Thanks! to IPCC members for your on-going support for PC Project

- PC Project brochures distributed at ACMG by Drs. Bale & van Steensel.
- Letters written & PC brochures sent to all PC patients tested and to referring physicians by Drs. McLean & Smith (more than 150 distributed).
- Cells sent from Dr. McLean to Dr. Landthaler for tests with siRNA.
- Grant proposals reviewed by IPCC members.
- News articles received from Drs. McLean and Kaspar.
- Sample genetic testing forms received from Dr. Bale.
- Referrals to other clinicians and researchers by many IPCC members.
- Emails, guidance, advice, encouragement from many IPCC members!

JID 2004 PC Symposium Proceedings Publication

We have approval from the JID to publish the 2004 PC Symposium Proceedings. Of course their editors will review material prior to final acceptance and publication.

PC Project has agreed to fund this effort with a grant of $25,000.

Now, dear friends, we are counting on you to respond to this opportunity and work together to produce a valuable and definitive publication on PC.

We have transcribed and reviewed all of the presentations and all the discussions. At first we had hoped these would be a basis for the JID articles. This is not the case.

Although the transcripts may not be useful in preparation of the published articles, these materials have been very helpful in forming PC Project goals (see page 2), in revising our Grant funding approaches, and in developing the vision for the JID publication.

Sancy Leachman will coordinate this project and she has used the transcribed Symposium materials to develop an approach and outline for the publication. The PC Symposium proceedings will be the definitive publication on PC. It will be complete and comprehensive — a valuable reference tool for scientists and clinicians.

We need your support and the collaborative effort of all IPCC members to accomplish this goal. Sancy will contact you shortly regarding this JID publication.

If you would like a copy of the transcription of your presentation (unedited and phonetically typed!) please request via email from Mary.Schwartz@PC-Project.org.

PC Project Grant Award Announcement at SID Conference April 28, 2004

We have selected the SID conference as the venue to announce the 2004 PC Project Grant Awards.

The grant proposals are currently being reviewed by several IPCC members.

The approach to funding grants was revised during discussions at the 2004 PC Symposium. We asked each applicant to request only those funds necessary so that we can fund more grants and undertake collaborative approaches.

We are grateful that several IPCC members have found outside funding for specific activities which will benefit PC research and some research is already moving forward.

Thanks! Thanks! Thanks!
IPCC Founding Members & 2004 Symposium Attendees

<table>
<thead>
<tr>
<th>Name</th>
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<tr>
<td>Sherri Bale, Ph.D.</td>
<td>Roger Kaspar, Ph.D.</td>
<td>Frances Smith, Ph.D.</td>
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<td>Ralph R. Bradley, M.D.</td>
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<td>Mario R. Capocchi, Ph.D.</td>
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<td>Jiang Chen, M.D.</td>
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<td>Philip Fleckman, M.D.</td>
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<td>Kyonggeun Yoon, Ph.D.</td>
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<td>Olga Igoucheva, Ph.D.</td>
<td>Leonard M. Millstone, M.D.</td>
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<td>Aleksej Kansky, M.D.</td>
<td>Dennis R. Roop, Ph.D.</td>
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1 Organizer/Chair

Next IPCC Meeting — May 3, 2005 New Orleans (prior to the 2005 SID Conference)

PC Project Goals & Progress February 2004 - April 2004

- Research Goals
- Support Goals

PC Project has received IRB approval through WIRB.
2004 Grants

The PC Project Grant Awards were announced on April 28 in Providence, RI prior to the SID meeting. More information is available on the website. Grants selected are:

Leonard Milstone, M.D.
Yale University
Project Title: Inactivation of keratin 6a by sequence-specific Gene Targeting

Dennis Roop, Ph.D. and
Jiang Chen, M.D.
Baylor College of Medicine
Project Title: Generating an inducible mouse model for Pachyonychia Congenita

W.H. Irwin McLean
Ph.D., D.Sc., and Frances
Smith, Ph.D.
University of Dundee, Scotland
Project Title: Drug discovery for the treatment of Pachyonychia Congenita

Maurice A.M. van Steensel, M.D.
University Hospital Maastricht, The Netherlands
Project Title: Gap junction regulation of keratin expression

Philip Fleckman, M.D.
University of Washington
Project Title: National Registry for Ichthyosis and related disorders

Additional funding was established for PC Project Core Resource needs in coordinating clinical, genetic and patient-related activities in support of PC patients and researchers. Sancy Leachman, M.D., Ph.D., University of Utah will administer these funds.

Five Gold Stars to all grant awardees for their prompt and positive response to post-award communications —

(1) Quarterly progress goals have been set with the first target date 1 August 2004. A report will be in the next IPCC newsletter.

(2) Post-award reviews are being completed by Drs. Ervin Epstein, Rudolph Leube, Maurice Seidman and others to further our collaborative efforts and enhance grant potential.

(3) On-going collaboration including sharing of reagents, discussion regarding setting up the best screening assay and exchange of other ideas among the IPCC members.

Be part of this exciting collaborative effort! We’ll have a conference call in mid-June. Contact PC Project (877-628-7300 or Mary of Sancy by email) if you’d like to participate in that call.

JID—July 1 Deadline.

I. Introduction (pp. 3-5) Sancy Leachman

II. Clinical and Pathological Features of Pachyonychia Congenita (pp.16-20) Philip Fleckman

IV. The Strength of the HUGO Database Irwin McLean

V. The Genetic Basis of Pachyonychia Congenita (pp. 24-33) Frances Smith

VII. Genetic & Pharmaco-clinical Approaches to Correction, Modification or Regulation of Gene Expression in Autosomal Dominant Genodermatosis Roger Kaspar

VIII. Goal Oriented Integration of Academia and Industry Philip Fleckman

IX. Advertisement to become a part of IPCC (p. 60) Maurice A.M. van Steensel, M.D.
**Next IPCC Meeting**
May 3, 2005—New Orleans
(prior to the 2005 SID Meeting)
IPCC Welcome Dinner—May 2, 2005

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**PC PROJECT GOALS & PROGRESS**
February 2004 - May 2004

- Research Goals
- Support Goals

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**IPCC MEMBERS**
*new this quarter
**PC Project Grant award

Sancy Leachman, M.D. Ph.D.
Organizer & Chair
*Anonymous
Sherri Bale, Ph.D.
Ralph R. Bradley, M.D.
Mario R. Capecci, Ph.D.
**Jiang Chen, M.D.
*John J. DiGiovanna, M.D.
*Ervin Epstein, M.D.
**Philip Fleckman, M.D.
C. David Hansen, M.D.
Olga Igoucheva, Ph.D.
Aleksej Kansky, M.D.
Roger Kasper, Ph.D.
Gerald G. Krueger, M.D.
Markus Landthaler, Ph.D.
*Rudolph Leube, M.D.
Alfred S. Lewin, Ph.D.
**Irwin McLean, Ph.D., D.Sc.
**Leonard M. Milstone, M.D.
**Dennis R. Roop, Ph.D.
*Michael Seidman, Ph.D.
**Frances Smith, Ph.D.
Bhaskar Thyagarajan, Ph.D.
**Maurice van Steensel, M.D.
Pauline Wong, Ph.D.
Kyonggeun Yoon, Ph.D.

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**IRB Approval & IPCRR begins**

On April 12, 2004, PC Project received approval from Western IRB for the International PC Research Registry (IPCRR). Registration has begun!

We are pleased that in the first 3 weeks, 19 patients have completed initial screening and received the Questionnaire. PC Project is arranging for clinician review and validation as well as for genetic testing when requested by the participants. When researchers need information or participants, we plan to be ready with quality data.
THANKS IPCC members for your on-going support for PC Project. For example:

- Referrals continue for new IPCC members (see list).
- Roger Kaspar has offered ongoing consultation and an opportunity to speak with those at OOPD (Office of Orphan Product Development).
- Len Milstone and Phil Fleckman met with 10 PC patients at the FIRST Conference in July in Kansas City, KS.
- Irwin McLean and Frances Smith hosted 19 PC patients at a PC Patient Support Meeting in Dundee, Scotland, Sep 3–4. Sancy Leachman, Colin Munro, Edel O’Toole, and Maurice van Steensel gave clinician support. The meeting was enormous success.

COLLABORATION. Sancy Leachman set up an important conference call in mid-June to facilitate continued collaboration among grant recipients. THANK YOU to all participants for being so generous and open and willing to share.

2004 GRANT UPDATES

Philip Fleckman: National Registry for Ichthyosis and related disorders. We were just advised that FIRST and GeneDx have joined us in support of this effort.

Rudolph Leube: Creation of Cellular Models for PC. Dr. Leube has provided excellent collaborative input as an active participant in the post-award grant review and the conference call.

W.H. Irwin McLean & Frances Smith: Drug discovery for the treatment of Pachyonychia Congenita. A specialist, Dr Yiwei Zhao, from China, has been recruited to work with Frances Smith on this project.

Leonard Milstone: Inactivation of keratin 6a by sequence-specific Gene Targeting. “I now have my clones of mutant luciferase CHO cells ready to test, using the upstream K6a triplex target site.” Dr. Milstone initiated collaborations with several others and has been given a supplemental grant to involve Dr. Michael Seidman (of the NIH) who will make new oligos for this project.

Dennis Roop & Jiang Chen: Generating an inducible mouse model for Pachyonychia Congenita. Update from Dr. Chen: “The most difficult part of the construction of the targeting vector has been completed earlier this month. Right now, I am in the middle of selecting clones in which the wild type MK6a is replaced by partially humanized N171K-K6a. Then, I only need to insert the neo cassette, before the first targeting vector is complete.”

Maurice A.M. van Steensel: Gap junction regulation of keratin expression. Update from Dr. van Steensel includes this overview of status (1) All mutants of interest are cloned; (2) Confocal laser scanning microscopy expertise gained; (3) First test runs with fusion proteins in 3T3 cells performed; (4) Novel gap junction gene mutation identified, clinical studies performed and published. Functional characterization of the mutation in progress; (5) Cultures of keratinocytes, HaCATs and HeLa started” Dr. van Steensel also reported a new clinical POP trial of novel pharmaceutical agent which my be of interest for PC.

Sancy Leachman: PC Project Core Resource Grant. Activities this quarter included a Patient Support Meeting in Kansas City, KS (July 2004) and a Patient Support Meeting in Dundee, Scotland (Sep 2004), a number of physician referrals for patient’s special needs, continued Registry consultations and genetic counseling.

IRB APPROVAL was given Sep 20 to the PC Project Registry so that we can take biopsies as well as receive and store biopsies, tissue blocks, and glass slides.

2005 IPCC MEETING ST. LOUIS (prior to SID) IPCC Dinner & Social May 3, 2005 IPCC Sessions 9:30 to 4:00 May 4, 2005

Excellent sessions on PC for physicians and scientists will be presented throughout the day on May 4th.

Let us know if you’d need travel assistance, or you’d like to submit an abstract or suggest someone for a presentation. Please contact us at IPCC@PC-Project.org or call 877-638-7300.
**Location of PC Patients**

<table>
<thead>
<tr>
<th>Country</th>
<th>City/Area</th>
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<tbody>
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<td>Australia</td>
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<td>WA</td>
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<td>USA - LA</td>
<td>Wales</td>
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**IPCRR Statistics**

- 136 Individuals identified with PC
- 122 Registered with PC Project
- 32 Questionnaires Completed
- 17 Genetic Test Results Available
- 6 Waiting Test Results

**IPCC MEMBERS**

- *new this quarter*
- **PC Project Grant award**

Sancy Leachman, M.D. Ph.D
Organizer & Chair

Sherri Bale, Ph.D.
Ralph R. Bradley, M.D.
Mario R. Capecci, Ph.D.
**Jiang Chen, M.D.**
John J. DiGiuliana, M.D.
Ervin Epstein, M.D.
**Philip Fleckman, M.D.**
C. David Hansen, M.D.
Olga Igocheva, Ph.D.
Aleksej Kansky, M.D.
Roger Kaspar, Ph.D.
**Paul Khavari**
Gerald G. Krueger, M.D.
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**Leonard M. Millstone, M.D.**
*Colin Munro, M.D.*
*Edel O’Toole, M.D.*
**Dennis R. Roop, Ph.D.**
**Michael Seidman, Ph.D.**
**Frances Smith, Ph.D.**
Bhaskar Thyagarajan, Ph.D.
**Maurice van Steensel, M.D.**
Pauline Wong, Ph.D.
Kyonggeun Yoon, Ph.D.

**Publication Incentive Bonus.** The first publication bonus award has been made to Frances Smith for her article on PC which will be published in an upcoming issue of the BJD. We encourage all IPCC members to publish PC data and to let us know of your publications.

**A gift for you!** In appreciation of your support for PC, and in support of DEBRA UK, we’re happy to send you this special CD. You’ll definitely recognize one of the ‘super stars.’ Enjoy!
JID UPDATE All of the articles except the Clinical and Pathological Features of PC have been completed and are in the final stages of editing. It is anticipated that the final version will be submitted to the JID in January, 2005 and the editors have agreed to expedite our review in an effort to have it published before the Society of Investigative Dermatology Meeting in May, 2005. Although we had hoped for earlier completion of this project, because of the delay, we have been able to perform an in-depth review of the literature, which has resulted in the development of a comprehensive bibliographic resource available to everyone. This includes English language translations of over 50 foreign language articles, performed by Dr. Karen Leube's translation services. We never realized that inclusion of Rudolph Leube would bring such great side benefits - thank you both. We have also done a preliminary analysis of the PC questionnaire data and have obtained outstanding clinical and pathological photographs which will be included in the manuscripts. Finally, as you can see from the summary of mutation testing data on the back, we have confirmed mutations in 35 PC participants so far. The newly identified mutations from our study will also be included in the JID Proceedings. Thanks so much to all of you who have made the creation of this update on PC possible!

2004 GRANT UPDATES

Philip Fleckman: National Registry for Ichthyosis and related disorders. Funding completed for this Registry.

Rudolph Leube: Creation of Cellular Models for PC. This effort is underway.

W.H. Irwin McLean & Frances Smith: Drug discovery for the treatment of Pachyonychia Congenita. The K6a promoter has been cloned and verified and is being put into the luciferase plasmid for drug screening in the new year. The K6a constructs for other IPC projects are completed.

Leonard Milstone: Inactivation of keratin 6a by sequence-specific Gene Targeting. (1) We now have clones of CHO cells containing a single copy of the K6a-mLuc reporter. One set of clones have the polypurine strand of the TFO site on the sense strand with respect to the mLuc (e.g. mLuc38), the other clones have the polypurine strand of the TFO site on the antisense strand with respect to the mLuc (e.g. mLuc37).

Both clones have very low background fluorescence and both show substantial signals (i.e. correction of the stop codon mutation in the mLuc) after the addition of a single-stranded donor oligo. In these model systems we are now testing the hypothesis that triple binding can increase the frequency of mutation correction. We are testing two purine oligos, one with standard bases and phosphorothioate-protected termini; the other has several of the Gs replaced with 7 deazaguanine to potentially increase binding. (2) We are ready to transfuse the K6aGFP into test cells as soon as received.

Deniss Roop & Jiang Chen: Generating an inducible mouse model for Pachyonychia Congenita. Since we had trouble purifying the previously reported “near-ready” targeting construct from its wild-type form, we had to modify the original mouse K6a genomic DNA clone by exchanging the kanamycin resistant gene on the PI plasmid backbone with chloramphenicol resistant marker before making further modifications. The exchange of drug resistant genes has been completed. Now, we are working on the partial replacement of the wildtype mouse K6a sequence with the mutant sequence of the human K6a gene.

Michael Seidman: Supplemental Grant with Leonard Milstone. We have completed the synthesis of one of the chemical precursors for the oligonucleotides and are now in the midst of the synthesis of another of the precursors. There are three precursors that are unavailable commercially and must be synthesized. We have enough of the third to allow for some initial, small scale, oligonucleotide synthesis.

Maurice A.M. van Steensel: Gap junction regulation of keratin expression. PC grant fund helped in research on a disease called oculo-dento-digital dysplasia showing that yet another gap junction protein influences nail and skin growth. Some possible therapeutic applications for PC. [Will be published American Journal of Medical Genetics.]

Sandy Leachman: PC Project Core Resource Grant. We have held a number of consultations with physicians regarding care for their PC patients; biopsies were taken from 4 PC patients for analysis; tissue samples were collected during a patient surgery providing opportunity for further pathological analysis. In addition, patient consultations and genetic counseling have been completed for the IPCRR.

2005 IPCCC MEETING
ST. LOUIS (prior to SID)
May 3, 2005
IPCC Dinner & Social
May 4, 2005
IPCC Sessions
9:30 to 3:00

Thanks to Dennis Roop and SID staff for arrangements for our PC sessions on May 4. Please let us know whether or not you will attend. All grant recipients will be presenting a status report.

Please let us know if you need travel assistance, or if you'd like to submit an abstract or suggest someone for a presentation related to PC.
Thanks to Marcus Landthaler for sticking with it and getting some excellent siRNAs designed and tested for further use... Great news!

PC Project is delighted to report that effective January 1, 2005, Roger Kaspar will head a new ‘skin delivery’ research firm focused specifically on delivery for PC. This is a great boost to PC goals.

### Location of PC Patients

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### IPCRR Statistics

- 152 Individuals Identified with PC
- 140 Registered with PC Project
- 44 Questionnaires Completed
- 35 Genetic Test Results Received

### IPCC Members

**New this quarter**

- Sancy Leachman, M.D. Ph.D., Chair
- Sherri Bele, Ph.D.
- Ralph R. Bradley, M.D.
- Mario R. Capucci, M.D.
- **Jiang Chen, M.D.**
- Bernard Cohen, M.D.
- John J. DiGiovanna, M.D.
- Jon A. Dyer, M.D.
- Ervin Epstein, M.D.
- **Philip Fleckman, M.D.**
- Jennifer Hand, M.D.
- C. David Hansen, M.D.
- Olga Igocheva, Ph.D.
- Alan Irvine, M.D. FRCP, MRCP
- Aleksiej Kansky, M.D.
- Roger Kaspar, Ph.D.
- Paul Khavari, M.D., Ph.D.
- Gerald G. Krueger, M.D.
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- Bhaskar Thyagarajan, Ph.D.
- **Maurice van Steensel, M.D.**
- Pauline Wong, Ph.D.
- Kyonggeun Yoon, Ph.D.

**PC Project Grant award**