MESSAGE FROM THE EDITOR

Hello from London. We are now like many others recovering from the Covid19 pandemic and wondering when the second wave might come. I hope you are all safe and well. It is rather strange talking to my patients over the phone or by video and 90% of them say....so when can we come and see you again, doctor. I am not fully convinced by virtual dermatology, although I think it has a place for patients who are stable and live far away. Our managers think it is a great idea. The laboratory is opening with reduced capacity because of social distancing, but everyone is being flexible to get their work done.

We are all now experts on Zoom, Webinars and Microsoft Teams. The annual IPCC meeting before the SID became a virtual effort. Thanks to Xiang-Li Tan and Albert Wu for participating. The French PC patient support meeting planned for June was postponed, but will be rescheduled as soon as it becomes possible. Hopefully, life will settle down to a new normal and we will have opportunities to meet again.

I am looking forward to going to Ireland soon.

'Sheer, bright-shining spring, spring as it used to be, Cold in the morning, but as broad daylight Swings open, the everlasting sky Is a marvel to survivors.'
- Seamus Heaney

DISCOVERING PPK

By Eli Sprecher, MD, PhD

Palmoplantar keratodermas (PPKs) have always been regarded by clinicians as diagnostically challenging. Patients often display overlapping clinical features which are not in themselves discriminative enough to pose a definitive diagnosis. Is there a need for posing a diagnosis in families with PPKs? There is. Not only to allow for proper genetic counseling to be delivered but also because some of these conditions are sometimes associated with non-cutaneous features which require specific surveillance or interventions (e.g. cardiac arrhythmias).

More recently, the need for accurate diagnosis has become even more acute with the advent of possible therapeutic options for PPK patients. In this context, morphology is not enough anymore to guide PPKs classification. Pathogenesis-based grouping may actually point to common therapeutic solutions. For example, there is a growing number of PPKs associated with abnormal proteolytic or anti-proteolytic activity in the epidermis such as keratolytic winter erythema due to increased expression of the protease cathepsin B (Ngcungcu et al., 2017) or Nagashima-type palmoplantar keratosis (Kubo et al., 2013) and exfoliative ichthyosis (Pigors et al., 2016) due to decreased activity of protease inhibitors.

Now a new form of autosomal recessive palmoplantar keratoderma associated with peeling skin has been found to result from loss-of-function mutations in vaspin, an inhibitor of proteases such as kallikrein 7 (Mohamad et al, 2020). The PPK-causing mutations were found to result in increased kallikrein 7 activity which in turn led to enhanced degradation of desmoglein 1 and corneodesmosin. This nicely explains the two major cardinal features of this new disease (PPK and peeling skin) as desmoglein 1 deficiency has been previously associated with PPK while lack of corneodesmosin results in different forms of peeling skin syndromes.
This novel form of PPK and other types of PPKs associated with abnormal proteolytic activity in the epidermis may be amenable to emerging therapies aimed at restoring protease inhibition in the skin.

**VALO Clinical Trial Update**

Palvella is happy to announce the VALO Phase 2/3 clinical trial remains on track with anticipated completion this fall. Because of dedicated PC patients, supportive caretakers, excellent clinical trial coordinators, and the commitment of lead principal investigators, the VALO study has continued in spite of the challenges of COVID-19.

In the next few months, several smaller studies will be conducted, which are needed for FDA approval of this investigational therapy. In addition to these smaller studies, the extension trial will also open. For additional information visit pachyonychia.org/valo/ or clinicaltrials.gov.
Recent Publications

pachyonychia.org/research-articles/


PC Awareness Month

June is Pachyonychia Congenita awareness month, a time for patients around the world share their PC stories and raise the profile of PC. Here is a sampling of the submissions for the first #PCSidewalkChallenge:
Patient Viewpoint

Hi, my name is Tara. I’m 23-years old, and I was diagnosed with PC at the age of two. I have PC-K16. Living with PC is not easy. It affects you on an emotional and physical level.

I would like to start out by talking about the physical pain and then get more into the emotional pain. The emotional pain is what I believe is the worst part of the disease and affects you most. I would like everyone to bear with me for a second and close your eyes. Imagine yourself barefoot with no shoes, no socks, just your bare feet and nothing else. Now, imagine yourself stepping on a bed of misshapen, sharp, hard rocks. Stand there for a second as gravity does its job and pushes your feet deeper and deeper into the rocks. Now, you may open your eyes. I bet that made you feel a little bit uncomfortable. Well, that’s how I feel every day. My pain fluctuates in intensity, meaning sometimes it’s bearable, and sometimes I’m at the point where I can’t even stand. But I’m one of the lucky ones. My PC was genetic, not spontaneous like the others. My father has PC, and I’m lucky because I grew up learning how to manage the pain that comes with PC, but the one pain none of us seem to know how to relief is a never-ending itch.

As a female, I grew up feeling a bit of pressure to be perfect. When I was younger I did not care much about what people thought about my PC until I started being bullied in elementary school for how I looked. This is what led me to feel self-conscious about my PC, and I tried my best to hide it. I honestly cannot remember the last time that I left the house without socks on or went ten minutes without nail polish on. Whenever people ask me why I walk weird, I say it’s because of a sports injury that never healed, even though I’ve never played sports. I stuck with this lie for years. It took me seven years to come out and tell my best friend the truth. I felt like I needed to lie to my friends because I did not want them to treat me differently. I did not want them to see me as someone who is broken, and I did not want them to ask me if I was okay or if I needed a break. I know my limits and I know when the time comes, I’ll push through the pain to do what I want to do.

A few years ago, my family and I went on a trip to Italy. We did a lot of sightseeing, which required a lot of walking. Now, the one place I really wanted to see on this trip was the Vatican. We got a tour of the Vatican Museum, which was great, and it was fine up until halfway through, when the pain started. I was at the point of dying from pain and my family kept telling me, “If you’re in pain, let’s go,” but I kept saying, “No, I really want to see this museum.” When we finally finished our tour, I was about to collapse. My sister gave me a piggyback ride to the taxi stand, where we got back to the hotel and I fell, crying from the pain.

One of my biggest fears with PC is passing it down to my children and having them go through the things that I had to go through. I hope one day there’s a cure, so no one has to experience going through this.