



# IPCC News

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## International Pachyonychia Congenita Consortium

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**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 IPCC 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 anti-sense 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 triplex 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 transfect the K6aGFP into test cells as soon as received.

**Dennis 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 wildtype form, we had to modify the original mouse K6a genomic DNA clone by exchanging the kanamycin resistant gene on the P1 phage 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.]

**Sancy 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 IPCC 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!

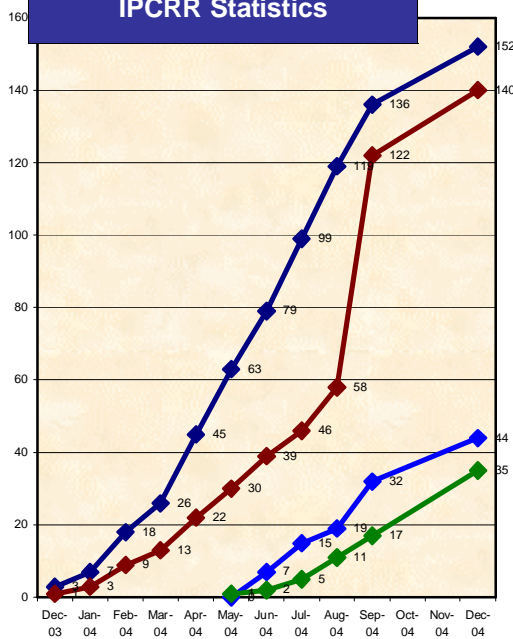


PC Project is delighted to report that effective January 1, 2005, **Roger Kaspar** will head a new 'skin delivery' research firm focused specifically on delivery for PC. This is a great boost to PC goals.

### Location of PC Patients

Australia 13	USA - IN 1
Brazil 1	USA - LA 1
Canada 8	USA - MA 1
England 19	USA - MD 1
Finland 2	USA - MI 1
France 5	USA - MN 5
Italy 1	USA - NY 17
Netherlands 8	USA - OH 5
Scotland 2	USA - OR 3
Sweden 6	USA - PA 2
Unknown 9	USA - SC 3
Wales - 1	USA - TX 9
USA - CA 6	USA - UT 7
USA - CT 2	USA - VA 1
USA - FL 1	USA - WA 6
USA - IL 5	Total 152

### 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 Bale, Ph.D.

Ralph R. Bradley, M.D.

Mario R. Capecchi, Ph.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 Igoucheva, Ph.D.

• Alan Irvine, M.D. FRCPI, MRCP

Aleksej Kansky, M.D.

Roger Kaspar, Ph.D.

Paul Khavari, M.D., Ph.D.

Gerald G. Krueger, M.D.

Markus Landthaler, Ph.D.

• Birgit Lane, Ph.D.

Rudolph Leube, M.D.

Alfred S. Lewin, Ph.D.

\*\* Irwin McLean, Ph.D., D.Sc.

\*\* Leonard M. Milstone, M.D.

Colin Munro, M.D.

Edel O'Toole, M.D.

• Phoebe Rich, 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.

\*\* PC Project Grant award

