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*


Save the date
The 15th annual International Pachyonychia Congenita Consortium (IPCC) symposium, May 7-8, 2019 in conjunction with the SID in Chicago, IL. More details for this meeting will be coming early 2019. Until then, please contact PC Project with any queries.

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.

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.
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.
Medical Panel Question and Answer Session

A PC kid, Cian, with a few of his heroes Braham, Roger and Wes

Life is not meant to be endured.
Life is meant to be enjoyed.

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2018 PeDRA Annual Meeting Photos

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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