PC Project Working Together for PC Patients

The PC Project continues to provide services to patients with pachyonychia congenita. In this newsletter, we update you on new developments at PC Project including data from the patient registry, new publications, a profile of Pierre Coulombe from our Medical and Scientific Advisory Board and an update on development of topical rapamycin as a treatment for PC.

The key programs of PC Project are:

- **The IPCRR (patient registry)** founded in 2004 it is one of the most important achievements of PC Project with over 700 PC patients now enrolled in 47 countries.

- **The International PC Consortium (IPCC)** to encourage and support collaborative research efforts to find a treatment for PC.

- **Newsletters** both for patients and for the IPCC members to inform and unite these communities.

- **Annual PC Patient Support Meetings (PSM)** where patients meet, teach and support one another and effectively defeat the overwhelming loneliness caused by an ultra rare disease.

- **Publications** to continue to bring attention to PC and explain the debilitating nature of this disorder, emphasize the need for treatment and highlight important research achievements.

- **Pachyonychia.org** website with accurate and current information on all things related to PC.

PC Project wants to express its deep gratitude for each of you - our dear friends old and new. Thank you for all you do to help PC Project, PC Patients and in moving PC research forward.

Why is the Skin of our Palms and Soles So Much Thicker?

Dr Anissa Chikh, Dr Thivi Maruthappu and Prof David P Kelsell, Centre for Cell Biology and Cutaneous Research, Blizard Institute, Queen Mary University of London, London

Keratinocyte hyperproliferation and inflammation are common to many skin disorders such as psoriasis, atopic eczema and palmoplantar keratodermas (PPKs) including Pachyonychia Congenita (PC). The PPKs are characterised by different patterns of hyperproliferative thickening of the palms and soles, and can often exhibit painful callous formation. Previously, the Kelsell group showed that inherited dominant mutations in RHBDF2, the gene encoding iRHOM2, are the genetic basis of the inherited syndrome Tylosis with Oesophageal Cancer (TOC) characterised by the development of a painful keratoderma in childhood and a 95% likelihood of developing Oesophageal cancer >65 years old.

The group recently published their research in Nature Communications 2017, and described an important role for iRHOM2 as a master regulator of stress responses in skin. They identified that iRHOM2 is a novel regulator of the cytoskeletal response to physical stress through its interaction with keratin 16 (K16) in humans and mice. This has important implications for PPKs, wound healing,
inflammatory skin disease and cancers. They showed that iRHOM2 regulates thickening of the footpad epidermis where TOC-associated iRHOM2 is characterized by palmoplantar thickening, upregulates K16 with robust downregulation of its type II keratin binding partner K6. In contrast, iRHOM2 loss results in reduced K16 expression and rhbdf2–/– mice have a thinner epidermis in the footpad compared to control mice. These findings shed light on a novel role for iRHOM2 in regulating the epithelial stress response and contribute to our understanding of the molecular mechanisms underlying hyperproliferation of the palmoplantar epidermis in both physiological and disease states. Moreover, as PC can be caused by mutations in Keratin 6 and 16, it could be intriguing to determine the contribution of iRHOM2, and its interaction with these particular keratins in the development of keratoderma in PC.


UPDATE ON PC PROJECT AND PALVELLA’S EFFORTS TO RAPIDLY ADVANCE NOVEL, HIGH STRENGTH TOPICAL RAPAMYCIN TO PC PATIENTS

Wes Kaupinen, Palvella

With the enthusiastic and ever-willing help of PC Project and scientists and clinicians worldwide, Palvella Therapeutics continues to make meaningful progress on its development of an enhanced formulation of topical rapamycin to be evaluated in a Phase 2/3 safety and efficacy study commencing in 2018. The study builds on the compelling scientific rationale of rapamycin in PC first elucidated by Dr. Roger Kaspar and the TransDerm team, as well as the early directional clinical evidence generated from the oral rapamycin study and multiple topical rapamycin studies in PC. This study will be the first properly designed and adequately powered study to evaluate the efficacy of topical rapamycin in pachyonychia congenita.
While the TransDerm team discovered certain proposed direct mechanisms of action in pachyonychia congenita (Hickerson et al., Journal of Dermatological Science, 2009), further therapeutic effects of rapamycin in PC are likely derived from its known anti-inflammatory properties (Weichhart et al, Nature Reviews, 2015) and anti-angiogenic properties (Guba et al, Nature Medicine, 2002), each of which are important given the documented inflammation and hyper-neovascularization (Polydefkis et al, Pain, 2016) which are likely major contributors to PC disease pathogenesis.

Palvella’s efforts over the last several months have been acutely focused on two areas: i) Development of a high strength and rigorously tested formulation of topical rapamycin that has product attributes that are acceptable to both PC patients and global regulatory authorities; and ii) Careful selection of efficacy outcomes measures, i.e. endpoints, for inclusion into the clinical study. Endpoint selection is by no means trivial for PC given the multi-factorial presentation of the disease as well as the scarcity of clinical studies in PC, i.e. limited precedent from which to work. Palvella has recruited some of the world’s leading clinical trial design experts, including the former Director of the FDA’s Dermatology Division, to help address this issue. The clinical relevance of a narrowed list of potential efficacy endpoints, many of which are designed to objectively evaluate function and ambulation in PC, have now been validated through survey work directly with PC patients. Next steps for Palvella include proper interactions with regulatory authorities before initiating the clinical study later this year.

Thanks to everyone who has been a contributor to advancing this development program. The level of collaboration put forward from all corners of the PC world will one day make for a great case study of the results that can be achieved from a patient-first partnership among a patient advocacy group, the clinical and scientific communities, and industry. Special thanks are extended to Phil Gard who has played a vital role in ensuring the ‘voice’ of PC patients worldwide has been incorporated into the formulation development process. Phil has gone above and beyond the call of duty by traveling to Guildford, UK to meet with many of the world’s leading topical formulation scientists to provide valuable feedback on what product attributes would be most valuable to PC patients. We look forward to keeping everyone updated on the exciting progress.

UPCOMING PC & EB PL-PFDD MEETING

PC Project will participate in an Externally-led Patient-Focused Drug Development Meeting (EL-PFDD) with FDA officials.

This FDA meeting will take place the morning of April 6, at the College Park Marriott Hotel in Hyattsville, MD, near FDA headquarters. Approximately 50-75 PC patients and caregivers will share their voices through panel presentations, electronic polling and moderated audience discussions. (After a shared luncheon with PC patients, EB and EBS patients will have a similar meeting in the afternoon.)

The Patient’s voice has historically been absent from the drug development process until a drug was approved by the FDA or when a clinical trial was failing and the FDA wanted input from actual patients to understand the problem. Now, the FDA wants to hear patient voices at the beginning of the process and throughout. Patient engagement is now a priority for the FDA.

PC patients are thrilled to be part of this historic opportunity to tell FDA officials about living with PC, managing PC, and what meaningful treatments will look like for patients.

As a researcher or clinician, if you are interested in attending this meeting either in person or through a live webcast, please email PC Project at info@pachyonychia.org.
PC Patient Problems and Solutions - Leukokeratosis

The IPCRR shows that 54% (424/792) of all genetically confirmed PCers have leukokeratosis (K6a has the greatest percentage who say they have leukokeratosis at 89%, K6b 25%, K6c 18%, K16 35%, K17 26%) and only 16% report the leukokeratosis as somewhat painful. The majority of PCers do not have pain or discomfort with leukokeratosis. It is not malignant or pre-malignant and can be aggravated by stress, spicy food, alcohol and smoking. Some patients rinse their mouth with warm water with a tiny pinch of salt or antiseptic mouthwash, such as Gly-oxide if sore or thickened. One patient mentioned that L-Lysine tablets help (available from health food stores).

Genetic Testing

Genetic testing for patients enrolled in the IPCRR is currently performed using a gene panel of nine genes including the five PC associated keratin genes (KRT6A, KRT6B, KRT6C, KRT16 and KRT17) plus four other genes; DSG1 (striate PPK), GJB6 (Clouston syndrome), AAGAB (punctate PPK), and TRPV3 (Olmsted syndrome). Mutations in these latter four genes result in phenotypes with overlapping/similar features to PC ie focal palmoplantar keratoderma, which can lead to misdiagnosis. Diagnosis at the molecular level by genetic testing confirms/ ensures the correct clinical diagnosis enabling appropriate care and genetic counselling.

As of January 2018 the IPCRR has enrolled over 1,000 patients. Clinical and molecular data has been collected from 792 PC patients (431 families) in over 47 countries. 114 distinct PC mutations have been identified. The majority of PC mutations are heterozygous missense mutations with a small number of insertion/deletion and splice site mutations.

After submitting their IPCRR clinical questionnaire, clinical photographs and participating in a clinical consultation some individuals (67) have been identified as not having PC (or any of the disorders we test for) and therefore no testing has been performed. Others (135), identified as unlikely PC, but with likely candidate genes have undergone testing by Sanger sequencing or the gene panel. Mutations have been identified in some of these (see below), others with no mutation may have other disorders including psoriasis of the nails.

63 individuals have been confirmed by genetic testing (by Sanger sequencing or the 9 gene panel)

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<thead>
<tr>
<th>#</th>
<th>Gene/Disorder</th>
<th>#</th>
<th>Gene/Disorder</th>
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<tbody>
<tr>
<td>5</td>
<td>AAGAB/punctate PPK</td>
<td>7</td>
<td>FZD6/recessive nail dysplasia</td>
</tr>
<tr>
<td>1</td>
<td>AIRE/APS Type 1</td>
<td>3</td>
<td>KRT1/PPK</td>
</tr>
<tr>
<td>1</td>
<td>CAST/PLACK syndrome</td>
<td>7</td>
<td>KRT9/PPK</td>
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<tr>
<td>2</td>
<td>COL7A1/dominant DEB</td>
<td>1</td>
<td>ITPKC/Kawasaki disease</td>
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<tr>
<td>15</td>
<td>GJB6(Cx30) Clouston syndrome</td>
<td>1</td>
<td>INSR/Rabson-Mendenhall syndrome</td>
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<tr>
<td>8</td>
<td>DSG1/striped PPK</td>
<td>10</td>
<td>TRPV3/Olmsted syndrome</td>
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<tr>
<td>2</td>
<td>DSP/skin fragility woolly hair</td>
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to have a disorder distinct from PC.

Recent Publications


2017 International PC Consortium (IPCC) Symposium in Portland, Oregon
INTRODUCTION

In this May newsletter, we update IPCC readers on the recent meeting of PC patients with the FDA to discuss future therapies for PC which was a huge success. We profile Dr Frances Smith, the PC Project Chief Geneticist who has worked on PC for over 20 years! Emily Warshauer from the University of Colorado writes about Keratin 24. Finally, PCer Rylee Defebaugh writes about how she copes with plantar pain.

FDA officials listen & learn about PC

The PC Externally-led Patient Focused Drug Development (EL-PFDD) meeting with FDA officials on April 6, 2018 was a huge success!

With over 100 PC patients participating in person or via the live webcast, patients successfully communicated to key FDA officials the impact of PC on their lives, how they manage their PC and what a meaningful treatment will look like.

Patient input and experiences were expressed through panel presentations, live polling and audience participation. Patients who attended remotely submitted their answers to open-ended questions online. All answers will be incorporated into the official Voice of the Patient Report for FDA.

An impressive number of FDA officials attended the meeting - 24 in person and 18 via the webcast. This was a record amount of FDA officials to attend an externally led patient drug development meeting.

Why was this meeting so important for PC patients, FDA officials, industry partners, scientists, and clinicians?

1. FDA officials who listened at the meeting will make critical decisions regarding future treatments for PC.

2. While FDA officials will seek out medical literature and input from clinical experts, most FDA reviewers will have little if any personal knowledge of PC from their time in practice. Neither the published literature, nor the clinical expertise can fully capture the experiences of what patients experience day-to-day. It is only patients (and their caregivers) who have that knowledge to share.

3. There isn’t always unity between patients and clinicians on what the most pressing unmet medical needs are, especially when a disease is as ultra-rare as PC. PC patients were able to express to FDA officials what those unmet needs are in a compelling way. The Voice of the Patient Report from this meeting will be used by FDA as a standard for PC.

4. FDA needs to know it is designing clinical trials that will generate empirical evidence on outcomes that are important to PCers. What a patient describes as the greatest burdens of a condition can lead to the appropriate selection of outcome (baseline) measures. Knowing about the day-to-day impact of PC can help determine when and how to implement outcome measures in clinical trials.

5. Patient input at the meeting also focused on preferences for future treatments. The FDA recognizes that it is a judgement call as to whether the benefits of a drug outweigh the risks when it is making an approval decision. Thus, FDA heard the preferences of patients about future therapies; they can assign appropriate
weight to those things that are most important to patients when balancing those benefits against the risks of a product.

6. Finally, FDA saw real patients, with real pain and challenges. FDA officials have learned not only about PC, but that PC is a disease that needs effective treatments to reduce or eliminate the debilitating, painful burdens PCers live with every single day.

PC Project appreciates the IPCC members who were able to attend the meeting in person — Drs. Anna Bruckner, C. David Hansen, Roger Kaspar, Sancy Leachman and Joyce Teng. PC Project also appreciates James Valentine (consultant and moderator) and the support of its industry partner, Palvella including Wes Kaupinen and members of his team who attended in person.

### Sampling of EL-PFDD Live Poll

Which PC conditions have impacted your life? Check all that apply. N=103

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of PCers</th>
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<tr>
<td>Other</td>
<td>9</td>
</tr>
<tr>
<td>Trouble feeding as a baby</td>
<td>16</td>
</tr>
<tr>
<td>Leukokeratosis</td>
<td>59</td>
</tr>
<tr>
<td>Follicular hyperkeratosis</td>
<td>60</td>
</tr>
<tr>
<td>Painful cysts</td>
<td>35</td>
</tr>
<tr>
<td>Infections in nails or feet</td>
<td>69</td>
</tr>
<tr>
<td>Deep persistent itch in feet</td>
<td>56</td>
</tr>
<tr>
<td>Painful blood vessels/nerves in calluses</td>
<td>60</td>
</tr>
<tr>
<td>Painful calluses/blisters on hands</td>
<td>33</td>
</tr>
<tr>
<td>Painful calluses/blisters on the soles of your feet</td>
<td>99</td>
</tr>
<tr>
<td>Thickened nails</td>
<td>88</td>
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</tbody>
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Have you ever utilized a mobility assistance device (e.g. wheelchair, cane, scooter, walker or employed an alternative form of mobility (e.g. such as bikes, strollers, crawling, holding onto walls or rails, piggy-backing, holding onto another person, etc.

- **Yes, 85%**
- **No, never = 15 PCers**

Breakdown of Yes:
- Yes, on occasion, but not every week = 33
- Yes, at least once or more each week = 31
- Yes, at some point during every day = 33
In the absence of a cure, which single FUNCTIONAL improvement would be most important to your quality of life?

- Increase either the length of time I can walk or improve my ability to do activities that involve being on my feet = 81 PCers
- Reduce my need to use mobility aids or alternative aids (such as crawling, crutches, etc.) = 7 PCers
- Reduce the time required to manage PC symptoms = 8 PCers
- OTHER = 8 PCers

How has your PC changed overtime/with age?

- Stayed the same = 13 PCers
- Gotten better = 7 PCers
- Gotten worse = 80 PCers

In the absence of a cure, a clinically meaningful treatment for PC would: Select all that apply.

- Reduce the time required to manage PC symptoms = 39 PCers
- Reduce need to use mobility aids or alternative aids (such as crawling, crutches, etc.) = 37 PCers
- Increase either the length of time I can walk or improve my ability to do activities that involve being on my feet = 66 PCers
- Decrease Pain = 79 PCers
- Improve appearance of calluses, cysts, nails or other PC Symptoms = 53 PCers
EL-PFDD Meeting Highlights in pictures.
PC Patient Viewpoint

My name is Rylee. I’m 18 years old. I’m a senior in high school and have a spontaneous mutation of PC K6a.

Everything I do to manage my PC has to deal with treating the pain in my feet. One thing I do is try and keep my feet in a balance between wet and dry. I leave my socks and shoes on a lot to keep my feet from drying out. If my feet get too dry, my feet hurt more. The calluses get hard, like rocks, and they hurt super badly. They will crack and bleed. The worst is when they stick to my socks. I’ll have to put them in water, socks and all, in order to peel off the socks.

Still, it’s a hard balance. When my feet are wet and blistery, they hurt and when they are dry they hurt. It’s a lose-lose situation.

I regularly soak my feet in plain water. Soaking helps. It feels good and is soothing. It also helps them not to itch. This itch is so bad I’ll scratch them until they bleed. I can’t seem to get to the itch, no matter how much I scratch. To get the itch, I’ll rub my sock against my foot, because I don’t have good nails for scratching.

The worst thing about PC are the blisters and calluses. Every other symptom I have – the pain, the itching – is from the blisters and calluses. I have to pop the blisters with needles all the time.

My mom used to cut my calluses down with a razor blade till I was about 9 or 10 years old. She used to cut so close to the skin they would bleed. (There is a balance between cutting too much and not enough.)

Last year, I started taking tramadol. I take pain medicine each morning in order to go to school. The medicine takes the edge off. It takes the throbbing, sharp pain away. The hurt doesn’t go away, but I can stand up more.

I use the medicine to help me get through school, without using my crutches or wheelchair. But I do use my wheelchair every time I go to the mall, grocery store, concerts or on vacation.

None of these things – the medicine, the soaking… really stop the pain or how my calluses grow.

The only thing that help stop the pain is to limit my walking. Staying off of my feet is the only thing I can do.

I made my school schedule so all my classes are close together. I don’t eat in the lunchroom because it’s so far away. I bring my own lunch and eat in the library because it’s closer to where my classes are.

I also have a handicapped placard for my car and I use it at school every day.

In junior high, I walked a lot. I just can’t do that now. The pain in my feet hurts in my whole body. When I stand or walk too long, I feel like I’m going to pass out. I can only walk for about 10 minutes before my body shuts down. My legs go all red or purple and I have to sit down. I’ve even thrown up sometimes because of the pain.

Another way I manage my PC is by crawling. When I come home at the end of a day, I usually park my car in the driveway crawl from my car to my home because my feet hurt so badly. Inside my home I crawl 24/7. The only bad thing is crawling bruises my knees. I got to the point where my knees hurt so bad, I couldn’t even bend them.

If there was no cure for PC, I would at least want a treatment that would give me less pain. Everything starts with the pain. I can’t walk without my shoes because of the pain. I wouldn’t crawl if I didn’t have the pain.

I would like a treatment that would let me walk a lot longer. I wish I could take my dog on a walk. I’d love to be able to walk at the mall or go to a concert. I would love to walk on the beach without dying. I would like to be able to do some things other people my age do, like stand up at a sports game and cheer. I would love to have a typical teen job. The most simple things to other people are the hardest thing in the world for me.

Still, I’m always in a good mood. People call me Smiley Rylee. There’s no point in being negative. Because I have a disease that is so rare, my Dad always says, “You’re going to win the lottery.” But for me, if there is a good treatment out there that would make it so I don’t have this much pain and that I could stand or walk more, that would be like winning the lottery.
NEW KERATINS ON THE BLOCK
By Emily Warshauer, MD, University of Colorado

We all can relate to being the new kid on the block at some point growing up. Whether starting a new school, moving to a new town, state or even a new country, there may be a common thread of anticipation, enthusiasm, uncertainty and excitement. These days, keratin 24 (K24) is one of the new kids on the block and is stirring up a flurry of anticipation regarding the sort of critical role it will turn out to play in the biology of epidermal keratinocytes.

In the March 2017 publication of PLoS One, Min and colleagues explored K24, a 525 amino acid type I keratin protein found to have a high level of expression in keratinocytes, the placenta, colon and spleen. The authors investigated the localization of K24 and found it to be predominantly located in the upper stratum spinosum of the epidermis. They also explored the functions of K24 and found that it is required for terminal differentiation upon CaCl2-induction. In vitro studies further revealed that increased K24 in keratinocytes significantly altered the differentiation of primary keratinocytes and inhibited keratinocyte survival, inducing senescence, autophagy and apoptosis. Current evidence highlights the role of K24 as an anti-proliferative factor in the epidermis and potential differentiation marker, yet the full impact K24 may have on its surroundings in the epidermis still remains unknown.

In a review article of the May 2017 Journal of Investigative Dermatology, Pierre Coulombe addresses the incredible diversity of keratins in the context of being one of the largest gene families in the human genome. The emphasis placed on the study of this fascinating gene family for more than 25 years has led to a surge of discovery about the role keratins play in a great number of genodermatoses. The quest continues in the journey to address unanswered questions about keratins, both old and new on the playing field.

As new keratins such as K24 and others continue to make their debut, these keratins, which are newcomers on the block, will be extensively studied and evolve into established members of the keratin community. The potential for greater understanding is exciting as new keratins continue to be discovered, revealing both new and unorthodox roles for keratin proteins.


epidermolysis bullosa with muscular dystrophy but required cloning of the gene before genetic analysis could begin. With strong competition from several other groups we teamed up with one, Jouni Uitto’s lab at Thomas Jefferson University, Philadelphia, USA resulting in several trips to Philadelphia in the space of a few months by myself and Irwin to successfully complete the project. Later that year we returned to Jouni’s department to set up a research lab where I continued ‘gene hunting’ for various rare genetic skin disorders, and during which time we identified the fourth causative keratin gene for PC, KRT6B.

On returning to Dundee at the end of 1998, the lab had established an international reputation for discovery and diagnostics of rare keratinizing disorders. My passion for tracking down causative genes continued in Irwin’s lab with the ‘filaggrin experience’ and our discovery of the first filaggrin mutations in ichthyosis vulgaris and atopic dermatitis.

A few years before, in 2004, I was invited to the first International PC Project Consortium Symposium, in Salt Lake City USA. This was a highly motivated meeting of clinicians and scientists to set the aims and goals of PC Project. Subsequently, I established the genetic testing service for PC Project in Dundee and a few years later, we discovered the fifth keratin gene associated with PC, KRT6C. Alongside the diagnostics, other projects were established in the lab to develop therapeutics for PC including siRNAs and drug screening.

PC Project and Irwin’s lab, co-hosted the first European PC Patient Support Meeting in Dundee in 2004 – with around 15 patients and their families attending. The meeting was hugely inspiring for all of us – highly emotional for many patients who had never met anyone else with PC, educational for clinicians who so rarely meet more than one or two PC patients in a lifetime, and impacting for lab members providing inspiration for their studies. The success of this meeting led to biennial European PC patient meetings in and around Dundee.

In Oct 2015, after many years of pipetting, PCR and sequencing! I joined the small team at PC Project, and work from Dundee. Although not in the lab I oversee the genetic testing so am still very much involved in the diagnostics and providing patients with a definitive answer for what is causing their condition, as well as being involved in many other aspects of PC Project towards the ultimate goal of a treatment.

**Recent Publications**


INTRODUCTION
In this belated newsletter, we update you on recent developments with PC Project. We update readers on progress with topical rapamycin, recent publications and the upcoming PC patient Support Meeting in London. PC patients tell us how they look after their nails. We can all learn from PC patients and it is very useful for physicians to hear the ingenious ways that patients manage problems for which we currently have no good treatment.

PC PROJECT AND PALVELLA COLLABORATING TO INITIATE PHASE 2/3 CLINICAL STUDY OF PTX-022
By: Wes Kaupinen, CEO, Palvella Therapeutics

PC Project and Palvella have been working very closely over the last several months to prepare for the imminent initiation of the Phase 2/3 study evaluating PTX-022 (novel, high strength topical rapamycin, optimized for dermal targeting) for the treatment of PC. Significant progress has been made in recent months, the most important of which is: i) The selection of a final formulation to be evaluated in the Phase 2/3 clinical study; ii) Decisions around which efficacy endpoints to prioritize for the study. Notably, the final formulation has been architected specifically for the PC patient population, and it was selected after a rigorous testing program that included more than 20 prototype formulations evaluated by Palvella and their formulation partner MedPharm, a leading global topical formulation development company based in London, UK.

With regards to efficacy endpoints, as many of you are aware, hundreds of PC patients have willingly participated in qualitative and quantitative surveys to help narrow to specific efficacy endpoints. PC is truly a condition where the patients are the experts in the disease, and hence, the ‘voice of the patient’ will play a central role in the Phase 2/3 study. In addition to the tremendous response from PC patients, a Global Pachyonychia Congenita Working Group comprised of clinicians with expertise in PC as well as rare disease regulatory experts was assembled more than 16 months ago, and that group has worked diligently to iteratively narrow to efficacy endpoints for the study.

Overall, the meaningful progress made these last few months is a testament to the tremendous collaboration that defines PC Project and the PC community worldwide. More frequent updates on the upcoming Phase 2/3 clinical study will follow in the coming weeks.

IPCC SPOTLIGHT:
EDEL O’TOOLE MD, PhD, FRCPI, FRCP
Professor of Molecular Dermatology and Centre Lead, Centre for Cell Biology and Cutaneous Research, Blizard Institute, Barts and the London School of Medicine and Dentistry. Consultant Dermatologist, Royal London Hospital, Barts Health NHS Trust, London, UK

I was born in County Mayo in the West of Ireland. I was brought up in a small village called Leenane, on the border of County Mayo and Galway beside Killary Harbour, a 16 km long fjord-like inlet. Although it was very beautiful, it rained (with varying intensity) about 300 days out of 365. I am the oldest of seven children and my father was an agricultural scientist. When I was about 9 I decided that I wanted to be a botanist. Subsequently, I fell in love with the piano and I thought I might study for a degree in Music. At age 16, I decided I could always play the piano no matter what career I pursued, and chose to become a doctor. I obtained my medical degree at University College, Galway and subsequently trained in Internal Medicine and
Dermatology in Galway and Dublin. I acquired expertise in keratinocyte biology at Northwestern University, Chicago, where I was a Dermatology Foundation Fellow followed by a Howard Hughes Medical Institute Physician Scientist Fellow with David Woodley from 1994-1998. I relocated to London in 1998 to complete my Dermatology training, obtained my PhD and became a Senior Lecturer in 2001. I was promoted to Professor of Molecular Dermatology in October 2008 at Queen Mary University of London and became Centre Lead in 2015. Our Centre has diverse interests in epithelial biology including skin cancer, keratin biology, skin genetics, epidermal barrier, hair biology and stem cells. We also have a portfolio of undergraduate and postgraduate teaching in Dermatology and Plastic Surgery.

In my early years in London, I worked with Professor Irene Leigh who stimulated my interest in palmoplantar keratodermas (PPK) including pachyonychia congenita. PPK and Ichthyosis are my main clinical specialist interests. I have two big clinics a week at the Royal London Hospital in Whitechapel in East London. Tuesday is paediatric dermatology day and Thursday is adult dermatology (with a mix of inflammatory skin disease and genetic skin disease). I supervise the inpatient acute dermatology service for 2 months of the year. I am also the rare disease lead for my hospital for 100K Genomes, a big project in the National Health Service to sequence 100,000 genomes from patients with rare disease and cancer.

I first attended an IPCC meeting in 2005 and currently am on the Medical and Scientific Advisory Board of PC Project and participate in the monthly genetics meetings. Through attending PC Project Patient Support Meetings and also participating in the genetics meetings I have learned a huge amount about PC and PPKs from sharing clinical experiences with Eli Sprecher, Alain Hovnanian, David Hansen, Phil Gard, Frances Smith and Maurice van Steensel. I am also the current Chair of the Medical Advisory Board of the UK-based Ichthyosis Support Group.

In the lab, I have a fairly broad portfolio of research. Since working with David Woodley, I have been interested in extracellular matrix and my group works on type VII collagen and laminin and normal epidermal homeostasis, in particular with regard to epidermolysis bullosa. I also have 2 active basic science projects on harlequin ichthyosis and X-linked ichthyosis. In the East End of London, I see a lot of Bangladeshi children with severe eczema and these families have enrichment in variation in filaggrin. I have just recently started a new project to recruit over 1,000 Bangladeshi children and young adults for deep phenotyping (clinical and laboratory). This is an interesting new adventure. However, this does not compare to the adventures I have had with PC Project including near collapse from dehydration on the floor of the Grand Canyon and hearing issues for several months after a trip to Salt Lake City (Sancy and Roger are you listening)! Thankfully, I am now fully recovered.

In summary, I have really enjoyed my involvement with PC Project. Progress is being made and I can definitely see a better treatment for PC patients on the horizon. However, we can still do better for all of our patients and need to work together to achieve this.

**SOCIETY FOR PEDIATRIC DERMATOLOGY ANNUAL MEETING**

PC Project attended and participated with the Society for Pediatric Dermatology (SPD) at the annual meeting July 12-14, 2018 at Lake Tahoe. As the only patient advocacy group to be invited, this was a not-to-be-missed opportunity for PC Project to network and raise awareness among the 430 attendees. The goal of PC Project was for every single participant to learn about PC and PC Project, to join the IPCC (International PC Consortium) and to encourage every dermatologist there to invite their PC patients to join the International PC Research Registry (IPCRR).

In addition to brochures, PC Project handed out small treats with poems to educate researchers and physicians about the painful nature of PC and to entice attendees to visit the PC Project table that was located directly outside of the main presentation room. Thanks to a PC patient for his limerick-writing
abilities. The treats and the poems were enthusiastically received.

During the “Hurwitz Lecture—Lessons Learned from Great Thinkers,” Dr. Eulalia Baselga, the director of the Pediatric Dermatology unit at Hospital de la Santa Creu I Sant Pau in Spain, who has referred patients to PC Project and who attended the 2016 Spain and 2016 Edinburgh Patient Support Meetings, shared her positive experiences from attending PC Patient Support Meetings. Dr. Baselga told the group how she learned about current research at the patient meeting and how the meeting helped her own PC patient. Dr. Baselga encouraged doctors to attend patient support meetings with their patients. In addition, she gave an enthusiastic shout-out to PC Project!

Dr. Tracy Funk, Assistant Professor, Dermatology and Pediatrics at Oregon Health & Science University, who works with Dr. Sancy Leachman who was influential in PC Project's creation and a founding member of the International PC Consortium (IPCC), gave an informative 30-minute presentation called, “Update on Pachyonychia Congenita.” Dr. Funk also encouraged scientists and clinicians to learn more from PC Project.

Because there are many rare diseases, to have PC and PC Project talked about twice in one conference was extraordinary. PC Project met new researchers, physicians and medical students, and reunited with IPCC members and friends such as Anna Bruckner, Amy Paller, Joyce Teng and many others. Thanks to the Society for Pediatric Dermatology for the invitation to share their annual conference with PC Project.
**RECENT PUBLICATIONS**


Krupiczjc MA and O'Toole EA. *Plantar pain in pachyonychia congenita*. Br J Dermatol 2018;179:11-12 (Linked to Brill et al Br J Dermatol 2018;179:154-162)


Peter DCV, Thomas M, Wilson NJ, Smith FJD. *Skin fragility, woolly hair syndrome with a desmoplakin mutation - a case from India*. Int J Dermatol. 2018 Sep;57(9):e73-e75

**WHY ARE PATIENT SUPPORT MEETINGS IMPORTANT TO ACHIEVING THE MISSION OF PC PROJECT?**

Over 65 PC patients, plus caregivers, physicians, scientists and industry partners (approximately 140 people), will attend the 17th PC Patient Support Meeting in London, England, October 19-21, 2018.

Each year, PC Project hosts a Patient Support Meeting where PC patients and their families come together to learn from leading physicians and scientists who provide information and training on how to care for and live with this isolating, painful disease. These meetings are not only educational but emotional and even life-changing for PC patients who have never met another person with PC. In addition to adult sessions, meetings include sessions for teenagers and children who learn about the science behind PC, how to deal with pain, social issues, difficult questions, bullying, and how to stay focused on their positive strengths and characteristics.

Furthermore, PC Patient Support Meetings serve as an opportunity for clinicians, researchers and drug developers to observe and learn directly from PC patients. Various studies and focus groups conducted at Patient Support Meetings over the years have resulted in first-hand and greater knowledge about PC due to the benefit of having a gathering of rare patients to learn from.

Finally, the hope with every patient meeting is that PC patients and caregivers will leave encouraged, edified and more able to cope with this debilitating disease. Instead of feeling embarrassed and alone, patients will feel more positive about a disease they didn’t choose and feel empowered to live fulfilling lives in spite of the pain.

Quotes from Patients who have attended past Patient Support Meetings:

“At my first PSM meeting, for the first time I looked into the eyes of another person with the same disease, saw them move like me, and saw them use the same tricks that I use to get through their day. This gave me an immense feeling of no longer being alone and it’s a wonderful feeling. I would say that I’ve never been as happy and confident before the PC PSM experience.”

“Attending the PSM is the one best thing you can do to help the way you psychologically handle your PC. It has finally allowed me to be able to talk openly about my PC.”

“I have hope again.”

“Despite living with PC for my entire life (although not knowing what it was for most of that), I had never met another person with the condition. My life changed forever as I discovered the amazing community of patients, caregivers, physicians, scientists, and others who make up PC Project.”
This PC Patient Support Meeting is sponsored by Palvella Therapeutics and supported by a grant from Novartis Pharmaceuticals UK Limited. PC Project is extremely grateful to both of these organizations.

HOW PATIENTS CARE FOR PC NAILS

The PC community was asked how they trimmed their nails. PC nails vary between PCers in how they look, and patients trim them in different ways using many different tools. What works for one does not necessarily work for another. It is an individual choice of the tool to use, how often to trim, whether preference is wet or dry nails when trimming etc. Here is how one PCer, Roseann McGrath, has cared for her nails from childhood:

“I am a 52-year-old female, spontaneous PC-K6a mutation, where my PC presented at birth on my hands and feet. I was thankfully diagnosed shortly after my birth with having PC. As early as 6 months old, my mother & father used a General Electric (G.E.) manicure set to drill my tiny finger and toe nails weekly. As I got older I started to do it myself. In my early teens I began to use a Sears Craftsman Dremel Drill every other day on my finger nails and weekly on my toe nails.

In 2014, a fellow PCer told me about the “Upower” drill, which is just as powerful, but much easier to hold and handle then the Dremel. It is made by Urawa Corporation Upower Nail Filing System UP200C Series Controller. To this day I drill my nails down to get them as flat as I can. I paint my fingernails with a light beige nail polish to cover the green hue in our PC nails. I cannot “trim” or “drill” too low because my nerves grow through my nails, thus when they start to bleed I know I’ve gone too low. Conversely, I cannot permit my nails to remain too high, because the nails are sensitive from the thickness. Therefore, I must find the right balance of how thick or how low my nails can be. With this said, I err on the side of drilling down as far as I can to hide how thick they are and to try to make them appear somewhat normal. I unfortunately cannot hide my calluses and blisters on each finger (and foot) at each pressure point like I can my nails.”

Responses from others on tips and tools they use.

“Large pointed nail clippers (I affectionately refer to them as “hedge trimmers”) which work best on wet/soaked nails, or a Dremel tool with a dimmer switch on dry nails/skin.”

“Nails clippers for large dogs, small pointed nail clippers, Dremel and Emery board. I grind them with an electric manicure device every three weeks.”

“I use this (see left) once a week for the very thick nails of my son. Our son watches television with a favorite snack during the weekly trimmings.”

“An Emery board to maintain my nails. I’ve only been able to tolerate the Dremel on my fingers in the last couple of years. As a child, my dad soaked and trimmed my nails with a razor blade. A Dremel still hurts when used on the fingernails.”

“These are a few of my trimming tools (see right).”

“Dremel on the worst nails, nail clippers and an Emery board on the other nails.”

“I use a thing called the PediNova by Medicool. It’s essentially a Dremel tool but they provide different bits specifically for nail grooming. They include a sandpaper barrel attachment, but I find that gets incredibly hot.”

“Black & Decker drill with a fine sandpaper disk.”

“My nails are very thick, so when a podiatrist takes the clippers to them, it’s quite painful. I find that using a grinder is much more comfortable.”

“A spring-loaded toe nail clipper for the foot nails and a good nail file for the hand nails. Sometimes I use a single edge razor blade to help with the toe nails.”

SAVE the DATE

The annual International PC Consortium (IPCC) Symposium will be held May 7-8, 2019 in conjunction with the SID meeting in Chicago, Illinois.
FIRST-EVER PHASE 2/3 CLINICAL STUDY IN PACHYONYCHIA CONGENITA TO COMMENCE IN EARLY 2019

By: Wes Kaupinen, CEO, Palvella Therapeutics

On December 18th, Palvella Therapeutics issued a press release highlighting the receipt of a $10 million investment from Ligand Pharmaceuticals to support the Phase 2/3 study of PTX-022 (QTORIN™ rapamycin formulation) for the treatment of Pachyonychia Congenita. Ligand Pharmaceuticals is a publicly traded company that has a track record in partnering with leading biopharmaceutical companies to develop some of the world’s most important medicines. The planned Phase 2/3 study builds on smaller studies with low-dose topical formulations of rapamycin which together encourage a well-designed, sufficiently-powered evaluation of rapamycin’s efficacy in PC using a commercially-viable topical formulation. The news of this significant funding support comes after the FDA’s recent granting of Fast Track Designation to Palvella for PTX-022 for Pachyonychia Congenita.

The potential for mTOR inhibitors, including rapamycin, as a treatment modality for PC was initially discovered by Dr. Roger Kaspar who elucidated a direct mechanism of action of mTOR inhibitors on the causative mutant keratin genes in pachyonychia congenita. Palvella’s PTX-022 is a novel formulation of rapamycin that has been developed using a scientifically rigorous process in partnership with MedPharm Ltd, a leading topical formulation company that has been intimately involved in developing several topical treatments that have been FDA approved for a number of dermatologic diseases. PTX-022 leverages Palvella’s QTORIN™ formulation and delivery technology which employs a highly specific composition of excipients to enable distribution of mTOR inhibitors into the basal keratinocytes which harbor the mutant keratin genes in PC.

2018 represents a year of noteworthy progress for PC Project and Palvella Therapeutics, with the following milestones achieved:

- The historic FDA patient-focused drug development meeting on PC where PC patients courageously shared their personal stories of living with PC with 42 FDA officials
- The publication in Clinical and Experimental Dermatology by Dr. Joyce Teng and colleagues reporting two PC patients treated with topical rapamycin cream who experienced rapid improvement of pain and ability to ambulate
- FDA’s granting a Fast Track Designation which recognizes PC as a serious disease with an unmet medical need
- Ligand’s investment of $10 million which will accelerate the Phase 2/3 study of PTX-022 in PC

2019 promises to be an exciting year with the commencement of the Phase 2/3 clinical study which will initially be focused at several sites in the US. Sincere thanks to all who have contributed over many years to the advancement of this program.

IPCC SPOTLIGHT:
ALAIN HOVNANIAN MD, PhD

Prof. Alain Hovnanian research laboratory is based at the Imagine Institute for genetic diseases recently created at Necker hospital in Paris. His laboratory is affiliated to the National Institute of Health and Medicinal Research (INSERM) and Paris Descartes University. The laboratory focuses on the study and the development of new treatments for severe and rare genetic skin diseases, including epidermolysis bullosa, Netherton
syndrome and severe palmoplantar keratoderma such as Pachyonychia Congenita and Olmsted syndrome.

Hovnanian's laboratory has recently identified a new gene for Olmsted syndrome, initially in a 7 year old boy from Spain, and subsequently in 3 additional subjects from the USA through a collaboration with Prof Keith Choate from Yale University. This new gene, named ‘PERP’ is a component of desmosomes, which are specific structures which hold cells together in the epidermis. In these families, PERP mutations were located close to the end of the protein and caused a shortened protein which is likely to impair cell-to-cell adhesion. Of note, a different truncating mutation located in the beginning of the same gene caused complete lack of PERP expression resulting in a distinct genetic skin disease (erythrokeratoderma). In both cases, electron microscopy examination revealed that desmosomes lacked a central element, called ‘dense midline’ which suggests an immature state of cell-to-cell adhesion. These new findings identify PERP as an important component of desmosomes and further expand the genetic and clinical heterogeneity of desmosomal diseases and inherited palmo-plantar keratoderma. It is hoped that a better understanding of Olmsted syndrome, which is most often caused by TRPV3 mutations, and more rarely by PERP mutations, will help finding safe and effective treatments for this severe palmoplantar keratoderma and also for Pachyonychia Congenita.

Hovnanian laboratory team currently consists of 17 persons, including faculty professors, associate professors, tenure researchers, post-doctoral researchers, research engineers, technicians and PhD students.

**Giving Tuesday Success - Thanks to You!**

Because of you, and with the help of over 350 donors, we surpassed our Giving Tuesday goal and raised more than $80,000 for PC patients and research. This amount was matched by a generous donor and all contributions will continue to be matched for the rest of 2018. Your support is proof that combined efforts, big or small, equal impressive results.

On Giving Tuesday, as we saw your donations, along with your emails, personal fundraisers and shared social media posts, we were moved to tears by your goodness, generosity and love. Please accept our sincerest thanks.

As we continue to work together, we expect our hopes to be realized, and that one day all PC patients will enjoy pain free skin.

**Recent Publications**


Tous-Romero F, Vico-Alonso C, Calleja-Algarra A, Sánchez-Calvin MT, Palencia-Pérez S. *Thick nails, plantar keratoderma, follicular hyperkeratosis, and leukokeratosis associated with a...*


**British Journal of Dermatology**

**PC-Themed Issue**

Reminder: If you wish to submit a publication for the special PC themed issue of the BJD, please see the information below:

1. Dr. Edel O'Toole will serve as a guest editor for this edition.
2. Please email PC Project with the subject and/or title of your article as soon as possible, so we can inform the BJD how many papers to expect.
3. Submit your manuscript directly to the BJD when ready and as soon as possible (the final deadline is January 31, 2019.) BJD article submission guidelines/remit are available at https://onlinelibrary.wiley.com/page/journal/13652133/homepage/forauthors.html
4. Each submission should be clearly marked in the cover letter: For Themed Issue on Pachyonychia Congenita.
5. Submitted papers will go through the normal BJD review process.

**PeDRA Annual Meeting 2018**

PC Project was one of three patient advocacy organizations invited to present at dinner session at the 2018 PeDRA Annual Meeting in Colorado, October 25-27, 2018. The session was focused on the value of collaborations between patient advocacy groups and industry. Holly Evans, PC Project Patient Support Officer, presented the pathways PC Project has taken to help develop effective endpoints for clinical trials for Pachyonychia Congenita. This process has included patient focus groups and a number of patient surveys. Working with patient groups helps drug developers understand what kind of treatment is meaningful to patients. Working together to find effective ways to measure the efficacy of a drug is critical for both industry and patient advocacy groups.

PC Project is grateful to Sheila Rittenberg and the PeDRA team for the invitation, support and collaboration. In addition, seeing friends from the IPCC is always a joy.

Please see the last page of this newsletter to enjoy photos of IPCC members at the PeDRA meeting.

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**London PC Patient Support Meeting**

Over 140 Pachyonychia Congenita patients, caregivers, scientists, clinicians, and representatives from PC Project’s industry partner, Palvella, gathered in London on October 19-21, 2018 to share knowledge, encouragement and love. Thank you to the IPCC members who helped make this PC Patient Support Meeting a success. The following two pages have a collage of photos from the meeting.

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**Save the Date**

The 15th annual International Pachyonychia Congenita Consortium (IPCC) symposium, May 7-8, 2019 in conjunction with the S2D in Chicago, IL. More details for this meeting will be coming early 2019. Until then, please contact PC Project with any queries.
PC Children learned about their disease as well as tips on dealing with social issues, bullying, and focusing on their strengths and special talents.

Wes Kaupinen, Braham Shroot, Phil Gard, and Roger Kaspar.

PC Patients participated in large and small group discussions.
Collaborating with Industry

Power of IPCRR Patient Registry
1. We know who our patients are
2. We know where they are
3. We know the gene and mutation

www.pachyonychia.org/pc-data/
www.pachyonychia.org/patient-registry/

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