Dear Friends,

I hope you are enjoying the summer and that life is returning to more normality (albeit with caution) wherever you are in the world. In this newsletter, we update you on the IPCC symposium which was held virtually because of the pandemic. Although very informative and successful, we look forward to the improved interactions of face-to-face meetings.

PC research and clinicians are currently working on a very important document, the Pachyonychia Congenita Research Agenda. We hope we can use this to mobilise funders and other stakeholders to have an interest in PC. PC Project will host a virtual patient support meeting on November the 20th. This will be an opportunity for your patients to talk to others with PC and feel part of the PC community.

Please continue to encourage your patients to enroll with the IPCRR (International PC Research Registry) at pachyonychia.org/patient-registry/

**IPCC Symposium**

On June 28-29, 2021, PC Project hosted the 17th Annual International PC Consortium (IPCC) Symposium, “Innovations and Transformations”. This year, the meeting was a virtual gathering of doctors, scientists, and pharmaceutical representatives who listened to presentations about PC-related research and engaged in discussions on how to move the work forward.
Professors Eli Sprecher and Edel O’Toole co-chaired the meeting which featured 20 speakers. Over 100 people registered and on each day of the symposium, approximately 78 professionals attended. The co-chairs and the PC Medical and Scientific Advisory Board were thrilled at the attendance, the engagement, and more importantly, the new research that was presented. We are grateful that there is still so much interest in PC in the scientific and medical community. Not only did PC Project’s key collaborators participate in the meeting, the virtual format allowed many new people to attend and be welcomed to the IPCC community.

The symposium was held in a Zoom meeting style (not webinar style) so attendees could interact, discuss, and make personal connections. Seeing longtime friends as well as new faces was a delight for all.

To see the full program with abstracts and biographies visit pachyonychia.org/2021ipcc/.

A short summary of the main highlights is given below.

Alain Hovnanian spoke about activation of the epidermal growth factor receptor (EGFR) in Olmsted syndrome and treatment of patients with erlotinib, an EGFR inhibitor. Pierre Coulombe updated us on recent work from his laboratory showing that Keratin 17 regulates nuclear shape and chromatin organization. Sonja Lehmann gave an interesting talk on changes in mitochondria and lysosomes in PC. Kathy Green spoke about the cell biology of desmoglein-1 deficiency and an unexpected effect on melanocytes. In a complementary presentation, Akiharu Kubo spoke about diverse phenotypes of desmoglein-1 deficiency. Both Diana Blaydon and David Kelsell spoke about using the novel technique spatial transcriptomics to understand more about palmoplantar skin in iRhom2 and desmoplakin mutant/deficient mouse models. Joyce Teng and Christopher Bunick gave a joint presentation on structural modelling in PC and the implications for disease severity, pathogenicity and therapeutic interventions.

The biomechanical role of the keratin cytoskeleton was discussed by John Connelly. Other clinical presentations included a summary of clinical findings in 815 patients with PC identifying genotype-phenotype correlations (Liat Samuelov), a discussion of the association between PC-KRT17 and hidradenitis suppurativa (Mor Pavlovsky) and patient reported quality of life differentials in PC treatment (Albert Wu and Shari Lipner). Lynn Boyden described recent work on ASPRV1 mutations causing autosomal dominant lamellar ichthyosis with a palmoplantar keratoderma. Roger Kaspar spoke about his efforts to evolve siRNA therapy for PC. Using kinase inhibitors, Thomas Magin showed that keratin aggregation could be reduced in epidermolysis bullosa simplex keratinocytes restoring a functional keratin cytoskeleton. Finally, Wes Kaupinen and Braham Shroot gave an update on the VALO clinical trial.

**IMPACT OF THE INTERNATIONAL PC RESEARCH REGISTRY (IPCRR) DATA**

Have you ever wondered how the registry data is used? The following presentations were given during the recent IPCC Symposium based on new information gleaned from de-identified IPCRR data:

- Structural modeling guided understanding of genotype-phenotype correlation in PC. Joyce Teng, MD, PhD, and Christopher Bunick, MD, PhD, Stanford University and Yale University
- Revisiting pachyonychia congenita: a case cohort study in 815 patients. Liat Samuelov, MD, Tel Aviv Medical Center
- Prevalence and characterisation of itch in PC. Lloyd Steele, Academic Clinical Fellow in Dermatology at Barts Health NHS Trust, London
- Patient-reported quality of life differentials in PC management. Albert G. Wu, MD Candidate, New York Medical College and Shari Lipner, MD, PhD, Weill Cornell Medicine, Department of Dermatology
Co-existence of PC and hidradenitis suppurativa: more than a coincidence.
Mor Pavlovsky, MD, Tel Aviv Medical Center

All of those presentations were recently or are in the process of being published in medical and scientific journals. In the quest to find effective treatments, scientists and drug developers are using the registry data to learn more about PC, to advance PC research, and to develop therapeutics that may help PC and other rare skin diseases.

For clinicians, registry data is literally changing what is known about PC. Factual information teaches physicians what PC is (much more than thickened nails) and prevents doctors from prescribing treatments that are ineffective or harmful to patients. More publications about PC in high impact medical journals will enable improved recognition of PC by physicians so those with PC don’t have to live for decades without a proper diagnosis. Please continue to encourage your patients to participate in the IPCRR. www.pachyonychia.org/patient-registry/

Together we are making a difference!

PC Research Agenda

The writers of the PC Research Agenda have submitted an impressive master outline of where research for PC should be focused. Once this important document is finished, PC Project will use it to increase interest in stakeholders, such as rare disease biotechnology companies, scientists, pharmaceutical companies and government bodies and leverage support from funders such as the NIH. The Research Agenda will also be used to direct priority areas of research which may be funded in future pilot grant calls by PC Project.

VALO Study Update

Thanks for the tremendous support and interest this community has had in the VALO Phase 2/3 clinical trial, sponsored by Palvella Therapeutics, to evaluate the safety and effectiveness of the 3.9% rapamycin gel.

The following are some important things about this investigational drug and the trial:

- The VALO trials (the combined phase 2/3 and the extension study) are the farthest a treatment specifically for PC has ever gone on the path towards FDA/regulatory approval.
- Palvella and PC Project are working closely together on the design and implementation of the next clinical study in this journey. Patients in the VALO extension study needed to get off drug and begin to “wash out” in the event they would like to participate in another trial.
- The data from the previous VALO clinical trials have been meticulously gathered, analyzed, and learned from in order to prepare for future clinical trials for PC. You can find a summary of the top line VALO study results on Palvella’s website (www.Palvellatx.com) under press releases.
- Developing a drug is time consuming and extensive and almost always requires conducting more than one clinical trial. As part of this journey, as noted above, Palvella intends to run another study to further evaluate the effectiveness of this drug.
- Because the PC community is small, specific details about the results of the previous trial have not been publicly shared so as to not introduce patient bias for the next trial.

Currently, we anticipate that adult patients with PC-K6a, PC-K6b, PC-K6c, and PC-K16 in the US and UK with a genetically confirmed diagnosis of PC will be invited to participate. If you have patients in these countries and think they might be interested in participating, they will need to have a genetic testing report confirming PC.

PC Patient Support Meeting

PC Project will hold a virtual PSM on Saturday, November 20th. The precise schedule is yet to be determined, but this will be an interactive meeting with not only educational
presentations, but a chance for patients to talk with one another. If you are interested in PC or want to learn more about PC and how it affects the lives of those who deal with it every day, please save the date. More information will be coming soon.

**Recent Publications**

[link to more information]


- **A role for keratin 17 during DNA damage response and tumor initiation.** Nair RR, Hsu J, Jacob JT, Pineda CM, Hobbs RP, Coulombe
We would love to feature your research, lab news, and publications in our newsletter. Please email info@pachyonychia.org with information.

**PC Awareness Month: #WeAreUltra**

This past June, the PC community participated in the #WeAreUltra campaign for PC Awareness. Patients and their loved ones were invited to share photos of themselves, along with encouraging words for the PC community and to finish the sentence, “WeAreUltra...” During the month, photos and stories were shared, fundraisers were held, and direct donations to PC Project were made. And the funds contributed during the month were matched twice! The PC patient community and their supporters really are wonderful – kind of like the PC medical and scientific community.

Hello! I’m Vania and I’m 5 years old.

Even though I live with a very rare condition that can be debilitating at times, I fix my crown and remind myself that I’m a fighter and that my #UltraRare condition won’t stop me. Thank you for the care, research, and support that PC project provides to me. It’s because of them that I know I’m not alone.

Saludos, me llamo Vania y tengo 5 años.

Aunque vivo con una condición Ultra Rara que puede ser debilitante a momentos, me arreglo mi corona y me acuerdo que soy una guerrera y que mi condición Ultra Rara no me va detener. Gracias por el cuidó, investigación y apoyo que el PC Project brinda a mí. Es por ellos que se que no estoy sola.

I was born with a rare genetic mutation called Pachyonychia Congenita (PC). It’s caused by a mutation in one of my keratin genes that affects my hair, nails, skin, etc.

The most distinguishing symptom is blisters and callouses that form on my feet. They are painful and it often feeling like I’m walking on shards of glass.

This mutation has crushed me and controlled me for the longest time, but this past year, I’ve learned how to love it.

PC makes me the strong individual I am today!

I have Pachyonychia Congenita, otherwise known as PC, and so did my dad. He suffered his entire life, never knowing what he had. All he knew is that his feet weren’t normal and hurt tremendously.

I’ve led a pretty good life with this condition. You must, however, learn your limitations. For example, I don’t stay on my feet for more than two hours at a time. If I push it beyond that timeframe, I pay for it later on in the evening.

For all of you kids out there, you’ll learn what limitations you have. If you stick to that, you’ll still have good days and bad days, but at least you are not causing yourself more pain by going beyond what you can handle.

Remember: PCERS ARE #ULTRA