



International PC Consortium

Pachyonychia Congenita Project

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SUCCESS THROUGH COLLABORATION. I have learned that collaboration may not be ‘normal’ in the scientific field and may even be uncomfortable to some, so this Thanksgiving season I am filled with an overflowing appreciation for each of you and the amazing examples of collaboration within the IPCC. We want everyone’s research to be enhanced through IPCC relationships and through interactions with PC patients. Beyond our PC goals, it is our sincere hope that our efforts will benefit those with other disorders as well. Thank you, IPCC members for collaborating with each other and with PC Project. Mary

Mario Capecchi, distinguished professor of human genetics and biology at the University of Utah’s Eccles Institute of Human Genetics has won the **2007 Nobel Prize in physiology or medicine**. Our congratulations and admiration to Dr. Capecchi for this high honor. We remember that at the first IPCC meeting in 2004, Dr. Capecchi advised that ‘delivery’ would be a major challenge in our efforts for PC. We listened! We are focused to solve the delivery challenges and expect to have success in this area—thanks in part to Dr. Capecchi’s early warning and his willingness to collaborate, share and direct as we began our efforts to find ‘a cure for PC.’

In the midst of all the publicity following announcement of the Nobel Prize award, Dr. Capecchi took time to send this message to the IPCC: *“Your enthusiasm and dedication to making a difference for patients with Pachyonychia Congenita is extraordinary. I applaud your effort. I look forward to the upcoming siRNA clinical trials and wish them success. Best wishes, Mario R. Capecchi, PhD.”*

Jiang Chen is currently a research instructor of Dermatology and the Charles C. Gates Regenerative Medicine and Stem Cell Biology Program at the University of Colorado at Denver and Health Sciences Center (UCHSC). His research is focused on the development of inducible “knock-in” mouse models for ichthyosiform dermatosis, disorders of skin appendages, keratodermas of the palms and soles (including pachyonychia congenita) that are caused by dominant mutations of the epidermal keratinocyte genes. Utilizing existing epidermal skin disease

mouse models and various robust approaches and delivery systems, RNAi and lentivirus, he is also actively involved in the development of skin gene therapy strategies, aiming to target epidermal stem cells. Dr. Chen is also assisting PC Project in coordinating arrangements for the May 2008 IPCC meeting in Heifei, China.

Marcela Del Rio and Fernando Larcher (Epithelial Biomedicine Division, CIEMAT, Madrid, Spain) are participating with the Animal Models and Delivery Systems Group of the IPCC. For nearly ten years, they have devoted intense effort to the development and application of tissue engineering and gene therapy strategies to cure inherited and acquired skin diseases. Their team at CIEMAT includes both the Skin Regenerative Medicine Unit led by Dr. Marcela Del Rio and the Cutaneous Disease Modelling Unit led by Dr. Fernando Larcher.

Their studies in this field began with the development of a bioengineered skin based on the culture of human keratinocytes on top of a live fibroblast-containing fibrin matrix (a dermal equivalent) which demonstrated to be an efficient and robust tissue engineered product to treat severe acute skin losses such as large surface third-degree burns. At the same time they were also searching for pre-clinical applications of tissue engineered skin equivalents. In fact, the group came up with a methodology enabling the generation of numerous mice engrafted with a significant area of single donor-derived human skin. The system, named as the skin-humanized mice, is based on the grafting of fibroblast-containing, fibrin-based skin equivalents

described above using optimized surgical procedures.

This system emerged as a unique platform to evaluate both cell and gene therapy strategies. Using this system, they have already been able to establish faithful humanized models for several genetic skin diseases such as Dystrophic and Junctional Epidermolysis Bullosa, Xeroderma Pigmentosum, etc. Recently, in collaboration with Dr. Roger Kaspar (Transderm Inc, Santa Cruz, CA) they took the challenge of developing a humanized model of Pachyonychia Congenita (PC). To that end keratinocytes and fibroblast were isolated from a small skin biopsy taken of two PC patients. The cells were used to generate skin equivalents that were, in turn, grafted to recipient mice. To their delight, several mice were engrafted with PC skin. Having a large number of pachyonychia skin-engrafted mice from a single patient biopsy will enable us now to test novel pharmacological or gene-based medicines including siRNAs for this yet untreatable disease. We hope for success to be translated soon to PC patients.

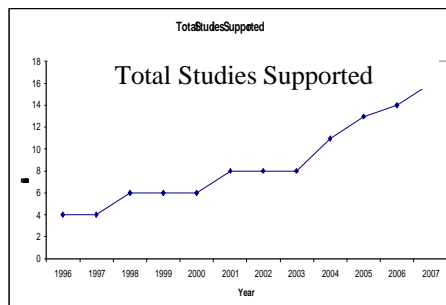
John DiGiovanna is Director of the Division of Dermatopharmacology and Professor in the Department of Dermatology at the Warren Alpert Medical School of Brown University. He is also an Adjunct Investigator at the National Cancer Institute, NIH. Since 1980, he has been involved in studies of the inherited skin disorders focusing on the disorders of cornification and the cancer prone genodermatoses. These studies aim to better understand the clinical manifestations and underlying causes of these diseases as well as improving

treatment. He works closely with investigators at the NIH in clinical, translational, and genetic epidemiologic studies of the inherited disorders of DNA repair, including xeroderma pigmentosum (XP) and trichothiodystrophy (TTD). Patients with XP develop dry skin, pigmentary abnormalities, have a high risk of skin cancer, and some have neurologic degeneration. TTD can be caused by mutations in the same genes, but has different clinical features including short brittle hair, developmental delay, photosensitivity, ichthyosis, and a broad spectrum of abnormalities. Ichthyosis including collodion presentation, nail changes, and less commonly keratoderma can occur in TTD. This work aims to better define the clinical and molecular abnormalities in these disorders as a framework for understanding the underlying mechanisms as well as developing better treatments.

Philip Fleckman heads the National Registry for Ichthyosis and Related Disorders which was funded by NIAMS in 1994 to identify individuals affected by the ichthyoses, confirm their diagnosis by specific clinical and histologic criteria, and enroll them into a registry. The purpose of the Registry is to improve understanding of the diagnosis, pathophysiology, and treatment of affected individuals.

610 individuals have been enrolled who are well characterized by clinical, histologic, biochemical and molecular means and are interested in participating in studies of their disorder. Cholesterol sulfate levels were determined in 171 subjects, and a “bank” of 119 biopsies read by expert pathologists and 168 DNA samples analyzed for mutations in genes underlying 12 disorders has been established. Validated quality of life information was also obtained. Sixteen studies have been aided by the Registry; the increase in studies supported as a function of time (see figure) reflects the continued usefulness of the data. Research registries are important tools for those who seek to understand and treat people with rare diseases. Beyond “validating” the disease for affected

individuals, they offer a broad perspective of the disease not possible from caring for a few affected individuals. In addition, they offer potential access to well-characterized subjects who wish to participate in studies of their disorder.



The paradox of research registries is that while the expensive part of running them – the startup, enrollment and characterization of enrollees, is well funded, the most useful part – supporting investigations of the disorders on which the registry focuses with acquired data and subjects, are poorly funded or not funded at all. Because of this, research registries are at risk for death at the time when they “come of age.” As new information and treatments for the ichthyoses emerge, the importance of maintaining and updating this valuable resource is apparent.

Peter Hull, Head of the Division of Dermatology, University of Saskatchewan, a clinical dermatologist and researcher, received the Canadian Dermatology Foundation “Practitioner of the Year 2007” from the Canadian Dermatology Association. Dr. Hull was recognized as an outstanding researcher, teacher and practitioner who had enriched dermatology by his hard work and dedication.

Dr. Hull has assisted PC Project at two Patient Support meetings (Dundee 2006 and Park City 2007) and is the newest member of the [PC Project MSAB](#).

He is participating with the IPCC Registry Working Group. The group intends to publish data from the Int'l PC Registry so that it will be available to all. Dr. Hull will also begin providing consultation services for PC patients.

Gerald Krueger has a long-standing interest in psoriasis. His work on the transplantation of involved and uninvolved skin to athymic mice in the early 1980s provided an early indication that without immune/inflammatory cells, there is no visible lesion of psoriasis. His psoriasis research also has a therapeutic aspect, focusing on the early phases of clinical trials using biological response modifiers as well as traditional agents.

He and Dr. Kristina Callis-Duffin started the Utah Psoriasis Initiative. This project is focused on identifying clinical phenotypes and their associated findings and on identifying genes/gene-sets that associate with or drive these unique phenotypes. Currently over 850 subjects with psoriasis have been phenotyped and enrolled in the Utah Psoriasis Initiative. The resource of having a large cohort of psoriasis subjects that are well characterized with DNA banked from their blood has already led to productive collaborations. A recent collaboration with Celera Diagnostics (Alameda, CA) led to the discovery of polymorphisms in two genes in the IL-12/IL-23 pathway that have a strong association with psoriasis. This finding gained additional significance because rapid, dramatic and long-lasting improvement is noted when monoclonal antibodies to IL-12/IL-23 are given to patients with psoriasis.

Edel O'Toole is a Clinical Senior Lecturer based in the Centre for Cutaneous Research in the Institute of Cell and Molecular Science and an honorary consultant dermatologist at Barts and the London. She is originally from Leenane, a small village in the West of Ireland famous for the film *The Field* and the scenic Killary Harbour. She was appointed to her current post in 2001. Her clinical interests are paediatric dermatology and genetic skin disease (including pachyonychia congenita [PC]), and students and post-docs in her group are working on many diverse aspects of keratinocyte biology. Rudolf van Koningsveld is studying the

signalling role of keratins (cytoskeletal proteins in keratinocytes) in cell-cell adhesion in PC. Emmanouil Papadakis and Monika Cichon are investigating the role of the receptor tyrosine kinase, Axl, in cancer invasion and apoptosis. Vera Martins, a PhD student from Portugal, is using small inhibitory RNA technology to look at the role of type VII collagen, a basement membrane protein, in cancer. Manuraj Singh is a Dermatology SpR on a MRC Clinical Training fellowship, who is studying varicella-zoster infection of keratinocytes, particularly stem cells, in collaboration with Judy Breuer. Edel also collaborates closely with David Kelsell on a number of projects including harlequin ichthyosis (a severe congenital skin disease) and the genetics of atopic eczema in the local Bangladeshi population. Edel enjoys the challenge of having parallel clinical and scientific careers and hopes that this dual relationship can result in her research leading to translational benefit for patients

Amy Paller, Head, Dept of Dermatology, Children's Hospital, Chicago, IL and current President of the Society of Investigative Dermatology and Dr.

Brandi Kenner-Bell have applied for IRB approval for a natural history study of PC patients. They are working with PC Project and the Int'l PC Research Registry.

Liz Rugg is an associate researcher in the Department of Dermatology at the University of California Irvine. Her research interests include keratin disorders and wound healing. One current focus of her research is the ability of chemical chaperones to reduce the cellular effects of mutant keratins. Keratin aggregates are a feature of many keratin disorders and suggest that mutant keratins have abnormal conformations. Chemical chaperones are compounds which help proteins fold correctly. Liz has evidence that these compounds can reduce the sensitivity of cells expressing mutant keratins to environmental stress. This raises the possibility that chemical chaperones may have the potential to alleviate symptoms in pachyonychia con-

genita and related conditions by reducing the formation of keratin aggregates and helping mutant keratins form normal filaments. Liz is hoping to investigate this further with the help of a grant from NIH.

Matthias Schmuth is an Austrian dermatologist with particular interest in disorders of cornification. His research is focused on trying to understand how mutations underlying disorders of cornification result in abnormalities of the epidermal barrier. He is working to increase understanding of the role of keratins 1 and 10, loricrin, transglutaminase-1 and filaggrin in epidermal structure and function through studies of patients with aberrant forms of these proteins. Dr. Schmuth runs a cornification clinic with Dr. Mary Williams at the University of California, San Francisco (UCSF). He is on the advisory board of the Foundation for Ichthyosis and Related Skin Types (FIRST) and recently has helped establish the first Austrian patient support group for disorders of cornification.

Eli Sprecher serves as deputy director for academic affairs of the Rappaport Institute for Research at the Technion, is heading the Medical Genomics Program and is the director of the Laboratory of Molecular Dermatology at the Department of Dermatology, Rambam Health Care Campus, Haifa, Israel. Sprecher's laboratory investigates the molecular genetics of inherited skin diseases with a particular focus on keratin disorders. Recently, this group succeeded to decipher the molecular basis of a rare autosomal dominant disorder, Naegeli-Franceschetti-Jadassohn syndrome, which manifests with reticulate hyperpigmentation, abnormal sweating, absence of fingerprints, but also shares some features with PC such as focal keratoderma and nail dystrophy. The disease was found to result from mutations in the gene encoding keratin 14, which is usually associated with the skin blistering disease, epidermolysis bullosa simplex (EBS). In contrast with mutations associated with EBS which disrupt the cell cytoskeleton, the mutations causing Naegeli-Franceschetti-

Jadassohn syndrome, were shown to lead to increased apoptosis in the epidermis basal cell layer, possibly pointing to the importance of non-mechanical functions of keratin molecules.

Alain Taieb, Head, Dept of Dermatology & Pediatric Dermatology at the National Reference Center for Rare Skin Diseases, Bordeaux, France and Dr.

Fanny Morice have formed an amazing collaboration with PC Project to conduct the Registry consultations for nearly twenty PC patients in France. Test results will be available shortly for many of these patients. This is a great example for other physicians.

Maurice van Steensel co-hosted a successful *1st World Congress on Genodermatology* in Maastricht, The Netherlands. A number of IPCC members participated and we trust this will lead to new collaborations and additional patient referrals to the PC Registry.

siRNA Clinical Trials Update

With financial sponsorship from PC Project, the drug TD-101 (an siRNA targeted specifically to inhibit only the mutant gene in patients with the K6a N171K mutation) has been manufactured under cGMP standards at Agilent Technologies, Inc. (Boulder, CO). The fill/finish process has been completed under cGMP standards at the University of Iowa (College of Pharmacy, Division of Pharmaceutical Service, Iowa City, IA). All of the necessary testing is being completed so Sancy Leachman can file the IND (Investigational New Drug) application with the US Federal Drug Administration. It is our hope the trial will be approved and begin early in 2008 under Dr. Leachman's direction.

We have received outstanding support from special consultants including Susan Srivatsa (Elixin Pharma, Encinitas, CA), Doug Kornbrust (Preclinsight Inc., Reno, NV) and Steven Hutcherson (Cyclix Ltd, Richmond VA) who have volunteered their skills to make this project a success. Thank you!

In this issue, we featured several IPCC members to show how each individual affects the overall IPCC success. Thanks to everyone who helped me collect and write this information. I hope to gather more for the next Newsletter. Mary

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