

COLLAGEN CONNECTION

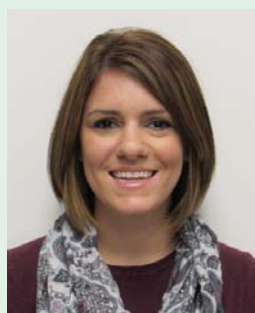
SUMMER 2018

Dr. Lafyatis Awarded NIH Centers of Research Translation Grant (CORT)

You are familiar with the old proverb that “it takes a village to raise a child.” Similarly, this adage holds true in the field of science. It takes a village of physicians, scientists, and research staff to bring new medical treatments to the clinic. In this issue, we are highlighting an exciting project by Dr. Lafyatis and his team at the University of Pittsburgh doing just that. This collaboration brings together some of Pittsburgh’s finest scientists, along with scientists from Boston University and Dartmouth, to study systemic sclerosis with the goal of identifying more effective ways to treat patients.

Dr. Lafyatis, the Director of the UPMC and University of Pittsburgh Scleroderma Center, was awarded a Centers of Research Translation Grant (CORT) focused on Systemic Sclerosis. This funding is provided by the National Institute of Arthritis and Musculoskeletal and Skin Disease (NIAMS) at the National Institutes of Health (NIH). The purpose of this funding is to have a team of scientists and physicians carry out interactive and coordinated research projects to address the challenge of understanding and treating systemic sclerosis from a translational approach. Translational research is the process of applying knowledge and discoveries obtained through basic laboratory research into development of new treatments and

Meet Our Staff



Christina “Nina” Morse is Laboratory Manager of the Scleroderma Center in the Division of Rheumatology and Clinical Immunology (DRCI) at the University of Pittsburgh. She has a Bachelor of Science from The Pennsylvania State University and has over 10 years of research experience in translational science, immunobiology and cancer. She has worked at the university for almost 9 years and joined the DRCI in July of 2016 working in the laboratory of Dr. Robert Lafyatis. Nina lives in the South Hills with her husband Tom and their children Paige and Owen. In her spare time she enjoys spending time outdoors with her children on the family farm.

therapies. Systemic sclerosis (SSc) is a severe scarring disease that affects many organs including the skin and lungs. Skin disease is painful and disfiguring, while lung disease can be lethal. Currently there are no approved treatments for this disease. This CORT is a highly coordinated, data driven, translational research at its finest focused on identifying and developing new treatment targets for systemic sclerosis.

To study a disease like SSc it is important to take such a large project and break it down in to smaller more manageable targeted projects. In this University of Pittsburgh run CORT there are three major projects each run by field leading scientists.

Project 1 is led by Dr. Robert Lafyatis and his staff at the University of Pittsburgh. The long-term goals of

this project are to discover biomarkers permitting more efficient testing of novel drugs for SSc patients, to dissect the cellular source and progenitors of cells expressing biomarkers in SSc skin and to study genes uniquely expressed by myofibroblasts, the cells that cause fibrosis (scarring) of the skin and lungs.

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Project 2 is led by Dr. Maria Trojanowska of Boston University along with co-investigator Dr. Elena Goncharova of the University of Pittsburgh. Project 2 focuses on Pulmonary arterial hypertension (PAH). In systemic sclerosis (SSc), PAH is a leading cause of morbidity and mortality. Moreover, patients with SSc-PAH have a poorer prognosis than patients with idiopathic PAH. To improve treatment options for SSc-PAH, a better understanding of SSc-PAH pathogenesis is needed. Although the exact pathophysiology of PAH is unknown, abnormal cellular metabolism caused by altered mitochondrial dynamics, is now considered an important contributor to pathological alterations in PAH. Drs. Trojanowska and Goncharova will use their breadth of experience to identify PAH treatments and investigate new drugs.

Project 3 is led by Dr. Rama Mallampalli with co-investigators Dr. Bill Chen and Dr. Daniel Kass. Their goal is targeting pro-fibrotic E3 ligases, a family of proteins that regulate how other proteins are broken down, in systemic sclerosis for therapeutic invention. This project will interact very closely with the other CORT projects and cores to discover the overlapping biology of dysregulated ubiquitin E3 ligases in SSc-PAH and SSc-skin disease. Recent studies completed by these investigators using a large number of idiopathic pulmonary fibrosis (IPF) and SSc lung samples have uncovered an array of several, previously unsuspected, molecular targets. In particular, they have identified two highly novel profibrotic signaling pathways in SSc fibroblasts. They plan to continue this work by targeting these pathways with new therapies being studied at the university Drug Discovery Institute.

To make sure that each project has the resources it needs to effectively

pursue their goals the CORT also has dedicated Cores that support the research projects. The Cores are also run by highly esteemed researchers and clinicians that focus their efforts and make sure that each team of scientists running the projects have all of the biological samples, data analysis support and lines of communication in place to make every experiment count. The Cores include:



The Administrative Core which is led by Dr. Robert Lafyatis and Dr. Robyn Domsic with the support of Nina Morse, the Scleroderma Center Lab Manager. The goals of this core are to provide scientific oversight of the program, facilitating communication with and among Project and Core investigators. This Core also plans an annual retreat and monthly CORT Executive Committee Meetings, coordinates external oversight review of the research. This core also solicits, reviews and manages Development and Feasibility grants to encourage additional new research throughout the five year project.

The Clinical and Biological Specimen Core is led by Dr. Robyn Domsic from the University of Pittsburgh along with co-investigator Dr. Robert Simms of Boston University. The essential function of the Clinical Core is to provide prospectively collected, longitudinal clinical data and associated biosamples on a well-characterized cohort of systemic sclerosis (SSc) patients. This clinical

data will be linked by date to the biologic specimens essential to the completion of the projects. The Clinical Core will build on two existing, dedicated Scleroderma Center longitudinal SSc patient cohorts at the University of Pittsburgh and Boston University Medical Center in order to accomplish this goal.

The Lung Tissue Core is led by Dr. Mauricio Rojas of the University of Pittsburgh. The specific goals of this core are to enrich our current biorepository of lung, skin and bone marrow stem cells procured from normal individuals and individuals with SSc. Dr. Rojas and his team are exceptional resources to the Projects and will assist program investigators in the design and implementation of experiments using biological specimens obtained from the lungs of SSc patients with interstitial lung disease or pulmonary arterial hypertension undergoing lung transplantation.

The Translational Genomics and Data Core is led by Dr. Michael Whitfield of Dartmouth University. The goals of this core are to provide high quality RNA-seq analyses for individual projects and process the resulting data in a rigorously controlled analysis pipeline to provide differential gene expression and patient subset assignments. Dr. Whitfield and his team will also provide a systems biology and network analysis of gene expression data in SSc, and perform metaanalyses of SSc clinical trials using both existing data, as well as new data generated as part of the CORT research projects.

To say the least, this is a massive undertaking with huge implications but these investigators are the best in the business and will certainly make the most of this opportunity to work together. The team has been meeting monthly since January and great things are already in motion.

A PATIENT GIVES BACK

In late 2015, Caroline Graettinger noticed a number of unusual symptoms that started with numbness in her hands and fingers, and within a month progressed to include loss of appetite, dry cough, shortness of breath, and debilitating fatigue. The symptoms were broad enough to be related to a number of conditions, but her primary care physician thought they definitely pointed to some type of autoimmune disease. After six months of more testing and input from multiple specialists, Caroline was referred to the Scleroderma Center and officially diagnosed with scleroderma.

“I have a spreadsheet that I tracked over time that has 27 different symptoms – all of which were significant and frightening,” Caroline said. “Scleroderma can be a really nasty, chronic condition, and the way to treat it is to manage it. Manage the symptoms, try to tamper down the autoimmune response to it, and just try to feel better and keep going.”

Some ways Caroline has managed her scleroderma is through medicine and iron infusions, physical therapy for her lungs, exercise to fight severe fatigue, and weight gain to offset the substantial amount of weight she lost in the first year of her diagnosis. Her husband, Tim, notes that she has shown major improvements since her initial symptoms.

“Caroline has really made some huge progress to the point where she’s taken a couple trips to Arizona and Florida,” he said. “She’s done a lot of walking and is back in the gardens again.”

Last year, Caroline and Tim even found another way to help with managing scleroderma. In June of 2017, she and her husband, Tim,



Caroline and Tim enjoying their hike

attended a scleroderma patient education conference where they were inspired to help start a local support group for patients and caregivers.

“A speaker from the Scleroderma Foundation talked about what they do and their mission. Then, he asked if anyone would be interested in trying to get a chapter or support group started locally again,” Tim said. “I looked around the room and didn’t really see any hands going up, but I had been thinking about it, so I raised mine. Since then, it’s been a great experience getting the support group started. We’ve been really happy with the turnout.”

The support group meets monthly, with about 20 members at each meeting.

“It’s been an enlightening experience for the both of us, and I think for all the other members of the group,” Tim said. “Everybody just walks away feeling kind of energized that we’re doing the best we can and we’ve got each other to talk to. So that’s really been gratifying, and we’re so happy to have been a part of getting that started.”

Caroline and Tim are grateful to be so close to the Scleroderma Center, compared to some patients who have to travel far, sometimes even by plane, to receive specialized care.

“I feel very fortunate to live within a reasonable distance to such a high-class center that is not only acting clinically to help patients, but is also leading the way in research in this area,” Caroline said. “There’s not a cure for scleroderma yet, but one of the things we love about the Scleroderma Center is that they are a research center, and they make their patients aware of the different clinical trials and research studies that they’re involved in.” Caroline has even participated in a few clinical trials, herself.

“I feel like I’m helping other patients by contributing information and data, and it gives me just another opportunity to ask questions about what’s going on in the field and what they’re doing at the center,” she said. Caroline and Tim encourage others to support the Scleroderma Center in any way that they can. Whether it be through the support group, as a patient participating in clinical trials, or through giving.

“There are ways for people to contribute online directly to the research going on at the UPMC Scleroderma Center if they’re interested,” Caroline said. “Anyway of helping advance the research toward treatment and a cure is important.”

To support the Scleroderma Center, contact Anne Immekus at ami16@pitt.edu or 412-647-2434. For more information about the support group or how to get involved, contact sfgrouppitt@gmail.com.



CLINICAL DRUG TRIALS AND OBSERVATIONAL STUDIES

Our Scleroderma Center is committed to participating in clinical trials. We feel it is a vital step in working together to find treatments for scleroderma. Without clinical trials, our field will not advance. If you are interested in participating in a trial or would like additional information regarding clinical studies at our Center, please contact one of our scleroderma clinical trials coordinators, Dana Ivanco at des2@pitt.edu or Maureen Laffoon at laffoonm@pitt.edu.

CURRENTLY ENROLLING PATIENTS:

The Effect of Atorvastatin on Microvascular Endothelial Function and Raynauds in Early Diffuse Scleroderma (TAMER):

This is a NIH-supported single-center study (being done only in Pittsburgh). The purpose of this study is to examine the effect of atorvastatin (trade name Lipitor) on Raynaud symptoms and small blood vessel function in patients with early diffuse scleroderma. Scleroderma is characterized by blood vessel injury, immune system activation and fibrosis. The blood vessel injury is thought to be important early in the disease, and many think this may be the reason most scleroderma patients experience Raynauds as the first symptom. While atorvastatin reduces cholesterol, it is recognized to have many positive effects beyond cholesterol reduction. These include

improvement of blood vessel function and reduction of fibrosis. It is believed that atorvastatin will improve blood vessel function and Raynaud symptoms in patients with early disease. Early disease means <3 years of scleroderma symptoms for this study. The trial is 16 weeks and half the patients will receive atorvastatin and half placebo. Atorvastatin (or placebo) is given as an "add-on" therapy. This means all medications can be continued while in this trial. There are only 3 visits over 16 weeks.

Evaluation of Brentuximab Vedotin for Diffuse Cutaneous Systemic Sclerosis: A Phase I/II Multicenter, Randomized, Double-Blinded Safety Study (BRAVOS):

Brentuximab vedotin (name brand Adcetris) is a drug that was developed and has FDA approval for the treatment of lymphoma. This research is being done to evaluate the safety and tolerability of brentuximab in the treatment of diffuse skin disease in scleroderma. Patients must be early in their disease with worsening skin to participate. Two of three patients will receive brentuximab vedotin, and the other individual, placebo. The study lasts 48 weeks and involves 14 visits. Patients will be able to remain on their current scleroderma medications.

Dimethyl Fumarate (Tecfidera), In Pulmonary Arterial Hypertension Associated With Systemic Sclerosis (DMF):

Dimethyl fumarate (DMF) is a drug approved for the treatment

of multiple sclerosis and psoriasis. DMF acts at multiple targets and has both anti-oxidant and anti-inflammatory properties. The NIH-funded four-center study will examine the safety of DMF in scleroderma patients, and if it improves patient function by increasing the distance scleroderma patients with pulmonary hypertension can walk. Half of the subjects will receive DMF and half placebo. Other medications can be continued throughout the study. This is a 36 week study with 6 visits.

An Observational Study of the Effect of Mycophenolate Mofetil (Cellcept) in Early Diffuse Scleroderma:

This is a NIH-supported single-center study (being performed only in Pittsburgh) to observe the effect of mycophenolate for the treatment of early diffuse scleroderma. Mycophenolate is one of the most commonly used medications to treat diffuse scleroderma and scleroderma-related pulmonary fibrosis, however we know little about how to predict who will respond well to the medication. Patients whose physician recommends they should be clinically treated with mycophenolate are eligible to be in this study. When in this study your doctor may change your medications at any time. We simply observe the effect of mycophenolate, collect data on its effect on skin, and collect blood and oral swab samples every 3 months for the first year a patient is treated with mycophenolate. This study can easily be combined with regular patient visits.

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial to Evaluate Efficacy and Safety of Lenabasum in Diffuse Cutaneous Systemic Sclerosis:

Lenabasum, formerly known as anabasum and also known as JBT-101 is an experimental (investigational) drug that is chemically similar to a chemical in cannabis, or marijuana. However, this drug has been designed to avoid the “high” feeling of marijuana. This research study is being done to test the efficacy of lenabasum when it is given to subjects with diffuse cutaneous scleroderma of < 6 years of disease. Lenabasum is entirely manufactured from chemicals, not plant or animal products. This is a 52 week study. Patients will be able to remain on their current scleroderma

medications. Two out of three will receive therapy in this study, and 1 in 3 will receive placebo. There is an open label extension study for this trial.

Evaluation of tofacitinib in early diffuse cutaneous systemic sclerosis:

Tofacitinib is currently approved in the US for the use in Rheumatoid Arthritis. This research study is being done to evaluate the safety, tolerability and efficacy of treatment of tofacitinib along with any possible efficacy descriptors, as a treatment for dcSSc when given to subjects with diffuse cutaneous scleroderma of < 5 years of disease. This is a 24 week study, 2 out of 3 will receive therapy in this study, and 1 in 3 will receive placebo. There is a 24 week open label extension study for this trial.

A Phase II double-blind, clinical trial addressing the treatment of patients with active and symptomatic scleroderma-related interstitial lung disease (SLSIII):

This study compares the safety and effectiveness of adding on pirfenidone to current mycophenolate (Cellcept) therapy for scleroderma-related lung disease. Pirfenidone is FDA approved for the treatment of pulmonary fibrosis. This research is designed to test whether combining pirfenidone and mycophenolate will result in a more rapid and possibly greater improvement in lung function than occurs when mycophenolate is used alone. There are 13 office visits and 11 phone calls over 18 months.

RESEARCH VOLUNTEERS NEEDED

The Division of Pediatric Rheumatology at Children’s Hospital of Pittsburgh of UPMC is currently conducting a clinical research study to determine the role that certain molecules found in blood samples play in the severity of rheumatic autoimmune diseases, like arthritis, scleroderma, and lupus. We are currently looking to obtain approximately 3-4 teaspoons of blood from healthy individuals to compare with blood samples from patients with these types of diseases.

Eligibility Requirements:

- Healthy children and adults who have not been diagnosed with a rheumatic disease
- Children and adults who have been diagnosed with a rheumatic disease
- A parent must be present to consent for their child’s participation

Questions?

Contact us:

Kathryn Torok, MD
Principal Investigator
Children’s Hospital of Pittsburgh of UPMC
(P) 412-692-5081
Kathryn.Torok@chp.edu



Pediatric Updates

SAVE THE DATE:

Please join us for the 2nd annual Scleroderma 5K Run/Walk Saturday, July 28 in Kersey, PA. This event is led and organized by a local group of pediatric scleroderma patients, and is a fun way to meet other families and support one another. Proceeds will benefit pediatric scleroderma research led by Dr. Torok and her team at Children's Hospital of Pittsburgh. For more information, look for updates soon at:

<https://runsignup.com/Race/PA/Kersey/Scleroderma5k>

SCORE STUDY: Identifying Juvenile Scleroderma Immunophenotype Subsets

Dr. Kathryn Torok is leading the Scleroderma Foundation Multi-Center Collaborative Research (SCORE) observational study in collaboration with the Childhood Arthritis and Rheumatology Research Alliance (CARRA) and 18 leading pediatric rheumatology centers throughout the United States and Canada. The goal of the project is to identify specific immunophenotypes (cell types, inflammatory protein profiles and antibody types circulating in the blood) of pediatric Systemic Sclerosis (SSc) and Localized Scleroderma (LS). Identifying immunophenotypes will biologically define clinical subsets of disease to help improve treatment and outcomes. Dr. Torok and her team believe there will be both shared and overlapping immunological profiles between SSc and LS, which will help determine measures of clinical disease outcomes, prognosis and potentially predict response to medications.

Enrollment is anticipated to begin this summer. For information, please contact the pediatric research coordinator: Kaila Schollaert-Fitch, k.fitch@pitt.edu.

KGS2!
Kids Get Scleroderma Too!
2018

October 26-27
Children's Hospital Colorado
13123 E 16th Ave, Aurora CO 80045

LEARN ABOUT SCHOLARSHIPS AND REGISTRATION BY JOINING THE EMAIL LIST:
Rocky Mountain Chapter: cbesselievre@scleroderma.org
Tri-State Chapter: mbbkadylak@sclerodermatristate.org

EVENT INCLUDES:
Halloween Costume Party - the evening of 10/26
 Hyatt Regency Aurora - Denver Conference Center - Ballroom
Workshops all day - 10/27 - with segments for all ages
 Children's Hospital - Colorado

Co-Sponsors
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The KGS2! (Kids Get Scleroderma Too) patient and family education conference sponsored by the Scleroderma Foundation will take place at Children's Hospital Colorado October 26-27, 2018. Dr. Torok and other pediatric scleroderma experts will be attending! Please see the flyer above for additional information.



We would like to thank the following donors for their support of scleroderma research



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Your contributions to the Scleroderma Center are greatly appreciated and help support research and patient education programs. You can remember or honor a loved one by using the envelope enclosed in this newsletter to send your donation.

For additional information on giving to the Scleroderma Center, please contact Rose Jandrasits at 412-864-1958 or krj13@pitt.edu.

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