MESSAGE FROM THE EDITOR

Greetings from London where we are still talking about Brexit. The European Society for Dermatological Research (ESDR) meeting in Bordeaux was very successful and PC Project was represented there. At the beginning of October I was back in France again at the European Reference Network for Rare Skin Diseases meeting. This has an ichthyosis and palmoplantar keratoderma subgroup (which includes PC) and aims to improve patient care throughout Europe. In this newsletter, we have updates from the VALO Clinical Study which is recruiting well in the USA, we congratulate Birgit Lane on her honorary membership of the ESDR and also report from the IPCC Symposium in Chicago earlier this year. Jack Padovano gives us some insights into living with PC. His comparison of living with PC to maintaining a bank account of steps is a great one and illustrates the thought that PC patients put into each step. The onus on all of us is to increase the number of steps that individuals with PC can take.

VALO PHASE 2/3 CLINICAL STUDY
By Emily Cook, Palvella Therapeutics

VALO recruitment continues to remain on track, with more than 60 PC patients having entered the study by Mid-October. Dr. David Hansen, Dr. Joyce Teng and Dr. Leonard Milstone have led the way by enrolling a significant number of PC patients at their respective institutions. Successfully recruiting a clinical trial at a site requires the investigator’s commitment to the study, engaging their clinical teams in meaningful ways and ultimately placing the patients at the center of the work. Palvella Therapeutics, and PC patients are fortunate to have these three individuals setting the pace and are deeply appreciative of their leadership. Several other investigators and clinical sites are actively enrolling into the study and Palvella is also very thankful for their investment in PC patients and the study. We look forward to spotlighting them in the future!

On the heels of the VALO study, Palvella Therapeutics is pleased to announce that an open-label extension study will be available for patients to continue taking investigational PTX-022 (QTORINTM rapamycin) for pachyonychia congenita. We look forward to updating you on this study status in the next newsletter!

For more information on VALO, Palvella Therapeutics’ Phase 2/3 study investigating PTX-022 (QTORINTM rapamycin) for pachyonychia congenita, please visit clinicaltrials.gov or pachyonychia.org/valo/

BIRGIT LANE HONORED WITH PRESTIGIOUS ESDR AWARD

Ellen Birgitte Lane (Birgit Lane) was presented with Honorary Membership of the ESDR, the ESDR’s highest honor, at the 2019 ESDR meeting. Edel O’Toole gave the citation and mentioned Birgit’s strong leadership in research, significant contributions to skin science including the discovery of many of the known keratins causing disease, mentorship of many successful individuals in epithelial biology and building partnerships between individuals, institutions and patient support groups. This prestigious award was presented by Edel O’Toole and David Kelsell at the 49th Annual ESDR meeting September 19, 2019 in Bordeaux, France. When she received this award Birgit said, “Thank you very much for this. I’m very honored and touched to get this award. And it’s especially nice to get an award for something you love doing.”

Birgit obtained her BSc and PhD in Zoology from UCL and after post-doctoral work at Cold Spring Harbour and Imperial Cancer Research Fund, she started her own research group. She was the Cox Chair of Anatomy and Cell Biology in Dundee from 1991-2009. In 2005, she went on sabbatical to Singapore and founded the A-Star Institute of Medical Biology and was the inaugural director from 2007 until 2018. She founded the Skin Research institute in Singapore in 2013 and is now it’s...
Chief Scientist. In Singapore over the last 14 years, she has championed skin research, building partnerships with other institutions worldwide and working with patient support groups including PC Project and DebRA Singapore. She currently works on understanding how keratin filaments function, what are the consequences of their failure, and how such knowledge can lead to strategies for therapy.

**PC Project at ESDR**

French PC patient, Marie Jose Billeau, and her daughter, Alice, represented Pachyonychia Congenita at the European Society for Dermatological Research (ESDR) annual meeting in Bordeaux, France on September 19-20, 2019. Marie and Alice shared materials about PC in French and in English with scientists from around the world and met with members of PC Project’s Medical and Scientific Advisory Board. In addition, they received contact information of new researchers who are interested in being connected to PC Project.

Thanks to attending IPCC members who visited with Marie and Alice, including Alain Hovnanian and David Kelsell, Birgit Lane and Edel O’Toole.

**Global Genes Features PC**

Global Genes, a worldwide organization that connects, empowers and inspires the rare disease communities, recently interviewed Janice Schwartz, PC Project’s executive director, in order to bring awareness to Pachyonychia Congenita and PC Project.

When asked what makes her hopeful, Janice replied, “All the advances in science that have potential applications now and in the future for PC make me hopeful. If I didn’t believe that one day, we will have effective treatments for PC, I would not be dedicating my time this organization. I’m also energized by the hope of others—not just the patients, but all the people who donate their wisdom and resources to this cause. We see lots of little miracles all the time. Sometimes I worry and wonder, “How is this going to work out?” And then somehow, things do work out, usually because of the goodness of people.”


**Pachyonychia Congenita Voice of the Patient Report now on FDA website**

Last year, PC Project submitted the Voice of the Patient Report to FDA from the Externally-led Patient Focused Drug Development (EL-PFDD) Meeting. This report is now on the FDA website. The definitive voices of real patients about the impact of PC on
their lives are official. (You may need to click the Meeting Reports tab to see the report.)
fda.gov/drugs/development-approval-process-drugs/external-resources-or-information-related-patients-experience

Or visit  https://www.pachyonychia.org/externally-led-patient-focused-drug-development-meeting-el-pfdd-with-fda/

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**SAVE THE DATE!**

**17th Annual International Pachyonychia Congenita Consortium (IPCC) Symposium**

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PC Viewpoint: A Bank Account of Steps

My name is Jack Padovano. I’m 56, live in San Diego and my genetic mutation is in keratin 16.

My PC shows up with thick calluses on over 50% of the bottom of both feet, cracks and occasional blisters along the middle and sides of most calluses, and thickened nails on 100% of my fingers and toes.

Like most people, I have a bank account. But not the kind you’re probably thinking. This one isn’t filled with money, but instead, it’s filled with the number of steps I can physically walk each day before tremendous pain sets in.

Just like a checking account filled with money, I spend very wisely, or try my best. Each withdrawal, or step I take is mentally recorded and physically felt, right down to my bones. Overnight while I sleep, the bank account is refilled before I wake up. The amount of the refill varies. If I overdraw from the account the day before by walking too much, I have fewer steps in the account. If I got a good night’s rest, and monitored my walking, the account is completely filled up.

On my best day, I can walk down a long city block without thinking once about the pain. On my worst day, I simply refuse to walk. Period. Unfortunately, there are few best days. If I’m lucky, I get one per month. Most days I think about the pain with each and every step, including standing in place.

PC hurts both physically and emotionally. PC pain feels like someone is sticking pins and needles in the bottom of my feet. It’s a deep ache that cuts all the way to the bone. I treat the pain with hot water soaks, cold-water soaks, elevating my feet, rubbing creams, massage, Vaseline baths, Advil, and a lot of bitching, mostly under my breath. I treat my PC by pairing down the calluses once a week trying to navigate those pesky blood vessels and nerve endings that get cut and inflamed in the process. Nothing really works. The pain is constant and often makes me grouchy, sometimes to the point of lashing out to the people I love, work with, and even total strangers. I even think it contributes to my struggle with depression.

PC makes my fingernails ugly, so ugly that growing up other kids made fun of me. PC makes me walk “weird”, something we PCer’s affectionately call the “PC Walk”. But, kids being kids, they didn’t see any humor or have any compassion for my walk. I was just different and that made me a target for bullying. The really mean kids took to stomping on my feet, so hard I would fall to the ground and writhe in pain. And as those with PC can attest, the last thing we PCer’s need is more trauma to the feet.

PC also significantly impacted my parents. After my diagnosis at three years old my parents had a name for my condition. But that’s all they had…no treatment, no answer why, or especially, no cure. In fact, they were told the condition would most likely worsen to the point where I couldn’t walk. My mother was certain it was her fault. She would often say, maybe if I smoked less, ate differently, didn’t take aspirin, etc. etc. Today, we know none of that mattered. I’m a spontaneous case, meaning that my PC is not inherited.

As an adult, the bullying has stopped but is replaced by questions, mostly thoughtful and kind, but sometimes not. Questions I really don’t like to answer because the answers are never simple one-word answers.

PC changed my life, or better said, it IS my life. And because of its’ enormous power, I respect it and have learned to live side-by-side with it. It’s made me a stronger person and taught me how to be courageous by exposing it to doctors, strangers, and people who love me…not an easy task. It’s taught me how to stand up to bullies who have no interest in learning anything about PC except as way to call me out as different. Good life lessons.

Recently, I learned that the average person walks 10,000 steps per day, or 5 miles. I’m envious. That’s a big bank account. For me, I’m lucky to get a quarter mile, or 500 steps under my belt before the pain sets in. So, while my account may not be as rich as yours, I treasure every step I take.

Future forward, I worry that my condition will worsen as I get older. I know my pain has gotten progressively worse every year, particularly in the last 20 years or so. I can see it in my walk and feel it in my bones. My wish is simple. I want to stand and walk without excruciating pain. I hope and pray that’s not too much to ask.
Report of the 16th Annual International Pachyonychia Congenita Consortium (IPCC) Symposium

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Summary

The International Pachyonychia Congenita Consortium (IPCC) is a global group of scientists and physicians working to develop therapies for pachyonychia congenita, a rare genetic skin disorder. The research reported at the 16th Annual Research Symposium of the IPCC, held on 7-8 May 2019 in Chicago, IL, U.S.A is summarised here.

What’s already known about this topic?

Pachyonychia congenita (PC) is a rare genetic skin condition caused by a mutation in any one of five keratin genes (KRT6A, KRT6B, KRT6C, KRT16, or KRT17).

PC is characterized clinically by the triad of plantar keratoderma, plantar pain and variable nail dystrophy. Patients may also have other findings such as oral leukokeratosis, follicular hyperkeratosis and/or cutaneous cysts.

Plantar pain is severe and is out of proportion to that of non-syndromic callus formation, and it is the major symptom of concern for PC patients.

What does this study add?

We report on progress by scientists and clinicians from around the world who are working to understand the pathophysiology of PC and other keratinopathies.

We discuss ongoing scientific efforts to understand the role of inflammation in PC and work to translate that information into therapeutic treatments for PC.

We provide an update on the most recent advances in gene suppression or the modification of genetic expression as a treatment approach in PC.

We discuss the status of current therapeutic trials in PC as well as the need for collaboration between scientists, clinicians, patients, and industry to further advance PC treatment.

The 16th Annual Research Symposium of the International Pachyonychia Congenita Consortium (IPCC) was held in Chicago, IL, U.S.A. on 7-8 May 2019. The meeting was attended by approximately 60 scientists, physicians, and industry leaders from around the world who are devoted to understanding the pathogenesis and developing therapies for pachyonychia congenita (PC). PC is a rare genetic condition caused by the inheritance of a mutation in one of five known keratin genes (KRT6A, KRT6B, KRT6C, KRT16, and KRT17). The condition is characterized by plantar keratoderma, severe and debilitating plantar pain, and often nail dystrophy. Patients variably also have oral leukokeratosis, follicular hyperkeratosis and cutaneous cysts.

Day 1: afternoon session – Building the Foundation for Successful PC Studies

Janice Schwartz, Executive Director of the PC Project (Salt Lake City, UT, U.S.A.), opened the meeting with an announcement that the International Pachyonychia Congenita Research Registry (IPCRR) has now collected data from over 2,000 patients. The registry is an ongoing effort to identify, genetically test, and register patients with pachyonychia congenita. This process empowers patients and helps to advance scientific understanding and treatment of pachyonychia congenita. The registry is readily accessible and takes patient self-referrals or referrals from clinicians.

The first session of the meeting was chaired by Edel O’Toole (Queen Mary University of London, London, UK) and was entitled “Building the foundation for successful PC studies.” The session focused on cutting-edge basic science research that contributes to our understanding of PC and other keratinopathies, and that points to potential therapeutic targets for PC patients.

As the first speaker of the meeting, Birgit Lane (Skin Research Institute of Singapore) presented “Integrating the keratinopathies.” Dr. Lane’s team works on understanding how keratin filaments function and what the consequences are when they fail. She discussed the idea that keratinopathies, such as epidermolysis bullosa simplex (EBS), pachyonychia congenita (PC), and others might be productively grouped and studied together since the underlying similarities in the
pathogenesis of the disorders suggest that similar approaches could be taken to discover novel therapeutics. Dr. Lane discussed models that are being used to screen for compounds that reduce keratin aggregation with promising results. Her work demonstrates the need to better understand keratin biology in order to inform the development of targeted therapeutic modalities.

Furthering the discussion of keratin research, Pierre A. Coulombe (University of Michigan, Ann Arbor, MI, U.S.A.) presented his talk entitled “Novel roles for keratin in epidermal homeostasis and their significance for PC pathophysiology.” Dr. Coulombe’s team studies the genetic basis and mechanistic underpinnings of keratin mutation-based disorders, with a focus on EBS and PC. He reviewed what we have learned thus far from a Krt16 null mouse model for palmoplantar keratodermas (PPKs). The Krt 16 null mouse develops footpad lesions that mimic callus formation in PC patients, and the mouse model has been shown through murine and human comparative gene expression surveys to be an appropriate model for the study of plantar keratoderma in PC patients. Based on Dr. Coulombe’s discoveries, the development of calluses occurs in three stages: pre-PPK, PPK onset, and active PPK. In the pre-PPK stage, keratinocytes in the palmoplantar skin of the mice exhibit both defective terminal differentiation and a dramatic loss of keratin 9 expression. This downregulation of Krt9 expression in the Krt16 null mouse footpad is likely to be important, since Krt9 null mice develop PPK. A possible therapeutic approach in PC might be targeted upregulation of keratin 9. During the PPK onset stage in the Krt16 null mouse model, increased oxidative stress, including hypoxia, Keap1-Nrf2 signaling, occurs, and there is subsequently a lack of ability to return to normal homeostasis during the active PPK phase. Calluses in patients with PC also show evidence of reduced Nrf2 activity, highlighting the inflammatory cascade in PPK as a target for future therapeutic developments for PC.

The inflammatory response was also noted as important by Dr. David P. Kelsell (Queen Mary University of London Whitechapel, London, UK), who described his work on iRhom2 and the keratinocyte stress response in tylosis, a syndrome characterized by PPK and a high risk of developing oesophageal squamous cell carcinoma. Based on multiple lines of evidence generated in his laboratory, he showed that iRhom2 functions as a major regulator of the response to cellular stress and disease, particularly of keratin dynamics in response to stress and in p63-mediated signaling pathways.

Christopher G. Bunick (Yale University, New Haven, CT, U.S.A.) studies the biochemistry of intermediate filament assembly to understand how keratins function in PC. In his presentation “Keratin 1/10 A11 heterotetramer crystal structures provide a molecular basis for a novel knob-pocket mechanism governing intermediate filament assembly,” he discussed the importance of atomic resolution structures in understanding disease using ‘genotype-structure-type-phenotype’ models, highlighting the critical knob-pocket assembly mechanism within the K1 helix 1B domain, which is conserved among all type II keratins. Dr. Bunick’s work represents the first crystal structure of any keratin mutation associated with human skin disease and sets a precedent for future atomic resolution characterization of pathogenic PC mutants in intermediate filaments.

Thomas M. Magin (University of Leipzig, Leipzig, Germany) presented “Toward a compound-based approach for treatment of dominant keratin disorders.” His team has established assays to assess restoration of a functional keratin cytoskeleton in an effort to discover chemical compounds for the treatment of EBS and PC that prevent or revert collapse of mutant keratin cytosskeletons into protein aggregates. Such compounds would be applied locally or given systemically to patients. Compounds that modify keratin post-translationally are a focus. He has already identified a lead compound that decreased aggregation of keratin in cells with the EBS-associated K14R125C mutation by 50%. A screen of 5,000 bioactive compounds is currently underway to identify additional compounds that restore the keratin cytoskeleton.

The field of nucleic acid delivery as a potential treatment strategy for PC was another major theme at this year’s IPCC meeting. Robyn P. Hickerson (University of Dundee, Dundee, Scotland, UK) discussed the use of small interfering RNAs (siRNAs) to target mutant keratin expression, highlighting that intraleisional injection has been required in the past for delivery, given that the epidermal barrier precludes penetration of siRNA. However, pain with the injectable delivery method is a major problem in PC. Her IPCC presentation titled “Next generation ASOs (antisense oligonucleotides) for the treatment of PC” described her more recent work on nucleic acid-based therapeutics and strategies for delivery of these therapeutics. Her team, including speaker Michael Conneely (University of Dundee, Dundee, Scotland, UK), has developed novel ex vivo human skin models to evaluate delivery and efficacy of knockdown. Dr. Hickerson discussed promising ongoing research in collaboration with WAVE Life Sciences (Cambridge, MA, U.S.A.) that has increased the specificity of ASOs towards targeting at a single nucleotide mutation level, which previously required siRNA, and her goal of bringing these nucleic acid molecules to the clinic within the next few years.

Michael J. Caterina (Johns Hopkins, Baltimore, MD, U.S.A.) presented “Pain mechanisms in palmoplantar keratodermas.” Dr. Caterina’s team at Johns Hopkins is focused on the molecular and cellular mechanisms underlying neuropathic and inflammatory pain sensation. His recent work has been focused on mechanisms that contribute to pain in mouse models of hereditary palmoplantar keratodermas. Dr. Caterina discussed new research on specific neuroanatomical changes that might be associated with pain and itch in some, but not all, patients with palmoplantar keratodermas.
Alain Hovnanian (Imagine Institute and Necker Hospital, Paris, France) focuses on the study and development of new treatments for EB, Netherton syndrome and severe palmoplantar keratodermas such as PC and Olmsted syndrome. Dr. Hovnanian presented the final talk of the first session with “PERP, a novel gene causing Olmsted Syndrome” and discussed his co-discovery with Dr. Keith Choate of Yale University that variants in the PERP gene can lead to many of the features seen in Olmsted syndrome, including PPK. PERP codes for a component of desmosomes and is a downstream target of p63$^{13}$ which participates in epidermal cell adhesion. This discovery contributes to our understanding of the biological pathways involved in the development of severe palmoplantar keratoderma.

**DAY 2: morning session – PC and the Therapeutic Horizon**

The second session of the IPCC meeting, chaired by Amy Paller (Northwestern University, Chicago, IL, U.S.A.) and Roger Kaspar (Santa Cruz, CA, U.S.A) was titled “PC and the Therapeutic Horizon” and focused on the status of current therapeutic trials in PC as well as the need for collaboration between scientists, clinicians, patients, and industry to further advance PC treatment.

Dennis R. Roop (University of Colorado, Aurora, CO, U.S.A.) presented “An alternative method for delivering keratinocytes derived from patient-specific gene-edited iPSCs generated from patients with inherited epidermal fragility disorders.” He discussed work with colleagues, Drs. Ganna Bilousova and Igor Kogut, on the development of induced pluripotent stem cells (iPSCs) as a treatment for recessive dystrophic epidermolysis bullosa (RDEB). He noted that reprogramming fibroblasts with modified mRNA and miRNA is a non-integrative method of introducing genetic modifications in patient’s fibroblasts$^{14}$. He then discussed two means by which to deliver genetically modified cells into a patient. He is partnering with Avita Medical (Melbourne, California, U.S.A.), a company that manufactures a method for spraying dissociated cells onto patients. This method has been used effectively to treat burn patients$^{15}$ and may represent a plausible delivery mechanism for keratinocytes derived from gene-edited iPSCs that would obviate the need to develop sheets of skin for grafting. Moreover, spray delivery may be preferable in body locations that are traditionally difficult to graft, including the palms, soles, and oral cavity. Dr. Roop also discussed studies to increase the homing of modified mesenchymal stem cells, delivered intravenously, to areas of trauma or injury in internal epithelia.

Weston Daniel (Exicure, Skokie, IL, U.S.A.) presented ‘Topical application of DNA for dermatology’. He spoke about the properties of spherical nucleic acids (SNAs), nanoparticle constructs that are dense and radial arrangements of oligonucleotides. Dr. David Giljohann, founder of Exicure (Skokie, IL, U.S.A.), together with Dr Amy Paller (Northwestern University, Chicago, IL, U.S.A.), discovered that spherical nucleic acids readily penetrate epidermal cells in vitro and intact human skin in vivo$^{16}$. The oligonucleotide component of SNAs can suppress or modify disease gene expression, suggesting promise in the treatment of genetic skin diseases. Topical SNA-based therapies are currently in clinical trials for psoriasis with a goal to develop drugs for the treatment of rare genetic conditions.

Mark P. deSouza (FIBRX Derm, Inc, Berkeley, CA, U.S.A) presented ‘developing mechanism-based therapies for rare skin disease.’ He discussed lessons that he has learned over time regarding what makes for a good potential therapeutic drug, including a formulation that is stable, penetrates into the skin, is safe, and well tolerated. Eugene J. Sullivan (Palvella Therapeutics, Wayne, PA, U.S.A.) reviewed the unique challenges that are faced by drug developers in rare diseases. John D. Doux (Palo Alto Investors, Palo Alto, CA, U.S.A) shared his experience as an investor and discussed what investors look for in drug development. Braham Shroot, PhD (Palvella Therapeutics, Wayne, PA, U.S.A) discussed the development of a promising new high strength rapamycin formulation ‘PTX-022’, which is currently entering clinical trials for PC.

**Conclusions**

This year’s Annual IPCC Research Symposium reminded us of the ongoing efforts of the PC project and the IPCRR, which now includes data from over 2,000 patient participants and is a vast repository of important disease-specific information. This data is readily available to physicians and scientists who are working to further the understanding of PC pathophysiology and advancements in the translation of this scientific knowledge into therapeutic options for PC patients. Highlighted research with the potential for therapeutic development include targeting the inflammatory response in callosus development and suppression or modification of genetic expression via nucleic acid delivery or introduction of induced pluripotent stem cells. These potential therapeutic options move us closer to mitigating the debilitating pain that PC patients experience.

**References**


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