SCLERODERMA ASSOCIATION OF B.C.

# The Bulletin

Spring-Summer 2021 | Volume 3 Number 1

Scleroderma Association B.C.

## Spotlight on Research

## New Educational Sheets

# Summary




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# A Word from Our President


**Who would have thought that a year later, we would still be dealing with COVID-19. As we all move through this pandemic, what will our "new normal" eventually look like? As I write this, people are finally getting vaccinated, improving our outlook for the future. If you are unsure if you should get the COVID-19 vaccine, I suggest you go to the SABC website, click on the "COVID-19" tab and check out the links to an information sheet and a video under "Vaccine News". SABC and our Synergy of Three partners, Sclérodermie Québec and Scleroderma Manitoba, continue to work on improving our websites to ensure we provide relevant and up-to-date information for our members.**

## RESEARCH

SABC has recently been recognized by the St. Paul's Foundation for the many years of financial support of the Scleroderma Clinic. Your donations have contributed to over $600,000 raised for the SABC Research Project, other programs and specialized equipment. A plaque has been installed in the Lung Centre's patient waiting room, located on the 8th floor of the Providence Building.

We were also invited to celebrate the 'breaking of ground' for the new St. Paul's Hospital. An exciting future of patient care and research is ahead.

In this issue of The Bulletin, we are once again excited to share two additional articles about research. It is fantastic to see how committed these researchers are for such a rare disease.

## VIRTUAL SEMINARS

To meet our mission statement of providing Patient Support, Education and Research, we are continuing to offer various educational programs using Zoom. This is a great opportunity to share knowledge with patients, caregivers and associated medical professionals all over the province. In January, we offered a ***Wound Care seminar*** with RN and wound care specialist, Lauren Wolfe, providing valuable information to all but especially to those suffering from digital ulcers. If you missed it, the recording is on our website under "Videos". In March, we worked virtually with UBC's Patient & Community Partnership for Education to share our experiences as patients living with this disease with health sciences and medical students. We were thrilled to have the privilege to provide scleroderma awareness to our future health care professionals. Then in April we learned about Scleroderma & Cannabis with Greenleaf Medical Clinic's Dr. MacCallum and Fonda Betts.

### SAVE THE DATE:

**Our Virtual AGM & Conference will be held on October 2, 2021. Keep an eye on our website for details regarding the program and how to participate.**

## JUNE AWARENESS

I am once again excited to participate in this year's now **2nd Annual Virtual Fundraising Campaign**. The campaign gives our family and friends the opportunity to support us by spreading scleroderma awareness and raising money for research. SABC is committed to every penny raised supporting research here in BC or across the country, as lucky for us, there are many unique and important research projects to support at a wide variety of facilities across Canada.

While I really miss seeing everyone in person, going virtual still gives us a chance to participate in this year's **"Moving to Cure Scleroderma".** Virtual fundraising events allow us to connect with others in an innovative way for a shared cause without having to be in the same location.

***Personal Note: I know I have said this before, but you will be amazed how easy it is to join in the fundraising. People do really care about you.***

# Jen's Story

## "SCLERO WHAT…?!"

**In the winter of 2015, everything in my life changed after my diagnosis of systemic diffuse scleroderma. I spent the next several weeks paralyzed by fear trying to process all the information I was given by my doctors. I wondered how the trajectory of this disease would unfold for me and my family. Little did I know I was about to enter the fight of my life.**

Rewinding the clock, I was a competitive athlete holding provincial records in cross-country running, skiing and cycling. I spent a lot of time in my 30s and 40s participating in half and full marathons. I also enjoyed triathlons and teaching fitness classes. I worked for 25 years in the social service field serving and supporting adults with developmental disabilities. I was passionate about my volunteer projects in the community and always had positive goals in my back pocket.

Within weeks of my diagnosis, I noticed my body changing dramatically. My skin was tight and purple. Raynaud's attacks were frequently occurring, and I had developed digital ulcers on my fingers. Arthritis had set into my joints making walking and daily activities more challenging. I developed severe gastrointestinal involvement and lost 35 pounds. Every step I took felt as if I were walking on broken glass. Fatigue followed me around the house like a haunted ghost. I had fibrosis in the bottoms of both my lungs and had now gone from running marathons to becoming short of breath walking up my basement stairs. Mentally I had to come to terms with the fact that I may never run again. The emotional part of managing this disease was daunting. Fear and anxiety became part of my new normal. This was by far the darkest time in my young adult life. I had no idea what lay ahead of me. I was running low on hope.

Around two months into these unchartered waters, I read a young girl's story of scleroderma. I was incredibly inspired by her courage, resilience, and positivity in moving forward with her journey. Despite all the challenges she faced, she did not let this disease define her. I knew at that point I needed to change my perspective for the future and become my own self advocate.

I began to focus on well-researched and credible articles. I connected with positive support groups, the SABC and became an area representative in Kamloops. I attended both provincial and national conferences that provided a wealth of resources including SPIN (Scleroderma Patient Intervention Network). I had the privilege of connecting with other women in Kamloops who lived with and endured the challenges of this misunderstood disease. They became my mentors and friends. My family and friends supported me whole heartedly. I took in all the medical expertise from my compassionate team of scleroderma specialists at St. Paul's Hospital. I worked collaboratively with my doctors looking for the best possible treatments. It was a comfort to know I was not alone in fighting and managing this disease.

Five years ago, I was not sure which direction I was headed. I had tried several drug therapies that were unsuccessful in slowing down the progression. Two years ago, with the support of all my doctors, we found a treatment plan that worked to stabilize the progression of my disease and improve the quality of my life. I am not going to lie and say that I am not concerned about what lies ahead of me but am grateful to be out hiking with my dogs and enjoying all the things in my life I am passionate about.

I am also excited to share that this year I will be running 5 kilometres (yesss!) in support of the SABC's fundraiser, "Moving To Cure Scleroderma". Together, we will spread awareness and raise funds for scleroderma research in B.C.

Thank you for reading my story. My desire in sharing is that other newly diagnosed people will take away a sense of hopefulness, feel less isolated and motivated to move forward positively in their own journey. Although this disease impacts our lives daily, it does not define us.

# MOVING TO CURE SCLERODERMA



**100% OF THE FUNDS RAISED SUPPORTS SCLERODERMA RESEARCH HERE IN BC AND ACROSS CANADA**

**Virtual events are an opportunity to participate and connect with others over a shared cause without having to be in the same location. Join one of our teams, fundraising while engaging in an activity of your choice and capture it! Or simply support a team by donating online. Continue to practice social distancing while walking, hiking, bicycling, running, holding a virtual family activity or doing relaxed stretching at home. Your options are endless, and the choice is yours to be as energetic, adventurous, or creative as you want to be.**

## WAYS TO PARTICIPATE

### Go to our website sclerodermabc.ca, then to the Moving to Cure Scleroderma

**1 MAKE A DONATION**
to one of our teams or a particular participant

**2 JOIN THE FUNDRAISING EFFORTS BY JOINING ONE OF OUR TEAMS**

The fun continues afterwards when we share how we participated, so make sure to take pictures or videos and send them to SABC's:

**Valerie Doyon at valerie.doyon@alumni.ubc.ca.**

Include your location and any other details you would like to provide. The SABC will create a slideshow that includes your "Moving to Cure Scleroderma". We want to demonstrate how we all came together in the month of June to raise awareness and funds to support scleroderma research. We also encourage you to share your participation through Facebook (don't forget to tag us: @ScleroAssnBC)

### Questions regarding participation?

**Contact SABC's David Queen at dq.sabc@telus.net**

With the support of you, our families, friends and community, we can make this event truly special and we can really make a difference!

*This is our 10th year for The Scleroderma Ride for Research. Knowing that my family and friends will once again support me, in any way they can, is exciting. Raising money for research gives me hope. I can't wait for 2022 when the 11th year will be in person!* – Rosanne Queen, Vancouver

*This is my fourth year participating and raising awareness on Vancouver Island. I enjoy that this connects us as a community as well as brings our friends and family together to show our support.* – Jackie Alexander, Campbell River

*While we still must stay apart this year, we can all contribute to scleroderma research by participating virtually in raising money and awareness. Support our "Moving to Cure Scleroderma - Victoria" and we'll look forward to seeing you in person next year!* – Linda Barnes, Victoria

*I've never wanted anything to do with fundraising. Last year for the first time ever I was involved in fundraising for scleroderma. I was surprised at how many friends donated because they care about me. I'll definitely be involved again this year.* – Pat Thomasson, Coquitlam

*This will be our first-year fundraising in Squamish and we hope to raise lots of money to support the cause!!* - Beth Miller, Squamish

*Kamloops is looking forward to raising both awareness and money for scleroderma research in BC in the 2nd Annual "Moving to Cure Scleroderma" fundraiser.* - Jen Beckett, Kamloops

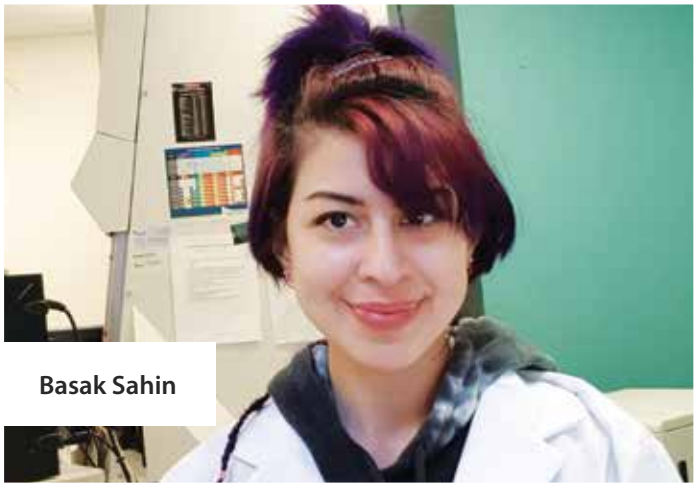
**FOR MORE DETAILS PLEASE VISIT: sclerodermabc.ca**

# Spotlight on Research
## SABC Research Program

**It was the summer of 2017 when many of us, patients and supporters alike, marched into the Scleroderma Clinic/Pacific Lung Health Centre on the 8th floor at St. Paul's hospital, rolled up our sleeves, and bared our arms to provide blood and skin samples. Some of us arrived at the clinic from all parts of B.C. as we know, Scleroderma is a rare disease with few specialists practicing in remote regions of the province. We signed-up to be participants in a Scleroderma research study titled Circulating and Cellular Biomarkers for Lung Disease in Systemic Sclerosis (SSc) and Idiopathic Pulmonary Fibrosis (IPF) or known to most of us as simply The Scleroderma Association of B.C. Research Project.**

### IT'S ALL ABOUT THE miRNAs

What we knew at the time of signing our consent forms and offering up our blood and skin is that the researchers would analyze our samples, looking for 'biomarkers' which are indicators of normal or abnormal biological processes or disease. Specifically, researchers would be assessing ribonucleic acid (RNA) which is the material that expresses DNA genes. Small sequences of RNAs, or microRNAs (miRNA), are vital in gene silencing, or the 'turning off' of gene expression. Because the levels of several miRNAs have been found to be abnormal in several conditions including SSc, researchers would be measuring the levels of miRNA sequences in our samples to identify if they are, in fact, potential biomarkers (predictors) of SSc and IPF. For example, if a patient's sample has a lower amount of a given miRNA sequence compared to a supporter's or 'control' sample, perhaps that low level is a biomarker or predictor for SSc. Discovering which miRNA sequences are too low or too high and correcting these imbalances could lead to effective treatment of skin damage in patients with Scleroderma and treatment of lung damage in patients with IPF only and in patients with both Scleroderma and IPF.



Basak Sahin

The SABC Research Project researchers are known to us all as Drs. Jim Dunne, Kevin Keen, Pierce Wilcox, Chris Ryerson and research coordinator Fran Schooley. **But there are many more experts, working behind the scenes on this project, analyzing our samples, collating the data and reporting out the results. One of these experts and the focus of this article is Basak Sahin**. Basak is a research technician at the Molecular Phenotyping Core of UBC Centre for Heart Lung Innovation at St. Paul's Hospital and has been with the SABC Research Project since the beginning. She works directly with Beth Whalen, the lab manager and supervisor and the two are each other's backup and support. Also on the research team is Iris Yao, this year's student who presents and reviews consent forms with study participants and Gurpreet Singhera who kindly volunteered to help with the western blot lab tests.

Basak's background is in molecular biology and genetics and she worked with small RNAs and nano/microparticles during her graduate studies. Basak became interested in working on the SABC Research Project while attending one of Dr. Dunne's infamous lab 'hurricane meetings', described as consisting of 15 minutes of brainstorming any number of different research ideas. Due to Jim's contagious enthusiasm (and long-standing relationship with the team at the Centre for Heart Lung Innovation), Basak joined the project in 2016, bringing with her the much-needed expertise for the start of the miRNA arm of the study.

# SABC Research Program

Basak Sahin, Gurpreet Singhera and Beth Whalen

Speaking of enthusiasm, Basak is familiar with the SABC being the main source of support for this study, both financially and in terms of spreading the word. Basak has also joined Scleroderma patients, their friends and family members at the annual June fundraiser, SABC's Scleroderma Ride for Research in Stanley Park. The support for research certainly contributes to Basak's enjoyment in working on the project. In her own words, **"There is always something new and exciting happening".** She continues to be energized after Jim's research meetings, reading up and delving further into study ideas, pouring over spreadsheets, reviewing needed inventory and planning, planning, planning.

The SABC Research Project is just one of many projects Basak works on, though our study is the one she is most involved in. Basak's role in the project has involved the hands-on lab work in extracting the RNA from the blood and skin biopsy samples, preparing the extractions for sequencing and conducting the required lab tests. Basak also generates sheets of spreadsheet data that regularly end up in Dr. Keen's inbox, knowing he will make sense of them!

Basak explained in more detail exactly what has been happening with our samples. After collection at the clinic, the research team are called to pick-up the samples with instructions of which arm of the study the sample belongs to. Samples are coded with a unique ID to ensure patient confidentiality and the blood processed into different aliquots of plasma, serum, buffy coat and the RNA tube. The skin biopsy samples were used to grow fibroblast cells. Samples are continually stored until the researchers have enough patient and control samples to run a set of experiments.

Much work has gone into extracting and sequencing of RNA from the RNA tube aliquots and the fibroblasts grown out of the skin biopsies. Additional experiments include the use of qPCR and NanoString technology to validate the molecular signatures seen in the sequencing. Also performing ELISA, western blot and flow cytometry tests to identify and measure protein concentrations in the plasma and serum , even sending plasma samples to Dr. Martin Fritzler in Calgary to test for additional protein signatures.

She explains the research is really trying to figure out the pathogenesis or how the disease develops. Basak states, "**SSc can manifest in many different ways, causing different symptoms in different individuals seemingly without rhyme or reason. When that happens, it is hard to put your finger on a specific gene or pathway and say, hey this is where the problem is, lets fix that**. We know what happens, but we do not know why. We want to pinpoint the source(s) where things are going awry, because there is really very limited knowledge of Scleroderma.

We want to dive deep into the biology and figure out what exactly is going wrong to cause all the different symptoms. It is never a very viable option to keep treating the symptoms and not the source itself. Treating the symptoms is maybe going to slow down the disease progression or make it more comfortable for the patients to live with it, but not stop or reverse the disease itself".

# SABC Research Program

According to Basak, the main goal of the SABC Research Project is to understand how all these pathways are interacting to cause the multitude of results and to try and understand which proteins, RNAs and DNA interact to make this complex machinery work (or in some cases, not work). The team is hopeful they are on their way to identifying a pathway that may be one of the main culprits in the disease progression. Identification is the first step which leads to understanding which leads to maybe one day, fixing it.

Basak continues with **"one of the things we think might be causing the disease and the variety of symptoms is an issue with cell to cell communication**. You have many different types of cells in your body, each with a different specialization. Cells need to 'talk' to one another to make this incredibly complex machinery that we call our bodies work properly. They achieve this communication by packing up and sending out 'envelopes' (called extracellular vesicles) to each other. Inside the envelopes are 'letters' consisting of proteins, RNA, DNA and most importantly for our research, miRNA, tiny RNA particles that carry information to regulate gene expression.

What happens when the cell is not able to pack the envelopes properly? When the letters inside are incomplete or different from what they need to be? We want to figure out which envelope is deficient or which cell type is having problems composing their letter. Then we can come up with a targeted strategy to fix the communication problem".

Basak mentions another goal of researching SSc is to be able to stratify patients into main and disease subgroups. Stratification will provide better, more personalized patient treatment for their specific prognosis. The preliminary research results do indicate a few molecular signatures may have been identified (validation of results pending). There are people that get interstitial lung disease (ILD) and those that do not, there are people who have a more diffuse disease and people whose symptoms are more limited. We want to know why this is and what makes people get such different prognoses.

We all know that understanding how a disease works leads to more precise treatments and cures. Adding to the existing knowledge base using basic science eventually leads to better therapies in the clinic for the patients.

**Thank you so much Basak for being SABC's first Spotlighted Researcher!**

**MICHELE GERVAIS**
Vice-President
Scleroderma Association of B.C.

**FOR DOCTORS ONLY:**

Please direct referrals to Dr. James Dunne
Tel: 604-732-4993 — Fax 604-732-4984

# Establishing the Individual Immune Identity Card of Scleroderma Patients

## An Essential First Step Toward Personalized Therapy

**JEAN-LUC SENÉCAL, MD, FRCPC, MCRA**
Scleroderma Research Chair
Professor of Medicine University of Montreal

**At the request of several provincial scleroderma (Scl) associations, I am pleased to provide an overview of recent research carried out under the University of Montreal Scleroderma Research Chair.**

**For the past several years, an advanced program of translational research on Scl is in progress in Montreal at the Research Center of the Centre Hospitalier de l'Université de Montréal (CHUM). This program results from a close collaboration between the Laboratory for Immunoregulation, directed by Marika Sarfati, MD, PhD, an immunologist and basic scientist, and the Laboratory for Research on Autoimmunity, directed by the undersigned, a rheumatologist and clinician researcher specialized in the care of Scl patients.**

### THE RATIONALE FOR A PERSONALIZED APPROACH TO TREATMENT

These scientists are closely collaborating on an exciting and state-of-the-art novel Scl research project aimed at changing the often poorly efficacious "one size fits all" approach to therapy of Scl into ***personalized medicine***, i.e. the prediction of Scl progression in individual patients and predicting whether they will respond to drug treatment. The ultimate goal of personalized medicine is the use of therapies specifically developed and individualized to target the disease mechanisms specific to a given Scl patient. We and others believe that this approach is much more promising because it will be based on identification of the disease mechanisms that are present in individual Scl patients very early in Scl and that this will predict their disease course, thus allowing therapies to be tailored to the individual Scl patient.

Until recently, exploring these mechanisms was not possible other than on a small scale but exciting new (and costly) technologies are now available on a very large scale commensurate with the high cellular and molecular complexity of Scl.

### THE NEED FOR EARLY THERAPIES IN SCL

But before explaining more in-depth our project and its potential high relevance to Scl patients, providing some essential background is needed. Scl is a potentially life-threatening and incurable disease. Although physicians do not like to admit it, ***most therapies in Scl (as in many other diseases) are given after the fact***, i.e. after a single or several organs are involved. For example, if moderate or severe lung fibrosis develops, attempts are made to treat with immunosuppressive and/or anti-fibrotic drugs, hoping at least to stabilize the patient's condition. Sometimes this is not possible and lung fibrosis progresses so much that lung transplantation is necessary, showing the limits of current medical therapies. There is a profound need to develop early and preventive therapies in Scl, i.e. treatments administered before the development of severe manifestations in the patients at-risk. >>

## THE CENTRAL ROLE OF THE IMMUNE SYSTEM

This lack of efficacy is not surprising in light of the extremely complex pathogenesis of Scl comprising four cardinal disordered mechanisms that ultimately lead to Scl symptoms through involvement of the skin and internal organs. Thus, ***autoimmunity*** (attack of the immune system against one's self leading for example to the production of autoantibodies in the blood that are highly specific for Scl) and ***inflammation*** combine with widespread ***involvement of small blood vessels*** (causing Raynaud's phenomenon, i.e. blanching of the digits on cold exposure) and ultimately ***fibrosis*** (excessive production of collagen leading to hardening of the skin and internal organs). Scientists have become aware that many cells (mononuclear phagocytes, fibroblasts, myofibroblasts, endothelial cells, vascular smooth muscle cells, to name but a few), hundreds of genes and hundreds of molecules (cytokines and many others) participate into Scl pathogenesis. ***Since inflammation precedes fibrosis, the immune system is at the core of the disease process and therefore its study is critical***. But how can such immune complexity be deciphered?

## THE NEW CONCEPT OF PRESCLERODERMA

Two breakthrough discoveries by our research team started to answer this daunting question and provided major clues as to where to start. First, in 2008, we reported in the leading rheumatology journal worldwide that, in almost ***all patients with Scl, an immune signature of the disease (i.e. Scl-specific autoantibodies in the blood) is present many months and often years before manifestations typical of Scl are noted*** by the patient and her doctor (such as thickening of the skin or lung involvement) [(1)]. This discovery focused attention on a very important and previously neglected period in the Scl time course that is now universally designated as prescleroderma (preScl). Our discovery raised three key questions:

- 1° Since patients with preScl eventually develop full-blown Scl, what are the pathogenic disease mechanisms active in the preScl phase?
- 2° Can these mechanisms predict the future course of the disease and involvement of specific organs?
- 3° Can these mechanisms be targeted early by novel or existent therapies to change the future course of Scl?

However, at the time, advanced technology to explore in-depth the cellular and molecular mechanisms of early Scl was not yet available. Therefore we decided to tackle these questions by developing an experimental (animal) model of Scl for which Dr Sarfati is an expert. An animal model is useful because it allows analysis at a greater level of biological complexity, i.e. closer to humans, than is possible in the test tube. Also, it allows therapeutic manipulations that would be unethical in humans.

## COPYING HUMAN SCLERODERMA INTO MICE

The successful development of this model was ***the second breakthroug***h. Said shortly, we succeeded into ***copying human Scl into mice***. Not only did our model replicate the four cardinal mechanisms of Scl, it also replicated the Scl phenotype, i.e. clinical manifestations such as skin thickening and lung involvement. Moreover, since we had previously identified preScl as a potential critical period for early therapeutic intervention, as seen above, we proceeded to therapeutic manipulations (antibiotic therapy to change the gut microbes) during the corresponding preScl period in the mouse model. The results were dramatic, indicating ***a profound effect on disease severity when therapeutic manipulation was applied specifically during preScl***. This discovery was published in 2017 in a top international dermatology journal with an accompanying editorial [(2)].

## NATIONAL SUPPORT

I wish to emphasize that the development of the model, originally supported by Sclérodermie Québec, was also generously supported by donations from Maureen Sauvé, Scleroderma Canada, Scleroderma Society of Ontario and the Scleroderma Research Chair, which allowed us to generate strong preliminary results and to obtain a research grant from the Canadian Institutes of Health Research (CIHR). Thus, we used these private donations as leverage to obtain highly competitive public funding ($ 575,740, 2015-2019; success rate: 9%). Currently, we are supported by Sclérodermie Québec, the Research Chair and by donations from the Scleroderma Associations of British Columbia, Manitoba and Saskatchewan, emphasizing the national stature of our program.

## PRESCLERODERMA: A NOVEL POTENTIAL THERAPEUTIC WINDOW

Taken altogether, these 2008 and 2017 discoveries, both in preScl patients and in the experimental model, ***identified preScl as a new and potentially very important therapeutic window*** for Scl patients. Therefore, it became critical to study in-depth at the cellular, molecular and gene levels patients with preScl in order to characterize early immune mechanisms, compare them with disease mechanisms active in full-blown Scl and identify potential novel therapeutic pathways and molecular targets. Remarkably, over the past few years, technological breakthroughs occurred that now permit analysis of disease mechanisms at an unequalled and extraordinary level of cellular, molecular and genetic complexity. >>

# University of Montreal Scleroderma Research Chair

## THE FACSYMPHONY

Thus, in late 2018, the CHUM Research Center, with support from Sclérodermie Québec and the Canadian Foundation for Innovation, acquired a cutting-edge instrument from Becton-Dickinson (BD) called the ***FACSymphony, a multiparameter flow cytometer that allows complex molecular analyses at the single-cell level*** that were not possible previously. As many as 30 (and in the near future up to 50) molecular characteristics of a single Scl cell can now be identified using only limited amounts of blood and small skin biopsies (3 mm) from Scl patients, thus enabling to comprehensively study their immune profile in blood and at barrier tissues. Over the past several months, Dr Sarfati and Heena Mehta, PhD, Research Associate, have become experts at using the FACSymphony and its complex results consisting of big data that require artificial intelligence-based software and computational biology for interpretation. The power of this new technology is extraordinary and will lead to the identification of unsupected pathogenic cellular subpopulations and new disease mechanisms.

## A GROUND-BREAKING RESEARCH PROTOCOL

Having mastered the FACSymphony, our expert team composed of Dr Sarfati, Dr Mehta, Sabrina Hoa, MD (a rheumatologist and clinician researcher who has completed a 3-yr Scl fellowship and a Masters in epidemiology at McGill University), Martial Koenig, MD (an internist specialized in Scl and the first author of the 2008 manuscript) and the undersigned undertook and are now completing, despite COVID19-related containment, ***a new research protocol with the aims of characterizing the overall immune landscape in Scl and preScl and establishing specifically "the immune molecular and cellular identity card" in individual Scl patients***.

The study design takes stock of our discoveries of preScl and our mastery of the unequalled analytical power of the FACSymphony. ***Results will provide important novel therapeutic targets, the inactivation of which may prevent Scl progression. We anticipate the potential discovery of a "protective" immune profile, that may suggest novel therapeutic targets and strategies to protect patients from progressing to full-blown Scl***.

## THE RHAPSODY

However, a key instrument was missing to maximize the identification of novel potential therapeutic targets. ***Additional state-of-the-art technology was needed to provide transcriptomes (all the messenger RNA molecules) of the targets identified by flow cytometry. This equipment, also from BD, is the Rhapsody, a single-cell analysis system that provides the expression of hundreds of genes across tens of thousands of single cells in parallel***. Like the FACSymphony, with which it operates in tandem, the Rhapsody is expensive and requires access to highly valuable patient biological samples. Therefore we wished to optimize the number of analyses on the same sample as much as possible and this is what justified the rapid acquisition of the Rhapsody, as the same precious patient samples used in the FACSymphony can be reused in the Rhapsody. Moreover, we recently had the opportunity to test the potential of the Rhapsody through a loan of demo equipment by BD. ***Put simply, not having the Rhapsody would deprive our research project from its potential therapeutic applications***.

## A SUCCESSFUL NATIONAL EFFORT

Given that the CHUM Research Center did not own a Rhapsody and that our team did not have the financial resources for its purchase, Sclérodermie Québec launched a national fundraising appeal. We are extremely pleased that $88,000 were raised in March and April 2021, that will allow the purchase of the Rhapsody. We thank for their generosity Scleroderma Canada, the Scleroderma Association of B.C., the Scleroderma Association of Saskatchewan, Scleroderma Manitoba, the Scleroderma Society of Ontario, Sclérodermie Québec and Scleroderma Atlantic.

## CONCLUSION

Technological advances are now providing extraordinarily powerful tools to establish the individual immune identity card of Scl patients. As we are taking our first step toward personalized therapy, these tools raise hope for all Scl patients. Partnerships between patients, basic science researchers and clinician researchers, and generous support from provincial and national organizations are critical to improve the life expectancy of Scl patients, and ultimately find a cure for Scl. Our team is proud of the national support for its projects. We are accountable and we deliver. <<

**JEAN-LUC SENÉCAL, MD, FRCPC, MCRA**
Scleroderma Research Chair
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1. Koenig et al. Arthritis Rheum (2008) 58: 3902-3912. doi: 10.1002/art.24038.
2. Mehta et al. J Invest Derm (2017) 137:2316-2325. doi: 10.1016/j.jid.2017.06.019.

# CAPILLAROSCOPY AND COMPLEMENTARY OBSERVATIONS

**France Joyal, M.D. and Martial Koenig, M.D.,**
internists and researchers, CHUM.

**Definition**

**Nailfold capillaroscopy is a simple, non-invasive, painless examination mainly performed on the hands that allows the study of small blood vessels, called capillaries, located around the nail beds. After depositing a drop of oil to make the skin more transparent, the periungual capillaries are observed under a microscope.**

The observation of animal and human cells began more than 300 years ago, and the addition of a magnifying glass 100 years later allowed the observation of capillaries at the surface of the skin. Over 100 years ago, significant changes in capillary morphology have been observed during scleroderma; and, in the last 40 years, studies have been carried out showing the morphological evolution of capillaries in relation to scleroderma-specific antibodies.

**CAPILLAROSCOPY AND COMPLEMENTARY OBSERVATIONS**

# THE FUNCTIONS OF THE CAPILLARIES

The capillaries, so named for their resemblance to hair, although they are ten times smaller, are the smallest visible vascular structure on the skin. They form a loop that connects the smallest end of the arteries to that of the veins. They act as a barrier that filters certain structures, bringing essential nutrients to the surrounding cells and capturing waste products that are then eliminated by other organs.

With today's high-magnification microscopes (from 50 to 200 times) their shapes can be accurately revealed thanks to the red blood cells that circulate in them and which define their contours since their walls, made up of just a few cells, are too thin to be visible.

# WHY PERFORM A CAPILLAROSCOPY?

Diagnostic criteria for scleroderma have gradually evolved, as these were initially based on the degree of skin and lung involvement (1980). Later, the growing interest of clinicians and researchers in this disease, the introduction of capillaroscopy, the notion of Raynaud's phenomenon and the discovery of scleroderma-specific antibodies have led to the development of new diagnostic criteria (1988, 2001).

Since 2013, following a consensus between American and European physicians on what are the key features for diagnosing scleroderma, new diagnostic criteria are being used. These criteria are based on a points-scoring system that relies on the presence of certain physical aspects (cutaneous and pulmonary), Raynaud's phenomenon, capillary abnormalities and specific antibodies found in 85% of cases (anticentromere (ACA), anti-topoisomerase, anti-Th, anti-RNA Polymerase 3).

## CAPILLAROSCOPY AND COMPLEMENTARY OBSERVATIONS

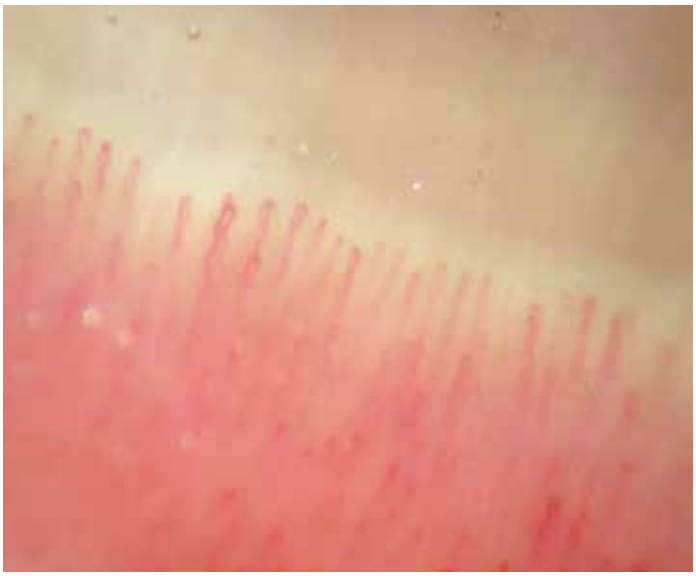


**Figure #1**
Normal pattern: row of hairpin-like capillary loops

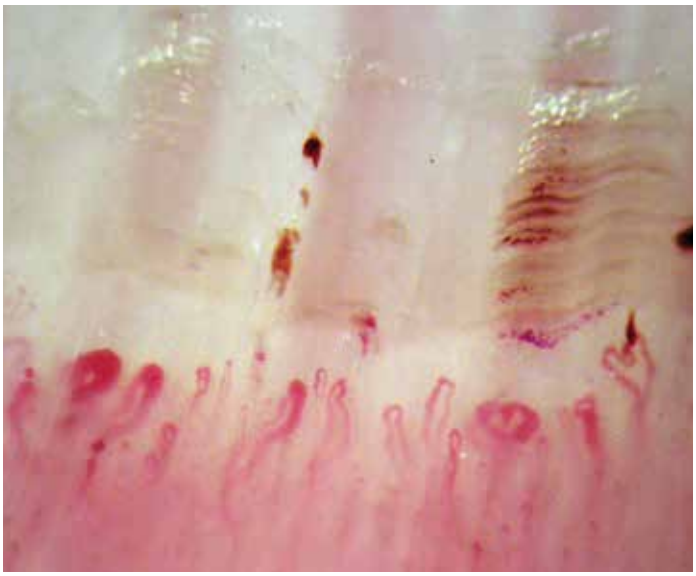


**Figure #2**
Scleroderma pattern with positive ACA antibodies: successive hemorrhages, enlarged and disorganized capillaries

### CAPILLARY CHANGES IN SCLERODERMA

The presence of specific abnormalities of the nailfold capillaries provides further evidence for supporting the diagnosis of scleroderma

especially in the absence of specific antibodies (15% of cases). An examination is required when a patient develops symptoms in the hands, whether or not these are related to Raynaud's phenomenon. Capillary abnormalities are not necessarily related to the number of fingers affected or the frequency of episodes of capillary discoloration.

In scleroderma, the walls of the capillaries and the surrounding tissue appear to change more or less rapidly depending on the antibodies detected and disease duration: normal pattern appears as a row of hairpin-like capillary loops (figure #1) become disorganized. The capillary loops enlarge, at more than 50 µm (figure #2), they thrombosed (self-destruct) and disappear with or without a trace of bleeding. They may cluster together and are often visible as small red dots on the skin

surface (capillary telangiectasias) with little evidence of replacement of the missing vessels (angiogenesis). Changes in capillaries have been observed up to 15 years before the onset of skin or other internal organs involvement during scleroderma. However, some patients with long-standing scleroderma may have normal capillaries.

Nailfold capillaroscopy alone does not allow for the diagnosis of scleroderma in all cases because the capillaries may also be enlarged in patients with other autoimmune diseases such as lupus erythematosus and dermatomyositis. Capillaroscopy findings should thus be interpreted according to some specific questions, the clinical examination and the antibodies detected.

Capillaroscopy remains an important tool for the early diagnosis of scleroderma. The pathophysiological mechanisms leading to changes in the number of capillaries, their shape and arrangement during the course of the disease are still poorly understood, as is the relationship with the antibodies detected. Fortunately, research continues to provide a better understanding of this disease and to identify treatments that are not only curative but also preventive.

# COVID-19 AND VACCINATION

FEBRUARY 2021


**COVID-19 is the disease caused by the coronavirus SARS-CoV-2, a new virus first detected in December 2019 in the city of Wuhan, China.**

**In March 2020, the World Health Organization declared the outbreak of COVID-19 a global pandemic. In Manitoba, in February 2021, we are in the second wave of this pandemic with more than 31,386 cases and more than 884 deaths.**

**To date, no medication is recommended to prevent or treat coronavirus infection. However, supportive treatments may be offered depending on the symptoms experienced and their severity. Although specific treatments are being studied and tested in clinical trials to assess their safety and efficacy, there is currently no evidence-based treatment available for COVID-19.**

**Vaccines for COVID-19 have been studied in clinical trials and approved for use against this disease. This raises the hope for a return to a life situation free from the adverse consequences of COVID-19.**

## COVID-19 AND VACCINATION

### VARIANTS OF COVID-19

SARS-CoV-2, the virus that causes COVID-19, will naturally develop mutations, which are changes to the genetic material in the virus over time.

When there have been several significant mutations to the virus then it's called a "variant".

Genetic variants of viruses, such as the one that causes COVID-19, are common and expected.

Several variants of the virus that causes COVID-19 are circulating around the world:

The United Kingdom (UK) has identified a variant called B.1.1.7 with a large number of mutations in the fall of 2020. This variant spreads more easily and quickly than the other variants. In January 2021, British experts reported that this variant may be associated with an increased risk of death compared to other virus variants, but further studies are needed to confirm this finding. It has since been detected in many countries around the world, in the United States in late December 2020 and in Canada in January 2021.

In South Africa, another variant called B.1.351 was detected in early October 2020. Cases caused by this variant were reported in the United States at the end of January 2021.

The two new variants of concern from the United Kingdom and South Africa include mutations that appear to make the virus more infectious, allowing it to spread more easily. However, they do not appear to affect the severity of the disease.

In Brazil, a variant called P.1 appeared and was first identified in four travellers from Brazil, who were tested during a routine screening at an airport in Japan in early January. This variant was first detected in the United States in late January 2021

### MONITORING OF VARIANTS

The Public Health Agency of Canada works with provinces, territories and other partners to monitor and identify variants of concern in Canada, including the United Kingdom and South Africa variants. Monitoring for genetic changes in the virus allows us to better understand the potential impact of the mutations.

At this time, there's no evidence that some variants have an impact on drugs and the authorized vaccines efficacy. Pfizer and Moderna's vaccines appear to have some efficacy against these two variants. Research is underway to assess this efficacy.

Given the limited data on the new variants, more research is needed to confirm these early findings. The Canadian and global medical, public health and research communities are actively evaluating these variants and other significant mutations.

### TRANSMISSION

- The time period in which an individual with COVID-19 is infectious remains uncertain.
- An asymptomatic person is contagious.
- A person may be infectious for up to 3 days before showing symptoms (pre-symptomatic infectiousness).
- Viral RNA levels appear to be highest just before or soon after symptom onset.
- Humans can be re-infected with SARS-CoV-2.
- Currently, we do not know whether the presence of antibodies indicates immunity to re-infection, and if it does, how long that potential immunity lasts and what is the potential severity of subsequent infections.

COVID-19 AND VACCINATION

# VACCINATION AGAINST COVID-19


## CHRONOLOGY OF EVENTS AND DEVELOPMENT OF COVID-19 VACCINE

- On March 11, 2020, the World Health Organization (WHO) declares COVID-19 a pandemic.
- Intensive research of vaccines and drugs.
- International collaboration to develop and produce large quantities of vaccines, to be made available as quickly as possible.
- First vaccine is available in December 2020.
- Research program with 20 years of RNA-based technology, but first used and licensed for human vaccines.
- Fast-track approval process for COVID-19.
- Two vaccines authorized in Canada to date (Pfizer and Moderna).
- The Government of Canada has signed advance purchase agreements for seven promising COVID-19 vaccines with the following companies: AstraZeneca; Johnson & Johnson; Medicago; Moderna; Novavax; Pfizer; Sanofi Pasteur/GlaxoSmithKline.
- Most COVID-19 vaccines under development block the S protein, preventing the virus from entering and infecting human cells. These COVID-19 vaccines incorporate fragments of coronavirus that help induce an immune response in the body.
- Vaccines from more than one company will be used for vaccination against COVID-19 to vaccinate the population as soon as products are available and authorized by Health Canada.
- Vaccination is free of charge and only reserved for people in priority groups.
- Adults under 60 years of age who have a chronic disease such as scleroderma or a health condition that increases the risk of complications from COVID-19 will be vaccinated following those over 60 years of age. Next in line are adults under 60 years of age who do not have a chronic disease or health problem that increases the risk of complications, but who provide essential services and have contact with users; and then the rest of the adult population.
- Following an agreement with Novavax, the production of their COVID-19 vaccine will take place in Quebec and should begin this year.

COVID-19 AND VACCINATION

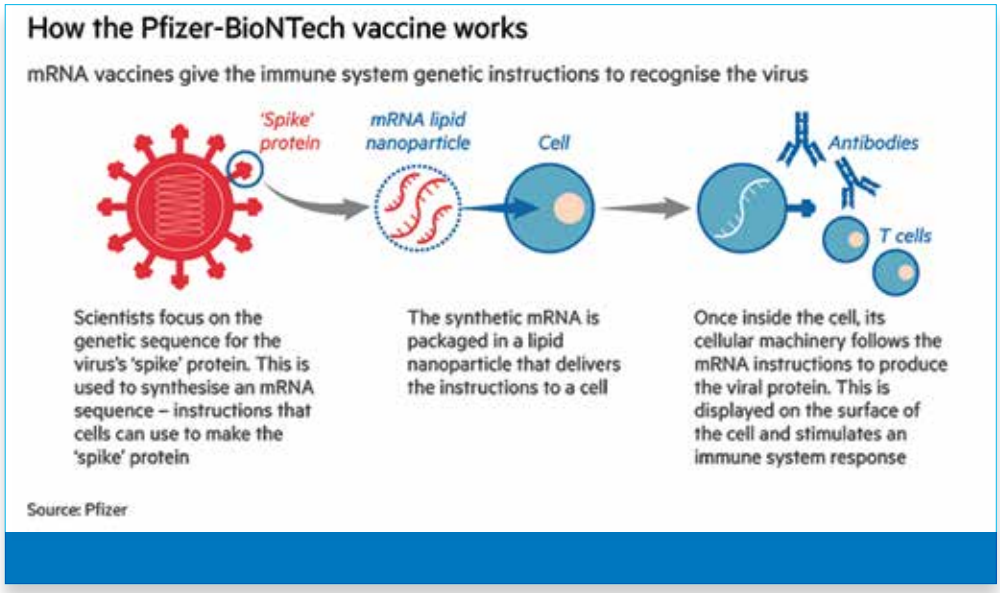
# PFIZER AND MODERNA VACCINES

These two COVID-19 messenger RNA (mRNA or messenger ribonucleic acid) inactivated vaccines have been in use in Quebec since mid-December 2020.

The messenger ribonucleic acid, messenger RNA or mRNA, is a highly purified transient copy of a portion of the DNA corresponding to one or more genes. mRNA is used as an intermediate by cells for protein synthesis.

## THE MESSENGER RNA OF THESE TWO VACCINES

- Provides cells with the genetic instructions for making the SARS-CoV-2 virus S protein (spike protein).
- Is surrounded by lipid particles allowing entry into host cells.
- The mRNA prompts the infected host cells to produce the S protein.
- The S protein, recognized as foreign, triggers the immune response.
- The mRNA and spike protein are then eliminated by the immune system.
- The efficacy of these vaccines is 92% 14 days after the first dose and 95% 7 days after the second dose.
- The duration of the protection is currently unknown.



COVID-19 AND VACCINATION

# IMMUNOSUPPRESSED PATIENTS

**Scleroderma patients are particularly vulnerable to COVID-19, especially if they suffer from pulmonary fibrosis or pulmonary arterial hypertension, or if they are taking corticosteroids or immunosuppressive drugs. These patients are commonly immunosuppressed and may have severe lung problems.**

The National Advisory Committee on Immunization (NACI) recommends that a complete COVID-19 vaccine series may be offered to individuals who are immunosuppressed due to disease or treatment in the authorized age group in this population, if a risk assessment deems that the benefits outweigh the potential risks for the individual, and if informed consent includes discussion about the absence of evidence on the use of COVID-19 vaccine in this population. (Discretionary NACI Recommendation).

Further research will provide more information for immunosuppressed or immunodeficient patients.

Strict adherence to the protective measures and recommendations can significantly reduce the risks of contagion. Let's hope that vaccination will contribute to a quick return to a life free from all these constraints.

## REFERENCES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- MSSS (Québec Minister of Health and Social Services)
- **QIC (Québec Immunization Committee)**

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  *Related material in English:* The Institut national de santé publique du Québec (INSPQ) - Public health expertise and reference centre - COVID-19. *(Most of their work can be found on the* French COVID-19 section*)*
- National Advisory Committee on Immunization (NACI)
- CDC (Centers for Disease Control and Prevention)
- PIQ (Québec Immunization Program)
  - Related material: COVID-19 vaccine
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  Related video in English: Vaccination against COVID-19 - Formation - Scientific Rationale for Quebec's SARS-Cov-2 Vaccination Recommendation. Chantal Sauvageau, MD. M.Sc., FRCP(C) and Gisèle Trudeau, MD., M.Sc., INSPQ, January 26, 2021, McGill University.
- **Videoconference broadcast on the website of the Association des Sclérodermiques de France**: Les vaccins de la Covid-19 et les immunodéprimés (in English: COVID-19 vaccines in immunocompromised patients), Professor Eric Hachulla, Internal Medicine and Clinical Immunology, Claude-Huriez Hospital, Lille University Hospital, and Professor Jean-Luc Cracowski, Pharmacology Department, Grenoble University. (In French only)
- Related material in English: Canadian Rheumatology Association Position Statement on COVID-19 Vaccination and British Society for Immunology statement on COVID-19 vaccines for patients who are immunocompromised or immunosuppressed.
- Who can take the Pfizer-BioNTech COVID-19 vaccine? WHO, 8 January, 2021.
- Wikipedia


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# PULMONARY FIBROSIS IN SYSTEMIC SCLEROSIS

**Dr. Sabrina Hoa, MD MSc FRCPC,**
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**Systemic sclerosis (SSc, systemic scleroderma) is a disease characterized by abnormalities in the functioning of small blood vessels and of the immune system, ultimately leading to inflammation and excessive fibrosis (hardening) of the skin and various organs. When the inflammation and fibrosis reach the lungs, it is called «interstitial lung disease» (ILD) or «pulmonary fibrosis».**

## WHO IS AT RISK OF DEVELOPING PULMONARY FIBROSIS IN SYSTEMIC SCLEROSIS?

Pulmonary fibrosis is a common manifestation of systemic sclerosis, being present in about half of the patients. However, pulmonary fibrosis is severe in only about 15% of patients. Patients who are men, of Black race, with the diffuse form of systemic sclerosis, with anti-topoisomerase I (Scl-70) autoantibodies or who have cardiac, muscular or upper gastrointestinal disease may be at higher risk of developing severe pulmonary fibrosis.

## WHAT ARE THE SYMPTOMS OF PULMONARY FIBROSIS?

Pulmonary fibrosis often presents itself silently in the early stages of the disease. With more severe involvement, patients may have symptoms of fatigue, decreased exercise capacity, shortness of breath and a persistent dry cough. However, in a sedentary patient, pulmonary fibrosis may remain asymptomatic even in more advanced stages of the disease.

PULMONARY FIBROSIS IN SYSTEMIC SCLEROSIS

# HOW IS PULMONARY FIBROSIS DIAGNOSED?

**Physical examination may reveal abnormalities during the auscultation of the lungs with the stethoscope. A chest X-ray may reveal more advanced changes in pulmonary fibrosis, but a high-resolution chest CT scan is a better test to detect pulmonary fibrosis in its earliest stages. Pulmonary function tests (PFTs) are useful to measure the severity of lung function impairment. The six-minute walk test, during which blood oxygenation and walking distance reached after 6 minutes are measured, can also be useful in assessing the severity of the disease.**

**Because pulmonary fibrosis in systemic sclerosis is often silent, periodic screening is recommended in all patients, knowing that appropriate treatment started early will result in better outcomes.**

## WHAT ARE THE TREATMENTS FOR PULMONARY FIBROSIS?

According to current guidelines, indications for initiating treatment for pulmonary fibrosis are:

- the presence of respiratory symptoms attributable to pulmonary fibrosis;
- moderate to severe involvement as evidenced by thoracic CT scan and pulmonary function tests;
- worsening of pulmonary fibrosis as evidenced by thoracic CT scan or lung function tests.

There are now two classes of medications used in the treatment of pulmonary fibrosis associated with systemic sclerosis. First, immunosuppressive medications, such as mycophenolate mofetil (Cellcept®), cyclophosphamide and rituximab, work by decreasing the activity of the immune cells responsible for inflammation. These medications can slow the progression of pulmonary fibrosis associated with systemic sclerosis. Mycophenolate is commonly used as a first-line treatment because a randomized trial showed that it is as effective as cyclophosphamide and has a better safety profile.

Recently, a randomized trial also showed that an anti-fibrotic medication, nintedanib (Ofev®), is effective in slowing the progression of systemic sclerosis-associated pulmonary fibrosis compared to placebo. Nintedanib is now approved by Health Canada. Although this medication is new in its use in systemic sclerosis, it has already been used for several years in the treatment of idiopathic pulmonary fibrosis (IPF).

When a medication is started for the treatment of pulmonary fibrosis, the patient is assessed monthly with blood tests to detect side effects of the medication. Pulmonary function tests are repeated every 3 to 6 months to determine the effectiveness of the treatment. Success is currently defined as stabilization of the disease.

Research studies are underway to determine whether earlier treatment in the mild stage of pulmonary fibrosis could be effective in preventing more severe involvement over the years. Considering that immunosuppressive and anti-fibrotic treatments may cause side effects, the decision to begin treatment should be made after assessing the risk of toxicity of the treatment compared to the expected benefits.

To reduce the risk of complications associated with certain infections when taking immunosuppressive medications, it is recommended to get the flu shot once a year and to get vaccinated against the pneumococcal bacteria (a cause of severe pneumonia) every five years. If the patient is a smoker, it is recommended to quit smoking to avoid further damage to the lungs. In patients with gastroesophageal reflux disease (GERD), it is recommended that this condition be treated aggressively in order to prevent further damage to the lungs due to reflux and aspiration of gastric contents into the lungs.

Home oxygen administration can be used for patients with very severe pulmonary fibrosis. Finally, in very advanced cases not responding to treatment, an autologous stem cell transplant or a lung or heart-lung transplant may be considered after a detailed medical and multidisciplinary assessment.

## IN SUMMARY

Pulmonary fibrosis is a common and potentially serious complication of systemic sclerosis. Careful monitoring by treating physicians and appropriate early treatment can improve the quality of life and life expectancy of patients with systemic sclerosis.

# Community Contact Representatives

## CONNECT WITH THE SCLERODERMA COMMUNITY IN YOUR AREA!

**Give us a call, send us an email, and meet other people living with scleroderma.**

### VANCOUVER

**We are seeking a volunteer representative.**

Please contact Rosanne Queen at **604-984-9425**

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The realization and mailing costs of a magazine are important elements of the budget of a charitable organization such as ours.

For this reason, we want to emphasize the generous gesture of our partner, Boehringer Ingelheim Canada Ltd which, thanks to an educational grant, made production, printing and distribution of this Spring Bulletin possible.

# HOW SCLERODERMA CAN AFFECT THE HUMAN BODY

**The symptoms of scleroderma vary greatly from person to person, so that patients will not necessarily develop all the complications of the disease.**

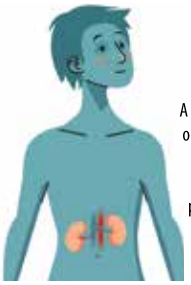
**The symptoms of the disease may be visible, as is the case when the skin is affected, or the symptoms may be invisible, as when internal organs are affected.**

## SYMPTOMS AND MANIFESTATIONS OF SCLERODERMA

### SKIN HARDENING
Thickening and loss of elasticity of the skin on different parts of the body. Hence the name «scleroderma», which means hard skin.

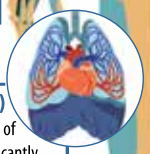
### PULMONARY FIBROSIS
A potentially serious complication where normal lung tissue is gradually replaced by scarred fibrotic tissue, making it difficult to breathe and deliver needed oxygen to the body.

Pulmonary fibrosis causes shortness of breath and also sometimes a dry cough.



### RENAL CRISIS
A renal crisis, which is due to an acute obstruction of arterioles and capillaries in the kidneys, leads to a sudden and sharp increase in arterial blood pressure. The symptoms are those of a hypertensive crisis: new and severe headaches, marked shortness of breath (left heart failure), and even epileptic seizures (convulsions). This is a very serious complication which requires urgent medical attention. Often during a scleroderma renal crisis, the kidneys stop functioning and dialysis (filtering the blood to avoid uremia) is then needed.

### BLOOD VESSELS
The narrowing of the arteries, small blood vessels, and capillaries, can lead to many complications, including the development of pulmonary arterial hypertension (PAH), digital ulcers, and other conditions.



### PULMONARY ARTERIAL HYPERTENSION (PAH)
Increased pressure in the pulmonary arteries due to the narrowing of small arteries in the lungs. Blood flow to the lungs is significantly restricted, making the heart work harder to pump blood through the lungs.

As arterial blood pressure rises in the pulmonary arteries, small pulmonary vessels slowly become clogged (a process which may take several years). This occurs through fibrosis of the small vessels, eventually leading to thrombosis, and the blood can no longer reach all parts of the lungs. Thus, it becomes more difficult for the lungs to supply enough oxygen to the body.

Sustained high blood pressure in the arteries of the lungs puts a strain on the heart, making it more difficult to circulate the blood through the lungs. Over time, this can eventually lead to congestive heart failure, particularly the right side, what is referred to as right heart failure (RHF). Right heart failure is indicative of significant PAH and is a serious complication of scleroderma.

**PAH results in one or more of the following symptoms:**

- Shortness of breath on exertion and at rest
- Palpitations (heart rhythm disorder)
- Fatigue
- Chest pain
- Dizziness
- Temporary loss of consciousness (syncope)
- Swelling of the ankles and legs



### SCLERODERMA FACES
Hollow eyes, pinched nose, thin pursed lips, mask-like face, small puckered mouth (microstomia), and peri-oral folds.

Thinning lips and facial muscle atrophy can make the teeth appear more prominent.

### EYES
Dry eyes caused by a decrease in tear production.

### TELANGIECTASIA
Small dilated capillaries visible on the face and hands, sometimes referred to as «spider veins».

### RAYNAUD'S PHENOMENON
Raynaud's is present in up to 95% of people with scleroderma. Whitening of fingers and/or toes triggered by cold or severe stress. The whiteness phase can be followed by a blue phase and then a red phase.

### SCLERODACTYLY
The skin of the fingers, which have become infiltrated with collagen (fibrosis), may look full and sausage-like. Functional loss or decreased range of motion.

### CALCINOSIS
Calcium deposits under the skin that may require antibiotics to cure occasional infections and sometimes surgery to drain calcium deposits and relieve pain.

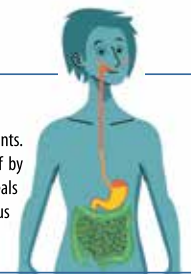


### DIGITAL ULCERS
Ulcers occur on the fingertips or on the top of the fingers. They are painful and difficult to heal.

In the most severe cases, it can lead to necrosis and amputation may be needed.

### SKIN PIGMENTATION
Dark or pale spots occurring in one-third of patients.

### DIGESTIVE SYSTEM
Gastrointestinal disorders affect the vast majority of patients. Gastric reflux is a common symptom that manifests itself by a burning sensation radiating up to the throat after meals and may cause inflammation of the lining of the esophagus (esophagitis reflux) if left untreated.





### MUSCLE AND JOINT PAINS
Joint pain is common. It is caused by inflammation of the joints and tendons, which quite often leads to joint swelling and stiffness that can become quite debilitating.

Muscular pain (myalgia) can be intermittent or continuous. It can also be associated with muscle weakness (myositis). Symptoms include difficulty in climbing stairs, lifting objects and getting up, and also difficulty swallowing.

**SCLERODERMA ASSOCIATION OF B.C.**
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Scleroderma Association B.C.