and Prof. Giuseppe Lauria.

PATIENT SUPPORT MEETING 2014—On October 26-28, approximately fifty PC patients will gather in Edinburgh for the annual PC Patient Support Meeting. The meeting is co-sponsored by PC Project and PC-UK at the University of Dundee. All interested physicians and researchers are invited to attend. Please contact PC Project for additional information and to arrange any travel stipends available.

PATIENT SUPPORT MEETING 2015—On June 26-28, we expect approximately 60-70 PC patients will gather at the Marriott Airport Hotel in Newark, NJ for the annual PC Patient Support Meeting. Again all specialists are invited.
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W. H. Irwin McLean, Roger L. Kaspar, Frances Smith, Eli Sprecher

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Webmeeting 1st Wednesday monthly
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PHYSICIAN NETWORK

Quarterly Webmeetings, Annual IPCC Meeting

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The ripple effect of a single keratin is likely far more extensive than initially thought in the early days of keratin discovery. It is well known that the keratin family contributes to the intermediate filament network within keratinocytes and has a critical impact on the epidermis and greater skin as a whole. Yet, keratins may also have an influence that even transcends the skin as evidenced by their intrinsic connection with neuroendocrine pathways, highlighted in two recent articles.

Based on an earlier discovery that the neuropeptide hormone, prolactin, profoundly impacts keratin expression, research in this area was inspired and the door was opened to the possibility that elements of the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-thyroid (HPT) signaling axes may play a major role in the skin. Last summer, in the *British Journal of Dermatology*, Yuval Ramot and colleagues utilized the highly specialized human hair follicle organ culture microdissection technique to explore the role of thyrotropin-releasing hormone (TRH) on different hair and epithelial keratins. They found that TRH functions as a novel and powerful regulator of many keratins, including K6, K16 and K17, relevant to pachyonychia congenita.

To complement previous studies, Yuval Ramot and colleagues in *Bioessays* this past July, continued to investigate numerous other endocrine mediators of keratin expression and acknowledged the impressive effect of opioids, catecholamines, PTHrP and endocannabinoids among others. Reflecting on new potential treatment for pachyonychia congenita, they contemplated alteration of keratin expression via neuroendocrine pathways. The use of combination therapy was suggested, either as a possible means to enhance siRNA delivery or coupling TRH or an endocannabinoid analog with retinoic acid or a statin. Of note, prior to focusing on this therapeutic approach, it is important to assess whether the endocrine mediators have a direct effect on the keratins and also to identify how much of the diverse hair and skin phenotypes of patients with keratin disorders is actually even due to neuroendocrine influences.

Not only are keratins under the regulation of neuroendocrine mediators, they may in fact also regulate important endocrine functions as exemplified by a recent article by Alam et al suggesting that K8 may be involved in glucose homeostasis.

How far do we need to zoom out in order to gain a full understanding of the relationship between keratins and endocrine systems? Similar to an island which is never alone but rather exists as a remarkably beautiful and intricate network forming an archipelago, no keratin is an island either. Continuing to develop and maintain a broad approach when it comes to understanding the extensive and complex nature of the keratins will provide insightful new perspective and ideas for innovative therapeutic modalities for pachyonychia congenita and other keratin disorders.

**References**


HEY, YOU NEVER KNOW...
This was the slogan for the New York Lottery for many years and was effective in getting people to ‘take a chance on winning.’

Although I am not in favor of lotteries, when I heard this slogan discussed recently, I thought how much this applies to what we are trying to do at PC Project. We want to invite, involve, encourage and empower each of you — our medical and scientific experts — to ‘take a chance’ that together we may find effective treatments or even a cure for Pachyonychia Congenita.

There are lots of risks along the way and the chances of winning often seem too small to pursue, but we must not stop our quest.

Educational outreach and awareness of the facts about PC remain a high priority. Textbooks and older articles contain a great deal of information that is not correct. We understand that often there was only a single case available on which to base the data.

However, although we have more than 25 publications in recent years, using the data gathered over the last 10 years in the International PC Research Registry (IPCRR), an author recently has asked us for help in responding to these comments by a reviewer

(a) Reviewer states ‘there is a sex bias in PC.’ Not true. Presently, we have 288 males and 305 females in the IPCRR with genetically confirmed PC.

(b) Reviewer states “it is widely known that K17 affects only hair and would not affect palms or soles.” Not true. The images on our website, the details of nearly 100 patients with genetically confirmed PC who have mutations in K17 show that PPK (as well as cysts) are main features of this PC type.

Hey, you just never know…so we have to keep publishing and gathering accurate data.

We are so hopeful that some of the clinical studies that are underway or planned. Here are a few of these

(1) Topical Rapamycin. The data from the Phase 1b Clinical Trial headed by Roger Kaspar, TransDerm and Jean Tang, Stanford will be unlocked in early 2015. We hope these results can be reported at the next IPCC meeting.

(2) Cream delivery siRNA. An exciting article was recently published by the McLean laboratory. (Listed below in Recent Publications). The intent is to further develop this through a collaboration of IPCC members.

(3) Botox. We continued to have patient-reported results of effective pain relief through injections of Botox into the plantar keratoderma. We are seeking partners to establish a study that will help to set up guidelines for the treatment.

(4) Nail removal. Len Milstone led efforts to query PC patients who had experienced nail removal. At the time of that study/survey, we had 25 PCers with at least one nail removed. Cynthia Carver DeKlotz is preparing that data for publication. We now have over 50 PCers with at least one nail removed and are looking for partners to extend and repeat this survey/study to help establish better guidelines and methods for this treatment.

(5) At the PeDRA meeting held in early November in Chicago, we presented our major clinical challenges (a) rarity of the disease (b) intense pain as the major debilitating feature and (c) delivery of drug to affected skin. We will pursue several of the proposals from PeDRA:

- Fractional CO2 Laser to treat cysts was proposed by Andrew Krakoswki, (UC San Diego) and we hope to have a few trial patients in a small study

- New software that creates a heat map of affected areas was presented by Anita Haggstrom (*) and we hope to see if this may be applicable on PC images.

(6) We are seeking authors to collaborate on a number of articles for which we have the data and case studies. For example, four cases of newborns with PC who were treated for thrush and experienced ‘failure to thrive.’
**SHOPPING FOR PC**

You have all done so much for PC research. However, it’s that time of year when people around the world are gathering with friends and family to celebrate a wide range of holidays. If your gatherings include a little shopping, consider doing yours online through any of the following organizations.

Without costing you a penny more than what you are already purchasing, you can help PC Project raise much needed funds to support our work.

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### iGive.com

Shopping with iGive returns an average of 3% of your purchase at more than 1,500 retailers back to the charity of your choice at no extra cost to you.

To get started, go to [www.igive.com](http://www.igive.com), fill out the short form, and choose PC Project as your charity of choice.

We have partnered with Goodshop so that now you can feel great about your online shopping!

Goodshop gives you the best coupons for thousands of stores like Target, Apple, Amazon, Petco and more AND a percentage of what you spend on virtually every purchase is donated to our cause! Plus, with the Goodshop app for iPhone and iPad, you can shop, save, and give on the go.

Go to [www.goodshop.com](http://www.goodshop.com), complete the quick signup form, choose PC Project as your charity of choice, and then shop away!

A sister site to Goodshop, Goodsearch donates to your cause just for searching the Internet.

### shopping with iGive

It’s well known that you can find pretty much anything you’re looking for on Amazon, and now, the stuff you buy can benefit the causes you love.

Go to [smile.amazon.com](http://smile.amazon.com), log in with your regular Amazon login info, select PC Project as your charity, and shop like normal.

0.5% of your qualifying purchases will be donated back to PC Project through the Amazon Foundation.

### Goodsearch

Simply go to [www.goodsearch.com](http://www.goodsearch.com), choose PC Project as your charity, and then search just like you would on Google, Bing, or Yahoo. A penny is paid to PC Project for every search you make!

**RECENT PUBLICATIONS**


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