SCLERODERMA & RAYNAUD'S UK

RESEARCH IMPACT REPORT

A RETROSPECTIVE REVIEW

30 YEARS OF FUNDING THE BEST RESEARCH TO TRANSFORM PATIENT LIVES

CONTENTS

WELCOME

DAME CAROL BLACK, PRESIDENT

I first started to study scleroderma at Bristol University as a young doctor. At that time little was known about the disease, and the survival and quality of life of patients were poor.

These have both improved markedly, and the efforts of the two UK charities founded to tackle the issue, the Raynaud's & Scleroderma Association and the Scleroderma Society, now merged as Scleroderma and Raynaud's UK (SRUK), played a considerable part in this improvement. Over the last 30 years, the charities' combined focus on funding research has led to a real change in outcome for patients and has supported many researchers in their quest to understand what causes scleroderma and how to treat it effectively.

Starting from a community of a few isolated researchers, the support of SRUK has meant that we now have a larger research community here in the United Kingdom whose work has made a real difference to patients.

There have been many advances in our knowledge about the condition and its various subtypes, better understanding of the science, and identification of therapeutic targets, leading to better survival outcomes for people with these conditions.

The work of the UK research community, enabled and supported by SRUK, is highlighted within this report, which outlines some key research studies that made significant inroads into our understanding of these conditions.

The history of SRUK and its predecessors is to a large extent the story of those with lived experience of the disease. It is because of these determined, devoted and brave people that SRUK is able to continue funding research which year-on-year has led us closer to a full understanding of the disease and hopefully a cure.

The voices of the SRUK community lie at the centre of this report, a deliberate choice. For them we have come a considerable distance, but not yet far enough. Scleroderma has still not given up all its secrets, and until it has done, further scientific research will be crucial, and the support of SRUK enormously valuable.

Together, we can make a big difference.

SUE FARRINGTON, CHIEF EXECUTIVE

We owe a huge amount to the drive and determination of our two legacy charities, the Raynaud's & Scleroderma Association and the Scleroderma Society, and in particular to the tireless work and dedication of Anne Mawdsley OBE, who made funding for research a key priority.

Over the last 30 years there has been considerable progress in the diagnosis, management and treatment of scleroderma and Raynaud's. During this time the charities have supported a range of national and international collaborations and special interest groups and enabled many young scientists to carry out research into scleroderma and Raynaud's phenomenon.

But there is a long way to go. We still do not fully understand the biology of these conditions, treatments often have unwanted side effects, and scleroderma remains incurable.

As SRUK we will build on the great work to fund research and support innovation. As part of the drive to achieve our vision of a world where no one has their life limited by scleroderma and Raynaud's, we have looked both backwards, reviewing the impact of the research we have funded, and forwards, through the development of a new research strategy.

We thank our supporters and all the researchers whose hard work has led to significant improvements in the diagnosis and treatment of people with scleroderma and Raynaud's. We look forward to building on these successes in the future and hope that you will continue to support us.

WHO WE ARE

Scleroderma and Raynaud's UK is the only UK charity dedicated to improving the lives of people with either scleroderma or Raynaud's phenomenon. Our vision is a world where no-one has their life limited by scleroderma and Raynaud's. Our mission is to improve the lives of everyone affected by scleroderma and Raynaud's. We do this by investing in research, improving awareness and understanding of the conditions and providing information and support to all those affected.

Our values are central to all of our work and represent who we are as a charity. We are:

- Collaborative
- Driven
- Trusted
- Compassionate

We currently support over 162,000 people each year. Our aim is to reach out to every single person who has a Scleroderma or Raynaud's diagnosis, providing them with the information and support they need.

By creating connections between people with the conditions and professionals, we have built a motivated community that shares knowledge and support, works in partnership on research projects, and speaks up about scleroderma and Raynaud's.

We are here to improve awareness and understanding of these conditions, to support those affected, and ultimately, to find a cure.

"SRUK gave me the chance to make friends with people who really understood my situation, extending my support network. They also provided my parents with information and addressed their concerns."

CONNOR, A MEMBER OF THE SRUK COMMUNITY

OUR HISTORY

Scleroderma & Raynaud's UK was formed in 2016 from the merger of the Raynaud's & Scleroderma Association and the Scleroderma Society.

"SRUK helps me put my mind at rest, and I know that I am lucky to have been diagnosed recently rather than 20 years ago, as I have access to provisions and information."

NINDER, A MEMBER OF THE SRUK COMMUNITY

A STRONG LEGACY

The Raynaud's and Scleroderma Association (RSA) and the Scleroderma Society both had a rich history of providing excellent support services to the community and investing in research to improve knowledge and understanding of these conditions. Between them they funded over £10 million in research, leading to many research breakthroughs highlighted in this report.

The Raynaud's and Scleroderma Association (RSA) was founded in 1982 by Anne Mawdsley, who was chief executive until 2012. It started as a support group for people with Raynaud's, becoming the RSA after Anne developed scleroderma.

The Scleroderma Society was also established in 1982 and while their main focus was to provide support for people with scleroderma and their families, they too funded research, during the period 1990 to 2015.

129

GRANTS AWARDED SINCE 2000

208

PAPERS PUBLISHED BY RESEARCHERS & CLINICIANS

WHAT IS SCLERODERMA AND RAYNAUD'S?

£

THE COMBINED INVESTMENT IN RESEARCH TO DATE

10M

RAYNAUD'S PHENOMENON

Raynaud's phenomenon (also referred to as Raynaud's syndrome – or just Raynaud's for simplicity) is an extremely common but under-recognised condition, affecting 10 million people in the UK today.

The condition, caused by an over-sensitivity of small blood vessels to temperature change, mainly affects the **fingers and toes**. After detecting a temperature change the affected blood vessels rapidly tighten, choking the blood supply and **cutting off oxygen** to the affected area. This is what causes the classic **whitening** of the extremities. Upon warming, the blood vessels relax back to their normal width, allowing the blood to flood back to the oxygen-starved tissue and this triggers bursts of acute burning pain.

Raynaud's can itself be subdivided into **primary** and **secondary** types. Primary Raynaud's can affect anyone, but the small fraction who develop secondary Raynaud's are at an increased risk of developing scleroderma.

Secondary Raynaud's differs from primary Raynaud's in that it is associated with **autoimmune conditions** and is more serious. It can cause ulcers to develop on the fingers and toes and lead to a calcium build up in soft tissue that can be particularly painful, a condition known as calcification or calcinosis.

Secondary Raynaud's affects **97%** of people with scleroderma and treatment can only relieve symptoms. A cure isn't yet on the horizon.

"SRUK's 30-year journey, of which I've been part of for 25 years, has been a really important time – it has seen us move from a rare, unknown disease to a disease which is better understood and now to one where we are beginning to make more progress for therapy."

PROFESSOR CHRIS DENTON

SCLERODERMA

Scleroderma is a rare autoimmune condition where the body's immune system becomes overactive and attacks healthy tissue. It affects about 19,000 people in the UK and 2.5 million worldwide. It is poorly recognised or understood. There is no cure, and patients' quality of life is impaired and their lifespan is reduced.

The name comes from the Greek: 'sclero' for hard and 'derma' for skin. The first noticeable symptom is hardening of the skin, caused by the body producing too much collagen. This excess collagen (fibrosis) may also affect joints, tendons and organs and can stop the body from functioning normally. There are two main types of scleroderma, **localised** scleroderma and **systemic** sclerosis. An early symptom of systemic sclerosis is Raynaud's phenomenon.

Systemic sclerosis

Systemic sclerosis affects the body's internal organs as well as the skin. There are two main types of systemic sclerosis: **limited** systemic sclerosis and **diffuse** systemic sclerosis. People with limited systemic sclerosis have often lived with Raynaud's syndrome for a long time. Usually progressing **very slowly**, the condition often only visibly affects the hands and arms below the elbow, the feet and legs below the knee and the face.

Symptoms can also include thickening of the skin, heartburn and problems with swallowing. With diffuse systemic sclerosis, it is more likely that the whole body will be affected, and there can be **life-threatening complications** involving the heart, lungs and kidneys. Common symptoms include tiredness and joint pain and stiffness.

Localised scleroderma

The two types of localised scleroderma are called **morphea** and **linear**. In morphea scleroderma, hard, painless patches of smooth shiny skin are seen on the trunk or another part of the body, usually with **no other symptoms** or problems. In linear scleroderma, a line of hard, shiny skin appears along an arm or leg. This skin is miscoloured or scarred and often feels **tight and uncomfortable**. Linear scleroderma must be monitored carefully in children because it can affect limb growth.

30 YEARS ON: The impact of research

Over the last three decades the two founding charities of SRUK, the Raynaud's and Scleroderma Association (RSA) and the Scleroderma Society, have funded over 100 research grants, spending more than £10 million on cutting edge science.

This has had a sizeable impact on the research field, helping make huge inroads into our understanding of the conditions. Over 200 science papers have been published by our scientists and clinicians, providing the inspiration for further scientific insights, which have ultimately translated into benefit for the communities we serve.

Our founding charities have funded science at all levels from building our knowledge about the very basic mechanisms underlying the conditions through to pioneering new methods of earlier detection and diagnosis. We are now in the incredible position of being able to accelerate research even further than it's been before, and this is all due to the pioneering work that has been carried out through our communities working together.

We know that earlier detection and better diagnosis of these conditions is vital if patients are to receive timely treatment and care. Early diagnosis of scleroderma is life-changing and can be life-saving. The RSA supported many research projects that have led to improvements in the detection and diagnosis of Raynaud's and scleroderma. Both charities funded work that has led to the discovery of clinical biomarkers and the development of medical technologies that can detect and monitor progression of the conditions.

Much of the current treatment that is available to people with the conditions today relies on our knowledge of the basic mechanisms underlying their development. These treatments are available because research, significantly funded by SRUK, has improved our knowledge of the role fibroblasts play in the build-up of collagen, and how our natural defence system can turn on itself to damage healthy tissue.

Scientific research, and by direct extension, medical treatment was revolutionised by the advent of biomolecular investigation into the roles that genes play. SRUK was funding research into these areas at the very start of the revolution, and the results have identified possible treatment targets that could improve the quality of life for people living with Raynaud's and scleroderma.

1985
5 year survival
60%

2018
5 year survival
85%

5 year survival
60%

1 year survival post renal failure
25%

5
Types of treatment to treat the symptoms

3
Specialist centres

5 year survival
85%

1 year survival post renal failure
80%

10
Types of treatment to treat the symptoms

6
Specialist centres

Over the last 30 years funding has helped:

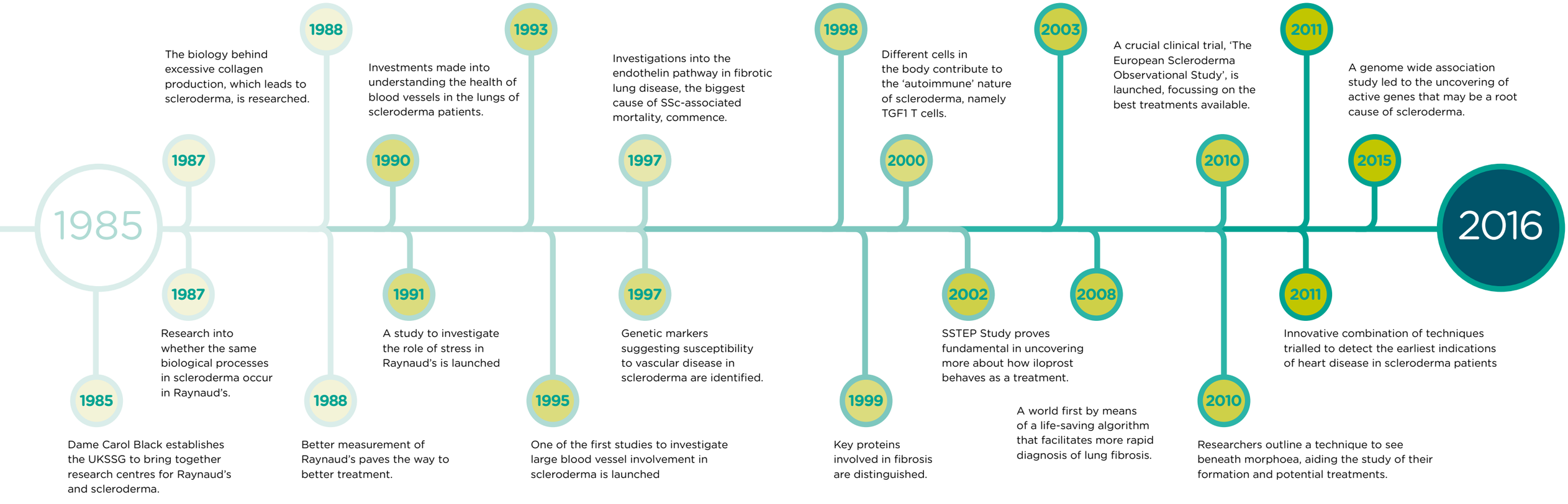
- Build the research community base in the UK
- Allow clinicians to detect the condition earlier
- Develop a more effective classification to enable better diagnosis
- Develop the best treatments available
- Increase understanding about the cause of these conditions

The cumulative effect of this support over the last 30 years means that today, survival outcomes are much improved, quality of life is significantly more positive and there are more treatments available.

At SRUK, we firmly believe that research saves lives. Research has been the key in improving the rate of survival 5 years post diagnosis, resulting in a huge increase from 60% to 85%. Research is the reason that renal crisis is no longer leading cause of mortality, and it's the reason why we now have more than 10 types of treatments that are available to treat the complex symptoms of scleroderma and Raynaud's.

Although it's the full breadth of research that was funded over the last 30 years that have resulted in these changes, we have selected case studies to demonstrate how the work we have funded has resulted in key discoveries contributing to the substantial improvements noted in the figure.

These case studies not only highlight the work, but also the tireless dedication of our researcher clinician community who worked hand in hand with people living with the condition to give them a better future more quickly.



UNDERSTANDING THE CAUSE OF SCLERODERMA AND RAYNAUD'S

Part of the challenge in treating scleroderma and Raynaud's is that the causes and biological mechanisms remain a mystery.

As a less well-funded research field, there are many unanswered questions which block progress. Answering these questions is as important as developing a new medicine, indeed it is essential if we are to develop new treatments. And for that to happen, we need to understand the causes behind scleroderma and Raynaud's.

Over the last 30 years, there have been significant advances in understanding the underlying biological processes of scleroderma. In particular, we now understand enough about the mechanisms of excess collagen production causing fibrosis that we can start to identify therapeutic targets. Since as early as 1987, work has been underway to understand how collagen synthesis is regulated in fibroblasts in scleroderma patients[1], as well as whether similar processes take place in people living with Raynaud's.

Even then, it was known that Raynaud's occurs due to issues with blood flow to the hands and feet, and that people with severe Raynaud's are more likely to develop scleroderma. And so, in 1990, knowing that life-threatening pulmonary hypertension is a major complication of scleroderma, the two charities funded a project to understand the pathology of the blood vessels that carry blood between the heart and lungs (pulmonary vasculature) in people living with systemic sclerosis[2]. To try to elucidate further the origins of Raynaud's (and therefore for many people, the origins of scleroderma) a study was launched in 1991 to investigate whether stress plays a significant role in the development of the condition[3]. Although the results were inconclusive, this study represented a real shift in trying to understand the causes of the conditions.

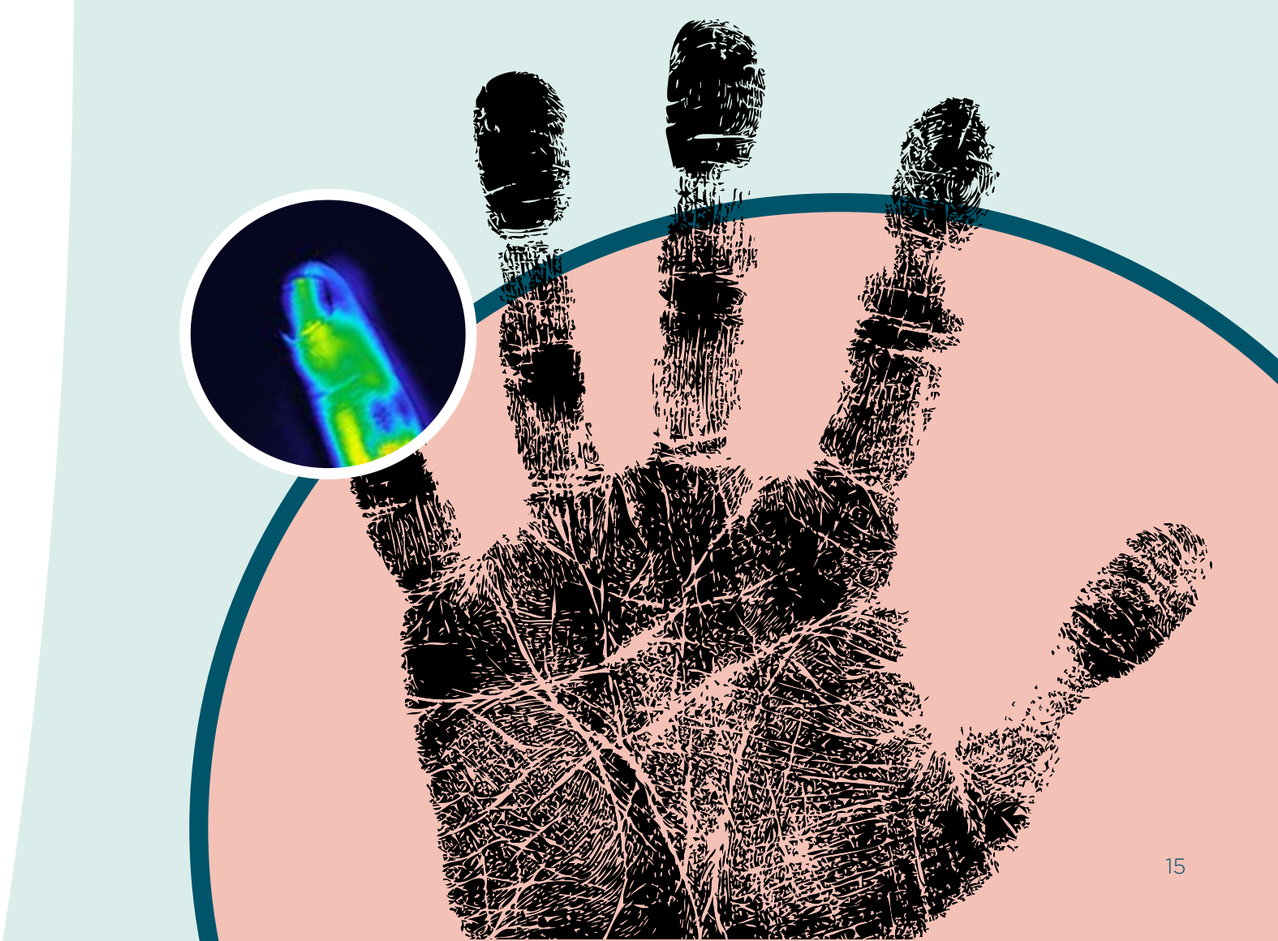
The late 1990s and early 2000s saw many breakthroughs in biomedical research, which meant that investigators have been able to dive much deeper into the molecular mechanisms underlying these conditions. One of the first studies that was able to take advantage of these changes was in 1997, when the role of the endothelin pathway in fibrotic lung disease was investigated. Components of this pathway can act as vasoconstrictors (molecules that tightenblood vessels) and as a result of this work we now understand the crucial role the endothelin pathway plays in pulmonary hypertension.

In addition, work started in the 1980s which identified a link between impaired production of nitric oxide (a powerful blood vessel relaxant) and lung fibrosis[4]. Further work by other research groups has looked at a previously unstudied protein called transgelin to see whether it has a role to play in the regulation of scarring in people who live with scleroderma[5], while other research has looked at the role of vascular pathways in the scarring process.

We've highlighted case studies to demonstrate some of the key work that has been conducted to understand why and how scleroderma and Raynaud's occur. Here are 3 key case studies that have investigated why thickened skin patches (morphea) occur, why the immune system starts attacking its own body, and why some people will develop scleroderma and Raynaud's and why others will not.

"My expertise is in trying to understand what are the main pathways which are the root causes of scleroderma: i.e. inflammation, fibrosis, which immune cells drive that, and then trying to understand the molecules involved. We then make animal models to try and see which treatments could be the most effective, moving ever closer to patients. Hopefully our research then allows us to link up with big pharma companies to test experimental drugs in a phase 1 trial."

PROFESSOR DAVID ABRAHAM



KEY BREAKTHROUGHS

THE ROLE OF INTERLEUKIN-6 IN FIBROSIS[6]

Professor David Abraham, University College London

A pioneering study at University College London discovered that Interleukin-6 (IL-6), a molecule heavily involved in inflammation, played a significant role in increasing the severity of systemic scleroderma. This insight was so important that a major pharmaceutical company has now launched two clinical trials to test drugs that can block it.

Professor Abraham has devoted his career to understanding the biology that underpins scleroderma, becoming world-renowned in the process.

One particular molecule that Professor Abraham has focussed on has been IL-6. He led a detailed analysis of the role of IL-6 in scleroderma, comparing levels in the skin of people with systemic scleroderma with disease-free volunteers. Professor Abraham's team found a clear increase in the amount of IL-6 in people with scleroderma, particularly those with diffuse disease, with the IL-6 at its highest in fibroblasts and endothelial cells that line the blood vessels. A particularly exciting finding was that high levels of IL-6 were directly associated with more severe skin involvement and worse long-term survival.

This discovery was important enough that researchers from the UK and the US were able to get support from Roche, one of the world's biggest pharmaceutical companies for two major clinical trials of a drug called tocilizumab that can seek out and bind to IL-6, reducing its effect.

Professor Abraham's work into the cellular and molecular causes of fibrosis are constantly pushing back the barriers of our understanding of the disease, providing a pipeline of exciting targets for future medicine.

UNDERSTANDING THE FORMATION OF MORPHEA IN SCLERODERMA[7]

Professor Ariane Herrick, University of Manchester

In a world first, this team developed a way of seeing beneath morphoea, patches of scleroderma-affected skin. By using a combination of advanced scanning technologies they have found a way for researchers to study the formation of untreatable morphoea, paving the way towards future treatments.

Part of the difficulty in understanding these diseases is that so much happens beneath the skin, making understanding the mechanics of the disease tricky. One classic condition associated with scleroderma is skin thickening. In localised scleroderma, thickening of the skin (and sometimes underlying muscles and fat) occur in a condition called morphoea.

Whilst morphoea isn't life threatening it can cause severe disabillity and disfigurement. A lack of understanding of the condition has prevented the development of any treatment. Professor Herrick was determined to understand the mechanics of this problem. So, she and her team turned to advanced physics for solutions.

In the way that archeologists combine ground penetrating radar, aerial observaton and close up examination to unlock ancient history, Professor Herrick and her team tested a variety of different methods to peer beneath the skin, a world first in studying morphoea.

The first two techniques tested were called High Frequency Ultra Sound and Optical Coherence Tomography.

Both of these work in similar ways, bouncing sound or light off the tissues. These richochet off different layers within the skin, and the patterns of these echoes can then be turned into a picture, potentially revealing the effects of scleroderma and Raynaud's beneath the surface. Of the two, Optical Coherence Tomography offered the most useful insight, but Professor Herrick's determination meant that she did not stop at one way of imaging. She combined this imaging with two techniques to monitor the pattern of blood flow. The simplest of these was thermal imaging, estimating blood flow based on warmer patches on the skin. The more advanced physical tool was a technique called Laser Doppler Imaging. This beams a specific colour laser light through the skin with the colour of the laser light chosen to reflect from red blood cells. Professor Herrick used a revolutionary version of Laser Doppler Imaging that went further than any commercially available system, adding a second colour of light which let her study blood flow at different levels of the skin.

Professor Herrick's work has established a non-painful, highly useful way that researchers can study the changes to a patient's skin without painful biopsies, helping scientists gain a deeper understanding of morphoea, providing the foundations for future research and treatments.

A GENOME WIDE ASSOCIATION STUDY LED TO THE UNCOVERING OF ACTIVE GENES THAT MAY BE A ROOT CAUSE OF SCLERODERMA

2015

A GENOME WIDE ASSOCIATION STUDY: GETTING TO THE ROOT OF THE PROBLEM[8]

Professor Chris Denton, Royal Free Hospital/University College London

A team of world class scleroderma scientists at the Royal Free Hospital made a breakthrough, uncovering a potential mechanism behind pulmonary hypertension, one of the biggest risk factors in scleroderma. They defined genes that may be involved in blood vessel changes, potentially identifying those patients most at risk of this deadly complication.

Every single thing that a cell can do, from colouring your eyes through to conducting thoughts across your brain, depends on a detailed and complex instruction manual called the genome. There are thousands of different instructions (or genes) that make us who we are. Yet cells don't follow all the genes all the time. A nerve cell and a skin cell behave very differently, and this is because they subscribe to different parts of this instruction manual.

The symptoms of a disease occur because cells start to follow instructions that they normally ignore. Sometimes this is because the cells themselves are faulty, other times it is because something, perhaps a bacteria or virus, is stressing the cell, changing its behaviour. In scleroderma, something causes the immune system to begin attacking the body, and these attacks cause damage to the cells, which defend themselves by changing the genes they use. In areas of extreme damage where repair is impossible, the cells form scar tissue.

If we can understand which genes are in play for scleroderma or Raynaud's, we can begin to anticipate how each person's disease will behave, and begin to explore ways to intervene or even correct the problem.

This is not a simple challenge, yet it is one to which Professor Denton has devoted almost 25 years of research, becoming a world authority in the process. His work is improving the ability of doctors to predict how scleroderma may behave, identifying which patients will respond best to certain treatments and helping to develop new treatments.

Using cutting-edge techniques to study the genes involved in different forms of scleroderma, Professor Denton's team uncovered a cluster of active genes that normally help control blood vessels and may be linked to many symptoms of scleroderma, including pulmonary hypertension, a major risk factor in diffuse systemic scleroderma.

They discovered that the highly specialised cells that normally line our blood vessels start to follow incorrect genetic instructions, transforming them into a different type of cell without some of their specialised properties. The consequence is that the blood vessels become very leaky, contributing to pulmonary hypertension, possibly by allowing a type of white blood cell that helps form scar tissue to cross the blood vessel wall and interact with the tissues beneath.

These major advances in understanding the mechanisms and genes behind some of the most serious scleroderma symptoms has opened up many opportunities for trialing new treatments, opportunities that Professor Denton's team are ready to build upon.

IMPROVING DIAGNOSIS AND MANAGEMENT OF THE CONDITIONS

"It's exciting that we are already seeing clinical benefits this early into the trial. Forming a relationship with an organisation that is determined to improve the lives of people with scleroderma helps build the foundations for future successes."

PROFESSOR MAYA BUCH

A diagnosis of scleroderma can represent, for some people, a severe prognosis. This is often because many people are diagnosed quite late, when the condition has progressed so far that there is a significant impact on their lives.

If the condition can be detected at a much earlier stage, then treatments that are less invasive can be given that will slow down or even halt the progression of this condition.

It is therefore vital that tools and techniques are developed to spot the first signs of a disease progressing from Raynaud's to the more serious scleroderma. There have been steady inroads into this area over the last 30 years, with significant momentum gathering over the last decade.

A huge amount of work has been undertaken into identifying biomarkers, biological molecules that can act as indicators of early stage scleroderma; from genetic markers for vascular disease (developed at Ninewells Hospital in Dundee)[9], through to identifying cell surface receptors at the Royal Free[10]. In particular, researchers at Leeds University have worked to identify biomarkers that can be used over time as a measure of how far scleroderma is progressing in a patient[11]. This means that not only would we be able to identify early stage scleroderma, but we might also be able to track how quickly the condition is progressing and therefore give appropriate treatments. Diagnostic tools to identify early stage scleroderma also represent an area of investment. A particular example lies in the investigation of skin autofluorescence as a way to measure oxidative stress in people living with the early stages of systemic sclerosis[12]. Although this tool is currently undergoing extensive validation at the University of Manchester, the funding provided by SRUK means that the possibility of developing a non-invasive tool for early detection has just become much closer.

Once the conditions are diagnosed, then management becomes even more crucial as for some people a diagnosis can lead to severe and fast disease progression. The broad spectrum of scleroderma conditions can be highly variable, ranging from very mild through to a disease that involves multiple organs in ways not seen in other diseases. Medicine has progressed in such a way that its tools are often set up to understand one condition at a time. For systemic scleroderma this renders many of them ineffectual. It is essential that doctors are able to understand the extent that different organs are affected and the severity of each person's scleroderma so they can deliver the most effective treatment.

Funding has been awarded over the last few years to ensure that these tools can be created. Some of this work includes the assessment of the Hand Ischaemia Score, which was undertaken by a partnership between the University of Cambridge and Addenbrooke's Hospital[13], and found that the Score could be used as a robust scoring system to assess hand blood flow in people with either Raynaud's or scleroderma.

Access to patient data, such as time to diagnosis and treatments given, has become hugely important over the last few years. Data enables clinicians to improve diagnostic practice, determine the best treatments and monitor patient health. That is why we have ensured that the Royal Free Hospital in London was able to install a patient database which will hold clinical data for more than 3,000 patients followed over 20 years[14]. The collection of this data means that clinicians will be better able to determine whether diagnosis of scleroderma and Raynaud's is improving over time.

We have highlighted three key case studies that showcase the impact of early diagnosis and consistent management of the conditions.

NAILBED MICRO CAPILLAROSCOPY: A TOOL FOR EARLIER DIAGNOSIS[15]

Dr Graham Dinsdale, University of Manchester

Scientists at the University of Manchester developed an essential diagnostic tool that can pick up the earliest signs of scleroderma in patients with Raynaud's Phenomenon. Led by Dr Graham Dinsdale, they overcame significant technical difficulties to develop a long sought-after method of spotting microscopic changes to the nailbed capillaries. This work has increased the chances of diagnosing early, helping to minimise the effects of the disease for many people.

The smallest blood vessels we have in our bodies are called capillaries. In normal Raynaud's these capilaries are unaffected, but if the disease is progressing into scleroderma, it leaves its first marks on the tiny capillaries, scarring and distorting them. Spotting this damage early gives doctors the best chance to manage the disease, minimizing the window where lasting systemic damage can occur.

Unfortunately, detecting this capillary damage reliably is hard. All people are built slightly differently, with no typical 'sign' of scleroderma. The solution is to monitor changes to the capillaries in the hand over time, but the hundreds of meters of capillaries in just one hand makes it hard to compare the same area. It is all too easy for doctors to miss the warning signs, and finding a way to help is a huge technical challenge.

This has changed. For 12 years a team of scientists at the University of Manchester, led by Dr Graham Dinsdale and Professor Ariane Herrick, have been tackling this challenge. Their breakthrough insight was to develop computer software that can weave individual images of capillaries into a detailed and highly reproduceable image. At a glance doctors can now see the entire nailbed, and compare it with the entire nailbed from a previous date to look for the signs of the disease. The research has unlocked a solution that is equipping doctors with the tools they need to monitor people with Raynaud's, something which could be the difference between lifelong disability and a relatively normal life.

SPOTTING THE WARNING SIGNS OF HEART DISEASE[16]

Professor Maya Buch, University of Leeds

This team is currently trialling a pioneering combination of techniques that can detect the earliest signs of heart problems in scleroderma patients, something that has been previously impossible. By using state of the art scanners and medical implants, this trial has already seen life-saving results and looks set to make a significant difference to the monitoring of this disease.

As many as 1 in 3 people with systemic sclerosis will develop heart problems. The disease can cause swelling of the heart and disturbance of heart rhythm (arrhythmias) that may cause sudden death. Identifying patients most at risk has been a real challenge.

Professor Buch used cardiac magnetic resonance imaging (CMRI), a non-invasive technique that provides highly detailed images of the heart and can detect the earliest signs of damage.

She tested the technique on systemic scleroderma patients with no clinical symptoms of heart disease. Astonishingly, the scanner found that a quarter of these patients already had scarring in their hearts.

But Professor Buch's work hasn't ended there. Just because a doctor is aware that there is scarring on the heart, it doesn't help them deal with any incidences of rapid degeneration. So Professor Buch is now also implanting a monitoring device in the upper chest to detect arrhythmias. Through a combination of scanning and the monitor, Professor Buch will be able to detect potentially life-threatening complications at the earliest stage.

Although this trial has only just begun, the combination of technologies has already flagged one patient who needed a pacemaker and another who needed urgent drug intervention.

STAGING INTERSTITIAL LUNG DISEASE: A WORLD CLASS SYSTEM FOR CLINICAL DIAGNOSIS[17]

Professor Carol Black, Professor Athol Wells, Professor Chris Denton, Royal Free Hospital/Royal Brompton Hospital

A team of world-leading clinicians and scientists developed a life-saving algorithm that allows clinicians to easily and rapidly diagnose lung fibrosis without the need for expert referral. Led by Professor Carol Black and Professor Chris Denton from the Royal Free Hospital and Professor Athol Wells from the Royal Brompton Hospital, this team's solution is one of the most important advances in scleroderma diagnosis in recent years.

Fibrosis of the lungs has become the number one cause of death in people with systemic scleroderma. For people with the most severe lung disease it is important to treat aggressively, suppressing the underyling immune response. But these treatments are harsh and can have severe side-effects. It is therefore vital for doctors to know which patients have the most advanced lung fibrosis so they can treat appropriately.

Unfortunately the standard way of assessing lung function just wasn't good enough. There is too much variability, and the complexity of achieving an accurate understanding is beyond all but the most experienced doctors.

Professor Black and her colleagues combined High Resolution Computed Tomography, a technique that takes accurate cross-sectional x-rays of the body and reconstructs an internal view of the lungs, with standard tests of the lung's performance. The revolutionary element was to create an algorithm that can draw on this information and classify a patient's degree of lung disease severity. They developed this test by working with over 200 people with scleroderma, and then evaluated their final model. Incredibly, in the trials, after only 10 minutes of training, doctors with less than 2 years of experience were able to classify the severity of disease as accurately as highly experienced radiologists. This technique has put the ability to assess a potentially fatal aspect of scleroderma into the hands of doctors everywhere and has gone on to become the international standard for assessment, quite literally revolutionizing a vital part of scleroderma medicine.

RESEARCH HAS LED TO THE DEVELOPMENT OF THERAPIES TO TREAT SYMPTOMS

10 TREATMENTS

DEVELOPING THE BEST TREATMENTS

The complex nature of scleroderma, in combination with many of the remaining unknown factors about this condition, mean that developing effective and non-toxic treatments has always proven to be difficult.

However, this did not stop our researchers. Their tireless dedication over the last 30 years means that there are now more than 10 types of treatments available, ranging from natural remedies through to treatments such as vasodilators and immunosuppressants.

In 1989, it was understood that in order to improve treatment for Raynaud's, work was needed to accurately measure the number and severity of Raynaud's attacks, and the RSA funded a study to answer these questions[18]. In parallel we also funded a project to assess how effective vasodilators can be in treating Raynaud's[19]. This has had a direct impact on the now available iloprost treatment for people living with severe Raynaud's.

Commonly used treatments such as iloprost and other vasodilators were first assessed by RSA and Scleroderma Society funded researchers who looked at the potential value of nitric oxide donor drugs as vasodilators[20]. The effect of iloprost on cardiovascular involvement in systemic scleroderma was analysed in a study funded over an eight year period by the RSA[21]. Pilot studies were also funded to understand whether a local delivery of a vasodilator by a technique known as iontophoresis would increase blood flow in the fingers so that digital ulcers could be better treated[22].

In addition to vasodilators, work has been undertaken to identify effective non-invasive treatments such as the laser and intense light pulsed treatments on spider veins that are sometimes found on the face, hands and forearms of people with scleroderma[23].

More recent work has focused on identifying molecular therapeutic targets to enable a more focused approach to addressing the root causes of the conditions. For example, since 2000 we have funded a series of studies that have helped to define the key role of the cytokine Transforming Growth Factor Beta and other proteins released by immune cells in the immunological response in scleroderma[24]. The impact of this work has meant that we can now identify key targets in the immunological response that can be modified to downplay the autoimmune response. This, alongside other work currently funded, means that we have more sophisticated treatments that will not only increase life expectancy but also improve quality of life.

Here are four highlights from the last 30 years.

"I'm still hoping that we'll be able to get a molecule that is a proper anti-fibrotic and will be able to target fibrosis and fibroblasts. I'd like to be able to say that the basic science has been used a lot and has been translated to form an effective therapy for patients."

PROFESSOR DAVID ABRAHAM

REGAINING BOWEL CONTROL: A NON-INVASIVE TREATMENT[25]

Dr Anton Emmanuel, University College London

Loss of bowel control is a particularly unpleasant symptom of scleroderma. A team from University College London Hospital pioneered a painless method of helping patients regain some bowel control. By electrically stimulating certain nerves in the leg, Dr Emmanuel's technique has helped improve the lives of a number of patients and is now being considered by the NHS as a possible standard treatment, benefiting conditions far beyond scleroderma.

Of the many symptoms of scleroderma, gut problems are amongst the most common and least discussed. Almost 8 in 10 people with systemic scleroderma find the immune system attacks their guts. For some people this damage stops them absorbing vital nutrients, sometimes resulting in the need to be drip fed. For other people the damage affects a person's bowel control. Not only is this life altering, but it can affect a person's sense of dignity and confidence in life.

Unfortunately loss of bowel control is not an area well understood or well treated. Regaining control over this most fundamental of bodily functions could do a lot to improve the impact of this disease. And work by Dr Emmanuel, supported by SRUK funding, has found a method for giving patients back some control over their bowels.

Dr Emmanuel was able to lay the foundations for this work, showing that faulty nerves could well be the reason for loss of bowel control in people with systemic scleroderma. Nerves work by passing electrical signals from one nerve cell to the next at high speed, and it is these nerve signals that control muscles. Dr Emmanuel led a pilot study to see whether stimulating specific nerves in the leg with electric pulses could help restore some of the muscle control in the gut. The results showed that a 12 week course of this painless and minimally invasive procedure led to clear improvements and a reduction in the number of bowel control incidents reported by the patients. This exciting development could soon become a standard treatment, with NICE currently assessing its use.

DIGITAL ULCERS: TREATMENT FROM AN UNLIKELY SOURCE[26]

Professor Carol Black and Professor Chris Denton, Royal Free Hospital

Digital ulcers are debilitating and can cause life-threatening complications. Taking inspiration from other medicines, Dame Carol Black and Professor Chris Denton from the Royal Free Hospital helped shape NHS treatment guidelines, using drugs such as Viagra to increase blood flow to the hands and feet, slowing the development of ulcers far more simply and cost-effectively than with the original treatment recommendation.

In scleroderma and Raynaud's, damage to the skin and blood vessels can stop blood reaching fingers and toes. If the cells in these areas can't get enough oxygen and nutrients from the blood they will begin to die, forming ulcers which are a significant cause of health complications, often causing infection, gangrene and even amputation, and dramatically altering the life of the affected individual.

To slow or even halt the development of digital ulcers, drugs called prostanoids increase blood flow to the affected area, stopping the cells from dying and forming ulcers. The problem with these drugs is that they need to be delivered into the veins. Teams led by Dame Black and Professor Denton helped build the case for using cheaper alternatives that could do the same job. One such drug is sildenafil which is very famous for increasing blood flow, albeit under its brand name Viagra. The work by Professors Black and Denton played a big part in the adoption of these treatments by the NHS, adding a cheap and highly useful medicine to the doctor's tool kit for controlling this disease.

THE EUROPEAN SCLERODERMA OBSERVATIONAL STUDY[27]

Professor Chris Denton, Professor Ariane Herrick, Professor Maya Buch Dr Voon Ong, Dr Francesco del Galdo, Europe Wide

Without additional SRUK funding, one of the most important international clinical trials of scleroderma treatments would not have been completed. As a result, an international consortium of scientists, led by Professor Chris Denton, were able to show the benefits of suppressing the immune system at all stages of early diffuse scleroderma, using a revolutionary study design that is becoming the benchmark for future studies.

Suppressing the immune system is an essential for treating severe cases of diffuse scleroderma, halting the damage. But suppressing the immune system is not without consequences, and the question as to whether it should be used for people with the earliest signs of diffuse scleroderma was unanswered. A clinical trial was needed. But trials on rare diseases are difficult as it is hard to get enough participants to be confident in the results.

To overcome the challenges of testing treatments on rare diseases, scientists and clinicians from 19 countries joined forces to recruit as many early-stage diffuse scleroderma patients as possible for the European Scleroderma Observational Study.

Led by Professor Denton and involving many clinician partners of SRUK (including Professor Herrick, Dr Voon Ong and Professor Maya Buch) this team showed that there was little difference between different types of immunosuppressant, but that there was a survival benefit to beginning treatment as early as possible.

As important as this finding is, it is arguably less important than the collaborative set up of the trial itself. This multi-national, multi-drug approach represented a game-changing way of testing medicine in scleroderma and will now serve as the benchmark worldwide when designing future clinical trials to test advanced treatments.

The goal is now to make a topical treatment that can be easily applied and will rid a person of a painful condition.

A TOPICAL TREATMENT FOR CALCINOSIS[28]

Professor Richard Winpenny, University of Manchester

Calcinosis is a debilitating problem, not just in scleroderma but in other diseases like arthritis too. This team led a revolutionary project to develop a treatment that can dissolve them.

Calcinosis is the formation of painful, hard lumps over the skin, particularly at pressure points such as joints. Unsurprisingly this can be debilitating. Professor Richard Winpenny and Professor Ariane Herrick were interested in learning what these lumps are actually made of, and crucially, whether treatments can be given to dissolve them safely, and SRUK made this a reality, continuing their long tradition of identifying promising projects at an early stage and giving them a chance to flourish.

Using advanced chemistry, the team assessed various reagents that might have the necessary properties to dissolve calcinoids, combining them with a ‘nanotechnology’ delivery system that can transport this chemical across the skin and into the calcinoid. The goal is now to make a topical treatment that can be easily applied and will rid a person of a painful condition.

BUILDING THE RESEARCH COMMUNITY IN THE UK

As we've shown, huge strides have been made in the areas of diagnosis and management, treatment and understanding the cause. But if we are going to make positive steps in the fight against scleroderma and Raynaud's, then it's vital that we have the right environment where research into these conditions can thrive. Some of the activities which have contributed to this development are outlined below.

FACILITATING AND SUPPORTING COLLABORATION: THE UK SCLERODERMA STUDY GROUP

Funding has helped to nurture and grow a vibrant community of some of the best scleroderma and Raynaud's clinicians, helping establish world-leading research groups.

But it's not just about supporting excellent individuals, it is also about building a community.

Dame Carol Black, SRUK's President, established the UK Scleroderma Study Group (UKSSG) to bring together centres interested in researching and treating scleroderma and Raynaud's.

Together with SRUK's Vice Presidents, Professor Christopher Denton & Professor Ariane Herrick, they built a forum where experts from across the UK share ideas, form partnerships and design and support a series of ground breaking studies.

NURTURING TALENT: DR JOHN PAULING AND DR VICTORIA FLOWER

Investing in future generations of researchers is essential to increase capacity and grow the scale of research being undertaken.

For rare autoimmune conditions like scleroderma, clinicians are often at the frontline in treating and looking after patients. In order to develop new and more effective treatments, it's critical that our clinicians are supported in their ambitions to further their scientific understanding of the conditions, as well as investigate promising areas of research. This is why over the years, a number of promising clinicians have been funded to undertake a PhD in the field, allowing them to grow and develop further.

Dr John Pauling, a consultant rheumatologist from Bath, was supported to begin a clinical research career focussed on scleroderma. In 2009, John was awarded the Dando Fellowship, jointly funded by the RSA and the Royal College of Physicians, for his research on dysfunction of small peripheral blood vessels in primary Raynaud's and scleroderma. During his fellowship, John received the BIRD Davies-Maitland Scholarship prize and the RNHRD Researcher of the Year award. He was later appointed consultant rheumatologist at the Royal National Hospital for Rheumatic Diseases in Bath.

Another clinician supported by SRUK to obtain her PhD is Dr Victoria Flower. She is taking small samples of skin from scleroderma patients and studying the interplay of molecules and the effects of scarring and damage on the blood vessels[29]. By funding a PhD for this talented young clinician, SRUK is continuing the tradition of developing the future stars of scleroderma and Raynaud's research, people who will be instrumental in transforming this disease.

3
PHD STUDENTS SUPPORTED

SUPPORTING GREAT IDEAS:
PUMP PRIMING INNOVATION

For many researchers, getting support for research projects can be tricky and may be the deciding factor on their future research careers. A key strategy for SRUK has been to back those innovative projects at a stage when big funding bodies and pharmaceutical companies aren't ready to commit or provide top up funding to ensure the success of clinical trials. This has led to numerous breakthroughs that otherwise may not have happened, which in turn have contributed to the longevity of many of our clinician researchers' careers. This longevity means that the researcher clinician community can continue to develop the best treatments available for people living with the conditions.

For example, this type of funding meant that a trial to test the efficacy of vasodilators, a previously unexplored treatment, could take place in people with Raynaud's. Today, vasodilators are one of the most commonly prescribed treatments for people with the condition.

"SRUK recognized the importance of not just funding good research but also of funding young doctors who want to develop a real interest in this field. It's not just about funding science to learn about the pathogenesis of the disease, but also about getting clinicians and rheumatologists in the country really interested in it, knowing that they will then spend the next 30 years of their career devoted to this disease."

DR JOHN PAULING

"Taking time out of my medical training and getting closer to the science gives me huge opportunities to improve my skills as both a clinician and a researcher. I see a future for me in specialist in systemic scleroderma and this funding from SRUK allows me the space to focus on this fascinating problem".

DR VICTORIA FLOWER

2

FELLOWSHIPS AWARDED

(JOHN PAULING & JILL BELCH)

"Some of the most important clinical studies I've been part of have been supported by SRUK. They are fantastic at providing vital add-on grants that have allowed us to extract the maximum value from clinical projects. This is a really cost-effective way of making a big difference and something I am extremely grateful for."

PROFESSOR CHRIS DENTON

AN AMBITIOUS FUTURE

Our vision for the future is ambitious but simple. No person with Raynaud's or scleroderma should suffer from their condition. People will be diagnosed quickly, and given the perfect treatment that manages their presentation of the condition.

Getting to this stage will not be easy, but both we and our scientists won't stop until this is a reality. SRUK is already investing in this future. With the help of our dedicated supporters who make this work possible we are putting in place the infrastructure and capacity to accelerate progress.

As part of our commitment and dedication to investing in the most important areas of research, we are developing an innovative research strategy. We will be publishing this as a separate report.

We firmly believe that the day will come soon when not a single person will have their lives limited by these painful and debilitating conditions. We also firmly believe that research holds the key to a better future.

We can only do this with your support, so that we can continue to invest in the most relevant and innovative research that will bring us to a future where no one has to suffer alone.

313K
INVESTED IN OUR FIRST TWO YEARS

IN THEIR FIRST YEAR, SRUK HAVE INVESTED £145K IN 4 GRANTS, AND £167,665 ON 4 GRANTS IN THE SECOND YEAR

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30 years of funding the best research to transform patient lives.

KEEP THE RESEARCH GOING

Scleroderma and Raynaud's UK (SRUK) is the only charity in the UK dedicated to improving the lives of people affected by scleroderma and Raynaud's. We exist to improve awareness and understanding of these conditions, to support those affected and ultimately to find a cure.

SRUK relies entirely on the support of our community to continue our work and thanks to that support we have been able to invest over £10 million in research to date. As you have read, that research has already led to better survival outcomes, improved treatments and advances in our knowledge.

JOIN OUR COMMUNITY

This is just the start of what we can achieve, and you can make that happen.

There are many ways that you can help us continue to invest in innovative research work to improve the quality of life of everyone with scleroderma and Raynaud's through the focus on better diagnosis, precision medicine and continuing to research the causes. This can be from making a donation to taking part in an event or becoming a member. Whatever you choose to do will make a difference to everyone living with and affected by scleroderma and Raynaud's.

If you would like to join our community, you can become a member and get exclusive access to our quarterly SRUK Magazine or sign up to our monthly E-news for useful tips and updates.

To find out more about how you can get involved contact the SRUK team:

Call: 020 3893 5998

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For support and information call our Helpline on: 0800 311 2756