International Pachyonychia Congenita Consortium (IPCC) Symposium

Innovations and Transformations

June 28-29, 2021

A virtual meeting

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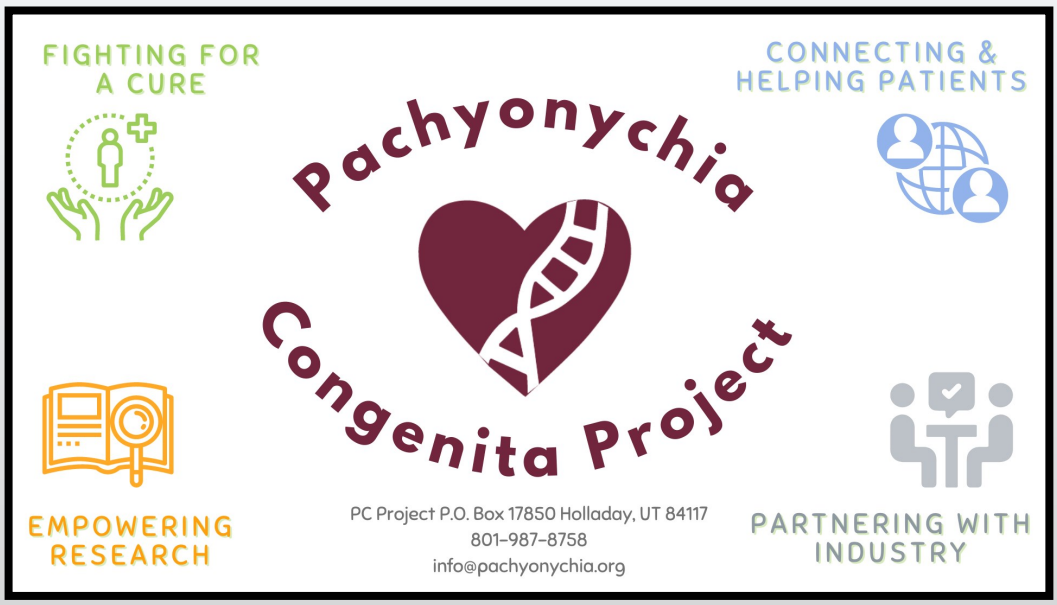


About Pachyonychia Congenita Project

PC Project connects patients, researchers, medical professionals, and industry partners in a united and global effort to help those who suffer from the painful and debilitating effects of Pachyonychia Congenita (PC), a rare genetic skin disease.

The **International Pachyonychia Congenita Research Registry (IPCRR)** gathers data from patients through an online registry and provides free genetic testing to those who join. Patients in the registry are offered individualized support and are notified of studies for PC treatments, advances in research, and activities such as online forums and patient support meetings. Please refer your patients with severe PPKs to PC Project for a definitive diagnosis: https://www.pachyonychia.org/patient-registry/

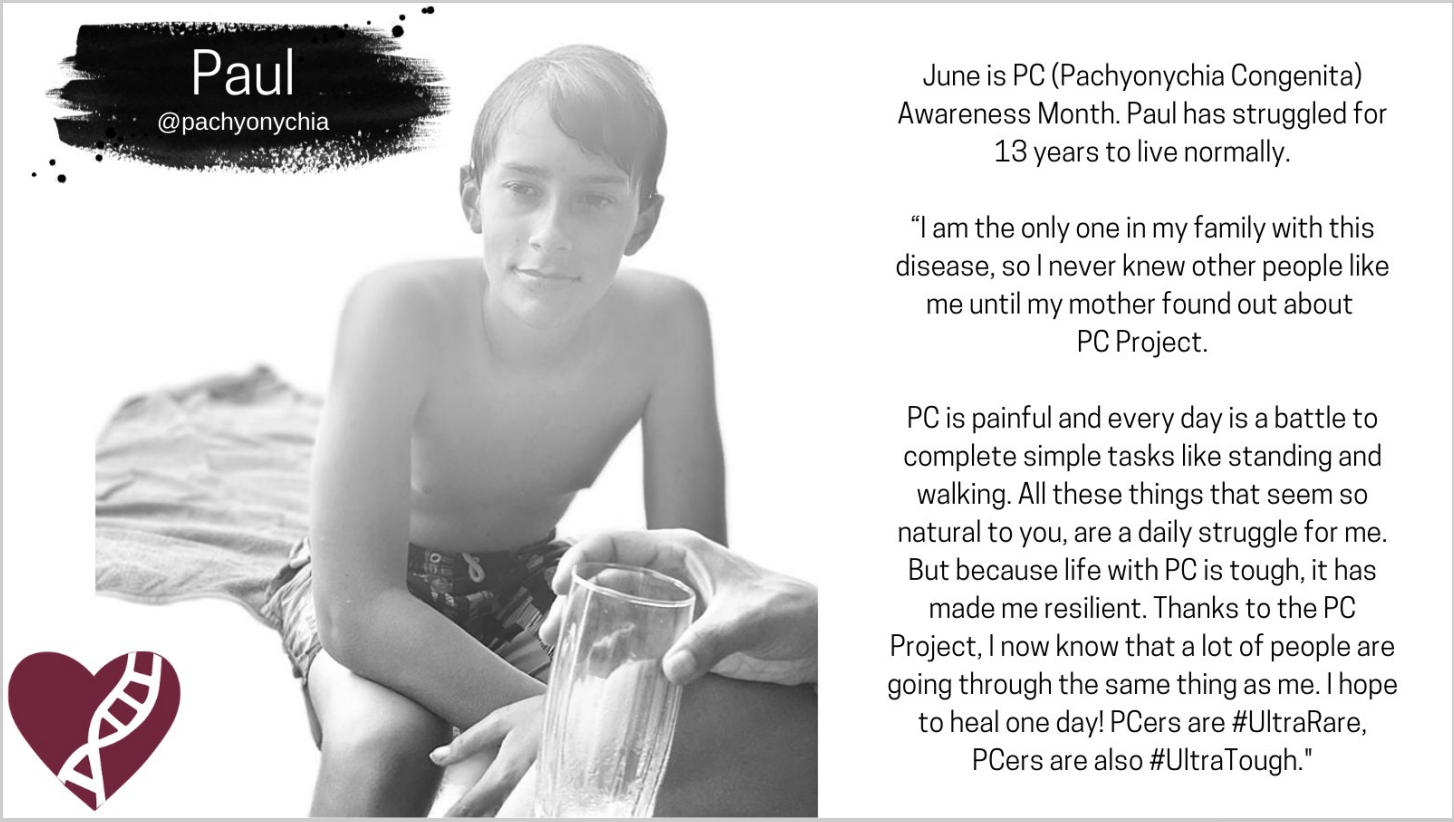
PC Project sponsors the **International PC Consortium (IPCC)** which facilitates collaboration among scientists, physicians, and other professionals interested in advancing research and translational therapeutics for PC. De-identified data from the registry is freely shared and available for research. PC Project invites all interested physicians, scientists and industry partners to join the IPCC, a special group, founded and fueled by love for these patients with severe unmet needs.

Thank you for helping us achieve our vision: A day when those who suffer from PC will live without excruciating pain, isolation, and embarrassment.

Table of Contents

Click on underline to jump to each section

- June 28th Schedule
- June 29th Schedule
- Speaker/Chair Biographies
- Registered Attendee List
- Presentation Abstracts
- Thank You



Monday, June 28, 2021

8:00-11:00 MDT (Click on underlined sections for more information.)

8:00 am *Welcome from PC Project*
Janice Schwartz, Executive Director, PC Project

The Innovation Day
Chair: Eli Sprecher, MD, PhD

08:05 am *How Desmosomes Help Drive Tissue Form and Function*
Kathleen Green, PhD, Northwestern University Feinberg School of Medicine

08:20 am *Mouse PPK models*
David P. Kelsell, PhD, Queen Mary University of London

08:35 am *A rationale for the interplay between expression and function for intermediate filament proteins*
Pierre A. Coulombe, PhD, University of Michigan

08:50 am *Spatial transcriptomics of iRhom2 mouse model paw skin*
Diana Blaydon, PhD, Queen Mary University of London

09:05 am *Mitochondria and lysosomes in PC pathogenesis*
Sonja Lehmann, RWTH Aachen University

09:20 am *Coffee/Tea/Comfort break (Break out rooms available)*

09:35 am *Biomechanical analysis of the keratin cytoskeleton and its role in cellular mechano-sensing*
John Connelly, PhD, Queen Mary University of London

09:50 *am* *ASPRV1 mutations cause dominantly inherited ichthyosis*
Lynn Boyden, PhD, Yale University School of Medicine

10:05 am *Structural modeling guided understanding of genotype-phenotype correlation in PC*
Joyce Teng, MD, PhD, and Christopher Bunick, MD, PhD, Stanford University and Yale University

10:20 am *Open discussion Basic research – Hypes and Gaps*
Moderator: David Kelsell, PhD, Queen Mary University of London

10:35 am *Open discussion: Between clinical and basic research: bio-banking*
Moderator: Eli Sprecher, MD, PhD, Tel Aviv Medical Center

10:55 am *Wrap-up*
Janice Schwartz

Tuesday, June 29, 2021

8:00-11:00 MDT (Click on underlined sections for more information.)

8:00 am *Welcome from PC Project*
Janice Schwartz, Executive Director, PC Project

The Transformation Day
Chair: Edel O'Toole, MD, PhD, FRCPI, FRCP

08:05 am *Revisiting pachyonychia congenita: a case cohort study in 815 patients*
Liat Samuelov, MD, Tel Aviv Medical Center

08:20 am *Phenotypic and pathogenetic heterogeneity in desmoglein 1 deficiencies*
Akiharu Kubo, MD, Keio University School of Medicine

08:35 am *Prevalence and characterisation of itch in PC*
Lloyd Steele, Academic Clinical Fellow in Dermatology at Barts Health NHS Trust, London

08:45 am *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

09:00 am *Co-existence of PC and hidradenitis suppurativa: more than a coincidence.*
Mor Pavlovsky, MD, Tel Aviv Medical Center

09:15 am *Coffee/Tea/Comfort break (Break out rooms available)*

09:30 am *Toward a chemical compound-based therapy for EBS*
Thomas M. Magin, PhD, Leipzig University

09:45 am *A new case series of Olmsted syndrome subjects confirms EGFR activation and that targeted systemic EGFR inhibition shows remarkable efficiency and acceptable side effects.*
Alain Hovnanian, MD, PhD, Imagine Institute, Necker Hospital, Paris

10:00 am *Are fully-modified therapeutic siRNAs the answer for PC?*
Roger Kaspar, PhD, Ayni Therapeutics

10:15 am *Phase 2/3 Trial – Next steps and what's been learned for future PC clinical studies*
Wes Kaupinen, and **Braham Shroot, PhD,** Palvella Therapeutics

10:35 am *Open discussion. Clinical research in PC – in/out-comes*
Moderator: Joyce Teng, MD, PhD, Stanford University

10:55 am *Wrap-up*
Janice Schwartz

2021 VIRTUAL IPCC CHAIRS & PRESENTERS BIOS

Diana Blaydon, PhD

Lecturer, Blizard Institute, Queen Mary University of London, London UK

After obtaining a PhD from University College London, I joined David Kelsell's group at the Blizard Institute to study rare, inherited skin conditions. During this time, we identified novel genes associated with a number of genodermatoses, including palmoplantar keratodermas (PPKs) and peeling skin. My research interests now lie in understanding the molecular mechanisms underlying maintenance of the skin barrier, particularly in response to stress, primarily through the study of proteins associated with PPKs.

Lynn M. Boyden, PhD

Yale University School of Medicine, Department of Genetics

Lynn Boyden has a PhD in Genetics from Yale University. She has discovered the genetic basis of 11 Mendelian disorders affecting bone density, blood pressure, electrolyte metabolism, and skin.

Christopher G. Bunick, MD, PhD

Associate Professor of Dermatology, Yale University

Dr. Christopher Bunick, MD, PhD is a dermatologist and physician-scientist with over 25 years involvement in structural biology research. As an undergraduate at Vanderbilt University, he trained with Dr. Gerald Stubbs in crystallography and fiber diffraction of filamentous plant viruses. This research sparked an interest in long, filamentous systems, which is reflected in his current work on intermediate filaments, particularly keratin function in the skin barrier. After completing medical school and the MSTP at Vanderbilt and dermatology residency at Yale, he performed a postdoctoral research fellowship at Yale University with Nobel Laureate Thomas Steitz. Most recently, his research has shed light on mechanisms of action of oral drugs for acne vulgaris, bringing his work from bench to bedside.

John Connelly, PhD

Reader in Bioengineering, Centre for Cell Biology and Cutaneous Research, Queen Mary University of London

Dr. Connelly completed his PhD in Bioengineering from the Georgia Institute of Technology, and he carried out further postdoctoral training in Prof. Fiona Watt's laboratory at the University of Cambridge. He is currently a Reader in Bioengineering at Queen Mary University of London, and the main research interest of his laboratory is the biomechanical regulation is skin homeostasis and repair. Dr. Connelly and his team have developed a range of engineering tools, technologies, and model systems to dissect the mechanisms of mechano-sensing within the skin.

Pierre A. Coulombe, PhD

G. Carl Huber Professor and Chair, Department of Cell & Developmental Biology, University of Michigan Medical School

Dr. Pierre A. Coulombe, a native of Montréal, Québec, Canada, serves as the G. Carl Huber Professor and Chair of the Department of Cell & Developmental Biology at the University of Michigan Medical School. He holds a joint appointment in the Department of Dermatology and is a member of the Comprehensive Cancer Center at the same institution. Dr. Coulombe has a long-standing interest in understanding keratin protein function in the context of tissue homeostasis and response to stress in skin epithelia and related tissue.

Kathleen J. Green, PhD

Joseph L. Mayberry Professor of Pathology and Professor of Dermatology
Northwestern University Feinberg School of Medicine

Dr. Green is the Joseph L. Mayberry Professor of Pathology at Northwestern University and Professor in the Department of Dermatology. She serves as Associate Director for Basic Sciences in the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, Illinois. Dr. Green's research focuses on how cadherins and their associated proteins direct tissue morphogenesis and differentiation. Her work on the structure, assembly and function of intercellular junctions called desmosomes led to discovery of their involvement in diseases of the skin and heart

Alain Hovnanian, MD, PhD

INSERM UMR1163, Imagine Institute, Necker hospital for sick children, Paris University

Alain Hovnanian is Professor of Genetics at Necker hospital for sick children at Paris University, and the director of an INSERM research laboratory on genetic skin diseases at the Imagine institue for genetic diseases in Paris. He has a long-standing interest in rare and severe genetic skin diseases with high unmet medical needs, including epidermolysis biullosa, Netherton syndrome, Darier and Hailey-Hailey diseases and severe palmo-plantar keratoderma such as Pachyonychia Congenita and Olmsted syndrome. Hovnanian's team has recently identified PERP as a new gene for Olmsted syndrome. His team, in association with Dr April Zhang's and Dawn Siegel's team from Medical College of Wisconsin and colleagues from George Wahington University School of Medicine, USA, and from Curitiba Hospital, Brazil, have recently shown that targeted inhibition of the mTOR and/or the Epidermal Growth Factor Receptor is a very effective therapy for Olmsted syndrome (Zhang A. et al. JAMA Dermatol, 2020).

Roger L. Kaspar, PhD

Ayni Therapeutics

Roger L. Kaspar, Ph.D, is CSO and founder of Ayni Therapeutics, a company focused on developing novel skin therapeutics, including inhibitors based on RNA interference (RNAi). Dr. Kaspar received his doctorate from the University of Washington (Seattle) in biochemistry (David Morris) and performed post-doctoral work at M.I.T. (Lee Gehrke), Stanford University (Helen Blau), and Chiba University (Tomohito Kakegawa). After serving on the faculty at Brigham Young University (Utah) in the Department of Chemistry and Biochemistry, he left academia to work at SomaGenics and later was a founder and CEO at TransDerm, which was acquired by Allergan in 2018. Most recently, he founded Ayni Therapeutics to build on the foundation and acquired IP assets created at TransDerm to develop novel skin therapies. Drawing on his expertise in the area of post-transcriptional gene regulation, his current efforts are focused on designing highly potent and selective therapeutic siRNAs that target disease-causing genes in skin disorders, including pachyonychia congenita.

Wes Kaupinen

Founder and CEO, Palvella Therapeutics

Mr. Kaupinen brings more than 17 years of entrepreneurial life sciences experience as an operating executive and early stage investor, including having worked closely with several companies that have secured FDA approvals of novel treatments for high unmet indications. Prior to Palvella, Mr. Kaupinen served as Senior Vice President of Corporate Development and Commercialization at Insmed (NASDAQ: INSM), a global commercial stage biopharmaceutical company focused on rare diseases.
Mr. Kaupinen earned an M.B.A. from The Wharton School of the University of Pennsylvania, and a B.A. in Economics from The University of Virginia.

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David P. Kelsell, PhD

Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London

My research largely focuses on understanding the genetic and disease mechanisms underlying monogenic skin disorders with a particular interest in keratodermas linked to cardiomyopathy, hearing loss and oesophageal cancer. My group is currently funded by the Medical Research Council, British Skin Foundation and Cancer Research UK. I was awarded the Chanel-CERIES award for skin research in 2016. I was the first non-clinical president of the European Society of Dermatological Research (2018-2019).

Akiharu Kubo, PhD

Department of Dermatology, Keio University School of Medicine

Akiharu Kubo received his MD from Osaka University in 1994, followed by dermatology residency training at Osaka University and cell biologist training at Kyoto University. In 2006, he moved to Keio University School of Medicine, where he made seminal discoveries on the roles of tight junctions in the skin barrier and skin homeostasis, and determined novel pathogenetic mechanisms in Nagashima-type palmoplantar keratosis and porokeratosis.

Sonja Lehmann

RWTH Aachen University, Institute of Molecular and Cellular Anatomy

My name is Sonja Lehmann and after studying biology and biomedical sciences, I became a member of the group of Dr Nicole Schwarz in the Institute of Molecular and Cellular Anatomy at the university hospital in Aachen (Germany) in 2016. After completing my master thesis, I continued the research on Pachyonychia congenita as a PhD student by investigating fundamental molecular abnormalities in PC, with the aim of providing ideas for novel therapeutic options in the future.

Shari R. Lipner, MD

Associate Professor of Clinical Dermatology, Director, Nail Division, Weill Cornell Dermatology

Dr. Lipner is an expert in nail disorders, including fungal diseases, inflammatory disorders, genetic syndromes and nail tumors. She is a member of the Women's Dermatologic Society, and Council for Nail Disorders, where she serves as Board of Director. She is also the President of The Dermatologic Society of Greater New York and co-chaired the Atlantic Dermatological Conference in 2019. She is the recipient of multiple honors and awards including the AAD Presidential Citation, AAD Academic Dermatology Leadership Program Award, Women's Dermatologic Society Mentorship Award, Weill Cornell Leadership in Academic Medicine Program Award, and the JAAD Editorial Mentorship Award. Dr. Lipner has authored over two hundred peer-reviewed publications, numerous book chapters, lectures nationwide, and is a frequently sought out by the media for her expertise.

Thomas M. Magin, PhD

Professor of Cell and Developmental Biology, University of Leipzig, Institute of Biology

Thomas Magin is chair of Cell and Developmental Biology and head of department at Leipzig University. Since 2015, he coordinates a German Research Council-funded priority program (SPP1782) of 22 PIs which studies the role of epithelial intercellular junctions in mechanotransduction and chemical signaling. His group investigates the function of keratin proteins during epidermal differentiation, regeneration and disease, with a focus on Epidermolysis Bullosa Simplex (EBS). A main aspect of his work centers on the development of a chemical compound-based therapy for EBS to be delivered locally or systemically.

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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, Queen Mary University of London

Edel O'Toole is a clinical academic and Centre Lead of the Centre for Cell Biology and Cutaneous Research, Blizard Institute, Barts and the London School of Medicine and Dentistry with an active research group working on rare and common genetic skin disease biology and is also an honorary consultant dermatologist at the Royal London Hospital, Barts Health NHS Trust. She trained in Medicine at University College, Galway, Ireland, followed by general medical and dermatology training in Dublin and London. She was a Dermatology Foundation followed by a Howard Hughes Medical Institute Post-Doctoral Fellow with David Woodley at Northwestern University in Chicago from 1994-1998. Her specialist clinical interests are ichthyosis and palmoplantar keratodermas. She is the current clinical lead for the British Association of Dermatologists Dermatology and Genetic Medicine network. She is Chair of the Medical Advisory Board of the Ichthyosis Support Group, is on the steering committee of Pachyonychia Project and is actively involved in 100K Genomes, a gene discovery project within the NHS. She is on the board of the ESDR.

Mor Pavlovsky, MD

Head of the Pigmentation Disorders Clinic, Division of Dermatology, Tel Aviv Sourasky Medical Center

In 2006, Graduated MD degree, Ben-Gurion University, Beer Sheva, Israel

In 2013, completed a residency in dermatology, Department of Dermatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

In 2018, completed a research fellowship, Laboratory of Molecular Dermatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

Now, head of the Pigmentation Clinic, Department of Dermatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel and a researcher in the Laboratory of Molecular Dermatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

Liat Samuelov, MD

Division of Dermatology, Tel-Aviv Medical Center

Dr. Liat Samuelov received her MD degree from the Sackler faculty of medicine, Tel-Aviv University and graduated Magna cum Laude in 2008. She specialized in Dermatology at the Tel-Aviv Medical center in 2009-2014. During her residency she spent almost a year at the lab of Prof. Ralf Paus, University of Luebeck, Germany (2010-2011) performing hair follicle research as a part of a Minerva scholarship. Following her residency, she performed a research fellowship at the Department of Dermatology lab of Prof. Richard Gallo at the University of California San Diego (UCSD) and between 2016-2017 she completed a Pediatric Dermatology fellowship with Prof. Amy Paller and Dr. Anthony Mancini at Lurie Childrens' Hospital, Chicago. Since 2017 she serves as the vice chair of the Division of Dermatology, Tel-Aviv Medical Center. She has co-authored over 40 scientific publications and several book chapters. Her research focuses on genetics of skin diseases, atopic dermatitis, pediatric dermatology and hair disorders. Dr. Samuelov holds a senior lecturer position at the Sackler Faculty of Medicine, Tel-Aviv University.

2021 VIRTUAL IPCC CHAIRS & PRESENTERS BIOS

Braham Shroot, PhD

Founder and CEO, Palvella Therapeutics

Braham Shroot PhD with over 40 years experience in drug discovery and development has been Chief Scientific officer of Palvella for the past 5 years. Pachyonychia Congenita has a fertile scientific knowledge base thanks to the legacy created by many talented investigators. They, along with the critical understanding of patients needs provided by PC projects, have provided the springboard for the Palvella team to create a therapeutic platform to be at the service of PC patients.

Eli Sprecher, MD, PhD

Chair, Division of Dermatology, Deputy Director General for R&D and Innovation, Tel Aviv Sourasky Medical Center, Frederick Reiss Professor of Dermatology, Sackler Faculty of Medicine, Tel Aviv University

Eli Sprecher received his MD and PhD degrees from the Hebrew University of Jerusalem and specialized in dermatology at the Rambam Medical Center, Haifa. He spent a post-doctoral fellowship at Thomas Jefferson University, Philadelphia. He became Chair of the Department of Dermatology at the Tel Aviv Medical center in 2008, Professor of Dermatology at the Sackler Faculty of Medicine, Tel Aviv University in 2010 where he also received the Frederick Reiss chair of Dermatology in 2014. He also served as Deputy Director General for Patient Safety till 2019 and is now Deputy Director General for Research and Development at the Tel Aviv medical center. He has co-authored over 300 scientific publications, has mentored over 40 students and has received numerous national and international prizes and honors. His research focuses on the genetic basis of skin diseases. His group aims at understanding the molecular genetics of both simple and complex traits, deciphering their pathogenesis and then attempting at translating this new knowledge into innovative therapeutic tools.

Lloyd Steele, MBChB(Hons), BMedSci(Hons), MRCP(UK), PGCert(MedEd), FHEA

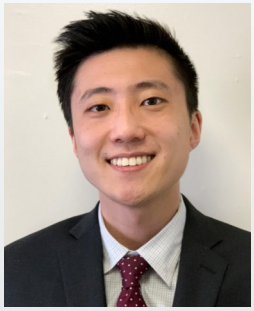
Academic Clinical Fellow in Dermatology at Barts Health NHS Trust, London

Dr. Steele is a second-year resident in Dermatology based in London in the UK. His research interests are in genomics, machine learning, and improving dermatology care through data-driven outcomes.

Joyce M. C. Teng, MD, PhD

Professor of Dermatology & Pediatrics, Department of Dermatology, Stanford University

Dr. Teng is a professor of Dermatology and Pediatrics at Stanford University. She also serves as the chief of pediatric dermatology and director of fellowship training. Dr. Teng's has broad clinical interests in rare genetic skin disorders and inflammatory skin diseases. Her translational research focuses on understanding pathogenesis of genetic disorders and targeted therapy discovery.



Albert G. Wu

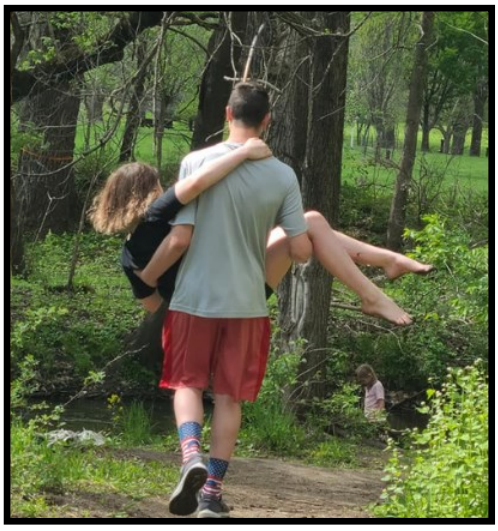
New York Medical College, M.D. Candidate, Class of 2022, Co-President, National Dermatology Interest Group Association

Albert Wu is a third-year medical student pursuing dermatology at New York Medical College. He has co-authored several research papers and poster presentations on a range of skin disorders and systemic disparities within medicine with Dr. Lipner serving as his mentor. He is passionate about medical education and genetic dermatoses, and currently serves as Co-president of the National Dermatology Interest Group Association(DIGA), which serves as a centralized platform of educational, research, and career exploration opportunities for medical students. In his free time, he enjoys birdwatching and exploring the local barbeque scene.

We need you!

Because PC feet hurt, sometimes we need a lift.

- If you have research or drug development ideas to share with PC Project or if you want to present at a future IPCC Symposium, please contact us at info@pachyonychia.org.
- If you have patients with painful PPKs, please refer them to the International PC Research Registry where they will be supported by our global patient community and receive a genetically confirmed diagnosis. www.pachyonychia.org/patient-registry/



2021 IPCC REGISTERED ATTENDEES

Maria Amparo Acosta Aragon
Cauca University
Colombia

Khalid Al Aboud
King Faisal Hospital
Saudi Arabia

Dario Leonardo Balacco
University of Birmingham
United Kingdom

Ajoy Bardhan
University Hospitals Birmingham NHS Foundation Trust
United Kingdom

Justine Bassett
Imagine Institute - Inserm U1163
France

Colton Baumler
UC Davis
United States

Susan Bayliss
Washington University School of Medicine
United States

Diana Blaydon
Cell Biology and Cutaneous Research
United Kingdom

Lynn Boyden
Yale University School of Medicine
United States

Liora Braiman
Kamari pharma
Israel

Al Bravo
United States

Christopher Bunick
Yale University
United States

Sandra Ceron
Universidad del Cauca
Colombia

Jiang Chen
Stony Brook University
United States

Anissa Chikh
St Georges University of London
United Kingdom

Keith Choate
Yale University
United States

Jennifer Chu
Blizard Institute
United Kingdom

Michael Conneely
University of Dundee
United Kingdom

John Connelly
Blizard Institute
United Kingdom

Maria-Laura Cossio
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Chile

Pierre Coulombe
University of Michigan Medical School
United States

Steven Daveluy
Wayne State University
United States

John Doux
United States

Jonathan Dyer
University of Missouri
United States

2021 IPCC REGISTERED ATTENDEES

Holly Evans
Pachyonychia Congenita Project
United States

Mark Field
EptivA Therapeutics
Germany

Philip Fleckman
University of Washington
United States

Paula Fron
MOCA, Aachen
Germany

Tracy Funk
OHSU
United States

Phil Gard
United Kingdom

Anju George
Christian Medical College, Vellore
India

Reza Ghohestani
Texas institute of Dermatology
United States

Sharon Glick
SUNY Downstate Health Sciences University
United States

Kathy Goin
Palvella
United States

Emilio Gonzalez
Canvax Biotech
Spain

Antoni Gostynski
Maastricht University Medical Center +
Netherlands

Kathleen Green
Northwestern University
United States

Ankan Gupta
CMC, Vellore, India
India

David Hansen
University of Utah
United States

Adrian Heagerty
University Hospitals Birmingham, UK
United Kingdom

Marie-Louise Henry
University of Michigan
United States

Angela Hernandez-Martin
Hospital Infantil Universitario Niño Jesús
Spain

Robyn Hickerson
University of Dundee
United States

Alex Hinbest
Yale/Wesleyan
United States

Minh Ho
Yale University School of Medicine
United States

Alain Hovnanian
Necker hospital
France

Alan Irvine
Trinity College Dublin
Ireland

Roger Kaspar
Ayni
United States

2021 IPCC REGISTERED ATTENDEES

Wes Kaupinen
Palvella
United States

David Kelsell
QMUL
United Kingdom

Andrew King
Wayne State University
United States

Daniela Kramer
DermatoSPA
Chile

Akiharu Kubo
Keio University School of Medicine
Japan

Sofia Labbouz
Royal Hallamshire Hospital
United Kingdom

Birgit Lane
Skin Research Institute of Singapore
United Kingdom

Sonja Lehmann
University Hospital RWTH Aachen
Germany

Rudolf Leube
RWTH Aachen University
Germany

Shari Lipner
Weill Cornell Medicine
United States

Ivan Lomakin
Yale University
United States

Thomas Magin
Institute of Biology, Leipzig University
Germany

Sajid Malik
Quaid-i-Azam University, Islamabad
Pakistan

Lucile Marchal
Institut Imagine
France

Michael McGrath
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Blizard Institute
United Kingdom

Amy Paller
Feinberg School of Medicine at Northwestern
United States

Amit Parikh
United States

2021 IPCC REGISTERED ATTENDEES

Rutu Patel
PriMed Strategy LLC
United States

Mor Pavlovsky
Tel Aviv Sourasky Medical Center
Israel

Vu Van Quang
Department of Pediatrics, Haiphong University of Medicine and Pharmacy, Vietnam

Neil Rajan
Newcastle University
United Kingdom

Laura Ramos
Queen Mary University London
United Kingdom

Dennis Roop
University of Colorado
United States

Liat Samuelov
Tel-Aviv Medical Center
Israel

Jana Schieren
Institute of Molecular and Cellular Anatomy, RWTH Aachen University

Matthias Schmuth
Medical University Innsbruck
Austria

Nili Schutz
Kamari Pharma
Israel

Janice Schwartz
Pachyonychia Congenita Project
United States

Nicole Schwarz
University Hospital RWTH Aachen
Germany

Braham Shroot
Palvella
France

Robert Silverman
United States

Cory Simpson
University of Pennsylvania
United States

Tycho Speaker
AbbVie
United States

Eli Sprecher
Tel Aviv Sourasky Medical Center
Israel

Lloyd Steele
Blizard Institute
United Kingdom

Peter Steijlen
Maastricht University Medical Center
Netherlands

Umi Tahara
Keio University School of Medicine
Japan

Joyce Teng
Stanford
United States

Asli Tolun
Istanbul Technical University
Turkey

Jouni Uitto
Thomas Jefferson University
United States

Michel van Geel
Maastricht University Medical Center
Netherlands

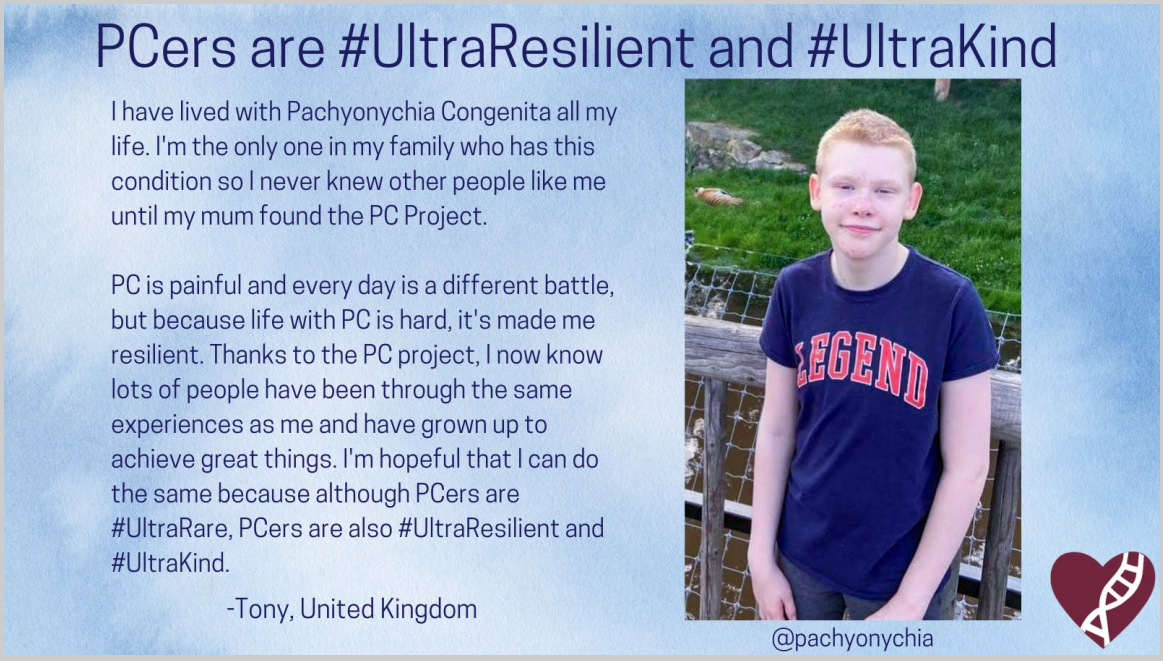
2021 IPCC REGISTERED ATTENDEES

Emily Warshauer
University of Colorado
United States

David Wen
University of Birmingham
United Kingdom

Albert Wu
New York Medical College
United States

I am ultra rare because I am strong and brave, but also sweet and loving. #IAmUltraRare
Thank you PC Project for being part of my life!



2021 IPCC PRESENTATION ABSTRACTS

Presentation Title	Abstract
A new case series of Olmsted syndrome subjects confirms EGFR activation and that targeted systemic EGFR inhibition shows remarkable efficiency and acceptable side effects.	Olmsted syndrome (OS) is a very rare and often severe form of palmo-plantar keratoderma (PPK) most often caused by dominant mutations in the transient receptor potential vanilloid-3 gene (TRPV3) encoding a thermosensitive calcium channel. A majority of TRPV3 mutations causing OS are missense mutations resulting in constitutive activation of the channel leading to abnormal keratinocyte activation. TRPV3 forms a signaling complex with epidermal growth factor receptor (EGFR) by which TRPV3 activation results in EGFR activation. We previously reported remarkable efficiency of oral erlotinib, an EGFR inhibitor, in 4 young patients on all disease symptoms, including pain, pruritus, calluses and PPK, resulting in a significant improvement of the quality of life of these patients.
Alain Hovnanian **Justine Basset, Lucile Marchal, Yaser Diab, Felicidade Santiago, Luna Azulay, Kelly Cordoro, Mathilde Bonnet des Claustres, April Zhang, Anna Yasmine Kirkorian, Flora Frascari, Paul Mercer, Flora Watanabe, Michael McGrath, Evgeniya Petrova, Dawn H. Siegel, Emmanuelle Bourrat, Renee Howard, Alain Hovnanian**	Here we report a 2-year follow-up of these 4 patients (now aged 4, 4, 14 and 16 years), and the treatment of 5 new patients (5.5, 20, 22, 40, 58 years of age) with oral Erlotinib for at least one year. Each patient is heterozygous for a TRPV3 missense mutation which was previously reported. All patients presented with a severe form of OS with painful, often fissured, thick and diffuse hyperkeratosis of their palms and soles, or thick and inflammatory calluses on their soles. In addition, some patients had macerated hyperkeratotic and inflammatory plaques in their axillary, inguinal and or intergluteal folds. All patients suffered from severe pruritus and painful lesions, walking was very strenuous and painful resulting in a very poor quality of life. In situ EGFR activation was assessed by proximity ligation assay which revealed a significant increase in EGFR homodimer formation in lesion skin compared to non-lesion skin in the patients studied. The Mammalian target of rapamycin (mTOR) pathway which is activated downstream following EGFR activation was significantly increased as shown by a marked increase of pRPS6 immunostaining in the epidermis of lesion skin in OS subjects. These observations prompted targeted EGFR inhibition in the new patients using oral Erlotinib. Treatment was initiated at approximately 2 mg/kg/day in a single dose, at distance from a meal and was adjusted to clinical efficiency and tolerance. Clinical response was assessed with visual analog scales for pruritus and pain and/or Children's or Adult Dermatology Life Quality Index. Adverse effects were monitored throughout treatment. Efficiency was observed as early as 4 weeks after treatment initiation and manifested as a significant reduction of pain and pruritus, and a progressive resolution of a majority of hyperkeratotic lesions. After a few months of treatment, calluses, hyperkeratosis of palms, soles and folds showed almost complete resolution in some patients, marked improvement (significantly smaller, thinner and less inflammatory lesions) in other patients. However, thick hyperkeratotic palms and soles persisted in other patients but were devoid of inflammation and pain. Pain treatments could be quickly discontinued. Overall, the quality of life of all patients significantly improved within the first months of treatment, allowing walking, improved weight bearing, physical and social activities. The most frequent side effects included abdominal pain, diarrhea, skin dryness, transient hair loss and acneiform eruptions on the face and the trunk. These adverse events were less frequent in children then in teenagers and adults. They were only partially improved by symptomatic treatment or reduction of Erlotinib dosage. This study provides further evidence that targeted inhibition of EGF signaling pathway, shows remarkable clinical efficacy in OS caused by TRPV3 mutations, and that its short- and long-term tolerance is most often acceptable. Such medications represent life-altering treatments for this orphan disease until more specific approaches targeting TRPV3 activation become available. Finally, the extent to which EGFR activation is involved in Pachyonychia congenital (PC) and other PPK is currently under investigation and could potentially open up the possibility of employing this family of drugs to treat PC.

2021 IPCC PRESENTATION ABSTRACTS

Presentation title	Abstract
A rationale for the interplay between expression and function for intermediate filament proteins. **Pierre Coulombe**	Keratin intermediate filament (IF) proteins provide mechanical resilience and adaptability to cells and tissues, and otherwise impact or regulate most major cellular processes, including proliferation, growth, differentiation, migration death and gene expression. Accordingly keratin IFs are highly significant determinants of the properties the cells and tissues expressing them and of their response to stress and other environmental determinants. Mutations altering the coding sequence of keratin proteins are causative for a broad range of diseases affecting skin and other epithelia. While an impact on cell and tissue mechanics is a recurring theme, there is increasing evidence that mutant keratin expression can alter cellular processes in a broad manner, with an associated impact on disease pathophysiology and clinical presentition. Pachyonychia congenita and related conditions provide vibrant examples of the broad array of tissue anomalies and clinical phenotypes that may result from mutant keratin expression. Progress in relevant fields has been significant in recent years and creates an opportunity to think differently about the interplay between expression and function of IF proteins, as well as about the puzzling phenotype-genotype correlations that typify many IF disorders.
Are fully-modified therapeutic siRNAs the answer for PC? **Roger Kaspar**	There are a host of dominant genetic skin disorders with high unmet medical needs including pachyonychia congenita (PC). It is well known that siRNAs can potently and selectively target mutant disease-causing mRNA expression and can have exquisite discrimination, including the ability to distinguish single nucleotide changes. The recent discoveries that siRNAs can be heavily chemically modified, allowing extraordinary longevity and prolonged inhibition of targeted liver gene expression as demonstrated in human phase 2 and 3 clinical studies, opens up highly promising opportunities to develop these inhibitors as therapeutics. The siRNA TD101 potently targets the PC-causative keratin 6a N171K single nucleotide mutation. The TD101 inhibitor was developed at TransDerm, Inc. and evaluated in a Phase 1b investigator-initiated clinical study. Although efficacy was apparent through lesion clearing and reduction of pain in the treated area, the intralesional injections were too painful (treatment required oral pain medications and a regional nerve block), and the longevity of treatment too short to move forward with additional clinical development using this first-generation siRNA. Ayni Therapeutics builds on the work performed at TransDerm and aims to transfer the lessons learned from others using full chemical modification of siRNAs. It is expected that this next generation of siRNA drugs will have increased in vivo potency, discrimination and, importantly, enhanced longevity for therapeutic use in skin disorders. Preliminary experiments show that fully-modified and cholesterol-conjugated TD101 siRNA derivatives are effective in knock-down experiments in cultured keratinocytes derived from PC patients and these studies will be expanded and extended to a mouse reporter model to determine the longevity of the treatment effect. If the human clinical results from liver studies are transferable to skin, this approach should be a boon for patients suffering from skin disorders, including PC, that have no approved treatment options.

2021 IPCC PRESENTATION ABSTRACTS

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ASPRV1 mutations in dominant lamellar ichthyosis **Lynn Boyden**	Via exome sequencing we show that mutations in *ASPRV1* cause a dominant form of palmoplantar keratoderma and lamellar ichthyosis, a phenotype that has otherwise been exclusively recessive. *ASPRV1* encodes aspartic peptidase retroviral-like 1, a mammalian-specific and stratified epithelia-specific protease important in processing of filaggrin, a critical component of the uppermost epidermal layer. The full-length protein is 343 amino acids and 37 kDa, but auto-cleavage generates a 14 kDa active enzyme (residues 191-326), with an active site at Asp212 essential to proteolytic activity. Eleven affected subjects in five unrelated ichthyosis kindreds were shown to be heterozygous for one of four previously unreported and damaging *ASPRV1* missense mutations. Two subjects have a mutation that arose *de novo*, and eight are within extended kindreds in which the mutation and disorder cosegregate, conclusively establishing that *ASPRV1* mutations cause this dominant form of ichthyosis. Mutation p.Lys199Glu is eight residues distal to the N-terminal auto-cleavage site, mutation p.Arg208Trp is four residues proximal to the active site, and mutations p.Arg311Pro and p.Pro314Thr are 12-15 residues proximal to the C-terminal auto-cleavage site. Crystal structure modeling of the active enzyme shows all four mutation sites are on the same surface and tightly clustered within the three-dimensional protein. Expression of mutant proteins demonstrates that *ASPRV1* mutations disrupt auto-cleavage and filaggrin processing, a function vital to epidermal barrier integrity. Because the skin disorder in subjects with *ASPRV1* mutations is a desquamation defect, keratolytic agents such as lactic acid and urea could be employed as pathogenesis-driven therapy. These agents have been used by two subjects so far, with almost complete resolution of non-palmoplantar scale.
Biomechanical analysis of the keratin cytoskeleton and its role in cellular mechano-sensing **John Connelly**	The keratin network of intermediate filaments provides keratinocytes with essential mechanical strength and resilience, but the contribution to mechano-sensing remains poorly understood. In our recent studies, we investigated the role of the keratin cytoskeleton in the cellular response to altered matrix rigidity. We found that keratinocytes adapted to increasing matrix stiffness by forming a rigid, interconnected network of keratin bundles, in conjunction with F-actin stress fiber formation and increased cell stiffness. Disruption of keratin stability by overexpression of the dominant keratin 14 mutation R416P inhibited the normal mechanical response to substrate rigidity, reducing F-actin stress fibers and cell stiffness. The R416P mutation also impaired mechanotransduction to the nuclear lamina, which mediated stiffness-dependent chromatin remodeling. By contrast, depletion of the cytolinker plectin had the opposite effect and promoted increased mechano-responsiveness and upregulation of Lamin A/C. Together, these results demonstrate that the keratin cytoskeleton plays a key role in matrix rigidity sensing and downstream signal transduction.
Co-existence of pachyonychia congenita and hidradenitis suppurativa: more than a coincidence **Mor Pavlovsky**	Background: The co-existence of pachyonychia congenita (PC) and hidradenitis suppurativa (HS) has been described in case reports. However, the pathomechanism underlying this association and its true prevalence are unknown. Objectives: We aimed at determining the genetic defect underlying the co-existence of PC and HS and to delineate a pathophysiological signaling defect jointly leading to both phenotypes as well as to estimate the prevalence of HS in PC. Methods: We used direct sequencing and a NOTCH luciferase reporter assay to characterize the pathophysiological basis of the familial co-existence of HS and PC. Results: Direct sequencing of DNA samples obtained from family members displaying both PC and HS demonstrated a missense variant (c.275A>G) in KRT17, encoding keratin 17. The KRT17 c.275A>G variant resulted in a significant decrease in NOTCH activity. A questionnaire distributed to all PC patients registered with the International PC Research Registry (IPCRR) revealed that 72 out of 278 responders reported HS-associated clinical features (25.9%). Limitations: HS prevalence among PC patients was assessed using a questionnaire rather than medical charts or physician assessment. Conclusion: The co-existence of HS and KRT17-associated PC is more common than previously thought. Impaired NOTCH signaling may predispose PC patients to HS.

2021 IPCC PRESENTATION ABSTRACTS

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How Desmosomes Help Drive Tissue Form and Function **Kathleen Green**	The evolution of multicellularity required that cells develop ways of coming together to form tissues and organs. While cell-cell adhesion molecules called cadherins were first seen in primitive invertebrates, as organisms increased in size and complexity new vertebrate desmosomal cadherins appeared that help tissues under mechanical stress such as skin and heart maintain their structural integrity. Expansion of the cadherin family also provided an opportunity for new functions that transcend adhesion to evolve. These functions are critical for creating the multi-layered epidermis that covers our entire body, providing protection against the sun, water loss, and pathogens in addition to mechanical insults. In our presentation we will describe how one of these desmosomal cadherins, a terrestrial and keratinocyte-specific molecule called desmoglein 1, integrates chemical and mechanical signals to promote stratification and help build the skin barrier. Beyond these structural roles, our data show that desmoglein 1 also harnesses paracrine signaling in the epidermis. Acute loss of desmoglein 1 stimulates the keratinocyte secretome to mediate alterations in melanocyte behavior simulating a tanning response. On the other hand chronic remodeling of the secretome in Dsg1-deficient patients is associated with skin inflammation and allergies. Collectively, our studies show how cytoarchitectural systems are structurally and functionally integrated within a complex tissue, and also how disabling specific nodes in the network contributes to human disease.
Mitochondria and lysosomes in Pachyonychia congenita pathogenesis **Sonja Lehmann**	The tightly regulated autophagy of cell organelles such as mitochondria is essential for functional differentiation of keratinocytes. If the autophagy process is disturbed, it can lead to epidermal thickening, as it is encountered in Pachyonychia congenita patients. During mitophagy, mitochondria are engulfed by autophagosomal membranes in order to isolate them for subsequent removal. This process is followed by fusion of autophagosomes with lysosomes, resulting in autolysosomes, which ultimately degrade mitochondria by providing the correct biochemical environment and different degrading enzymes. In our studies, we investigated the different steps of mitophagy in keratinocytes derived from human healthy individuals or PC patients by biochemical and fluorescent microscopy-based experiments. We could show that PC cells accumulate an increased amount of overaged mitochondria and autolysosomes compared to healthy cells. The underlying keratin 6a mutations thus cause impaired mitophagy, which might contribute to Pachyonychia congenita pathogenesis. These disturbances seem to be mainly caused by impaired lysosomal function and not the initial mitophagy steps. Thus we are now focusing on how PC keratin mutations influence autolysosomal recycling.
Patient-Reported Quality of Life Differentials in Pachyonychia Congenita Management **Albert Wu, Shari Lipner**	Pachyonychia congenita (PC) is an autosomal dominant disorder characterized by a constellation of findings, including palmoplantar keratoderma, debilitating neuropathic pain, onychodystrophy, follicular hyperkeratosis (FHK), and PC-induced cysts. Since standardized treatments are lacking, lifelong morbidities are often managed with lifestyle modifications and pain control. Our objectives were to compare the efficacy of therapeutic options used by PC patients for keratodermas, FHK, and PC-induced cysts.
Phenotypic and pathogenetic heterogeneity in desmoglein 1 deficiencies **Akiharu Kubo**	Various DSG1 mutations including a nonsense mutation at the C-terminal portion and missense mutations at the transmembrane portion cause palmoplantar keratoderma with/without additional phenotypes.

2021 IPCC PRESENTATION ABSTRACTS

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Prevalence and characterisation of itch in pachyonychia congenita **Lloyd Steele**	Itch is not well-recognized as a clinical finding of pachyonychia congenita (PC), but is anecdotally reported by patients. We assessed the prevalence and characteristics of itch in participants from the International Pachyonychia Congenita Research Registry (IPCRR) using a modified 11-item Leuven Itch Scale (LIS). Itch attributed to PC had been in the past month by 144/281 (51.2%) participants. It most frequently affected the feet at callus sites. Itch was described as tickling (31.3%), burning (28.5%), prickling (26.4%), and tingling (6.9%). Itch in the past month was significantly associated with PC genotype (P=0.001) and keratin domain affected (P=0.002), being most prevalent for KRT16 mutations (63.5%) and the head domain (100%). Despite an incomplete response rate of 31%, the high prevalence observed, together with its biological plausibility, suggest itch is a real phenomenon in PC.
Revisiting pachyonychia congenita: a case control study in 815 patients **Liat Samuelov**	Pachyonychia congenita (PC) is a group of autosomal dominant disorders caused by mutations in one of 5 keratin genes (KRT6A, KRT6B, KRT6C, KRT16, or KRT17). The establishment of an international registry containing both clinical and molecular data led to the development of a disease classification based on the mutant gene and associated features. Here we harnessed the same resource to clarify the prevalence of PC-associated clinical features, delineate phenotype-genotype correlations and identify prognostic features for disease severity. 815 individuals with confirmed keratin mutations registered in the International Pachyonychia Congenita Research Registry (IPCRR) were surveyed for clinical findings associated with PC. Data were analyzed using Student T-test, Chi-Square, ANOVA tests (for differences in means/proportions), Spearman correlation, logistic regression (for phenotype-genotype correlation) and Kruskal–Wallis tests. KRT6A mutations were most common and evident in 40% of cases. Plantar keratoderma and toenail dystrophy were the most common clinical findings, with plantar keratoderma most significantly affecting patient's quality of life. KRT6A mutations were associated with young age of onset, high number of fingernails/toenails involvement, oral leukokeratosis and hoarseness. Cysts and natal teeth were most common among patients carrying KRT17 mutations. In addition, we looked for statistically significant associations between genetic variants and clinical manifestations in a subgroup of patients carrying mutations found in at least 10% of the cohort. The KRT16 p.L132P mutation was significantly associated with younger age of onset, presence of palmar keratoderma oral leucokeratosis and a higher number of involved nails. By contrast, the KRT16 p.N125S and p.R127C mutations resulted in a milder phenotype featuring a decreased number of involved nails and older age of onset. Patients carrying the p.N125S mutation were less likely to develop palmar keratoderma while p.R127C was associated with an older age of palmoplantar keratoderma onset. Moreover, the KRT17 p.L99P mutation resulted in an increased number of involved fingernails and patients demonstrating 20-nail dystrophy, while the opposite findings were observed with KRT17 p.N92S mutation. Our study reveals novel and clinically useful prognostic predictors in PC, and more generally demonstrates the importance of large registry-based careful studies in rare disorders.
Spatial transcriptomics of iRhom2 mouse model paw skin. **Diana Blaydon**	Gain-of-function mutations in RHBDF2, the gene encoding the inactive Rhomboid protease iRhom2, underlie Tylosis with Oesophageal Cancer (TOC). TOC is characterised by a focal palmoplantar keratoderma (PPK) in association with oral and oesophageal lesions and a high lifetime risk of developing oesophageal cancer. We have shown that iRhom2 has an important role as an epidermal stress response protein, including in regulation of the stress-associated keratin 16. We have generated a CRISPR-Cas9 knock-in mouse model of TOC, which develops hyperkeratotic lesions on its footpads, similar to the focal PPK observed in TOC affected individuals. In contrast, Rhbdf2-/- mice display significantly thinner paw epidermis. We have applied spatial transcriptomics to the paw skin of these iRhom2 mouse models to gain additional insight into the role of iRhom2 in the stressed palmoplantar/paw epidermis.

2021 IPCC PRESENTATION ABSTRACTS

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Structural modeling guided understanding of genotype- phenotype correlation in PC **Joyce Teng, Christopher Bunick**	Genotype-structurotype-phenotype correlations seen with mutations in keratin genes (KRT6A, KRT6B, KRT6C, KRT16, KRT17) were investigated utilizing protein structure modeling. The functional importance of high frequency mutations in keratin structural domains were analyzed. Participants of the International PC Research Registry underwent genetic testing and completed a standardized survey on their symptoms. Our results support prior reports that painful keratoderma was prominent with KRT6A and KRT16 mutations. Nail involvement was most common in KRT6A and least common in KRT6C patients. Across keratin subtypes, patients with coil 2B mutations have greatest impairment in ambulation, while coil 1A domain is the mostly common affected region among all PC subtypes and affected patients frequently report emotional issues. Molecular modeling demonstrated that hotspot missense mutations in PC largely disrupted hydrophobic interactions or surface charge. The former may destabilize keratin dimers/tetramers, while the latter likely interferes with higher-order keratin filament formation. Understanding pathologic alterations in keratin structure provides insights to disease pathogenesis, severity and therapeutic development.
Toward a chemical compound-based therapy approach for EBS **Thomas Magin** **Kinase inhibition prevents epithelial damage in epidermolysis bullosa simplex via keratin and cell contact stabilization.** **Katrin Rietscher, Heinz-Georg Jahnke, Eric W. Lin, Cristina Has, M. Bishr Omary and Thomas M. Magin**	Epidermolysis bullosa simplex (EBS) is a dominantly inherited skin disorder caused by mutations in keratins K5 or K14 and occurs at a frequency of 1:20.000. Keratin proteins protect the epidermis against mechanical and chemical insults by forming an extensive cytoskeleton which is anchored to desmosomes to provide strong cohesion among epidermal keratinocytes. Severe K5 or K14 mutations collapse the cytoskeleton into cytoplasmic keratin aggregates, causing profound keratinocyte fragility and cytolysis. In severe EBS this leads to extensive epidermal blistering, pronounced inflammation and itch, complications which are potentially life-threatening. Given the absence of curative treatments, insights in the molecular pathology are crucial to devise rational EBS therapies. We and others have observed that several EBS-associated keratin mutations are accompanied by elevated keratin phosphorylation, a condition known to compromise the stress resilience of the keratin cytoskeleton. We hypothesize that elevated phosphorylation of keratins or of keratin-associated proteins such as constituents of desmosomes and of the actomyosin cytoskeleton, act in conjunction with EBS-associated keratin mutations to aggravate the EBS condition. Thus, the pharmacological inhibition of EBS-associated phosphorylation should represent a viable strategy for the treatment of EBS using local or systemic delivery of appropriate chemical compounds. This will not cure EBS but significantly improve the quality of life of patients. We examined select compounds known to interfere with protein aggregation by treating EBS and normal human keratinocytes for 24-48h. As a readout, keratin organization and aggregation were monitored by indirect immunofluorescence. Compound C1, already in clinical use, reduced keratin aggregation by 40% in patient-derived K14.R125C EBS-associated keratinocytes. C1 restored a functional and shear stress-resilient keratin cytoskeleton in an established epithelial sheet assay. Real-time impedance spectroscopy demonstrated a significant increase in impedance in PKC412-treated EBS-associated keratinocytes, supporting an improvement of epithelial cell junctions. In my talk, I will discuss potential C1 targets and their relevance for the treatment of EBS.

Thank You!

On behalf of PC patients worldwide, thank you for sharing your time and talents with us!