PC PROJECT ANNOUNCES
CHANGE IN MSAB AND IPCC
Since the founding meeting of the International PC Consortium (IPCC) in February 2004, many good things have been achieved through the IPCC. Members of the IPCC serve on the Medical and Scientific Advisory Board (MSAB) for PC Project and have provided consistent guidance to PC Project in patient support, the PC research registry, research projects and clinical studies. During these years, Sancy Leachman (one of the founding members of the IPCC) has contributed greatly to the success of these efforts. Dr. Leachman was the clinician for the 2008 clinical trial sponsored by PC Project, she has conducted more than 100 consultations for PC patients and has been co-author on many PC publications.

At this time, Dr. Leachman is heading a number of melanoma-related projects and grants and has asked to be involved “as a less active ‘specialty’ member for selected areas of expertise.” Sancy writes “I want to let everyone know how much I have enjoyed working with this group and how special the experience has been for me. I don’t think many people ever get this kind of opportunity and I feel truly privileged to have been a part.” Sancy also expressed her support for “the strong team that has been assembled (and is functioning so well).” We appreciate all that Sancy has contributed and look forward to her continued involvement with the IPCC. Her expertise will continue to be needed and utilized.

We welcome Eli Sprecher, MD, PhD (Tel Aviv, Israel) as IPCC Chair for 2011-2012. Also, Amy Paller, MD and Maurice van Steenest, MD, PhD have joined the PC MSAB. The May 2011 IPCC meeting will focus on setting the next goals for the IPCC and organizing to achieve those goals over the next years.

International PC Consortium (IPCC)
Annual Symposium
May 3-4 (Tuesday all day and Wednesday AM only) prior to SID
SID Translational Research Session will be Wednesday PM
JW Desert Ridge and Resort, Phoenix, Arizona
Please register to attend the meeting http://www.pachyonychia.org.
We have a few openings for speakers; please contact Mary Schwartz.

Pachyonychia Congenita Patient Support Meeting
August 5-7 (Friday evening, Saturday all day, Sunday AM only)
Philadelphia, Pennsylvania
We invite all physicians and scientists interested in PC or related keratin/skin disorders to the meeting.
We expect approximately at least 50 genetically-confirmed Pachyonychia Congenita patients will participate.
Please register to attend the meeting http://www.pachyonychia.org.

Editors Comment
We recognize the need for better delivery for effective treatments for PC and other skin disorders. Therefore, although not an IPCC meeting, we feel it is important to share with IPCC members the abstracts from the GO Delivery! Grant (NIH/NIAMS under ARRA funding) Second Annual Conference held Feb 10-12, 2011 in Park City, Utah.

Everyone is invited to participate in the GO Delivery! and test specific delivery methods. For further information contact Roger.Kaspar@TransDermInc.com.

GO Delivery! 2nd Annual Conference
KEYNOTE SPEAKERS
Irwin McLean, PhD, DSc, FRSE, University of Dundee. Small molecule and siRNA therapy for inherited skin disorders. The past two decades have seen tremendous progress in our understanding of skin diseases where a single gene is causative (monogenic disorders) or more recently, where multiple genes plus environmental factors are involved (complex traits such as atopic eczema). In the dominantly inherited keratin disorders including epidermolysis bullosa simplex (EBS), pachyonychia congenita (PC) and Meesmann epithelial corneal dystrophy (MECD), the mechanism is dominant-negative interference i.e. one copy of the gene is mutated, producing defective protein that binds to and interferes with the function of the normal protein present. An attractive way to treat these disorders is to exploit short-interfering RNA to selectively inactivate the mutant allele and allow the normal allele to function, which we are developing for EBS, PC and MECD. Alternatively, it may be possible to find small molecules to modulate keratin expression in a therapeutic direction. By chemical library screening, we recently showed that statins unexpectedly have an impact on keratin gene expression, which may be useful in some keratin disorders, such as PC. In atopic eczema, we identified filaggrin as a major predisposing gene. We are currently pursuing two small molecule drug discovery programmes aimed at restoring or enhancing filaggrin expression in the skin.
One of these projects, aimed at developing drugs to rescue nonsense mutations, is much more widely applicable in the genodermatology and genetics fields.

Amy Paller, MD, Northwestern University. Is genotyping important for the diagnosis and treatment of genetic skin disease?: issues and implications. During the past 30 years, the underlying genetic basis for more than 2000 genetic disorders has been discovered; approximately 20% of these disorders involve the skin and could be impacted by cutaneous gene therapy. These discoveries have improved our understanding of the basic science of skin function, helped us to untangle genotype/phenotype relationships, led to new classifications within groups of genodermatoses, allowed prenatal and preimplantation diagnosis, and provided the opportunity to initiate new therapeutic approaches, including cutaneous delivery of siRNA. However, to date, few individuals affected by genetic disorders involving the skin have been impacted in their clinical care by these gene discoveries. In fact, the minority of individuals in the U.S. with genodermatoses are aware of the underlying genetic basis for their own disease. The primary reason is the current cost of commercially available gene analysis and the difficulty in obtaining insurance coverage for genotyping. The lower cost of genotyping as a result of next generation sequence technology and the availability of targeted gene therapy interventions in the near future, including through siRNA delivery, will revolutionize our evaluation and management of patients with genetic skin disorders.

Dennis Roop, PhD, University of Colorado Denver. Exploring the therapeutic potential of induced pluripotent stem (iPS) cells for inherited skin diseases: an update. Besides symptomatic care, no effective therapeutic treatment is available for inherited skin diseases. Therefore, a stem cell/gene therapy based approach is the only option for a permanent corrective therapy for patients who suffer from these diseases. The discovery that adult human skin cells could be reprogrammed into an embryonic stem cell (ESC)-like state has had a dramatic effect on the fields of stem cell biology and regenerative medicine. The therapeutic potential of such induced pluripotent stem cells (iPSC) for tissue repair and regeneration is enormous. This procedure not only eliminates ethical concerns associated with generating ESCs from fertilized human embryos, but it also enables the delivery of truly personalized medical treatment since the iPSC would be generated from the same individual in need of treatment. Furthermore, the therapeutic use of cells derived from a patient’s own iPSC would potentially avoid the complication of immune rejection, which might occur if cells were derived from ESCs. Before iPSC can be considered for the treatment of inherited skin diseases, methods must be developed for the efficient differentiation of iPSC into keratinocyte lineage. We have now succeeded in developing a method for the efficient differentiation of mouse iPSC into functional keratinocytes capable of reconstituting a normal stratified epidermis, hair follicles, and sebaceous glands when grafted onto mice. This enabling technology will allow us to assess the feasibility of using iPSCs for the treatment of inherited skin disorders, using our genetically engineered mouse models that mimic these diseases.

ABSTRACTS

James Birchall, PhD, Cardiff University
Tycho Speaker, PhD, TransDerm Inc.
Microneedle delivery of nucleic acids.
Microneedles represent a simple and minimally-invasive method for depositing nucleic acids through the outer skin barrier for therapeutic applications. Whilst microneedle-assisted nucleic acid delivery has been reported previously further studies are required to ensure that clinical microneedle use will be effective and reproducible, i.e. the right device delivers the right amount of DNA to the right target at the right time, every time. We aim to contribute to this prospect through i) Employing novel imaging techniques to determine how various microneedle designs perform in human volunteers, ii) Using excised human skin to monitor the effectiveness of microneedle-assisted DNA delivery, iii) Conducting direct comparisons of nucleic acid delivery efficacy (reporter plasmid expressing luciferase/GFP fusion protein) from two microneedle array delivery platforms; soluble protrusion array devices (DNAwithin needle) and stainless-steel microneedle patches (DNAon needle), iv) Engaging with healthcare practitioners and the general public to capture the opinions of potential end-users of microneedle technology. An update on our progress in all of these areas will be presented, with particular reference to GO studies that demonstrate significant and continued levels of bioluminescence following both types of microneedle application and individual keratinocytes expressing GFP both in mouse and human skin equivalents grafted on immunocompromised mice (xenografts).

REMARKS

Carl Baker, MD, PhD, NIAMS/NIH.
Grand Opportunity (GO) skin delivery project. The availability of ARRA funds has provided a unique opportunity for NIH to fund worthy projects that might not otherwise have come into consideration. In particular, the Grand Opportunity program has allowed funding of projects such as this one that is allowing development of common reagents and skin models systems that will be made available to the research community to facilitate development of skin delivery technologies.

Erika Geihe, BA / Christina Cooley, BA, Stanford University. Guanidinium-rich molecular transporters (GR-MoTrs) for direct and microneedle assisted delivery of siRNA. GR-MoTrs have been shown to carry a wide range of molecular cargos across biological barriers, including small molecules, peptides, proteins, plasmids, probes, metals and imaging agents. We have recently developed a strategy that allows for the rapid synthesis of libraries
of modified GR-MoTRs that differ by design in their composition and thus ability to complex and transport various cargos. The synthesis and evaluation of a novel series of amphiphatic carbonate co-oligomers will be described including their ability to both bind and deliver unmodified siRNA into human keratinocytes. As a prelude to the application of this delivery strategy to dermatologic indications, we have also designed an assay to evaluate microneedle assisted delivery of GR-MoTR-conjugates in real time in mice. This hybrid technology has important ramifications for research and clinical use.

Emilio Gonzalez, PhD, Stanford University. Imaging of reporter gene expression in skin for optimization of nucleic acid delivery tools. Intravital imaging can be used to reveal the extent of delivery and patterns of gene expression in live animals over time. In vivo bioluminescence imaging (BLI) provides macroscopic patterns of gene expression and can be used for in vivo quantification of gene transfer, but the low resolution of this method prevents localizing cells that express the reporter gene within the tissue. In contrast, intravital fluorescence confocal microscopy is a high resolution imaging modality that can be used to localize fluorescent cells within the tissue and complements BLI. Confocal reflectance imaging of skin is currently used for clinical diagnostics (due to its high resolution that allows cell identification by morphological features (keratin, melanin, etc) but not functional information. Here we used BLI as a guide for imaging with a dual-mode (fluorescence and reflectance) confocal intravital microscope (VivaScope 2500) to study epidermal plasmid delivery. This was done using expression from reporter plasmids that were administered via intradermal (ID) injection. Various ubiquitous, constitutive promoters were evaluated and the optimal construct, from these comparisons, was selected. Using the VivaScope 2500 we have been able to identify and localize individual keratinocytes expressing green fluorescent protein (GFP) within the epidermis in mouse skin as well as human xenografts. These complementary imaging systems provide the foundation of a rapid noninvasive approach to validate different delivery technologies both globally, by BLI, and locally, with GFP expression in cells of the epidermis.

Robyn Hickerson, PhD, TransDerm Inc. Evaluation of siRNA delivery using an inducible reporter model. The development of siRNA therapeutics for treatment of skin disorders is hampered by delivery considerations. Despite recent progress in the development of in vivo delivery reagents and initiation of clinical trials for a number of indications, including those of the skin, there is a clear need for better delivery systems and more effective screening systems. We have developed an inducible model system in which siRNA delivery results in a positive outcome (light emission) rather than inhibition (as is traditionally monitored), which is more difficult to detect and quantify. This de-repression system uses a modified tetracycline (tet)-regulated system in which luciferase-2/ enhanced green fluorescent protein (Luc2/EGFP) bicistronic reporter expression is controlled by the interaction of the Tet-cycline-controlled Transcription Silencer (tTS) with the Tet Response Element containing seven repeats of the tet operator cloned into the human ubiquitin C promoter. Co-transfection of the reporter and repressor constructs results in repression of Luc2/EGFP expression. Reduction of intracellular tTS levels by delivery of TTS-specific siRNA de-represses reporter gene expression, which can be visualized using bioluminescence and fluorescence imaging.

Gunilla Jacobsen, PhD, Stanford University. Nanoparticle delivery of nucleic acids. Our work involves development of biodegradable nanoparticles (NPs) for delivery of pharmaceuticals with the goal to achieve sustained release as well as target specific delivery. In this presentation I will focus on results and methods specifically relevant to the delivery of siRNA. We have previously shown results of gene silencing using transdermal injection polymeric NPs, but were also left with several challenges to move forward such as (1) NP agglomeration, (2) NP size, and (3) need of shorter release times to obtain in vivo data using relevant mouse models. Another important aspect is delivery method and finding ways to avoid needle injections. An update on our approach will be presented, including the use of lipid NPs and a range of new polymers.

Dan Koon, BA, Lucid, Inc. In-vivo confocal microscopy of skin: applications in dermatology, industry, and pre-clinical research. Imaging is becoming an increasingly important tool for dermatologists who perform skin cancer detection and diagnosis, for researchers developing treatments for skin disease, and for industry scientists developing consumer skin products. Mounting evidence shows that physicians and researchers require more advanced methods for identifying skin disease. Simply put: we need better tools. Lucid, Inc. has pioneered in-vivo reflectance confocal microscopy (RCM). Its products, called VivaScopes®, provide a “window” for cellular imaging of skin and other living tissues for clinical dermatology and basic and clinical research applications. This “optical biopsy” technology is entirely noninvasive. Both reflectance and fluorescence confocal laser scanning microscopy are possible in certain multi-laser VivaScopes. This makes possible the use of various fluorophores to produce additional contrast during the imaging process. Lucid’s confocal microscopes are utilized across a broad spectrum of applications: human skin in vivo, excised tissue, and, recently, small animals. Researchers using these devices have published over 200 studies in refereed medical and scientific journals, presented dozens of invited talks, and innumerable other presentations at scientific and medical conferences. An overview of the technology and the applications within dermatology, industry, and research will be presented.

Maria Fernanda Lara, PhD, TransDerm Inc. Use of self-delivery siRNA loaded microneedle arrays to target CD44 in human skin.
skin models. Despite rapid progress in developing small interfering RNA (siRNA) as therapeutic agents to treat skin disorders, translation to the clinic has been hampered by two major delivery hurdles: the stratum corneum barrier and cellular uptake. Delivery (pressure mediated) of siRNA by intradermal injection results in effective knockdown of targeted gene expression but is painful and the effects are localized to the injection site. Our recent work demonstrated that self-delivery (sd) modified siRNA (Accell technology from Thermo Scientific, Dharmacon) does not require high pressure for in vivo delivery to mouse skin, making it attractive for patient-friendly delivery strategies. In this work, we have used sd-siRNA to target the endogenous human gene CD44. First, we treated human epithelial equivalents in vitro with CD44 sd-siRNA. A reduction of 70% of CD44 mRNA levels was observed in epidermal equivalents as measured by RT-qPCR relative to unmodified CD44-specific siRNA. Furthermore, daily treatment (over 10 days) of full-thickness human skin equivalents (Stratapex), grafted on immunocompromised mice, with micro needle arrays loaded with CD44 sd-siRNA resulted in 40-50% reduction of CD44 mRNA levels compared to grafts treated with ds-nonspecific siRNA. Further experiments using full-thickness human skin (from abdominoplasty surgeries) grafted on immunocompromised mice were underway. Taken together, these results demonstrate that sd-siRNAs are able to inhibit target gene expression in human skin models.

Devin Leake, PhD, Thermo Fisher Scientific. Overview/applications of Accell siRNA technology. To address delivery issues with RNAi molecules, we have developed a novel siRNA, named Accell siRNA, that is capable of cellular delivery without the use of other reagents (e.g. lipid solutions). This siRNA technology incorporates a chemical modification pattern that allows for both cellular uptake and targeted gene silencing. My presentation will provide an overview of the molecule's development and recent biological applications in vitro targeting TNFα, and in vivo targeting an antiapoptotic protein, KLF6, in an ovarian cancer model.

Michael Mandella, PhD / Hyejung Ra, PhD, Stanford University. New confocal designs and skin applications. Advancing molecular therapies for the treatment of skin diseases will require the development of new tools that can reveal spatiotemporal changes in the microanatomy of the skin and associate these changes with the presence of the therapeutic agent. For this purpose, we have evaluated a handheld dual-axis confocal (DAC) microscope that is capable of in vivo fluorescence imaging of skin, using both mouse models and human skin. Individual keratinocytes in the epidermis were observed in three-dimensional image stacks after topical administration of near infrared (NIR) dyes as contrast agents. This suggested that the DAC microscope may have utility in assessing the clinical effects of a siRNA-based therapeutic (TD101) that targets the causative mutation in pachyonychia congenita (PC) patients. The data indicated that (i) formulated indocyanine green (ICG) readily penetrated hyperkeratotic PC skin and normal calloused regions compared to non-affected areas, and (ii) TD101-treated PC skin revealed changes in tissue morphology consistent with reversion to non-affected skin compared to vehicle-treated skin. In addition, siRNA was conjugated to NIR dye and shown to penetrate through the stratum corneum barrier when topically applied to mouse skin. New confocal designs that will further the capability and utility of in vivo microscopic imaging is presented. These developments may enable an informative clinical endpoint to evaluate the efficacy of experimental molecular therapeutics.

Alison McBride, PhD, NIH/NIAID. Human keratinocytes are efficiently immortalized by a Rho kinase inhibitor. Primary human keratinocytes are useful for studying the pathogenesis of many different diseases of the cutaneous and mucosal epithelium and represent the ideal model for studying HPV infections in vitro. However, primary keratinocytes have a finite lifespan in culture that limits their proliferative capacity and clinical utility. We have found that treatment of primary keratinocytes, from several anatomical sites; with a Rho Kinase (ROCK) inhibitor greatly increases their proliferative capacity and results in efficient immortalization without detectable cell crisis. More importantly, the immortalized cells display characteristics typical of primary keratinocytes; they have a normal karyotype, an intact DNA damage response and are able to differentiate into a stratified epithelium. This is the first example of a defined chemical compound mediating efficient cell immortalization and this finding could have wide-ranging investigational and medical applications.

Xavier de Mollerat du Jeu, PhD, Life Technologies. Invivoj ectam ine® 2.0, new commercially available, reagent for in vivo delivery of siRNA. Delivering RNAi duplexes to the appropriate tissue remains a major bottleneck for the development of in vivo RNAi. In this study, we describe the development of Invivoj ectam ine® 2.0 a new in vivo delivery reagent, as well as Ambion® in vivo siRNA, a new highly potent and stable siRNA. After a single intravenous injection of 5mg/kg Factor VII siRNAs complexed Invivoj ectam ine® 2.0, we observed 90% mRNA and protein level reduction in liver for more than 3 weeks. We confirmed this mediated siRNA cleavage by 5’-RLM RACE and show a dose dependent effect with an EDS of <1mg/kg. In addition, we were able to knockdown 4 genes at the same time after a single injection of a mix of different siRNA complexed with Invivoj ectam ine® 2.0. We also demonstrated that Invivoj ectam ine® 2.0 can be delivered to other organs depending of the route of delivery used. Finally, Invivoj ectam ine® 2.0/ siRNA complex is safe and did not trigger any IFN response or liver toxicity.

Faye Rogers, PhD, Yale University. Triplex-forming PNA-peptides induce gene-targeted modification of stem cells. Gene correction of human genetic skin disorders represents a potentially effective strategy in the treatment of diseases that
have proven resistant to traditional small molecule therapies. During recent years, molecules such as triplex-forming oligonucleotides (TFOs) and peptide nucleic acids (PNAs), which bind sequence-specifically to duplex DNA, have been developed to selectively modulate gene expression. We have proceeded to expand upon this technology by investigating the ability of translocating peptides to enhance the epidermal delivery of such antigen agents. Several TFO/PNA peptide conjugates were designed to bind to the supFG1 reporter gene, which was used as a model system to measure epidermal chromosomal gene targeting. Specifically, we have investigated the ability of a covalently linked transport peptide fragment derived from the Drosophila protein, antennapedia (Antp), to improve the biodistribution of PNAs in the skin of transgenic mice, as measured by an assay for gene-targeted mutagenesis. Treatment of mice by intraperitoneal injection with a PNA-Antp conjugate induced targeted mutations in both the dermal and epidermal layers of the skin. Studies were also initiated to establish whether intradermal injection would be a more effective method of administration for delivery of these molecules to the epidermis. Results indicate that administration via this method dramatically improved the gene targeting capability of the PNA-Antp molecules, with a more than 10-fold increase of chromosomally induced epidermal mutations. Taken together, the results demonstrate that PNA-peptide conjugates can be effective reagents for in vivo gene targeting of skin disorders that affect the epidermis.

Janice Schwartz, PC Project - The need for “patient-friendly” delivery. The rare skin disorder pachyonychia congenita (PC) is an autosomal dominant syndrome that includes a disabling plantar keratoderma for which no satisfactory treatment is currently available. We have completed a phase Ib clinical trial for treatment of PC utilizing the first short-interfering RNA (siRNA)-based therapeutic for skin. This siRNA, called TD101, specifically and potently targets the keratin 6a (K6a) N171K mutant mRNA without affecting wild-type K6a mRNA. The safety and efficacy of TD101 was tested in a single-patient 17-week, prospective, double-blind, split-body, vehicle-controlled, dose escalation trial. Randomly assigned solutions of TD101 or vehicle control were injected in symmetric plantar calcanei on opposite feet. No adverse events occurred during the trial or in the 3-month washout period. Subjective patient assessment and physician clinical efficacy measures revealed regression of callus on the siRNA treated, but not on the vehicle-treated foot. This trial represents the first time that siRNA has been used in a clinical setting to target a mutant gene or a genetic disorder and the first use of siRNA in human skin. The callus regression seen on the patient’s siRNA-treated foot appears sufficiently promising to warrant additional studies of siRNA in this and other dominant-negative skin diseases.

Dmitry Samarsky, PhD, RXi Pharmaceuticals. Self-delivering RNAi compounds (sdrRNA): chemistry, in vivo efficacy and preclinical development for skin indications. Delivery is a major challenge for the development of RNAi therapeutics. To address it, RXi has developed a novel class of RNAi compounds termed “self delivering rRNA” or sDR RNA™, that combines beneficial properties of the RNAI and conventional antisense technologies. The combination enables robust cellular uptake of the molecules and silencing of the target genes. In vivo efficacy achieved using local administration of the new compounds, and potential clinical applications, including ophthalmic and dermal, will be discussed.

Gretchen Unger, PhD, GeneSequess, Inc. Passive topical administration of nucleic acids to skin by cell-targeted sub-50 nanometer capsules. Passive topical administration of nucleic acid drugs and vaccines is a desirable goal for patient-friendly manipulation of target cells in the skin. However, two major delivery challenges that have impeded development are 1) penetrating the stratum corneum, and 2) avoiding endosomal entrapment and degradation. GeneSequess has developed a novel sub-50 nanometer (s50) nanocapsule technology to deliver intact nucleic acids to intracellular sites in target cells. s50 capsules are directed to specific tissue and cells by formulating appropriate targeting proteins, peptides or antibody ligands to the crystallized capsule shell. The size and structure of s50 capsules allows for efficient penetration of the stratum corneum and, by co-opting the non-endosomal “lipid raft” pathway, intact delivery of nucleic acid cargo to the nucleus and cytoplasm of the target cell. Here we show in pilot studies using pig dermis organ culture as an established model for human skin, transcutaneous passage of plasmid-bearing s50 capsules with cell-specific targeting. We extended these studies of passive cutaneous delivery, using plasmid-bearing, fibronectin-coated s50 capsules, to in vivo time-course studies in murine paws where stratum corneum layers in footpads are approximately 50 um thick, demonstrating uniform transfection of underlying basal keratinocytes. In a further extension, using hyaluronan-coated s50 capsules together with a novel adjuvant, we demonstrated a functional response to model antigen after passive topical DNA vaccine administration in weanling pigs. Skin is a powerful immune organ, not conveniently addressed by current vaccination methods such as electroporation. Based upon these promising results, GeneSequess is pursuing further development of s50-mediated cutaneous delivery technology for nucleic acids.
INTERNATIONAL PACHYONYCHIA CONGENITA CONSORTIUM (IPCC)
Eli Sprecher, MD, PhD, IPCC Chair
The IPCC physicians and scientists agree to work together to develop PC therapeutics.

DIAGNOSTICS AND GENETICS TEAM — FRANCES J.D. SMITH, PhD, Chair
Sheri Bale, C. David Hansen, Leonard M. Milstone, Peter R. Hull, Jean Y. Tang

RESEARCH TEAM — ROGER L. KASPAR, PhD, Chair
James Birchall, Jiang Chen, Christopher Contag, Marcela Del Rio, Marianna Foldvari, Daniel J. Gibson, Emilio G. Gonzalez, Richard Heller, Robyn P. Hickerson, Yeu-Chun Kim, E. Birgitte Lane, Maria Fernanda Lara, Fernando Larcher, Irene M. Leigh, W.H. Irwin McLean, Leonard M. Milstone, Samir Mitragotri, Dennis R. Roop, Frances J.D. Smith, Tycho Speaker

PHYSICIAN NETWORK — ELI SPRECHER, AMY S. PALLER, MAURICE VAN STEENSEL – Co-chairs

Open Membership: Physicians and Scientists interested in collaborations for PC Therapies

Special Needs MSAB/IPCC

2386 East Heritage Way, Ste B, Salt Lake City, UT 84109 · www.pachyonychia.org · Phone 877-628-7300 · Email: info@pachyonychia.org
IPCC 8th Annual Scientific Symposium
Eli Sprecher, IPCC chairman, led a successful IPCC meeting in Phoenix, AZ on May 3-4 (just prior to the 2011 SID). We were pleased to have special guest, David Lane, attend the sessions and share comments. Special thanks to John McGrath and Sancy Leachman for interviews for the keynote address. Each attendee contributed to the progress and success of the IPCC efforts.

Goals Set for IPCC Physician Network
Headed by co-chairs Eli Sprecher, Amy Paller and Maurice van Steensel, the IPCC Physician Network (one of three working groups in the IPCC) set goals for 2011-2012 as follows:
- Public awareness and physician awareness
- Standard of care guidelines
- Multicenter clinical trials

Over the past years, ground-breaking advances have been made in PC therapeutics, with the application of novel technologies such as siRNA and the translation of basic findings into innovative therapeutic options (as for rapamycin). Despite this progress, it is clear that in order to reach definitive conclusions regarding treatment effects, controlled data are needed.

The limited number of eligible PC patients, the fact that they are living far apart, clinical and genetic heterogeneity in PC as well as country-specific variations in clinical trial-related regulations, all represent obstacles to the conduct of trials of sufficient size to reach statistically meaningful conclusions.

In an attempt to overcome some of these problems, a coordinated action between all IPCC members is mandatory. A possible strategy was put forward during the meeting, which is summarized in the figure.

What do you think?
Please send your ONE best idea for a multi-center clinical trial via email to info@pachyonychia.org. Once ideas are gathered, the steering committee will be organized. We have some data that suggests the following are all good candidates for a major clinical study:
- Glycopyrrolate (anticholinergic drug)
- Self-delivery siRNA
- Simvastatin
- Simvastatin AND either oxybutinin or tolterodine (anticholinergic drugs)
- Topical rapamycin

Other things that have been suggested or tried include: topical botox (under development; not yet available); topical ibuprofen (for pain; not FDA approved in US); gabapentin (proposed pain study to begin in August at the Patient Support Meeting may help determine what drugs may be most effective for which patients).

Best Practice Guidelines
At the IPCC meeting, Amy Paller led the discussion on developing ‘best practice’ guidelines. It was agreed that a survey needs to be conducted to gather additional information both
from patients and from physicians. The IPCC members divided into sections and questions for the two surveys were drafted. Immediately after the meeting, the surveys will be circulated to genetically confirmed PC patients in the IPCRR as well as to all physicians registered with PC Project.

**IPCC MEETING SUMMARY**

In addition to the Physician Network session on Wednesday, presentations and discussions were held on Tuesday with other IPCC working teams.

On Tuesday evening, IPCC members and guests were treated to an exquisite dinner at the private estate of one of the PC patients. A full measure of southwestern culture and hospitality was enjoyed including dinner by moonlight around the lovely pool landscaped with many varieties of cacti and other native plants.

**Frances Smith, Chair of the IPCC Diagnostics working team,** gave an update on the genetic analysis of new cases of PC. The reclassification of PC that was proposed at the 2010 IPCC symposium was discussed. Due to the clinical overlap between PC-1 and PC-2 a new molecular classification has been adopted where the subtypes of PC refer to the mutated keratin gene, for example PC-6a for a patient carrying a K6a mutation, PC-6b, PC-16, PC-17 and so on. PC-U will be used for cases where the causative gene is unknown.

Mutations in KRT6A account for almost 50% of published cases of PC, 24% of mutations are in KRT16, 23% in KRT17, 3% in KRT6B and 1% in KRT6C. Overall there are more than 85 different PC mutations. The majority of mutations are missense mutations, with a smaller number of insertion/deletion mutations and splice site mutations.

Two unusual cases were reported where individuals were found to be homozygous for dominant mutations in KRT17. In one family the offspring was from a known consanguineous marriage between two affected parents. Both mutations are known mutations in KRT17, but these are the first cases of homozygosity of a dominant mutation in a PC– associated gene. Clinically, individuals homozygous for the mutations were more severely affected than family members that were heterozygous for the respective mutation.

Unusually the homozygous individuals also presented with alopecia. Alopecia has not previously been associated with genetically confirmed cases of PC. However, since K17 is expressed in the hair follicle as well as other epidermal appendages it is possible that a homozygous missense mutation results in greater fragility of epithelial cells expressing K17 leading to a more widespread and severe PC phenotype that includes hair abnormalities.

Other presentations in the diagnostic section included:

- **Gabrielle Richard**—New approaches to the diagnostics of genodermatoses
- **Takashi Hashimoto**—Studies in Japan on PC and related keratin diseases
- **Adam Rubin**—PC Nails: Data regarding nails from 101 patients with pachyonychia congenita
- **Keith Choate**—Revertant mosaicism in ichthyosis with confetti
- **Jean Tang/Katrina Spanhurst**—Phenotypic differences between pachyonychia congenita patients with mutations in K6a and K16.

Conclusions: Phenotypic differences between patients with K6a and K16 mutations support adoption of a new classification system based on the mutant gene (PC-6a, PC-16). In addition, further information on successful treatment methods used by PC patients must be explored.

**Roger Kaspar, IPCC Chair of the Research Studies working team** gave an update on exciting work on topical rapamycin as well as on the GO Delivery! Grant which involves TransDerm, Inc., Stanford University and Yale University. Roger reported continued efforts into what is the most challenging hurdle remaining to develop siRNAs into an effective option—delivery!

As part of the GO Delivery! consortium, delivery technologies continue to be tested at TransDerm, including new ideas that have come forward in the past few months. In addition, a manuscript was recently submitted by Emilio Gonzalez (lead author of many that participated on the effort) that describes the resources available through the consortium for testing nucleic acid delivery as well as the ability of two microneedle delivery systems to deliver expression plasmids.

For those of you that are not familiar with the GO Delivery! project, there is a wealth of information available at a Wiki site that has been set up at www.go-delivery.com. The site is password protected but if you send an email to Andrea Burgon at andrea.burgon@transderminc.com, she will quickly send you a password.
Other presentations in the research studies section included:

**Fernando Larcher**—Modulating effect of normal fibroblasts on the PC phenotype in vivo

**Jiang Chen**—Exograft models for inheritable skin disorders caused by keratin mutations

**Kellie White**—Irritant injury as field injury: roles of ATP and EGFR

Numerous diseases manifest at sites of injury. Termed the Koebner Phenomenon, the mechanism behind this observation remains undefined. We have developed an in vitro system for studying the mechanism of irritant contact dermatitis using the model irritant sodium lauryl sulfate (SLS). SLS causes activation of the epidermal growth factor receptor, which occurs at least in part through release of ATP and activation of purinergic receptors on keratinocytes. ATP is known to be released by cells during times of injury. We believe treatment with SLS induces a general "field" injury to cells and that our model can be used to potentially explain why skin diseases may be induced by and localize to sites of injury.

**Hector Zambrano** — Gene Targeting of Chromosomal Keratin 6a Gene in Cells Using Small Oligonucleotides.

The use of triplex-forming oligos (TFOs) to foster introduction of sequence-specific alterations in chromosomal genes is well-established. The goal of the present work is to identify TFOs that enhance the frequency of KRT6a targeting. We conclude that some, but not all, keratin 6a sequence-specific TFOs enhance chromosomal gene targeting in reporter cells.

**JeanChristopher Chamcheu**—Development of effective therapies for keratin genodermatoses: concepts and lessons learned from EBS, EI and PC.

Hereditary keratin disorders of the skin and its appendages (hair, nail, palm, sole etc.) comprise a large group of clinically heterogeneous disfiguring blistering and ichthyotic diseases, primarily characterized by loss of tissue-specific integrity, blistering and hyperkeratosis in severely affected tissues, resulting from pathogenic mutations in keratin genes.

In concert these mutations with characteristic features have formed the basis for improved disease diagnosis, prognostic implication with recent proof-of-concept in therapy development. Typical examples include epidermolysis bullosa simplex (EBS), keratinopathic ichthyoses (KPI), pachyonychia congenita (PC) etc. Our Understanding the molecular genetic events underlying skin dysfunction has realistically initiated alternative treatment approaches which may provide novel therapeutic opportunities beneficial for affected patients. Animal and in vitro disease modeling studies have shed more light on in-depth knowledge of molecular pathogenesis, further defining the role of keratins in disease processes. Several such currently emerging models are useful steps towards the translational development of new gene and pharmacologic therapeutic strategies.

Given that the molecular basis for these monogenic disorders is well established, gene therapy and drug discovery targeting pharmacological compounds with the ability to reinforce the compromised cytoskeleton may lead to promising new therapeutic strategies for treating hereditary keratinopathies. Collectively, these approaches have unequivocally shown that both gene and pharmacological approaches are equally influential in the future outcome of therapies, and a recap of such knowledge would rapidly harness therapy development.

JeanChristopher summarized and discussed recent advances in the preclinical and clinical modeling and development of gene, natural product, pharmacological and protein based therapies for these disorders, highlighting the feasibility of new approaches for translational clinical therapy with a bias on my work in EBS and EI in relation to its applicability to PC research.

**Amy Paller**—Polyvalent oligonucleotide gold nanoparticles for topical delivery

**NOTE:** If you were unable to attend the IPCC meeting or would like to review any presentation, please send a request to info@pachyonychia.org.

**PUBLICATIONS**

The May 2011 issue of the Journal of Investigative Dermatology featured several articles related to Pachyonychia Congenita. We are so grateful to see this goal met which we set at the 2010 IPCC meeting. Copies of this issue are available on request from PC Project.


R.P. Hickerson, M.A. Flores, D. Leake, M.F. Lara, C.H. Contag, S.A. Leachman, R.L. Kaspar. Use of Self-Delivery siRNAs to Inhibit Gene Expression in an Organotypic Pachyonychia Congenita Model
R.L Kaspar, S.A. Leachman, W.H.I. McLean M.E. Schwartz


A Large Mutational Study in Pachyonychia Congenita

Y. Zhao, U. Gartnet, F.J.D. Smith, W.H.I. McLean. Statins Downregulate K6α Promoter Activity: A Possible Therapeutic Avenue for Pachyonychia Congenita

In addition to the articles in the May 2011 JID, other articles by IPCC members have recently been published. We appreciate these authors collaborating with PC Project and utilizing data from the International PC Research Registry (IPCRR).


Additional recent articles relevant to PC include the following. These are also available on our website at www.pachyonychia.org/Bibliography.


Kim JS, Lee CH, Coulombe PA. Modeling the self-organization property of keratin intermediate filaments. Biophys J. 2010 Nov 3;99 (9):2748-56


FUTURE PUBLICATIONS
There are other articles now being submitted and articles in preparation — and there is more to do. We invite interested authors to contact us — we have a list of topics that need attention and we are open to your ideas. Contact us at info@pachyonychia.org.

PC PAIN STUDY
Thanks to IPCC member Adrian Heagerty, PC Project intends to sponsor a PC Pain Study in collaboration with Dr. Barbara Hoggart, MD pain specialist at the EB Pain Clinic in Birmingham. The initial phase of the study will be at the Patient Support Meeting in Philadelphia Aug 5-7 with over 60 PC patients participating.

MONTHLY GENETICS MEETING
More than 30 patient cases were evaluated at the June 1 IPCC Genetics meeting and possible diagnosis suggested. A plan for evaluating the group of ‘nails only’ patients has been developed and the format is being prepared for future review of these cases which so far have no PC mutations identified.

FUTURE MEETINGS
IPCC Physician Quarterly Web Meeting
August 3rd (Wednesday) 12 noon MST
All Invited—Best Practices & Clinical Studies will be discussed.
For a link to the meeting, send an email request to info@pachyonychia.org.

Pachyonychia Congenita Patient Support Meeting
August 5-7, 2011
(begins Friday evening; ends Sunday noon)
Philadelphia, Pennsylvania
More than 60 genetically-confirmed PC Patients will attend this conference. If you are a physician or scientist interested in participating, please contact us as soon as possible at info@pachyonychia.org.

International PC Consortium (IPCC) 9th Annual Symposium
May 8-9, 2012 prior to SID
Raleigh, North Carolina
PC Project is a 501(c)(3) Public Charity registered in the USA

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These physicians provide patient consultations for the Int’l PC Research Registry (IPCRR) sponsored by PC Project

INTERNATIONAL PACHYONYCHIA CONGENITA CONSORTIUM (IPCC)

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These IPCC physicians and scientists have agreed to work together to develop PC therapeutics.

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PHYSICIAN NETWORK — ELI SPRECHER, AMY S. PALLER, MAURICE VAN STEENSEL – CO-CHAIRS


* Participated in the IPCC 2010-2011 Physician Network Web Conferences or Patient Support Meetings

Open Membership: Physicians and Scientists interested in collaborations for PC Therapies


1Special Needs MSAB/IPCC
2012 SPONSORED MEETINGS
International PC Consortium (IPCC) 9th Annual Symposium
May 8-9, 2012 prior to SID
Raleigh, North Carolina
Pachyonychia Congenita
Patient Support Meetings
France—June 9-10
Edinburgh, Scotland—Oct 28-30
Please submit abstracts by 1 Jan 2012 to info@pachyonychia.org for consideration for presentations at any of these meetings.

MEETING IN REVIEW
PC Patient Support Meeting (PSM)
August 5-7, 2011, Philadelphia, PA
We are grateful for generous support for this meeting received from Prof. Irwin McLean, University of Dundee (£2000) and Dr. Adam Rubin, University of Pennsylvania ($2500). The following presentations are available online at www.pachyonychia.org.

• What is Pachyonychia Congenita? Peter Hull
• PC Genetics Frances Smith
• The World of Keratins Gabrielle Richard
• What Is "Infection" Christopher Urban
• What Can Be Learned From A Nail Clipping? Campbell Stewart
• All About PC Nails Adam Rubin
• Why is Pain Important? Barbara Hoggart
• Becoming An Informed Partner With Your Medical Advisors David Hansen
• The Importance of Developing Best Practice Guidelines Albert Bravo

MOVING FORWARD: PC CLINICAL STUDIES AND CLINICAL TRIALS
Following the goals set at the May 2011 IPCC meeting, progress is being made for a number of studies and clinical trials.

PC Nails—nail clippings were collected at the PSM and analysis is on-going at the University of Pennsylvania under the direction of Adam Rubin.

PC and Pain—an IRB-approved in-depth study of PC pain was conducted at the PSM by pain specialist Barbara Hoggart (Solihull Hospital - Pain Management Clinic, UK) using a series of validated questionnaires and specialized equipment used to differentiate types of chronic pain including nociceptive, neuropathic and mixed pain.

PC Cysts—based on observations at the PSM, the need for more in-depth understanding of PC cysts was evident, and Phillip LeBoit (UCSF) has agreed to analyze patient samples as a first step in this study.

PC Treatment and Care: Best Practices—responses have been gathered from over 120 PC patients and nearly 25 physicians and the data is now being reviewed and analyzed in preparation for an upcoming publication.

Four Clinical Trials for PC were outlined during the IPCC Physician Quarterly Web Meeting held August 3, 2011 including Simvastatin presented by Peter Hull and Topical Rapamycin presented by Eli Sprecher. This web meeting can be viewed online at www.pachyonychia.org. The protocols for these two studies are outlined and the next steps toward administration of these trials is underway. The next siRNA clinical trial using microneedle delivery is also in development (see TransDerm press release Sep 2011 attached). The fourth clinical study is a topical gabapentin formula for pain relief being drafted by David Hansen.
FACTS ABOUT PACHYONYCHIA CONGENITA—2012 QUIZ (“don’t believe everything that’s published...”)
We hope members of the IPCC will have fun taking this quiz and will then help us spread these facts and share what is and what isn’t PC. Our comments are based on detailed data, photos and consultations from 323 genetically-confirmed PC patients and about 100 non-PC patients who have been misdiagnosed and have a different disorder. We now have over 450 confirmed with PC and the data is consistent with our initial findings.

TRUE OR FALSE
1. PC always involves fingernail and toenail dystrophy. T F
2. Thick nails are always evident at birth or shortly after for those with PC. T F
3. K6a/K16 and K6b/K17 are phenotypically similar and form PC-Type 1 and PC-Type 1 respectively. T F
4. A characteristic of PC is that all 20 nails are affected. T F
5. There are gender and ethnic bias in PC. T F
6. Some with PC only have nails affected and no other signs. T F
7. The most consistent characteristic of those with PC is plantar pain. T F
8. There is a ‘late-onset’ type of PC that starts in middle-age adulthood. T F
9. There is a ‘recessive’ form of PC. T F
10. PC calluses are always focal (not diffuse). T F
11. PC nails are always thickened ‘pincher-type’ nails. T F
12. Alopecia or other types of hair changes are typical of PC. T F
13. Most PC patients find retinoid treatment helpful. T F
14. Cysts are found mostly in those with mutations in K17 or K6b. T F
15. If PCers didn’t have children, the disorder would be eliminated. T F

HINT—only one of these is true!

ANSWERS—FROM UNPUBLISHED IPCRR DATA AND RECENTLY PUBLISHED PAPERS ON PC
1. There is no fingernail dystrophy for 21/31 patients with mutations K16R127C and K16N125S. See Tang, Jean Y et al, Genotype-Phenotype Correlations among Pachyonychia Congenita Patients with K16 Mutations, J Invest Dermatol 131: 1025-1028, 2010. Also, many with K6b or K17 mutations have mild or no nail changes.
2. K6b nail changes may not be evident until late childhood (ages 6-12).
4. 209/323 (or 65%) of those with confirmed PC have all 20 nails affected, but 114/323 (35%) have fewer than 20 or none of their fingernails affected.
5. There is gender bias in PC (male/152 and female/171). The statement that PC is more prevalent in ‘Slavic and Jewish’ populations is not supported by IPCRR data. The IPCRR now has patients from more than 50 countries around the world.
6. So far, no PC mutation has been found for any patient in the IPCRR with ‘nail changes only’.
7. TRUE. Although K6b and K17 may present milder plantar pain, all those with confirmed PC mutations have plantar pain, and the thickness of the callus may not directly correlate to the severity of pain.
8. So far, no PC mutation has been found for any patient in the IPCRR with ‘late-onset’ PC signs (i.e. after age 20).
9. No PC mutation has been found for the ‘recessive’ PC cases in the literature. A report of two homozygous cases will be published shortly (Smith et al, 2011 submitted for publication).
10. PC presents with both focal and diffuse keratoderma (see photos; all genetically confirmed PC).
11. There are many types of PC nails—thin, thick, pincher, and those that end prematurely (see photos; all genetically confirmed PC).
12. No hair changes have been proven in PC patients although hair changes have been found in one PC family. Also, alopecia is often an indicator of a Connexin mutation rather than PC.
14. 203/323 (63%) of all with PC mutations say they have cysts. K17=96%; K6a=72%; K6b=68%; K16=26%
15. 156/323 (48%) of genetically confirmed PC cases in the IPCRR are spontaneous.
Legend
a, b, c—dystrophic nails
d—dystrophic nails and palmar hypkerkeratosis
e, f, g—cysts
h—natal teeth
i—oral leukokeratosis (infant)
j—angular cheilitis
k—oral leukokeratosis
l—tongue; no leukokeratosis
m—follicular hyperkeratosis
n, o, p—focal and diffuse
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Open Membership: Physicians and Scientists interested in collaborations for PC Therapies

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**DEVELOPING PC ‘BEST PRACTICE’ GUIDELINES**

*Eli Sprecher, MD, PhD*

We are all too aware of the lack of information regarding the efficacy of the various treatment options available to Pachyonychia Congenita patients. To remedy this situation, a number of controlled trials are planned, but even once launched, will yield data only in the far future.

To obtain data albeit of a lesser quality, but readily available, the IPCC recently conducted a survey among PC patients in an attempt to generate a list of preferred therapies. The following table presents the raw data as collected during this electronic survey among more than 100 responders (5 = thought to best help, 1 = unlikely to help). We are now investing much efforts in analyzing the data, trying to characterize subgroups of patients who may be more likely to benefit from certain types of interventions.

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**Based on responses from 120 patients with genetically confirmed Pachyonychia Congenita—Sep 2011**

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**2012 PC PROJECT SPONSORED MEETINGS**

**International PC Consortium (IPCC) 9th Annual Symposium**

May 8-9, 2012 prior to SID
Raleigh, North Carolina

ALL INVITED — ABSTRACTS REQUESTED
Registration available at www.pachyonychia.org
Please submit abstracts to PC Project by 1 Feb 2012

**Pachyonychia Congenita Patient Support Meetings**

Roissy, France—June 8-9, 2012

IPCC members are invited to attend and participate.
Please email info@pachyonychia.org for details.
IPCC MEMBERS AND FOUR PC PATIENTS PARTICIPATE AT STANFORD, UCSF, UCDAVIS JOINT GRAND ROUNDS

Jean Tang, Roger Kaspar and Robyn Hickerson assisted four PC patients meet with nearly 100 residents on Saturday, November 19, 2011 at Stanford.

Involving multiple PC patients in educational outreach programs which provide a better view of the PC syndrome than single patient opportunities was a goal set at time IPCC. The Standard Joint Grand Rounds is the third event where PC Project has been invited to arrange for patient participation. Case study materials and interviews are provided prior to the meeting and detailed printed materials are provided to each attendee for the specific patients taking part.

If you would like to schedule PC patients for a Grand Rounds or other educational outreach program, please contact PC Project. Having multiple patients with varied mutations is essential.

IPCRR GENETICS TEAM

Team members participating in the Dec 2011 web meeting: Frances Smith, Eli Sprecher, Len Milstone, David Hansen, Edel O'Toole

The genetics team continues to have monthly conference calls between the physicians performing the consultations with new patients registering with PC Project and those carrying out the genetic testing in the lab in Dundee. In the majority of individuals with clinical features of PC we successfully identify mutations, both novel and recurrent, in the PC associated keratin genes, KRT6A, KRT6B, KRT16 or KRT17.

For about 10% of those clinically diagnosed with PC, a different disorder has been confirmed in the genetic testing, such as Connexin 30, EBS, etc.

However, there are a number of families within the PC Registry whose predominant clinical phenotype is hypertrophic nail dystrophy with no palmoplantar keratoderma or other features associated with PC. Full sequencing of the PC keratin genes has failed to identify a mutation in any of these families. We are now investigating these families for mutations in other genes that are candidates for a nail only phenotype.

There are also several individuals registered that have some features of PC plus some additional features. Full sequencing of the PC keratin genes and several other candidate genes has failed to identify a mutation in these cases.

Samples from these individuals will now undergo whole exome sequencing to identify the pathogenic mutations.

NOTE: Physicians interested in doing telephone consultations for the IPCRR registry, please contact PC Project for details, requirements, compensation schedule, etc. These consultations are extremely valuable in validating or correcting the patient-reported data.

IPCC PHYSICIAN NETWORK QUARTERLY WEBMEETING

Eli Sprecher led the discussion on development of Best Practices for PC and the on-going process of collection and analysis of data.

David Hansen provided a review of the 67 patients who were seen at the August PC Patient Support Meeting. One of the most striking findings at that meeting was the difference in disease presentation for those with K17 mutations. Although plantar pain is a problem for these patients, many of those with K17 mutations exhibit extensive cysts not seen in either K6a, K6b or K16 patients. For this reason, the dermatologists attending the PC Patient Support Meeting have determined separate measurement tools need to be used in studies involving K17 patients.

INT’L PC RESEARCH REGISTRY (IPCRR) AVAILABLE ONLINE

The IRB-approved IPCRR has enrolled patients since 2004 using a paper form to collect the patient reported data. The information is then validated by a qualified dermatologist and is manually entered into the IPCRR database. The 20-page questionnaire is now available in six languages (English, French, Spanish, Portuguese, German and Chinese).
Currently, queries are submitted to PC Project and de-identified data is regularly provided to physicians and researchers.

Early in 2012, the IPCRR will transfer to an online format where patients will be able to directly enter their own data. With the online registry, dermatologists will continue to conduct consultations to add, correct and validate the online data.

The new online IPCRR will allow patients to update information over time and allow a more complete life history and understanding of the development of various factors found in Pachyonychia Congenita patients and the impact of these symptoms at various ages.

The online version will provide access to de-identified data so that researchers will be able to directly query the data for their projects. Reports will be available both from the PC-specific data and through the broader GRDR registry which will include common elements of PC data and other rare diseases.

Also, the IPCRR data will be prepared in a manner to be consistent with the Global Rare Disease Registry sponsored by NIH Office of Rare Disease Research (ORDR) so that the specific PC data can be pooled with data from other rare diseases in a larger dataset while at the same time maintaining the confidentiality and specific details of the individual IPCRR registry.

A number of publications have utilized the IPCRR data. A series of nine articles on PC appeared in the May 2011 Journal of Investigative Dermatology. In addition, the following articles have recently been published:


**UPDATE ON PC STUDIES**

Each of the studies outlined at the May IPCC meeting continue to be developed. The patients are ready!

**PC CYSTS**—the final review for collection of cysts is in preparation and the mailing to patients will take place in early January.

**SIMVASTATIN**—several conference calls have helped to finalize details for this multi-center trial. Thanks to Peter Hull for conducting the initial 4-patient study, drafting the protocol and locating a CRO for the study. Thanks to Len Milstone for referral to the compounding pharmacist. Irwin McLean is coordinating the group effort to obtain funding for the study.

**TOPICAL RAPAMYCIN**—Roger Kaspar is continuing discussions with Pfizer so that topical rapa can be manufactured for this study.

**TOPICAL GABAPENTIN**—an off-label study of topical gabapentin will be conducted in early 2012.

**PC ‘EAR’ PAIN**—for children with PC-K6a this intense pain with first taste/swallow is debilitating. ENT specialists have indicated to PC Project that “First bite syndrome” is a known complication after parapharyngeal space surgery. The first case of this condition prior to surgery was reported in Lieberman SM, Har-El G. First bite syndrome... Head Neck. 2011 Oct;33 (10):1539-41. Epub 2010 Apr 29. We hope we can interest others in studying the PC condition.
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