SiRNA Clinical Trial Begins for PC. From drug development, to regulatory approval, to clinical trial, the experience has been amazing with countless collaborations among IPCC members. Many outside consultants volunteered their expertise in the preparation and filing of the IND with the FDA. This clinical trial milestone is also amazing because the timeline set in May 2007 was fully met: the IND was filed in early December 2007 (with the consultants constant help and guidance) and the Phase 1b clinical trial began as scheduled in January 2008. Sancy Leachman will provide information on the clinical trial at the May PC meetings in Kyoto, Japan (SID/IID) and Hefei City, China (IPCC).

IPCC Symposium 2008
Hefei City, China
May 18-20, 2008
In 2004, PC Project sponsored the First PC Symposium in Park City, Utah. That Symposium was the basis for the excellent progress has been made in PC research 2004-2008 and it is essential we again gather and evaluate the most effective strategies for scientific and clinical research — and delivery of therapeutics to PC patients.

The IPCC Symposium program is not finalized as yet and abstracts may still be submitted. Many of the following confirmed participants will be giving presentations:

- Jiang Chen
- Christopher Contag
- Marcela Del Rio
- Reza Ghohestani
- Robyn Hickerson
- Roger Kaspar
- Birgitte Lane
- Fernando Larcher
- Sancy Leachman
- Haihui Liao
- Irwin McLean
- Colin Munro
- Edel O'Toole
- Dennis Roop
- Elizabeth Rugg
- Frances Smith
- Eli Sprecher
- Virginia Sybert
- Yiwei Zhao

We want this to be an extraordinary event that will move the IPCC forward to new heights by forming new goals and projects. This is an ideal opportunity to set effective plans that will ensure success in our goal of developing therapeutics for PC. We also expect that successful development of PC therapeutics will benefit a much larger community of genetic disorders.

In addition to those listed above who are traveling to China for the IPCC meeting, we are delighted that a number of experts from within China will participate in the patient support activities of the meeting. Also, PC Project Director, Mary Schwartz, and two patient representatives from the US will attend the meeting in China.

If you would like to attend the IPCC Symposium in Hefei City, China, please contact us immediately at IPCC.China@pacyonychia.org.

SID/IID Kyoto, Japan
Satellite Meeting: PC Update
PC Project is sponsoring a half-day meeting in Kyoto, Japan on Tuesday, May 13th from 1:30pm—5:00pm, followed by a dinner that evening at Kiyamachi Restaurant, a place which reflects the elegance of old Kyoto.
The following have pre-registered for the PC meeting & dinner in Kyoto:

Susan Bayliss
Jiang Chen
Peter Elias
Reza Ghohestani
Robyn Hickerson
Alan Irvine
Roger Kaspar
Masahiko Kuroda
Birgitte Lane
Sancy Leachman
Masaharu Matsuzaki
Irwin McLean
Edel O'Toole
Amy Paller
Wilbool Piyawattanametha
Dennis Roop
Elizabeth Rugg
Frances Smith
Eli Sprecher
Mizutani Takayuki
Jouni Uitto
Anders Vahlquist
Mary Williams

If you (or others you know with an interest in keratin research) are attending the IID, please join us at this meeting and dinner. There is no registration fee, but we ask that you please pre-register so that we can ensure all are accommodated.

The link to the registration for the IPCC Kyoto is: 
[Register for Kyoto PC Meeting & Dinner](#)

The group discussion will be an essential part of the Kyoto “PC Update.” In addition to information on the siRNA clinical trial, several relevant presentations on delivery will be featured which will not be available at the Hefei City, China IPCC meeting.

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**Abstract of presentation at the PC Update Meeting, Kyoto 2008.** We are pleased to include this abstract from one of important presentations which will be given at the PC/Kyoto meeting. Abstracts from other presentations will be available in upcoming IPCC Newsletters.

**In vivo Three-dimensional Skin Imaging with a Handheld Dual-Axes Confocal Fluorescence Microscope**

W. Piyawattanametha\(^1\), E. Gonzalez\(^1\), M. J. Mandella\(^1\), H. Ra\(^1\), G. S. Kino\(^1\), O. Solgaard\(^1\), R. Kaspar\(^2\), and C. H. Contag\(^1\)  
\(^1\) Stanford University, Stanford, CA, 2 TransDerm, Santa Cruz, CA

The ability to non-invasively image skin pathology would be a boon for diagnosis of skin cancer and for evaluation of the effectiveness of therapies (including siRNAs) targeting genodermatoses including pachyonychia congenita. More than 1 million new cases of skin cancer are diagnosed each year in the US resulting in more than 10,000 deaths - a disproportionately large number of which is caused by melanoma. Invasive biopsies, in which skin lesions are removed and examined, are currently the primary means of diagnosis, but suffer from high false positive rates. Therefore, noninvasive techniques that minimize this error will significantly improve clinical diagnosis.

We demonstrate a Dual-Axes Confocal (DAC) fluorescence microscope capable of three-dimensional (3-D) *in vivo* real-time imaging in a handheld package (10-mm diameter), weighing less than 0.8 lb, that can fundamentally change the way skin clinical diagnosis has been performed. Genecreme\(^\circ\) (TransDerm, Inc.) containing fluorescent infrared dyes, can penetrate the stratum corneum layer of skin and in combination with DAC microscopy technology reveal the intricate structures of both the epidermal and dermal skin layers. The microscope not only helps determine whether a lesion is benign or malignant in real-time, but also facilitates micro-image mapping of the three-dimensional (3-D) volume and architecture of the tumor or lesion in question. The resulting data therefore contain functional and structural information of a lesion. The key technologies enabling miniaturization of the microscope are Microelectromechanical Systems (MEMS) and miniature-optics. The maximum imaging rate is 15 frames/second with a maximum field of view (FOV) of 700 × 300 µm\(^2\). The microscope achieves transverse and axial (FWHM) resolutions of 3 µm and 5 µm, respectively. Currently, the maximum imaging depth of the handheld microscope can go as deep as 300 µm in skin. A larger FOV (over 1 mm\(^2\)) of skin can be acquired by real-time “mosaicing” software integrating with our imaging acquisition system. The imaging demonstrations with sub-cellular resolution from the handheld microscope will be on both *in vivo/ex vivo* human and mice skin.
IPCC Physician Network
An IPCC goal for 2008 is to have an active ‘physician network.’ Saney Leachman has led this effort and we are pleased that we now have four physicians conducting the consultations/validation for the PC Research Registry. In addition to Dr. Leachman, these include C. David Hansen (US), Fanny Morice (France) and Peter Hull (Canada).

Research Registry Data
We now have nearly 200 questionnaires and approximately 150 individuals with genetic test results. We need to (a) publish the data effectively to overcome the misinformation that is prevalent and (b) formulate plans for studies that will discover new facts that make a real difference in the lives of PCers. If interested, forward a proposal and application to IPCRR.Study@pachyonychia.org.

Here are a few examples of the importance we see in having the data reviewed properly:

(1) Can PC patients benefit from retinoids? Although the general conclusion from data collected is that retinoids (a) do not relieve the pain, (b) have side effects that for most patients are not worth the thinning that may occur and (c) generally are not recommended to others by those patients who have or are using retinoids. However, there appears to be some basis for trying a controlled study using a very personalized approach (i.e. low dose, adjusting dose, on/off usage and so forth) with a close physician/patient interaction.

(2) Laryngeal involvement with PC: does the intervention worsen the problem? As we have studied the responses from PCers, we note that many have a ‘hoarse’ or low voice and a number have some comment about the larynx. However, it appears that only those who have had a procedure or intervention (i.e. surgery to remove keratin from the voice box, etc.), begin to have serious problems with the larynx. One hypothesis is that the intervention sets off the ‘wound healing’ response typical in PC. The only known PC-related death is related to laryngeal involvement. This needs careful research which could be life-saving.

(3) Sharp ear pain. What causes it and why does it diminish by adulthood? Although nothing has been published that we know of, children with PC often experience intense ear pain at each meal as they take the first bite of food. We’ve been asked ‘is this connected to PC?’ We assume it is, because we know firsthand that this ear pain exists in PC children. What is it? Can it be alleviated? What causes it to lessen by adulthood? (We know that follicular hyperkeratosis is also known to lessen by puberty and in adulthood.)

(4) How does circulation affect infection in PC feet? We’ve had several calls from older PCers with intense infections on their feet that persist despite repeated antibiotic treatments. Is there a connection between age and/or activity, and these infections?

Trans-Splicing Technology
5' Trans-Splicing Repair of the PLEC1 Gene (JID, Mar 2008; now available on-line)
Verena Wally1, Alfred Klausegger1, Ulrich Koller1, Hanns Lochmuller2, Sabine Krause2, Gerhard Wiche3, Lloyd G. Mitchell4, Helmut Hintsner1 and Johann W. Bauer1
1Division of Molecular Dermatology and eb house Austria, Department of Dermatology, Paracelsus Private Medical University, Salzburg, Austria; 2Department of Neurology, Friedrich-Baur-Institute, Ludwig-Maximilians-University of Munich, Munich, Germany; 3Max F. Perutz Laboratories, Vienna Biocenter, Institute of Biochemistry and Molecular Cell Biology, University of Vienna, Vienna, Austria and 4Retrotherapy LLC, Bethesda, Maryland, USA

“Like mutant keratin genes in PC, plectin mutations can cause dominant negative skin disease, leading to forms of epidermolysis bullosa, many of which are associated with muscular dystrophy that is frequently lethal. Using an RNA trans-splicing molecule to repair exons 2-9, Dr. Bauer's group was able to generate almost 60% of the normal protein levels in cultured patient keratinocytes and restored a normal immuno-histological staining pattern.” Lloyd Mitchell

SiRNA Clinical Trial News: Our international press release is posted at the PC Project website. Several additional news reports are linked at www.TransDermInc.com (“In The News” tab).

An impressive blog by Dirk Haussecker includes the PC siRNA trial is posted at RNAiBlogspot.

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International Pachyonychia Congenita Consortium (IPCC) Members - Feb 2008

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**DELIVERY SYSTEMS & ANIMAL MODELS**
Roger L. Kaspar PhD, Santa Cruz, CA, USA

**GENETICS**
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**PATIENT SUPPORT MEETING 2008**
W. H. Irwin McLean DSc FRSE, Dundee, UK

**REGISTRY**
Peter Hull MD, Saskatoon, Canada

2008 IPCC SCIENTIFIC MEETING
Xue-Jun Zhang MD, Hefei, China

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Xue-Jun Zhang MD, Hefei, China
Pingyu Zhou MD PhD, Shanghai, China

2008-2009 IPCC GENERAL MEMBERSHIP
We invite you to join one of the IPCC Working Groups.

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Kyonggeun Yoon PhD, Philadelphia, PA, USA
Yiwei Zhao PhD, Dundee, UK
Xue Zhang MD PhD, Beijing, China

Medical & Scientific Advisory Board (MSAB) member
IPCC Meeting at IID
Kyoto, Japan—May 13, 2008
A half-day session was held in Kyoto as all IPCC members were not available to attend the IPCC meeting scheduled for Hefei, China. The discussions continued at a dinner meeting, and evaluations show progress through the IPCC events in Kyoto.


Several of the IPCC members received awards at the IID meeting including Jouni Uitto, Pierre Coulombe and Irwin McLean. Congratulations! And thanks so much for being part of the IPCC and helping us succeed in our mission.

Presentations at the IPCC
siRNA Clinical Trial Update
Sancy A. Leachman
The twice weekly injections were completed in early May. However, the trial has a 3-month ‘wash out’ period required by the FDA and so is still ‘blinded.’

The injections were found to be so painful that Lortab and Valium were prescribed for the patient to use prior to each session. No negative side effects from the injections were observed during trial and additional tests following the injection period also appear to be positive.

An interesting set of photos was emailed by the patient during the IID meeting including the following:

The black line on the right foot is a pen mark by the patient showing where the callus had previously extended.

Treatment of pachyonychia congenita with plantar injections of botulinum toxin
Anders Vahlquist, MD/PhD
The botox treatment is welcomed by PC patients and appears to give relief from pain for a period of time. A study has been proposed to involve additional PC patients.

Comment on siRNA & Botox Clinical Studies
It was good to hear the early clinical data of the new siRNA therapy, and I’m sure many of us are confident that the results will improve with refinements in the delivery technique. Anders Vahlquist data (botox) are also pretty impressive, so one must be optimistic on both fronts. Congratulations once again to everyone pushing the research forward!

Robyn Eady

In vivo Three-dimensional Skin Imaging with a Handheld Dual-Axes Confocal Fluorescence Microscope
Wilbool Piyawattanametha, PhD
Christopher Contag Lab
Stanford University

This presentation showed remarkable images of skin cells using a new imaging system developed at Stanford University.

NOTE: Following the IPCC meetings in Kyoto and Hefei, China, Wilbool Piyawattanametha, Roger Kaspar, Chris Contag and other collaborators obtained IRB approval for the use of this imaging system in a small study involving one normal control and one PC patient. Results will be reported in the next IPCC Newsletter.

Keratin 6 regulation in sebaceous gland tissue: implications for glandular disorders
Pierre A. Coulombe, PhD
Johns Hopkins School of Medicine

Cysts are a major clinical feature of PC and this presentation provided a first discussion of possible new insight into the pathophysiology of steatocysts in PC and related disorders. A number of thoughtful questions were presented with research data in a series of excellent slides:
The presentation by Dr. Roop is one of the most impressive lectures at the IPCC meeting in Hefei (not only because he is my boss). Dr. Roop provided an update on the current status and most recent progress in novel therapies aimed at curing cutaneous diseases caused by single gene mutations, including ex vivo gene therapy, the promise of multipotent stem cells, bone marrow cell and epidermal stem cells as potential candidates in a permanent fix of Pachyonychia Congenita.

We know siRNA is a promising tool in tackling down mutant gene products. However, delivery is a critical limitation, which will hinder an effective and long-term improvement of PC symptoms.

I feel the IPCC needs to consider an out-reach program to have delivery addressed by establishing collabora-
tions. This is also supported by Dr. Birgitte Lane's talk of Other Keratin Diseases. Ex vivo therapy might be an alternative to intra-epidermal injection. (NOTE: A 'Delivery Summit Meeting’ is planned for early 2009. Details will be in the next Newsletter.)

PC researchers from China showed a vigorous PC research program in mutational screening. Clinical and genetic data has been collected per IPCRR protocol standards. This will greatly enhance the PC data base. Also, therapeutic approaches may be customized to adult and young PC patients.

MEETING COMMENTS
Yiwei Zhao and Liao Haihui
I think the Hefei meeting was very enjoyable and gainful as well. I think all of us learned a lot in that week. There are some feelings and impression that we would like to share with all of you.

First, we believe that the first day of the Hefei meeting (the Patient Support Meeting) was very unusual for all of you. We are sure that they had a very deep impression how the doctors and scientists from the IPCC communicated with patients, how they showed their sympathy and care, and how patient they were when facing the patients' inquiries. The relaxing and friendly atmosphere definitely brought a lot more interest and energy to the young Chinese scientists.

On the other hand, the scientific meeting on the second day was much more serious and professional. From what we saw and heard in Hefei, we think it was the first time for young scientists to take part in a discussion with so many questions and serious argument. Although they might not understand every conversation, but there was a lot they could learn not only about PC but also about the attitude and passion for science.

Most importantly, I really feel this meeting meant a lot to the Chinese patients, since most of them are from remote areas where there is a lack of doctors or proper medical treatment. They have very little knowledge about PC, let alone how to take care of themselves. And before this meeting, they never had any chance to meet other PC patients to share their feelings and their pain. Nor had they ever been able to discuss their problems with so many experts worldwide face to face.

So the Hefei meeting did bring a lot of love, hope and knowledge to the Chinese PC families, and they all knew that it would be impossible to have an opportunity like this without PC Project. The patients families appreciated the meeting very much although most of them can not express themselves in English. Many of them thought the same thing that "Now we know that we are not alone anymore and there are a lot of people in the world working on this disease although it is still not curable so far, and we also have now know this disease better and have learned how to do regular skin and nail care.”

Unfortunately, we didn't have many opportunities to talk with senior Chinese doctors and scientists, so we would not know what they thought about the meeting. However, we believe it was a nice meeting for them too. Anyway, we would like to
say thank you to everyone working for PC project on behalf of all the Chinese patients and young doctors and scientists. We hope the Hefei meeting was not the last meeting in China. We think we should have more communication with each other and we will all learn more from each other. That’s our point of view about this meeting.

PS: We also enjoyed the Yellow mountain trip.

CHINA IPCC MEETING
Attendees included Jiang Chen, Christopher Contag, Marcela Del Rio, C. David Hansen, Robyn Hickerson, Roger L. Kaspar, E. Birgitte Lane, Fernando Larcher, Sancy Leachman, Haihui Liao, W.H. Irwin McLean, Colin S. Munro, Edel O'Toole, Dennis R. Roop, Elizabeth Rugg, Frances J.D. Smith, Eli Sprecher, Virginia P. Sybert, Yiwei Zhao. The first day was set aside as a Patient Support Meeting:

Colin Munro writes: Delivering a talk on "What is Pachyonychia Congenita?" at the start of the IPCC China meeting presented familiar and new challenges. The familiar one was trying to share with a mixed clinical and lay audience the key messages about keratin biology and genetics and their relationship to skin disease; the new one has having to do so with semi-simultaneous translation into Mandarin. We got into our stride eventually, and I hope that some of what I was trying to say came over in a comprehensible manner.

The comfortable hotel venue was enlivened by the nightly wedding feasts and the catering for our own party provided many novel experiences. Thanks to the hard work of Professor Zhang and his team, and Mary’s indefatiguable organisational work, both the meeting and the trip to Yellow Mountain were rewarding: in themselves and for new and established professional relationships.

In the afternoon, two PC Patient Advocates (from US and Canada) led the ‘patient care’ discussion.

On the second day of the IPCC meeting in Hefei, the focus was on scientific presentations and included reports on several leading research topics including the following (summaries of all presentations are not in this Newsletter.)

Robyn Hickerson presented data showing the selective reduction of K6a in human keratinocytes by rapamycin (sirolimus) treatment and the results of a three-patient off-label clinical study. The results demonstrated subjective pain improvement as well as therapeutic response to rapamycin in callus character. Specifically, rapamycin greatly reduced the presence of painful cutaneous thromboses after reaching therapeutic serum levels. Topical formulations of rapamycin are being pursued in collaboration with the Paul Wender group at Stanford University. These studies are supported in part by an SBIR Phase 1 grant from the NIH. A clinical study using topical rapamycin is planned for later in 2008.

Roger Kaspar of TransDerm presented recent research done in collaboration with colleagues at Stanford University including Emilio Gonzalez, Qian Wang, and Chris Contag. We have developed a transgenic mouse model in which GFP expression is limited to the skin epidermis (mainly in the granular layer and stratum corneum). Intradermal injection into mouse footpad skin of a potent and selective siRNA targeting the reporter gene resulted in reduced GFP reporter expression, particularly near the injection site.

This new mouse model should prove useful for identifying, developing and optimizing effective systems for delivery of functionally active siRNAs.

Frances Smith presented a talk on 'The expanding world of PC mutations' - and gave a brief update on mutations found in new cases of PC including some novel splice site mutations. Also, she reported the first mutations in the third keratin 6 gene, KRT6C. Mutations in KRT6C have now been identified in three families who presented with focal palmoplantar keratoderma and minor/no nail changes.

Outside the formal meetings, many discussions and exchanges took place. Frances Smith spent some time talking with the young Chinese scientist who had performed the mutation analysis on most of the patients at the meeting and wanted confirmation of the results. Some samples were sent to the UK and the mutations have been confirmed, some of which are novel. Also, in informal sessions help was given in regard to manuscripts that are being prepared and minor corrections/comments were provided mostly needed due to language difficulties.

All attendees from the IPCC actively participated and a variety of options were considered on 'the best way forward for PC research.' Following the two-day meeting, a trip to Yellow Mountain proved an effective final event for IPCC 2008.
Clockwise from top left: Irwin, Peter, WP, Robyn, Roger, Dennis, Alan, Frances, Patrick, Pierre, Sancy, Birgit, Alan, Anders, Robin, Jouni and Hiroshi.

Left: traditional Japanese dinner enjoyed in the evening

IPCC
Kyoto, Japan
May 2008
IPCC Hefei, China 2008
Above: Yellow Mountain Group
Below: Sunrise at Yellow Mountain

Two IPCC super heros!
Left: Dr. Pingyu Zhou who arranged transportation in Shanghai in a most astounding manner and with great effort so that we could make our connections.
Right: Xianyong Yin, Secretary to Prof. Xuejun Zhang at Anhui Medical University who in addition to his studies and regular work, spent countless hours preparing for the IPCC meeting.

Thank you! Thank you! Thank you! Thank you!

Thanks to Roger Kaspar, Irwin McLean, Collin Munro, Eli Sprecher and others for photos.
**BIG NEWS: CLINICAL TRIAL**
The really BIG news at PC Project is the siRNA clinical trial. Although we are not able to provide details of the trial in this Newsletter, a full report will be issued shortly as soon as the FDA, OOPD, and publication requirements are fulfilled. In summary, however, we are very pleased.

**PUBLICATION INCENTIVES**
We want to encourage publications including data gathered through the International PC Research Registry (IPCRR) sponsored by PC Project. We believe a great deal of important information is now available from the more than 250 PC patients who have participated in the fully validated PC questionnaire and who have genetic testing completed.

We believe the IPCRR data will
(a) strengthen articles by providing a broader dataset than is usually available from a single case study and
(b) assist in making this data available to as many as possible and
(c) help to correct some old and incorrect information published before the genetic basis of PC had been established.

To help us achieve this goal, we have established guidelines and awards for published articles using IPCRR data. We want to avoid confusion as we move forward.

**PC PROJECT/IPCRR PUBLICATION GUIDELINES**
1. The data generated through the PC Project sponsored IPCRR is valuable and needs to be published. PC Project wants to encourage publications.
2. As you know, there can be confusion regarding authorship on papers and we want to avoid that confusion. Therefore, authors wishing to publish information based on IPCRR data need to register the planned publication with PC Project for pre-approval in order to avoid conflicts with others who may be preparing similar publications.
3. PC Project approval will include a deadline for submission. We recognize that sometimes deadlines will need to be adjusted or extended and that acceptance is not guaranteed. However, we believe the PC Project approval cannot be 'open-ended' or we fail in our role. Therefore, the permission will expire if the deadline for submission (or extended deadline) is not met.
4. IPCRR data includes but is not limited to: IPCRR questionnaire data, extraneous data from PC Project such as emails or special surveys, etc., as well as data from consultations, consultation notes, genetic testing results and data gained at Patient Support Meetings (PSM) or through follow-up based on PSM contacts.
5. We recognize fully that authorship can be tricky and PC Project wants to be fair to everyone. We've heard some comments that indicate there may be confusion as to who 'must' be cited on a PC Project/IPCRR paper. Here is our policy:
   5a. Authors are pre-approved when the publication is approved by PC Project. Others not listed should not be assigned to write the publication without PC Project approval.
   5b. The person writing the paper and the head of that lab obviously are authors on the paper. Others may be included, but PC Project has no agreement that all MSAB members or IPCC members are listed on papers unless they have an active role in that specific paper. The main authors who are approved by PC Project should determine who else should be listed on the paper (middle authors.)
   5c. There may be others involved in generating IPCRR data -- i.e. sometimes there is a referring physician. If there are others that PC Project knows of, this information will be provided at the time of approval for the publication by PC Project.
6. Acknowledgement to PC Project. In some instances it will be sufficient to simply reference PC Project in the acknowledgements section or credit PC Project for funding. In some cases PC Project needs to have an authorship role. We will work this out with individual authors.
7. PC Project has exclusive ownership of the IPCRR data and reserves the exclusive right to write papers on our own data and to solicit and engage authors for papers we want to publish.
8. PC Project will offer Awards (including cash awards) for anyone who has one of the proposed manuscripts accepted for publication. The type of award will be determined by an awards committee.

We welcome corrections and additions to our guidelines. We want to encourage additional quality publica-
**PUBLICATIONS IN PROCESS AND REQUEST FOR AUTHORS.** We've prepared a table listing the publications we hope will be completed in the coming months. These either (A) have been approved by PC Project or (B) are available to be assigned to an author and approved. The table includes the goal date for submission (when the approval ends and the article may be re-assigned if necessary.) We hope to hear from you and that you will help us by authoring a paper using IPCRR data. We look forward to working with you!

<table>
<thead>
<tr>
<th>Article Topic</th>
<th>Approved authors</th>
<th>Possible Journal for submission</th>
<th>Goal Date for submission for publication</th>
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<tbody>
<tr>
<td>Rapa study</td>
<td>Hickerson, Pho, Leachman, Kaspar (PC Project acknowledged)</td>
<td>JID</td>
<td>Submitted 17 Aug 2008</td>
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<tr>
<td>TD101 Clinical Trial</td>
<td>Leachman, Hickerson, Schwartz, Bullough, Boucher, Hansen, Eliason, Smith, McLean, Milstone, Kaspar</td>
<td></td>
<td>15-Sep-08</td>
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<tr>
<td>Humira study</td>
<td>AUTHOR NEEDED</td>
<td>?</td>
<td>15-Nov-08</td>
</tr>
<tr>
<td>Retinoid Data from IPCRR</td>
<td>AUTHOR NEEDED; we have an Aug 2007 draft by a PC Project intern that needs updating and reworking</td>
<td>?</td>
<td>15-Dec-08</td>
</tr>
<tr>
<td>IPCRR Data Update of 2005 JID publication</td>
<td>Leachman and others; authors needed</td>
<td>JID</td>
<td>15-Dec-08</td>
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<td>PC 'Ear' Pain: Salivary Glands?</td>
<td>Leachman and others; authors needed</td>
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<td>15-Jan-09</td>
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<tr>
<td>Case Reports - Secondary Infections</td>
<td>KaLynne Harris, C. David Hansen, Frances Smith, Peter Hull and Sancy Leachman</td>
<td>TBD</td>
<td>15-Feb-09</td>
</tr>
<tr>
<td>Analysis of PC keratoderma from photographs with mutation status correlation.</td>
<td>Majmudar, Vallari Majmudar, Frances Smith, W.H.I. McLean, Sancy Leachman, Edel O'Toole. (There may be referring physicians who will also be listed.)</td>
<td></td>
<td>15-Feb-09</td>
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<tr>
<td>PC Care based on IPCRR data</td>
<td>AUTHOR NEEDED.</td>
<td>AMA or other physician publication</td>
<td>15-Jun-09</td>
</tr>
<tr>
<td>PC and Laryngeal Involvement</td>
<td>AUTHOR needed. NOTE: Richard Haber is writing up a case study on this topic. We also need to gather ALL the case studies and write this up completely. The potential risk for PC patients needs to be reviewed. The published articles include non-PC families identified as PC patients.</td>
<td>?</td>
<td>on-going</td>
</tr>
<tr>
<td>Genetic Case Reports</td>
<td>Smith (and others as involved)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
tions about PC.

**CLINICIAN CONFERENCE CALLS**

The IPCC Genetics Working Group (headed by Frances Smith) has joined with the IPCC Registry Working Group (headed by Peter Hull) and the Clinician Advisory Working Group (headed by Sancy Leachman) on monthly conference calls to discuss the pending genetic testing for PC.

This collaboration is very effective. Drs. Smith, Leachman, Hull and Dr. David Hansen have participated. In some cases, where PC mutations have not been identified, the conference call discussion has identified other disorders possible based on the clinical photos, questionnaire data and interviews.

If you are interested in participating, please contact Mary Schwartz at PC Project who acts as coordinator for the calls.

**New PC Website**

A new website was launched for PC Project on August 1, 2008. We encourage you to register at www.pachyonychia.org. The site offers many features of importance to physicians, scientists, patients and the public. Additional features will be added regularly for registered members of the PC Website.

**Patient Support Meeting**

Under the leadership of Irwin McLean with Frances Smith assisting, a successful 3-day conference was held in Pitlochry, Scotland. A total of 161 individuals (including 59 PCers) attended the 2008 Patient Support Meeting. PCers were from Brazil, Denmark, England, Finland, France, Germany, Ireland, Israel, Poland, Scotland, Sweden, The Netherlands, USA and Wales.

**PUBLICATION NOTES**

Robyn P. Hickerson, Alexander V. Vlassov, Qian Wang, Devin Leake, Heini Ilves, Emilio Gonzalez-Gonzalez, Christopher H. Contag, Brian H. Johnston and Roger L. Kaspar.

**Stability study of unmodified siRNA and relevance to clinical use**

A stability study of K6a_513a.12 (TD101) and two other siRNAs was recently accepted for publication in the journal *Oligonucleotides*. These unmodified siRNAs demonstrated unexpected stability when incubated at high temperatures and in the presence of RNases found on skin and hair. It was also found that siRNAs can be stored at room temperature for over a year without loss of activity. One of the siRNAs studied in this publication targets the reporter gene in a fluorescent mouse model (L2G85) developed in Christopher Contag’s lab at Stanford. Intradermal injection of this siRNA resulted in reporter gene knockdown that lasted for two months. These data provide further evidence that unmodified siRNAs are well suited for formulation development and are viable therapeutic candidates.

**THE FOLLOWING ARTICLES ARE AVAILABLE ON THE PC WEBSITE.**

Click the link in this electronic newsletter or access at www.pachyonychia.org/Bibliography


**NOTE:** Current IPCRR data shows 75 individuals with K16 mutations and 130 individuals with K6a mutations in the IPCRR database.


**IPCC 2009—DELIVERY TO SKIN**

May 5-6, 2009 — Montreal prior to the SID Annual Meeting

Effective, patient-friendly delivery is essential to progress in skin therapies. Please mark these dates (May 5-6, 2009) and plan to attend this important IPCC symposium.

"Call for Speakers"

Please contact PC Project to recommend the top experts from all fields who should be invited to take part in these sessions on delivery.
NEWLY DESIGNED PC WEBSITE
We invite you to visit the site and register for full access. We will be adding features on a regular basis.
www.pachyonychia.org

STATIN OFF-LABEL STUDY
* SIROLIMUS (RAPAMYCIN)
* NEW IMAGING SYSTEM. A small patient study (normal control patient and PC patient) using a new imaging system developed by the Chris Contag lab at Stanford University has shown effective delivery to cells using GeneCream developed by TransDerm, Inc. Results are being prepared for publication.

Specific Mutations—Patients in the International PC Research Registry as of September 2008
Total Individuals = 283
Total Families = 121
Total Mutations = 53

K6a
Table: K6a

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Genetic Test Results September 2008
73 individuals (121 families) 17% K16
75 individuals in 34 families 24% K6a
130 individuals in 62 families 46% K6b
43 individuals in 17 families 10% K17
13 individuals in 7 families 7% K6c
36 individuals in 26 families 28% Other

These and other data and graphs from the IPCRR are available at www.pachyonychia.org

Animated genetics pages prepared by The University of Utah, Genetic Science Learning Center!!!
SIRNA Phase Ib Trial
Sancy A. Leachman, MD, PhD

A Phase Ib clinical trial evaluating an siRNA, TD101, was recently completed. This project was only possible because of the willing participation of the PC patient involved in this trial, as well as through support of the PC Project and the active participation of the International Pachyonychia Congenita Consortium (IPCC) membership. An FDA OOPD grant was received by Sancy Leachman to help support the trial. All of this support has been of vital importance to completion of the work, and also demonstrates support of this endeavor by a larger clinical and scientific research community.

TD101 is a siRNA that was developed through collaboration between TransDerm, Inc., PC Project, and other collaborators and consultants worldwide (see authorship of submitted paper below). TD101 was designed to selectively and potently target only the N171K keratin 6a mutant mRNA, without appreciably affecting the wild type K6a mRNA. The underlying hypothesis in the trial was that if TD101 was injected directly into a callus on the foot of a PC patient carrying the N171K mutation, that the mutant K6a would be selectively removed, and the clinical symptom of the disease (in this case the callus) would improve. In this trial, symmetric calluses were treated on both feet, one received vehicle and the other received TD101 in a double-blinded fashion. The primary purpose of the study was to evaluate the drug for toxicity, but efficacy measurements of the calluses and clinical examination by the physicians, as well as patient self-assessments, were performed regularly throughout the trial. The trial results revealed no major toxicities, although the intralesional injection of drug (into the exquisitely tender calluses) was painful at the time of injection, lasting even a few hours after the treatment (in both the vehicle- and TD101-treated callus). This pain at the time of injection necessitated pre-medication with acetaminophen, hydrocodone and diazepam, as well as a posterior tibial nerve block with lidocaine. Despite the pain at the time of injection, the drug was remarkably well-tolerated with no significant local or systemic toxicities. Indeed, even at the highest dose given, 2 mL of an 8.5 mg/mL solution, the maximal tolerated dose was not reached. However, because of the pain associated with the injection and the requirement for pre-medication, the decision was made not to proceed with the trial in additional individuals until a patient friendly, non-painful delivery method is developed. Overall, from the perspective of toxicity, the trial revealed that TD101 is safe, at least in this single-patient trial.

Although it is difficult to draw definitive conclusions from a single-patient trial, it also appears that TD101 showed some efficacy. Both patient and physicians examining the
patient produced data demonstrating improvement of the callus on the right foot and not the left. Unblinding of the data revealed that the right foot received TD101 and the left foot received vehicle.

Perhaps most impressive among the data was the development of an area of clearing of callus immediately surrounding the area of injection of TD101 (not observed in the vehicle-treated callus). This type of clearing of the callus has never been observed by the patient or physicians during any previous treatment of PC. Taken together, this proof-of-principle trial has led to great optimism among the group and alternative delivery methods are now being pursued to allow additional trials to proceed. Trial data have been submitted (First-in-human mutation-targeted siRNA treatment of an inherited skin disorder, authors: Sancy A Leachman, Robyn P Hickerson, Mary E Schwartz, Emily E Bullough, Stephen L Hutcherson, Kenneth M Boucher, C David Hansen, Mark J Eliason, G Susan Srimatsa, Douglas J Kornbrust, Frances J D Smith, W H Irwin McLean, Leonard M Milstone & Roger L Kaspar).

Additional PC patients that carry the N171K keratin 6a mutation have been identified in Ireland, Denmark and China. We believe this trial is the first stage in development of a well-tolerated and effective treatment for PC patients, as well as a new class of therapeutics that can be applied to beneficial to many patients with genetic disorders.

**STATUS OF THE IPCC**  
Mary Schwartz, Director, PC Project

Since 2004, our strategy has been to bring a PC therapeutic to the clinic as soon as possible. To this end, various siRNAs have been developed to target PC mutations, a 28-day mouse toxicology study (using intradermal injection of siRNA) was completed, an IND proposal submitted to the FDA, and a Phase 1b clinical trial was performed on one patient as approved by the FDA. The clinical trial exceeded our expectations in two ways. First, the pain associated with intralesional (intradermal) injections was much more intense than anticipated, necessitating oral pain medication and regional nerve blocks and precluding future trials using this delivery approach. Second, although the primary focus of the trial was safety (no adverse effects were observed), several efficacy parameters were measured and the effectiveness of the treatment was greater than anticipated. The “bull’s-eye” region of the foot receiving the siRNA showed marked improvement, including healthy non-PC skin that was no longer sensitive to touch. NOTE: The patient stated that this was the first time in her life that she could touch this area without any pain. (To view the patient’s video presentation about the trial, register at www.pachyonychia.org and click on videos on the drop-down list under the Scientist/Physician tab.)

New goals for 2009 for PC Project IPCC members include:

1. **Delivery! Delivery! Delivery!** Surprisingly few are actively working on nucleic acid delivery to skin. We want to achieve success in this area as quickly as possible and are devoting time and resources to this goal. If you or someone you know is working on delivery to skin, please contact us right away. Be sure to register now for a place at the **IPCC meeting on delivery** May 5-6, 2009.

2. Publish the data in our IPCRR registry on over PC 250 patients. If you wish to work with us as a co-author on this project, please contact us immediately.

3. Design, develop and implement an educational outreach program for PC. Seeing one PC patient, or even one family with PC, does not truly educate a physician about PC basics and the enormous differences between PC mutations. Also, it does not properly convey the intense pain suffered by PC patients. We invite IPCC physicians and scientists to work with. We believe we can deliver an outstanding and needed program.

4. Research and publish a **Guide for PC Care**. We need IPCC physicians who are actively treating PC patients to be part of this cooperative effort.

5. Move forward with Trans-Derm’s GeneCreme™ formulation for delivery to PC patients. In studies performed at Stanford with Chris Contag, Tony Oro, and their colleagues, this formulation was shown to deliver the imaging dye cardiogreen (aka indocyanine green) to callused skin as well as infrared dye-labeled siRNA to mouse skin. In both cases, dye was observed to penetrate the stratum corneum to the epidermis and in many cases to the dermis as assayed by a dual axis confocal fluorescence intravital imaging system developed by the Stanford team. We have enlisted a CRO to prepare a GLP-grade GeneCreme™ (both with and without siRNA) for testing in a 3-month rabbit toxicology study with the goal of treating patients as soon as possible with this more patient-friendly delivery system.

Please join with us in these efforts.
IPCRR Consultation / Genetic Testing Conference Calls
Frances Smith, Saney Leachman, Peter Hull, David Hansen

We have recently started monthly conference calls to establish discussions between the physicians doing the consultations with patients registering with PC Project and those carrying out the genetic testing. Clinical photographs and notes from each new patient are discussed before genetic testing commences.

The aim is to ensure that we are screening the PC genes only for those patients that have a reasonable chance of carrying PC mutations.

For rare cases that appear unlikely to have PC we will inform the referring clinician/patient as soon as possible. In some cases we may be able to indicate another diagnosis and either screen for it or suggest another lab that can perform that genetic test. PC Project will continue to provide patient help and support for these individuals with similar clinical features to PC.

In the next few calls we will also discuss a number of outstanding cases which have been screened for the PC genes but have failed to demonstrate detectable mutations. Clinical photographs/notes from these patients will be discussed and those that are likely to have PC will be retested to confirm that no mutation was missed. Based on the clinical presentation, several cases are thought to be unlikely to be PC and if necessary we will consult with the patient/referring clinician to ensure that we have not missed some crucial piece of clinical data. Again, depending on each individual case we may have an alternative diagnosis to suggest along with another lab that can perform genetic testing for the alternative condition.

Already these calls have been shown to be extremely beneficial to all those involved, including the patients to whom we are trying to get a correct diagnosis and test result as soon as possible. The calls have also been an outstanding opportunity for lively discussion regarding unusual manifestations of PC and hypotheses regarding the etiology of these manifestations. We have already identified a couple of new patients who likely do not have PC and we are waiting for further clinical information before starting genetic testing. We have also identified those cases most likely to be PC and are in the process of re-screening these samples. This re-screening process has permitted the identification of mutations in a couple of these samples which were missed on the first round of screening, probably due to a variety of reasons. Overall, these teleconferences appear to enhance our ability to correlate the clinical manifestations more closely with the genetic status to save resources when the diagnosis of PC is unlikely while simultaneously permitting more careful scrutiny of samples that deserve a second, more in-depth evaluation.

Would you like be one of the physicians who conduct consultations for the IPCRR? Do you wish to participate in the monthly review discussions? Please contact Mary Schwartz at PC Project.

NEW PUBLICATIONS


J Dermatol Sci. Therapeutic siRNAs for dominant genetic skin disorders...


(see pg 4 for publications in progress and authors needed listings as well as publications submitted since last IPCC newsletter)

GRANTS

We are pleased that two peer-reviewed government grants have been awarded to support PC clinical trials:

FDA OOPD (Orphan Product) (FD003553)
Pf: Sancy A. Leachman entitled, “Phase 1b trial of TD101 siRNA for pachyonychia congenita.” The aims of the grant are to identify additional PC patients and to conduct the Phase 1b trial.

NIH Phase 1 SBIR (R43AR056559)
Pf: Roger L. Kaspar entitled, “Pachyonychia congenita clinical trial using therapeutic siRNA” has as major goals to define the therapeutic window for TD101 siRNA and duration of mutant K64 knockdown effect following multiple treatments in PC patient-derived keratinocytes as well as determine the safety profile of TD101 in a 3-month rabbit toxicology study now in progress.
REQUEST FOR AUTHORS. As announced in the last IPCC Newsletter, we are giving awards (including cash awards) for publications based on IPCRR data and PC Project sponsored projects. We have validated data and photos on several hundred PC patients. We feel important publications can be developed from this resource. Please contact us if you have interest in the following publications or other related publications or projects utilizing IPCRR data. We will do everything we can to support your efforts and assist in moving your publication forward.

<table>
<thead>
<tr>
<th>Publication Title or Description</th>
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<th>Submit To?</th>
<th>Submission Goal</th>
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<td>Humira study</td>
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<td>15-Nov-08</td>
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<tr>
<td>Characterization of single-nucleotide specific siRNA, TD101</td>
<td>Hickerson, Leachman, Pho, Smith, Gonzalez-Gonzalez, Leake, McLean, Milstone, Kaspar</td>
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<td>1-Dec-08</td>
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<td>IPCRR Data Update</td>
<td>Hansen (other AUTHORS NEEDED)</td>
<td>JID?</td>
<td>15-Jan-09</td>
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<td>Retinoid Data from IPCRR</td>
<td>Gruber, Robert and Matthias Schmuth</td>
<td>TBD</td>
<td>15-Jan-09</td>
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<td>Analysis of PC keratoderma from photographs with mutation status correlation.</td>
<td>Vallari Majmudar, Leachman, Smith, McLean, Edel O'Toole [Other authors may include referring physicians]</td>
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<td>Case Reports - Secondary infection or a transgenic form of PC?</td>
<td>Kay Lynne Harris, Hull, Smith, Hansen, Leachman</td>
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<td>PC Care Guide</td>
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<td>&quot;PC Tarda - Is this PC?&quot;</td>
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<td>&quot;Thickened Nails - Is this PC?&quot;</td>
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Publications submitted this quarter that are sponsored by PC Project with IPCRR data and/or IPCC members

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<th>Publication Title</th>
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<td>Rapamycin selectively inhibits expression of an inducible keratin (K6a) in human keratinocytes and improves symptoms in pachyonychia congenita</td>
<td>Hickerson, Pho, Leachman, Kaspar</td>
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<td>TD101 Clinical Trial</td>
<td>Kaspar, Hickerson, Smith, McLean, Milstone, Boucher, Schwartz, Kornbrust, Srivatsa, Eliasen, Hansen, Leachman</td>
<td>PC Project sponsored TD101 clinical trial</td>
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<td>Keratin K6c mutations cause focal keratoderma</td>
<td>Neil J. Wilson, Andrew G. Messenger, Sancy A. Leachman, Edel A. O'Toole, E. Birgitte Lane, W. H. Irwin McLean, Frances J. D. Smith</td>
<td>PC Project co-sponsor of genetic testing</td>
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<td>siRNA silencing of keratinoctye-specific GFP expression in a transgenic</td>
<td>Emilio Gonzalez-Gonzalez, Hyejun Ra, Robyn P. Hickerson, Qian Wang, Wirbool Piyawattanametha, Michael J. Mandella, Gordon S. Kino, Devin Leake, Ariel A. Avilion, Olav Solgaard, Timothy C. Doyle, Christopher H. Contag, and Roger L. Kaspar</td>
<td>Emilio Gonzalez-Gonzalez is an outstanding PC Project Fellow</td>
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