



International PC Consortium

Pachyonychia Congenita Project

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Happy 2nd Anniversary IPCC! As we review progress since the 1st PC Symposium in Park City, Utah, February 2004, we see what one meeting, one conversation, one publication, and one group of dedicated researchers can achieve. We see amazing accomplishments by members of the IPCC in advancing research and moving toward effective therapies. For patients, while there is no cure and no therapy as yet, there is an effective community, a reason to hope, an opportunity to participate in the Registry and obtain genetic testing. Congratulations IPCC! Now, look forward and know that finding a cure and reaching a successful therapy for PC is absolutely our mission and our target. *Mary Schwartz*

GENE CAUSING ICHTHYOSIS VULGARIS DISCOVERED

PC Project CDA Research Fellow, Dr. Frances Smith, University of Dundee, Scotland has made a major breakthrough in the study of keratinizing disorders. She has identified the first mutations in a gene called filaggrin in patients with a relatively common skin disorder called ichthyosis vulgaris (a genetic condition causing dry, scaly skin). This work has arisen from a collaboration involving dermatologists and scientists in the USA, Ireland and Scotland. Mutations in the filaggrin gene were suspected as the cause of ichthyosis vulgaris for many years, but this gene is very large and has a complex structure which until now has defied any attempts at analysis.

Building on special techniques, she and her mentor Irwin McLean developed previously to analyze plectin, another large complex gene involved in skin disease, Dr. Smith solved these technical problems and identified the first mutations causing the most common keratinizing disorder - a genetic disease in the same "family" of disorders as PC and other keratin diseases.

Filaggrin is a protein found in the outer layers of the epidermis. It is made as a giant protein called pro-filaggrin which is then cleaved into a number of smaller identical proteins called filaggrin. These smaller proteins bind to keratins, including

the keratins involved in PC and other keratin diseases, and cause the keratin network to collapse. This leads to the formation of the outermost dead barrier layers of the skin, whose purpose is to prevent water loss through the skin and also to keep foreign organisms and chemicals out of the skin.

One of the amazing things about this discovery is that filaggrin mutations are very common in the population. By analyzing DNA from thousands of people around the world, Dr. Smith and colleagues have found that about 9% of people of European origin carry one or the other of two common mutations in the filaggrin gene. These mutations completely knock out the production of filaggrin and so about 9% of people in Europe and European Americans make only 50% of the normal amount of filaggrin. Another way to look at this is that more than 20 million people in the USA alone make only half the normal amount of filaggrin in their skin. The people who carry one filaggrin mutation have a very mild form of dry skin which can go unnoticed. People who carry two filaggrin mutations, about 1 in 500 people of European origin, have the full ichthyosis vulgaris presentation and suffer from extremely dry, scaly skin.

One might ask how all this relates to PC? Well, since 9% of people carry filaggrin mutations, then

9% of people with PC also carry a filaggrin mutation in addition to the keratin gene mutation that causes their PC. Since the filaggrin protein binds to keratin proteins as part of its function, it will be interesting to see what happens if you have both PC and a filaggrin mutation. One possibility is that this might make the PC worse, or, it might make it better, or, it might have little or no effect. Dr. Smith and her colleagues are now re-examining the DNA of PC patients, and patients with other keratin mutations, to see if filaggrin mutations affect the other disease one way or the other. This could be one of the so-called "modifier genes" that causes some PC patients to have a different severity of PC even though they have the same keratin mutation.

Dr. Smith's landmark paper on filaggrin has just been published online in the top genetics journal, *Nature Genetics*, and will appear in hard copy in the March issue.

IPCC MEETING 2007

May 2 - May 3

prior to the SID Annual Meeting
Philadelphia, PA

Please register on-line at

<http://www.pachyonychia.org/IPCC2006.html>

Submit abstracts for presentations or
posters by 15 March 2006

Submit requests for stipends or Young
Investigator Scholarships by 1 April 2006
Preliminary program available

TRANSDERM PROGRESS REPORT

TransDerm, a company devoted to identification and delivery of therapeutic agents for PC, has benefited immensely from interactions and collaborations with members of the International PC Consortium and PC Project through exchange of materials, ideas, and enthusiasm. TransDerm has focused on two major areas of investigation: (1) Identification of potent and specific inhibitors against the molecular targets responsible for PC and (2) Investigation of the best route for delivery of nucleic acid-based inhibitors (e.g. siRNAs) to the appropriate affected skin cells.

Potent and selective inhibitors. A complete sequence walk around the K6a N171K single nucleotide mutation site has been performed using siRNAs provided by Dharmacon. Two lead inhibitors have been identified that potentially inhibit mutant K6a N171K expression in tissue culture cells with little or no effect on wild-type K6a expression. These experiments are currently being extended to mice. Additional sequence walks for other mutations involved in PC are in the planning stages as well as mutations involved in other keratinizing disorders.

Identification of an efficient delivery route. Several routes of nucleic acid delivery to skin cells have been investigated including direct injection, preparation of "gene creams" and electroporation. Each of these has its own set of advantages and disadvantages. New and improved methods are being pursued "in house" as well as through joint projects with collaborators.

Other noteworthy events at TransDerm include:

- * Submission of a Phase 1 SBIR grant proposal on developing PC therapeutics to the NIH
- * Enlistment of a prominent consultant experienced in shepherding siRNA therapeutics through the FDA system and preparation of a product development plan
- * Near completion of negotiations for synthesis of large quantities of lead siRNA inhibitors for initiating toxicol-

ogy studies in minipig model in preparation for pre-IND and IND filing

- * Pursuit of intellectual property protection for identifying and using siRNAs to treat PC

- * Hosting of Dr. Frances Smith (PC Career Development Award (CDA) recipient) as visiting scientist

- * Participation in PC patient support meeting in Niagara Falls (sponsored by PC project)

- * Many presentations on PC given in academic, industry, and lay settings

- * Sponsorship of JID Symposium Proceedings

CETT PROGRAM

Thanks to Sherri Bale for alerting us to this new program. The website at www.cettprogram.org states, "Access to quality genetic testing for rare diseases is essential in the diagnosis and management of patients with inherited diseases... Currently the development of tests for rare genetic diseases is not keeping pace with the progress of knowledge of the genetic basis of disease." The CETT provides funding for researchers seeking to develop genetic tests for rare disorders. We are so fortunate to have PC genetic testing provided by Drs. McLean and Smith at University of Dundee and confirmed by Dr. Bale at GeneDx.

Congratulations to GeneDx on turning six years old on March 6 - Six on the Sixth in 2006!

PC PROJECT AWARDED NIH R13 GRANT FOR 2006 IPCC MEETING

Abstracts for presentations and/or posters should be submitted no later than March 15. Please submit requests for travel stipend or New Investigator scholarships on or before April 1.

This will be a major scientific meeting - we urge you to register as soon as possible and promote the event within your institutions

IPCC MEMBERS SUBMIT GRANT

IPCC members including Drs. Leachman, Roop, McLean, Milstone, Smith and Kaspar participated in the submission of a Center of Research Translation (CORT) proposal to the

NIH. Results will be announced in March 2006. Several independent R01 grants for PC have also been submitted by members of the IPCC.

EFFECTIVE ASSESSMENT STRATEGY

Sancy Leachman has submitted an abstract to the Society of Investigative Dermatologists based on the successful sample collection procedures conducted at the PC Niagara Falls Patient Support Meeting in August 2005. At that meeting, 31 PC patients used tape-stripping to provide skin for DNA analysis. The patients also provided shaved shards from affected areas.

In her abstract reporting the results of this sample collection study, Dr. Leachman concludes, "*these data demonstrate that expression levels of PC keratins can be assessed in shaved or tape-stripped skin.*" This measurement will be able to "*conclusively establish whether PC keratin expression has been successfully reduced in vivo.*"

NEW PC PUBLICATION

A new article on PC was posted on-line at www.GeneTests.org in January 2006 after nearly a year in preparation. Special thanks to Drs. Kaspar, Leachman, McLean, Milstone, Smith and van Steensel for this effort.

