

FIRST's Research Grant Program

FIRST officially launched its own Research Grant Program in early 2006. Our grant program promotes and strengthens investigation into the causes, treatments, and potential cures for ichthyosis and related skin types. Guided by the Foundation's Research Committee, which is comprised of knowledgeable physicians, scientists, and FIRST leaders, the office administers an annual granting program. Surveys of the ichthyosis community, specifically individuals affected with ichthyosis and their families, have indicated that research is their primary area of interest and their top priority for funds donated to FIRST. In response to this, FIRST has initiated this program to promote promising avenues of research by investigators who have a new or established interest in ichthyosis or a related skin type.

2014 and 2015 FIRST Grant Recipients



Dr. Britt Craiglow, Yale University: New Born Implications in Ichthyosis

Please join us in congratulating FIRST's 2015 Research Grant recipient, Dr. Brittany Craiglow of Yale University. Dr. Craiglow, a tenacious supporter of the FIRST community, was awarded a \$50,000 research grant for her collaborative study of newborn and early childhood complications and comorbidities that accompany the ichthyoses. Dr. Craiglow notes, "At present, there is no standard of care for the management of babies and children with these disorders and therapeutic

options are limited." She also states that her intention for the study is to offer investigators an enhanced understanding of these complications and establish an accepted clinical standard of care that could be tailored to the genetic diagnosis. "The study may also ultimately provide a foundation for the development of targeted therapies," said Dr. Craiglow.



Dr. Ryan O'Shaughnessy, University College, London: Therapeutic Avenues for ARCI by Targeting Common Pathways of Hyperkeratosis

(ARCI Lamellar Ichthyosis) Dr. Ryan O'Shaughnessy received \$50,000 from the FIRST Research Grant Program to continue his work in targeting the scaling pathways in ichthyosis. The research specifically focuses on understanding the mechanisms that cause scaling, and subsequently increasing the options for treatment. As explained by Dr. O'Shaughnessy, "Hyperkeratosis, or scaling, is a very common symptom in skin disease, with around 150 genetic ichthyosis and ichthyosis-related skin diseases leading to this thickening of the outermost layer of the skin. In many skin diseases this scaling is the most outwardly visible effect of the disease, and the one that patients would most want to treat. Current treatments for hyperkeratosis such as retinoids, although effective, are used without a full understanding of the molecular machinery behind the process. By better understanding the basis for scaling ("molecular mechanism") in ichthyosis, more directed protein or gene therapies could be developed that benefit patients, regardless of their specific genetic defect".

Ongoing Research Previously Funded by FIRST



A New Biomanufacturing Facility for an Inaugural Awardee - FIRST Research Grant Recipient, Dr. Dennis Roop

(Epidermolytic Ichthyosis) Generating Immortalized Cell Lines and iPS cells

Dr. Dennis Roop, internationally recognized leader in skin disease research, and his team at the Charles C. Gates Center for Regenerative Medicine at the University of Colorado, has been funded by FIRST's research grant program since 2006, supporting their cutting-edge work in epidermolytic ichthyosis (formerly known as EHK).

Dr. Roop is specifically working with adult cells of epidermolytic ichthyosis (EI) patients – essentially reprogramming, or “inducing” pluripotency, by introducing factors into these cells that are capable of removing all of the cell's memory, stripping it of all genetic coding as an adult cell, and reverting that cell back to an embryonic-like state. The reprogramming procedure gives the adult cells nearly the same pluripotent capabilities as embryonic stem cells. There are two advantages of working with iPS compared to adult cells: they can multiply for a more prolonged time than adult cells and gene correction strategies work more efficiently in iPS cells than in adult cells.

The long-term goal of Dr. Roop's work is to create iPS cells from individual patients, correct the mutant gene they contain, differentiate the iPS cells into

keratinocytes and then graft the corrected keratinocytes back onto the patient—in hopes that they will multiply and generate unaffected skin.

April, 2015 – Opening of New Biomanufacturing Facility

In 2007, Dr. Roop was named director of the Charles C. Gates Center for Regenerative Medicine at the University of Colorado, Anschutz Medical Campus. He had a long-range vision and when the new west wing of the Bioscience Park Center became available two years ago, Roop was one step closer to what he'd envisioned, a Good Manufacturing Practice (GMP) facility that will develop and manufacture investigational adult cell therapy products and therapeutic protein-based biological drugs suitable for investigational use in clinical trials. This type of biomanufacturing facility would mean that iPS cells could be grown in a clean and controlled enough facility so that they could be safely placed on or in humans. That vision became a reality April 6, 2015 when the Charles C. Gates Biomanufacturing Facility (GBF), a 14,000 square foot state-of-the-art manufacturing facility, opened its doors just steps away from Roop's laboratory at the Gates Center for Regenerative Medicine.

Genetically engineered mouse models for skin research: Taking the next step.
Journal of Dermatological Science (2008) 52, 1—12

A Recent Update from 2008 FIRST Research Grant Recipient, Dr. Robert Rice

Proteomic Analysis of Ichthyosis Structural and BioChemical Changes Underlying a Kera-Derma-like phenotype in mice lacking suprabasal AP1 transcription factor function

(ARCI lamellar, CIE) Dr. Robert Rice, 2008 FIRST research grant recipient, recently submitted an update to his research on protein cells, and the molecular basis for a variety of severities within the same genetic diagnosis. In brief, the update can be explained as follows:

Normally the epidermis forms a callus layer at the skin surface to protect us from our environment. This results from an intricate program of cell differentiation, where the cells synthesize new proteins in an orderly sequence. When this sequence is disturbed, various part of the program are deficient, often resulting in scaly skin and a damaged barrier to the environment. In the mouse model used in our research for scaly skin, a transcription factor was prevented from functioning in the epidermis, leading to a deficiency of some important proteins. To compensate, the epidermis made more of certain other proteins, where the resulting imbalance produced gross scaling. Studying this mouse condition may permit understanding how the protein imbalance occurs and how it produces scaling in patients with ichthyosis and related skin types.

Structural and Biochemical Changes underlying a Kera-Derma-like Phenotype in mice lacking suprabasal AP1 transcription factor function
Cell Death and Disease (2015) 6, e167

Checking in with 2006 FIRST Research Grant Recipient, Dr. William Rizzo

Ichthyosis and 12R-Eicosanoid Metabolism in Sjögren-Larsson Syndrome

(Sjögren-Larsson Syndrome) This study looks at a defective lipid (fat) metabolic pathway that is seen in Sjögren-Larsson syndrome (SLS) and several other genetic forms of ichthyosis. The study is relevant to the mission of FIRST and the interests of our members because therapy of the ichthyosis in SLS is non-specific. “Our research may lead to new approaches for cutaneous therapy for selectively bypassing the metabolic block in lipid metabolism and providing the metabolites that cannot be made by SLS patients,” said Dr. Rizzo.

The STAIR Consortium, an International Multi-Center, Collaborative Research Project

Most recently, Dr. Rizzo has partaken in the STAIR Consortium, an international multi-center, collaborative

research project focusing on genetic diseases that are caused by defects in Sterol (cholesterol) And Isoprenoid metabolism. "The funding from FIRST in 2006 helped us to bring the research to a new level and to the point where the NIH was interested in funding this unique, collaborative effort." The STAIR Consortium's goal is to establish the natural history of rare diseases, identify biomarkers for future therapy studies, investigate new treatments, discover new diseases, and train new physician-researchers to work on rare diseases.

Keith Choate, MD, PhD, Yale University School of Medicine: Gene Discovery Project

FIRST Clinical Scholar Award Recipient 2008

This research study seeks to comprehensively understand the genetics of ichthyosis and the biological implications of mutations in these genes. The study examines patient samples to identify mutations causing their skin condition and correlates these with physical findings in each person (their phenotype). To date, this program has identified three new genetic causes of ichthyosis and has ongoing studies to understand how these genes contribute to normal skin function and disease.

Dominant De Novo Mutations in GJA1 Cause Erythrokeratoderma Variabilis et Progressiva, without Features of Oculodentodigital Dysplasia *Journal of Investigative Dermatology November (2014) | doi:10.1038/jid.2014.485*

Heiko Traupe, MD, University Hospital, Münster Germany: Enzyme Replacement Therapy for TGM1 Autosomal Recessive Ichthyosis

FIRST Research Grant Recipient 2007 (ARCI Lamellar) This study focuses on enzyme replacement therapy for patients affected with a form of lamellar ichthyosis (transglutaminase 1-deficient autosomal recessive congenital ichthyosis). **Update as of 2014** - "We succeeded in restoring the normal histological architecture and normal skin physiology function as measured by transepidermal water loss in skin grafts of patients suffering from transglutaminase1 deficient-auto-

somal recessive congenital ichthyosis. These skin grafts were transplanted onto athymic (without t-cells) nude mice and treated with liposomes containing recombinant transglutaminase-1," noted Dr. Traupe. "One should note that there is quite some work that still needs to be done before this can enter the clinic."

This project was carried out in close cooperation with Dr. Karin Aufenvenne, Dr. Margitta Dathe, at the Leibniz-Institut für Molekulare Pharmakologie, and Dr. Fernando Larcher from the CIEMAT in Madrid, Spain.

Long Term Faithful Recapitulation of Transglutaminase 1- Deficient Lamellar Ichthyosis in Skin-Humanized Mouse Model and Insights from Proteomic Studies *Journal of Investigative Dermatology March (2012) 132, 1918-1921*

Suephy Chen, MD, Emory University - The Economic Burden of Cutaneous Disease in Ichthyosis Patients and Families

FIRST Research Grant Recipient 2007
There are no recent updates to this research project.

Highlights from the Report of the Working Group on Core Measures of the Burden of Skin Diseases *Journal of Investigative Dermatology (2007) 127, 2701-2706. d*

Amy Paller, MD, Northwestern University: Topical delivery of Keratin 10 mutation-specific siRNA-gold nanoparticles for epidermolytic ichthyosis

FIRST Research Grant Recipient 2012, 2013 (Epidermolytic Ichthyosis) This research study uses a new nanotechnology-based technique called 'spherical nucleic acids' (SNAs) to suppress the production of the abnormal keratin 10 gene that is the most common change leading to epidermolytic ichthyosis. Their goal is to discover a more precise mutation-specific topical delivery method. Recently, Dr. Paller and her team received, an NIH, SBIR grant, to continue working on this research project. An SBIR is a grant from the government that encourages a small company to collaborate with an academic institution to develop a useful, marketable product.

Topical delivery of keratin 10 mutation-specific siRNA-gold nanoparticles for epidermolytic ichthyosis (2012) Proceedings of the National Academy of Sciences of the United States of America

Proceedings of the National Academy of Sciences of the United States of America www.pnas.org/doi/10.1073/pnas.1118425109

Anders Vahlquist, MD, PhD and Hans Törmä, PhD, University Hospital, Uppsala, Sweden: Studies On the Pathophysiology and Novel Rationales for Epidermolytic Ichthyosis Affecting the Skin Barrier

FIRST Research Grant Recipients 2010, 2011, 2012 (Epidermolytic Ichthyosis) This research study supports the search for improved therapeutic options in EI by utilizing patients' cells or artificially produced mutant cells and exposing them to chemicals from a compound library to screen for other drugs with ability to protect the cytoskeleton.

Results were presented at the International Investigative Dermatology meeting 2013 (JID, vol 133, Suppl 1, S130, abstract 767).

Eli Sprecher, MD, PhD, Director, Department of Dermatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel and Dr. Dina Ron, Department of Biology, Technion-Israel Institute of Technology, Haifa, Israel: A Novel Regulator of Epidermal Differentiation

FIRST Research Grant Recipient 2006, 2007
There are no recent updates to this research project.

CEDNIK Syndrome Results from Loss-of-Function Mutations in SNAP-29 *The British Journal of Dermatology (2011) 164, 610-616*

Mason Freeman, MD, Massachusetts General: A Null Mouse Model of the Lamellar/Harlequin Ichthyosis ABCA12 Transporter

FIRST Research Grant Recipient 2009
There are no recent updates to this research project.

Endogenous β -glucocerebrosidase activity in Abca12^{-/-} epidermis elevates ceramide levels after topical lipid application but does not restore barrier function *Journal of Lipid Research March (2014) 55(3): 493-503.*

Current Clinical Studies Using FIRST Resources to Recruit Patients

Recent Studies Seeking Patient Participants

(Harlequin Ichthyosis) Kate Pawlowski, Genetics Department of Boston Children's Hospital:

This study is currently recruiting patients for a harlequin ichthyosis (HI) study. Boston Children's is collecting medical records of individuals with harlequin ichthyosis, and by reviewing these records, they hope to further the understanding of this disorder and how it affects people throughout their lives.

Contact: Kate Pawlowski

Phone: 857.218.5472

Fax: 617.730.0466

Email: katherine.pawlowski@childrens.harvard.edu

Collection of Blood Samples and Data from donors with Ichthyosis to Identify Potential Biomarkers – PrecisionMed, San Diego, California

As part of a clinical research study, Precision Med is collecting blood samples from volunteers who have been diagnosed with ichthyosis. Procedures for this single, one-hour study visit, will involve providing health/personal information and blood sampling. Participants will receive \$100 compensation at the time of the visit.

Contact: Tracy Savra, 858.847.0117 Ext. 214.

Temple University Itch Studies

FIRST's community of patients is eager to support studies that will advance treatments and make life with ichthyosis, or a related skin type, as comfortable and manageable as possible. FIRST members are participating in the following study currently underway to identify causes and treatment of *itch* as it relates to ichthyosis and related skin types

- Dr. Gil Yosipovich, Temple University - Phenotyping Itch in Atopic Eczema, Psoriasis, and Ichthyosis.

Please contact Temple Dermatology at 267.838.1094 or at TempleDermatology@gmail.com

Please check the FIRST website for *itch* study results and updates.

Aldeyra Therapeutics, Inc. Announces Open Enrollment for Phase II Clinical Trial of NS2 for Patients with Ichthyosis Due to Sjögren-Larsson Syndrome

The study is being conducted at the University of Nebraska Medical Center with FIRST MSAB (Medical Scientific Advisory Board) member, Dr. Bill Rizzo as the Principal Investigator. Find out more specific information regarding the SLS clinical trial, or contact Sara Jones by phone 402.559.1747 or email at saram.jones@unmc.edu if you are interested in participating or would like to learn more about the clinical trial.

About NS2

NS2 is an aldehyde-binding small molecule based on an innovative platform technology focused on trapping free aldehydes, which are toxic and pro-inflammatory mediators of numerous diseases. By decreasing aldehyde load, NS2 may mitigate excessive inflammation and address diseases where aldehydes are thought to mediate pathology.

More studies seeking patients with ichthyosis and related skin types can be found at: firstskinfoundation.org/research

Don't miss our Research Panel breakout session at the 2016 FIRST National Conference, San Diego – June 24-26. A panel of world-renowned scientists, working in the field of ichthyosis and related skin types, will present their research in-person, followed by a Q & A.

Please go to www.firstskinfoundation.org/research for up-to-the-minute updates on research funded by the FIRST Research Grant Program.