Ichthyosis Focus

F.I.R.S.T.
Foundation for Ichthyosis and Related Skin Types

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Relationship of Netherton Syndrome to Atopic Dermatitis

Peter M. Elias, M.D. and Mary L. Williams, M.D.

Clinical Characteristics and Differential Diagnoses:

Infants with Netherton Syndrome (NS) typically display total body scaling with extreme redness or inflammation, similar to that seen in patients with severe atopic dermatitis. They also often develop severe allergic reactions to food. Symptoms are commonly present at, or shortly after, birth. In older children and adults, a unique pattern, termed *ichthyosis linearis circumflexa,* may develop in which wavy or serpent-like areas of redness bordered by (double-edged) scale are present. Some apparently less-severe cases may present with excess scaling, but little redness, a milder variant of NS, termed "peeling skin syndrome." The skin changes are typically accompanied by diagnostic defects in the structure of hair, called *"bamboo hair"* or *trichorrhexis invaginata,* in which the weakened outer hair shaft collapses over or into the lower part of the hair shaft. These hair defects are not always present and even when present, only 20-50% of hairs display the abnormality. Therefore, since the hair abnormality may be absent in some patients, or develop several years later, the diagnosis is easily missed. These patients often carry alternate diagnoses, such as "congenital psoriasis," LI, CIE, or "severe atopic dermatitis." Although the clinical features in infancy can be confused with psoriasis (see below), a key distinguishing feature is that *thinning* rather than *thickening* of the stratum corneum occurs, which should suggest the correct diagnosis. Certain electron microscopic features also are characteristic of NS.

Patients with NS have a severe abnormality of their skin barrier (Fig. 1). When the skin barrier is defective, the body cannot retain its water, which is lost to evaporation. The barrier defect in NS may account for several other features of this condition. Infants with NS commonly have severe growth failure – initially with poor weight gain, later with lower rates of linear growth (height). This growth failure appears to be due predominantly to loss of calories through heat of evaporation. When water evaporates, it carries with it energy or heat. This is why sweating cools the body – but sweating is regulated by the body in response to its internal temperature. The water lost across the skin barrier is not regulated by body heat and so, to maintain body temperature, food calories (stored in the body as fat) must be burned to compensate for the heat loss. With a severe barrier defect – as in Netherton syndrome – an adult can lose as much as 1 1/2 to 2 quarts of water a day with

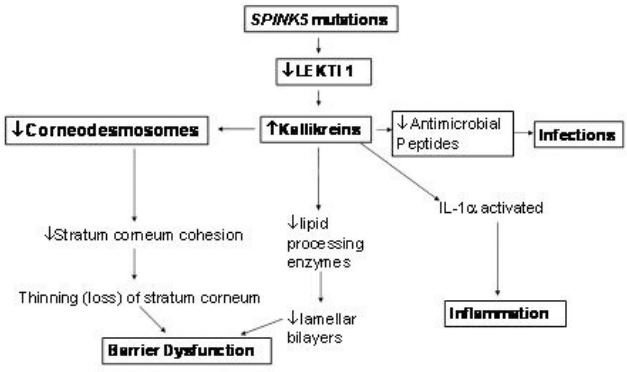

Figure 1: PATHOGENESIS OF NETHERTON SYNDROME

Relationship of Netherton Syndrome to Atopic Dermatitis *continued on Page 7*

Inside Ichthyosis Focus

Tele-Ichthyosis: a new online resource available to dermatologists (see pg. 5)

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Correspondence Corner

Dear Jean,

My name is Dawn Dombrowski/McDonnell. I receive your quarterly newsletter and often ponder whether I should write my personal story or not. When I begin to write, I find myself in tears rehashing past emotional hurts, and also being grateful knowing those of us who have any outward disfiguring disease or handicap possess gifts we are often unaware of until later in life.

I found solace in the recent spotlight article about John Paul. I was born on May 5, 1961 at North Shore Hospital–Cornell Medical Center, the first of 4 children. My parents were all of 21 & 22 at the time. They were childhood sweethearts who were strong in their faith, and college educated with science backgrounds in PE and medicine. The story for me at that time was bleak. I was diagnosed with complete congenital collodion ichthyosis. I was taken immediately after my mother gave birth, whisked away not to be seen. They didn't tell her anything. I don't think they knew. I was some freak of nature covered in brown with an extra layer of skin from head to toe inside and out.

My entire body was covered with scales. My mother was told that there was a possiblity that I would have no hair, sweat glands, or teeth, and extra precautions would need to be taken to prevent infection. I need not describe the unfortunate future for anyone with this disease. Often, I would hear the stories from my parents as they painfully described my fate and the enormous financial burden that they assumed they would endure at such an early age. When the doctors came in to suggest I be baptized before given last rites (that's how they did it then), my parents agreed. They had hope, faith, and determination to keep me alive. The prevailing thought then was to take overdoses of Vitamin A because, at that time, they believed there was something wrong with how I metabolized Vitamin A. I am grateful my parents did not choose that option.

A fund was started for the incredible costs it took to have round-the-clock nurses for three months. The expense far exceeded any salary my father would have made.

As I look back at my childhood, there are more emotional hurts than I can count. I was a sensitive child, and our family moved during some key elementary and high school years due to my father's job. Often, my mother was told she abused and burnt her child. I was faced with defending myself or explaining my disease. I learned to educate people, including school nurses performing regular head lice checks, who stopped short of asking what was on my head.

As time went on and years went by, I was faced with being half deaf due to the skin in my ears and on my ear drums, making a sensitive situation more sensitive because I couldn't really hear. In those days they didn't have special programs for everyone. You were just thrown in with the rest, no special attention; sink or swim. Sometimes I sank, sometimes I swam, finding my way from an ugly duckling to a swan.

As we moved a few times in elementary school to middle school and high school, from Long Island to New Jersey to Connecticut and Albany and then to West Chester, I became a stronger person each time. My disease changed over the course of my life. Many doctors,

Correspondence Corner *continued on Page 3*

Correspondence Corner *continued from Page 2*

lotions, prayers, inner struggles, and faith have only worked in my favor. Living in the Northeast, I learned that cold winters were not friendly to my skin. In the fall, I would often shed a thick layer of skin, leaving the aftermath of shedding similar to that of a snake shedding its skin. It was my secret. No one had to know. Early on, my disease appeared to disappear from my face, arms, and legs. It contained itself on my neck, stomach, and other areas one would not see if I covered it. My neck, looked like it was burnt but turtlenecks were fashionable in the Northeast. One winter my parents decided to go on vacation to Florida to get some sun and salt water on my skin and to leave the depressing cold weather of the Northeast. This was a tremendous help. Magic, the salt water, the heat, and sweat made my disease so much better! My parents had 3 more children; two girls with the disease, one in her lungs, one pretty bad on the head, and one son who is a carrier of the disease. After completing college on special handicap due to hearing issues and having an ear operation in the late 1970s, I have moved on mentally, physically, and spiritually. I touch people daily in whatever I do in school, in business, and volunteering. Like John Paul, I often thought about the religious life, but I did not act upon it. At 32, I met my husband and now have 3 beautiful children. None of my children have my disease and I am so grateful as I didn't know if they would. There isn't a day that goes by that I am not grateful for my parents, my family, and the challenges they endured choosing life for me and showing the way for me through tumultuous, self-doubtful times in the journey of life.

Today, I do not show any signs of my disease that you may notice. I am fortunate. What I have is not worth mentioning. The only thing left are the scars of hurt that permeate my mind when I go back to my childhood, leaving me with that much more compassion and understanding for the handicapped and all people faced with physical and mental challenges.

I do have some suggestions for those having this disease. Salt water and sunshine truly help relieve pain and help the scalp and ears. Aquaphor cream is a cooling sticky relief. It's hard to work with but it helps. Sally Beauty Supply Cure conditioner for hair and skin is absolutely fabulous. I buy it by the gallon for $5.00; there is no fragrance and it is cooling and clear. Also, for anyone having hard water in their home, this is disastrous for this disease. It's mandatory to get a water softener.

Other suggestions are to focus on inner strength, beauty, faith, the gifts you have been given, and the ability to face adversity in a world that is focused so much on the visual. It is vital to use our gifts and our minds through creativity, the arts, writing, music, and artistic design, reaching out to those who need the hope to face the challenges ahead.

In closing, I want to thank you for reading my story. It is my hope that I can come to the family conference with my sister and mother to give inspiration to others.

With an open heart for loving compassion for all those with skin disorders,

Dawn Dombrowski/ McDonnell

Members gathered in Mystic for Region 1 Meeting

Denise & Brian Merritt from New York

Members of F.I.R.S.T. and their families gathered in Mystic, Connecticut over the weekend of July 18, 2009 for the Region 1 meeting. This marked the first meeting of the new region structure. Seventy-three members, faculty, and F.I.R.S.T. staff, representing 9 states from Region 1, came together for this one-day meeting. Dr. Leonard Milstone, Dermatology Professor at Yale University School of Medicine, was the keynote speaker. His discussion touched on topics of skin care and how to best manage the treatments required for care. Dr. Milstone led a question and answer session after his talk. The afternoon was spent in break-out sessions facilitated by Keith Choate, MD, from Yale University and Kara Shah, MD, from Children's Hospital of Philadelphia. Each session was geared specifically for parents and caregivers or affected adults. Members also had the opportunity to spend time sharing product information and connecting with new friends. This was a wonderful opportunity for members to come together as a community.

Dr. Leonard Milstone takes time to read to some of the children

Jeff Gridley from Australia and Katie Smith from Massachusetts

Additional regional meetings were held this year in Houston, Texas on September 19, and Las Vegas, Nevada on October 3. In 2010, members will gather in Disney World for our biennial Family Conference.

The Hamill Family

Valerie Vitali from Massachusetts and Shawna & Diana Grady from Maine

Conference Chatter

The 2010 Family Conference

will be here before you know it!

June 25•26•27

in Orlando, Florida

The Vaseline Skin Fund is providing scholarships for families to attend the 2010 Family Conference in Orlando. These scholarships will include registration fees and hotel reimbursement. **All applications must be submitted by February 1, 2010.** If you are interested in this scholarship program, please complete the application on page 15 or complete the online application on our website, www.scalyskin.org.

Look for the Registration Form in the next issue!!

Tele-Ichthyosis:
a new online resource available to dermatologists

F.I.R.S.T. is proud to announce that a new teledermatology website has been created to assist local dermatologists with the treatment and diagnosis of patients with ichthyosis and related skin types. Thanks to members of our Medical & Scientific Advisory Board and the Lennox Foundation, this site is now available for your dermatologist to upload questions, documents, and images for input and consultation from ichthyosis and related skin type experts. The site uses a store-and-forward teledermatology approach in a secure, HIPAA compliant environment to facilitate communication between dermatologists dealing with this rare set of diseases.

So now, when your dermatologist needs assistance in a diagnosis, treatment option, or any other unanswered question or concern, he/she can simply go to our website (www.scalyskin.org) and click on the tele-ichthyosis link to upload your case. The case will be reviewed by our expert panel and a reply will be sent back in a timely and efficient manner.

This website is taking us one step closer to closing the gap for those affected in the ichthyosis community. No matter where you live, you and your doctor can now have access to reliable, expert, and cutting-edge information about your disease. Be sure to share this good news with your dermatologist so he/she can better serve you as a patient.

Currently, submissions are limited to dermatologists and a brief registration is required. We are grateful to the Lennox Foundation for funding this project in memory of Dane Christian Phelps.

News on the Hill

News on the Hill is a column to keep members current with the legislation in Washington, DC. This column is written by Angela Godby, Assistant Vice Chancellor for Federal Relations for the University of Texas System. She is affected with Lamellar/CIE.

Leading Genetics Researcher Sworn In As NIH Director

On August 17, 2009, Francis S. Collins, M.D., Ph.D. was officially sworn as the 16th director of the National Institutes of Health (NIH). Dr. Collins brings NIH a vast array of experience in genetics research.

Dr. Collins, a physician-geneticist, served as director of the National Human Genome Research Institute (NHGRI) at the NIH from 1993-2008. During that time, Collins led the Human Genome Project, the remarkable international project that was the first to completely sequence the human DNA instruction book. Dr. Collins has also made significant discoveries of specific genes for diseases ranging from cystic fibrosis, neurofibromatosis, Huntington's disease, and most recently, type 2 diabetes.

One of the first actions of NIH Director Collins was to reach out to key research institutions and patient advocacy organizations. Collins has placed significant priority on keeping the lines of communication open between NIH and these organizations.

In a recent meeting with advocates and researchers, Collins outlined his top priorities for NIH. These include ensuring that researchers apply the unprecedented opportunities in genomics to uncover the causes of specific diseases. Moreover, Collins placed a high priority on translating basic science into new and better treatments for all diseases, including rare diseases such as ichthyosis. Collins expressed strong support for a new program at NIH, the Therapeutics for Rare and Neglected Diseases (TRND), aimed at speeding the development of new drugs for rare and neglected diseases. All in all, the future looks bright for F.I.R.S.T. with Dr. Francis Collins at the helm of NIH.

Executive Director's Report

Dear Members and Friends of F.I.R.S.T.,

Despite the uncertain economy this year, plans are proceeding in a positive direction according to our strategic plan. We have accomplished quite a lot in the past 21 months and have remained relatively close to our original four-year timeline.

Recommended by our Research Review Committee, the Board of Directors approved the funding of three excellent research grants this year, totaling $225,000 (see page 8). Also, the office is now equipped with a new database, which has improved our donor management record keeping and strengthened our relationships with our members and donors.

We are making good strides in regionalizing the support network. Earlier this summer, a regional meeting in Mystic, CT, brought together members and families from the northeast region of the country. Other meetings in Austin, TX and Las Vegas, NV also provided an opportunity for friends and families to meet and learn from each other. Other plans are in store for the upcoming year, which will be directed by Moureen Wenik, our Program Director.

Under the direction of Eric Schweighoffer, the marketing committee is actively working on several key initiatives. Plans are underway to streamline and create impactful tools/materials and utilize the media to generate greater awareness and increase fund raising from the general public. Looking toward the future, F.I.R.S.T. will be upgrading our website and enhancing our educational materials to focus on specific areas in an affected person's lifecycle (childhood, preteen, teen, young adult, adult, and senior).

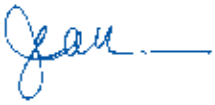
Our most recent accomplishment is the addition of our first-ever Development Director (fancy term for fund raiser), Greg Wilson, to join our staff. Greg started on August 17 and jumped in with both feet! After only his third day, Greg joined me, Moureen, and Lisa Breuning to volunteer at Camp Horizon in Millville, PA. There he met many children with various types and severity of ichthyosis. Greg is a welcomed (and much-needed) addition to our committed and hard-working staff (see page 14).

This November, the Board of Directors will be meeting for its biennial retreat in Philadelphia. The board members travel from all over the country and gather for a long weekend to discuss F.I.R.S.T.'s policies, programs, strategic initiatives, financial reports, and any other current issues. These retreats help to shape the future of F.I.R.S.T. and improve how we serve our members and the ichthyosis community.

We are getting things organized for the 2010 family conference in Orlando. Registration will be available in January. We are fortunate to be the recipient of a grant from the Vaseline Skin Fund (VSF). This grant will help fund scholarships for families to attend, defray child care costs, and reduce the registration fees for children. See page 15 for the VSF scholarship application. We had a record-breaking attendance last year in Chicago, but from "the word on the street," I think next summer will be even better attended. Be on the lookout for more information so you can book early!

When I write these reports, even I am amazed at the level of activity at F.I.R.S.T.! All of this would not be possible without the support from our committed membership and generous donors. Thank you. I look forward to serving you and continuing our mission—to educate, inspire, and connect those touched by ichthyosis and related disorders through emotional support, information, advocacy, and research funding for better treatments and eventual cures.

Sincerely,



Jean R. Pickford
Executive Director

accompanying losses of more than 1,000 calories! Infants with NS also are at risk for severe infections, again in large part due to a defective barrier (bacteria and viruses can more easily get across the skin into the body), but also possibly due to deficiency of (from enzymatic [proteolytic] attack) certain antimicrobial proteins that protect against infections in normal skin (Fig. 1). There is also an increased susceptibility to develop warts (a viral infection) in NS; and rarely, these cases can progress to skin cancers. Finally, patients with NS are at risk for excessive systemic absorption of topical medications, such as Protopic®.

Genetics: Netherton syndrome (NS) is caused by recessively-inherited mutations in a gene (SPINK), which encodes for a protease inhibitor, LEKTI. Loss of LEKTI results in a largely-unopposed attack on proteins by excess serine proteases on the epidermis (Fig. 1). A large number of different mutations have been described in NS, but all result in either absent or reduced LEKTI levels, and disease severity correlates with the extent of the increase in serine protease activation. Our recent studies showed that due to loss of LEKTI, attack by serine proteases can extend deep into the epidermis. Excess protease activity results in loss of stratum corneum (explaining the thinning, rather than thickening, of the stratum corneum), as well as degradation of enzymes that generate lipids required for barrier function. Since the stratum corneum is actually thinner than normal, NS can be thought of as a type of "unthyosis" or "ichthyosis-not." It is likely that these over-active proteases also degrade antimicrobial peptides that are part of the skin's defense against invasion by bacteria and other microorganisms. This could account for the increased risk of skin and skin-derived systemic infections in NS.

NS and Atopic Dermatitis:

Because NS patients often present with a rash that resembles severe atopic dermatitis (eczema), we asked whether the same or similar pathogenic mechanisms could be operative in atopic dermatitis (AD) (Fig. 2). Indeed, an increased incidence of SPINK5 mutations (single nucleotide polymorphisms, SNPs) has been noted in some families with atopic dermatitis and asthma. Moreover, as in NS, serine protease activity is increased in atopic dermatitis. Currently, AD is considered an inherited disorder of barrier function, in which allergens more readily cross the stratum corneum, eventually provoking the characteristic immunologic features of AD (it starts as the most common type of *ichthyosis, ichthyosis vulgaris, IV*). Similarly, the allergies in NS likely derive from increased penetration of allergens across the defective skin barrier. Therapies that reduce serine protease activity or decrease surface pH (acidification) hold promise not only for the treatment and prevention of AD (Hatano, Y, et al., 2009), but also for NS (Fig. 2). These approaches could also help to prevent progression of IV to AD.

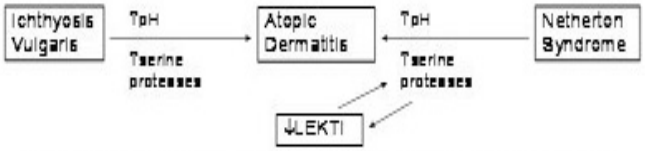


Figure 2: NS and atopic dermatitis exist along a disease spectrum that has as its key feature activation of serine protease in the epidermis.

F.I.R.S.T. Funds New Research Grants

The Foundation's Research Grant Program is pleased to announce the funding of worthy new research projects from the 2009 grant cycle.

Investigator: Heiko Traupe, MD
University Hospital, Muenster
$75,000
Lamellar/CIE

Project: In vitro and in vivo models for transglutaminase-1 deficient lamellar ichthyosis

Objective:
Enzyme replacement therapy has greatly benefited genetic skin diseases (e.g. Fabry disease) and holds great promise for lamellar ichthyosis (LI) due to transglutaminase-1 (TG1) deficiency and for other genetic types of LI. Because of the deplorable therapeutic situation, we want to develop a cream-based (topical) approach for enzyme replacement therapy for TGase-1 deficient LI. In work already supported by a previous F.I.R.S.T. grant, we established a) the expression (insect cells) and purification of large amounts of full length TGase-1, b) the encapsulation of TGase-1 in liposomes, c) the uptake of TGase-1 liposomes into primary keratinocytes of patients with TGase-1 deficient LI across the cell membrane, and d) demonstration of strong and specific TGase-1 activity within the keratinocytes treated with our liposomes. The next step will be to develop suitable in vitro and in vivo models that will then allow testing our TGase-1 liposomes. For this we intend to develop three-dimensional skin equivalents and to develop a skin humanized mouse model in which the human disease can be recapitulated.

Relevance to the mission of the Foundation for Ichthyosis & Related Skin Types:
The project wants to advance the field of development of a causative treatment for TGase-1 deficient LI by developing a) realistic in vitro models reflecting the human situation and b) by developing bio-engineered skin humanized mice. These mice will carry multiple small patches of LI skin and, in contrast to LI knock-out mice, will be viable. Thus we will create models that can serve as tools to test the effect of TGase-1 liposomes. This will be an important milestone in the development of enzyme substitution therapy for LI.

Investigator: Dennis R. Roop, PhD
University of Colorado, Denver

Project: Generating immortalized cell lines and iPS cells from EHK patients
$75,000
EHK

Objective:
There is no cure for epidermolytic hyperkeratosis (EHK). Therefore, novel gene therapy approaches become extremely attractive for this inheritable epidermal disease caused by single gene mutations in either keratin 1 or 10. In order to permanently correct epidermal diseases, it is necessary to design a therapeutic approach that is able to correct epidermal stem cells. Preliminary studies with a pre-clinical mouse model for EHK indicate the feasibility of ex vivo correction of mouse EHK cells followed by reconstitution of the skin in a graft model. Before this approach can be tested in humans, it is desirable to first test this ex vivo gene therapy with human EHK cells. For such purposes, large numbers of human EHK cells are required.

Relevance to the mission of the Foundation for Ichthyosis & Related Skin Types:
The aim of the proposed projects in this application is to generate EHK cell lines so that emerging therapies can be tested on human cells. Any therapy that is proven to be safe and effective using these cells will pave the way for clinical trials for EHK patients, thus meeting the priority of the research program and mission of the Foundation.

F.I.R.S.T. Funds New Research Grants
continued on Page 13

Grassroots Fundraising

Mattingly Dugan with her parents
Rodney and Louanna Dugan

3rd Annual Drive for a Cure held in New York

Chris and Michelle Dugan hosted their 3rd Annual Drive for a Cure Golf Tournament on Saturday, July 25, 2009 at the Brockport Country Club in Brockport, NY. The Dugans are aunt and uncle to five-year-old Mattingly Dugan who is affected with CIE. Even though the weather and this year's economic conditions were less than cooperative for the day, more than $1,000 was raised for F.I.R.S.T. They are making plans to do it again next year. Many thanks to the Dugans for their tireless efforts on behalf of our Foundation.

Beef & Beer held to raise money for F.I.R.S.T.

Jennell Williams from New Jersey, mother of 6-year-old Chad Erickson who is affected with X-Linked Ichthyosis, organized a Beef & Beer/Horseshoe Tournament to benefit our Foundation. The event was held on August 1, 2009 and raised $3,500 for F.I.R.S.T.

Denim Drive

Staff members at Accenture Supply Chain Management Community of Reston, VA, held a community meeting on Friday, August 21. At the meeting, there was a denim drive, highlighting non-profit organizations as beneficiaries. Scott Zailer, brother of Foundation member Jolie Cina, presented a slide show, with help from Jolie, which highlighted ichthyosis and F.I.R.S.T. The Foundation was the recipient of a portion of the funds raised at the meeting.

Coal Miners Combine Their Resources

Bob Martin of Australia has a granddaughter, Sophie Parsons, affected with ichthyosis. The men who work with Bob at the Springvale Coal Mines heard about Sophie and wanted to do something to help. They got together and made a donation to F.I.R.S.T. which totaled more than $10,000US. The generosity of these men is truly inspiring. Thank you to the Martin and Parsons families and in particular the Springvale Coal Miners.

Cathy & Sophie Parsons with Springvale Coal Miners who raised the funding

If you would like information on holding a grassroots fundraiser, please contact the Foundation office at (215) 619-0670 or e-mail us at info@scalyskin.org.

The Foundation is very thankful to all of our wonderful members for their hard work.
Grassroots fundraisers are a great way not only to raise money for F.I.R.S.T, but also to raise awareness about ichthyosis in your community.

Netherton Syndrome: Skin Inflammation and Allergy from Dysregulated Protease Activity

Alain Hovnanian, MD, PhD, Departments of Genetics and Dermatology
Necker Hospital for Sick Children ~ Paris, France

Following is part 1 of a 2-part article. In this segment you will read about:

- *A severe ichthyosis with constant allergy*
- *NS is caused by defective expression of a protease inhibitor*
- *Immunohistochemical and molecular diagnosis of NS*
- *Genetic Counseling and prenatal diagnosis*
- *What do we know about this protease inhibitor?*

In the Winter issue, you will read about:

- *KLK5 at the center of the disease mechanism in NS*
- *To which extent are these findings relevant to NS patients?*
- *Do these results lead to new treatments for NS?*

A severe ichthyosis with constant allergy

Netherton syndrome (NS) was first described by Comel and Netherton in 1949 and 1958, respectively. It is a rare disease, with an incidence estimated around 1 in 100,000 births, distributed worldwide. NS is among the most severe genetic diseases of keratinization, which has the very specific feature of always being associated with severe allergy, which manifests as eczema. It is transmitted in an autosomal recessive manner, i.e. parents are healthy carriers of a mutated copy of the disease gene, which they both transmit to their affected child.

NS is characterized by the clinical triad of redness and scaling of the skin, a specific hair abnormality, and severe eczema. Affected babies present at birth with generalized redness (erythroderma) and scaling of the skin. Complications are frequent during the neonatal period and can be life-threatening. These include severe hypernatraemic dehydration, systemic infections, failure to thrive, growth retardation, and sometimes lung and gastro-intestinal complications. Hair, eyebrows and eyelashes are often sparse, fragile, short, and grow slowly. By the age of one year, they show a highly specific feature named "bamboo hair" (or trichorrhexis invaginata) which is seen under light microscopy examination: the distal part of the hair shaft is invaginated within the proximal part, resulting in a "bamboo-like hair shaft." Later, affected children constantly develop severe allergy which manifests as atopic dermatitis (eczema of the skin with itching and elevated IgE levels in the serum), often associated with hay fever, multiple food allergies and sometimes asthma.

NS is caused by defective expression of a protease inhibitor

The underlying cause of NS remained elusive until 2000 when our group identified SPINK5 (Serine Protease INhibitor of Kazal Type 5) as the defective gene in NS (1). This came as a surprise, since SPINK5 encodes the protease inhibitor LEKTI (Lympho Epithelial Kazal Type Inhibitor), a family of proteins which has not previously been implicated in any disease. Proteases are enzymes which play many different roles in the human body, and their activity is regulated by specific inhibitors. This discovery, not only was a breakthrough in the understanding of the disease mechanism, but it immediately benefitted patients and their families for diagnosis and genetic counseling. Indeed, no diagnostic test for NS was available prior to the identification of the causative gene. Disclosure of the NS gene allowed molecular diagnosis of NS by SPINK5 analysis to be performed in each family. This also led to the development of LEKTI antibodies to design the first quick, easy and reliable diagnostic test of the disease by LEKTI immunodetection of skin sections from patient biopsies.

Netherton Syndrome *continued on Page 12*

Immunohistochemical and molecular diagnosis of NS

We and others have now studied a large number of patients from different cohorts worldwide. The vast majority of patients harbour mutations leading to the loss of LEKTI expression (2,3). This allows rapid and unambiguous diagnosis of the disease by immunohistological examination of a skin biopsy of the patient which shows complete absence of LEKTI in the most superficial living layer of the epidermis (granular layer).

Genetic counseling and prenatal diagnosis

The identification of SPINK5 mutations in NS families allows to confirm or to establish the diagnosis of NS, which is essential for genetic counseling. Indeed, due to its recessive mode of inheritance, a couple with an affected child is at 25% risk of recurrence at each pregnancy. The identification of the causative SPINK5 mutations in a given family offers early prenatal diagnosis of the disease (4). This is now performed at 10 weeks of gestation by fetal DNA analysis isolated from chorionic villus sampling. This is an outpatient procedure which is available in most specialized obstetric centers. This represents major progress since prenatal diagnosis of NS was not possible prior to the identification of the disease gene.

What do we know about this protease inhibitor?

LEKTI is a "super" serine protease inhibitor made up of 15 domains separated by linker regions. Each domain, except domain 1, has the potential to block target protease(s). LEKTI is produced as a precursor molecule which is quickly cleaved within linker regions to generate multidomain fragments. These proteolytic forms are secreted by keratinocytes into the extracellular space between the last living layer of the epidermis (granular layer) and the stratum corneum, where they inhibit their target proteases (5,6).

LEKTI is expressed in all stratified human epithelia, including the skin, the oral, and genital mucosa where it is expressed in the most superficial layers (3). LEKTI is thus expressed at the front side of the body defense. Interestingly, LEKTI is also expressed in the thymus, a lymphoid organ which is essential for the development of immunity. LEKTI is not detectable in haematopoietic cells, nor in the lung and the gastrointestinal track, but proteoltic fragments are detected in the blood circulation, suggesting a possible role at distance.

We have also studied how LEKTI affects skin cells in culture. LETKI is a protein that strongly inhibits enzymes that break down proteins (proteases). There is one area of the LETKI protein, in the middle of the protein (domains 8-11) that is most effective. This fragment strongly inhibits kallilkrein (KLK) proteases 5, 7 and 14, particularly KLK5 (7). Kallikreins are proteases which play important roles in the epidermis, including in the integrity of the skin barrier, and in preventing skin peeling (desquamation) and inflammation. Remarkably, the binding of this proteolytic fragment to KLK 5 depends on how the acid-base balance of the skin environment; is it strongly active at neutral pH (pH 7, in the deep layers of the stratum corneum), and weak at acidic pH (pH5, in the superficial layers of the stratum corneum or outermost area of the skin). Thus, the pH gradient of the SC allows the progressive release of KLK5 from LEKTI domains from the deep layer to its superficial layers, resulting in physiological desquamation of the most superficial layers of the skin. This fine regulation of desquamation is totally absent in NS due to the lack of LEKTI, resulting in fully active KLK5 in the deep layers of the SC. This leads to premature cleavage of intercellular adhesion structures ((corneo)desmosomes) and results in premature detachment of the outermost layers of skin.

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Netherton Syndrome *continued on next page*

Netherton Syndrome *continued from previous page*

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F.I.R.S.T. Funds New Research Grants *continued from Page 8*

Second year funded grant

Investigator: Mason Freeman, MD
$75,000
Lamellar/CIE

Project: Analysis of a Mouse Gene Deletion Model for the Lamellar/Harlequin Ichthyosis ABCA12 Transporter

Objective:
In humans, mutation of the ABCA12 transporter has been associated with ichthyotic skin diseases including the most severe of these, harlequin ichthyosis (HI). However, little is known regarding the activity of ABCA12 and its relation to the loss of skin barrier function and the hyperkeratosis seen in patients carrying ABCA12 mutations. Using funds provided by F.I.R.S.T. and the National Institutes of Health we have developed a mouse model with a targeted deletion of the ABCA12 gene and have shown this animal model reproduces the major features of the HI condition including a loss of the lipids that keep the skin from drying out. Like HI patients these mice also have a dramatic expansion and scaling of the outermost layer of the skin. Using mass spectrometry, a physical method that accurately measures the mass of molecules, we have profiled the lipids in the skin of the mice lacking ABCA12 and have found they have a profound reduction in linoleic esters of long chain omega-hydroxy-ceramides. Because these lipids are required for the barrier function of the skin, this result has given us important insight into how ABCA12 functions to allow normal development of the skin and how loss of ABCA12 activity causes harlequin ichthyosis. Excitingly, F.I.R.S.T. has funded our work for a second year and during this time we will be extending these results. In particular, in collaboration with Dr. Leonard Milstone, a member of the F.I.R.S.T. network of researchers and a dermatologist who provides care for HI patients, we have derived immortalized keratinocyte cells lines from the mice lacking ABCA12. Preliminary results indicate that these cells will also serve as a useful model to study the biochemical mechanism of ABCA12 function and should allow us to study the feasibility of re-expressing ABCA12 in these cells to correct their lipid transport defect. It is hoped that this work will provide methods and information that one day may lead to new therapies to treat patients with ichthyoses caused by the loss of ABCA12 activity.

Relevance to the mission of the Foundation for Ichthyosis & Related Skin Types:
This work is expected to lead to the generation of fundamental insights into the mechanism by which loss of ABCA12 function produces Harlequin and Lamellar Ichthyosis. In addition, multiple reagents required for the study of ABCA12 function, including expression vectors, anti-ABCA12 antibodies and a variety of ABCA12 cDNA mutant isoforms will be generated and shared with other investigators in the field. These tools will stimulate research in the field and will enable us (and others) to seek long-term NIH funding whose goal would be the production of the knowledge needed to develop new therapeutics for these disorders.

Meet the F.I.R.S.T. Staff

As part of our strategic plan, the F.I.R.S.T. staff has re-organized and shifted responsibilities. Following is a brief introduction to each member of our team.

Jean Pickford, *Executive Director*
Jean recently celebrated her 10 year anniversary as the Executive Director. Prior to coming to F.I.R.S.T., Jean was employed at the American Heart Association and National Tay-Sachs & Allied Diseases Association of Delaware Valley. She has been married to her husband, Steve, for 16 years. Together, they have 3 children, Matthew, Kellie and Erika, ages 11, 9, and 3. Jean holds various volunteer positions in the Home & School Association at her children's school. In her spare time, Jean enjoys spending time with her family, watching her children's sports & activities, going to the beach, and exercising (when she can fit it in).

Greg Wilson, *Development Director*
Greg is the newest member of the F.I.R.S.T. team, having joined us in August. Prior to joining the Foundation, Greg worked for the Sisters of the Order of Saint Basil the Great as their Director of Development. He also worked for the Boy Scouts of America across the greater Philadelphia and Lehigh Valley areas and expects to complete his Master's Degree in Nonprofit Management this December. Greg has been married to his wife Debbie for 3 years, and they are the proud parents of a brand new baby girl, Allison May, born on September 14. When not working or going to school, Greg's hobbies include home improvement projects, having made extensive renovations on his home in Boyertown. He also enjoys lawn care, gardening, watching or playing sports, cooking, and antique cars.

Moureen Wenik, *Program Director*
Moureen has been with F.I.R.S.T. for 2 1/2 years. She was previously employed with the YMCA organization for 20 years and still holds part-time positions with them as Teen Leader Coordinator and CPR Instructor with the YMCA of Philadelphia. Moe also serves as director of the Pennsylvania and Central Atlantic Area YMCA Teen Leadership School. She has been married to her husband Mark for 22 years. Together they have 3 children, Dylan, Saige, and Nolan, 19, 14, and 10 years. Moureen also holds many volunteer positions, including the Upper Moreland Township Park and Recreation Advisory Council, the Montgomery County Youth Aid Panel, and the Home and School Association at her children's school. In her free time she enjoys reading and spending time at her children's sports and extracurricular activities.

Donna Wiggins, *Membership Services Coordinator*
Donna will be celebrating her one year anniversary at F.I.R.S.T. in November. Prior to joining the Foundation, Donna worked in an administrative position at Tabor Children's Services for 2 1/2 years. She has been married for 29 years to her high school sweetheart, Bob. They have 3 children, Mac (23), Jenalee (22), and Garrett (17). Donna and her family have spent time in many regions of the country, living in Illinois for 8 years, then moving to Atlanta where they spent 4 years, and currently in Pennsylvania. For fun, Donna stays involved with her church and helps out where she can. She also enjoys crossword puzzles, going to the movies, or being at home watching a movie or playing board games.

Lisa Breuning, *Public Relations Coordinator*
Lisa just celebrated her 2 year anniversary with F.I.R.S.T. in September. Prior to coming to the Foundation, Lisa was a stay-at-home mother to her 2 children, Jennifer and Drew, ages 11 and 9 1/2. Before choosing to stay home with her children, Lisa worked for 10 years at the Jewish Federation of Greater Philadelphia Bux-Mont Regional office, where she was the office manager and then the Coordinator of the Women's Division. Lisa has been married for 17 years to her husband, David. In her spare time, Lisa enjoys watching her children's sports and extracurricular activities, going to the beach, reading, gardening, and doing Sudoku puzzles.

Cut here

Foundation for Ichthyosis & Related Skin Types, Inc.™

2010 Family Conference - Orlando, FL

Scholarship Application

Application Deadline: February 1, 2010

Name: _____

Address: _____

City: _____ State: _____ Postal Code: _____

Province: _____ Country: _____

Home Phone: _____ Work Phone: _____

Cell Phone: _____ Email: _____

How many people will be attending the conference? _____

Name: _____ Age: _____ Type of Ichthyosis: _____

Name: _____ Age: _____ Type of Ichthyosis: _____

Name: _____ Age: _____ Type of Ichthyosis: _____

Name: _____ Age: _____ Type of Ichthyosis: _____

Have you attended a F.I.R.S.T. Family Conference before? ☐ Yes ☐ No If so, when? _____

How many persons are you applying for a scholarship for? ____ Adults (14+) ____ Children (13 & under)

For what are you applying? _____ Registration Fees _____ Hotel Reimbursement

Annual Family Income: (please include a copy of Your most recent W-2)

___ Under $20,000
___ $21,000 - $35,000
___ $36,000 - $50,000
___ $51,000 - $60,000
___ $61,000 - $75,000
___ Over $75,000

Why do you want to attend the F.I.R.S.T. Family Conference? (Use additional paper if necessary)

_____

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Please return this form to the F.I.R.S.T. office by February 1, 2010.

Applications received after February 1 will not be considered.

F.I.R.S.T. and its officials reserve the right to disqualify any application that is incomplete.

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F.I.R.S.T. STAFF SPENDS THE DAY AT CAMP

Every summer, the American Academy of Dermatology sponsors Camp Discovery for children affected with skin disorders. This camp provides these children with the opportunity to enhance their self-confidence, learn from other children who have similar dermatologic conditions, and enjoy fishing, boating, swimming, water skiing, and arts and crafts. Camp Horizon in Millville, PA, held the week of August 15 – 22, 2009, is targeted to 8 to 13 year olds. They have a volunteer staff of past campers and AAD physicians and nurses. Every Wednesday afternoon, the volunteers are offered the opportunity to take some personal time for themselves. In an effort to keep the activities running smoothly for the children, volunteers from various agencies affiliated with the AAD offer their time to help with the camp activities. Every year, the staff of F.I.R.S.T. spends the afternoon at Camp Horizon helping out with activities with the children. This experience is very rewarding for us. We have the opportunity to get to know not only children whose families are members of the Foundation, but also children with other skin conditions, such as Alopecia Areata, Epidermolysis Bullosa, and Psoriasis. It is wonderful to see the kids just be kids and not have to worry about being "different" from the other kids. For many of the children, this is a rare opportunity to meet someone with the same condition as themselves. This year's trip to Camp Horizon took place on August 19, 2009. Each of us helped out with a different activity. Moureen made ice cream, Lisa helped some of the girls make flip flops, and Jean and Greg helped out with games. Despite a late-afternoon downpour, it was truly a rewarding day.

Back: Nicole McMillian, Jean Cahill, Jean Pickford, Lisa Breuning, Greg Wilson, Moureen Wenik, Derek Donovan. Front: Aubrey Mills, Ryan Balog, Marty McHale, & Mohammed Mehmood

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