

Centred on a cure

Professor David Abraham has focused his career on understanding fibrosis to better treat connective tissue diseases. Here, he discusses his current research activities and the future of biomedical research

PROFESSOR DAVID ABRAHAM



Could you describe your role as Director of the Centre for Rheumatology and Connective Tissue Diseases at University College London (UCL), UK?

My role is to oversee all aspects of the Centre's operations, including staffing and funding, supervising research, publishing in scientific journals, submitting grant applications, and recruitment and appraisals. I am also responsible for the teaching services the Centre performs for the University at both undergraduate and postgraduate level, and to ensure that research students are effectively supervised and prepared for a career in science. In essence, we want to attract, retain and develop the most gifted students and educate, train and inspire them to become the next generation of scientists and doctors at the national and international forefront of biomedical research and patient care.

What type of research are you conducting?

With my co-Director Professor Chris Denton, who is a clinician scientist, our main research focus is centred on the autoimmune/rheumatic connective tissue disease spectrum scleroderma (SSc). This disease has four main components: blood vessel damage, inflammation, autoimmunity and tissue scarring leading to widespread and organ-specific fibrosis. The majority of our work is aimed at understanding the genetic, epigenetic, molecular and cellular mechanisms that underlie these processes with a clear translational focus to identify candidates, which can be developed into new and more effective treatments for patients.

How much is known about the aetiology of SSc?

As with all autoimmune diseases, the precise aetiology of SSc is unknown. It is a complex condition with a multifaceted pathogenesis and

disease spectrum. Critical features include blood vessel disease and inflammation. Moreover, Raynaud's phenomenon is a near universal prodrome that occurs prior to developing SSc. There are also genetic components, and many studies have implicated an environmental influence, such as trauma, infection and exposure to toxic agents and oxidant stress. Therefore, in broad terms, epigenetics is widely believed to be important in the disease process. We are beginning to unravel the genetics, largely due to the application of new technologies such as genome-wide association studies. These alone have identified nearly 30 genes associated with the disease process; the most robust associations so far are with genes of the immune system.

To what extent will the understanding of complex pathogenic links between vasculopathy, autoimmunity and tissue fibrosis inform the development and use of targeted therapies?

From the natural history of the disease process, we believe there are linked pathogenic mechanisms. If we can determine which cell types are affecting the disease at different points or in different ways, we can develop targeted therapies. For example, damage to the blood vessel wall appears to promote the immune cells to escape from the blood into the tissues and cause inflammation, we can develop therapies that protect the blood vessel and dampen inflammation. Likewise, if we identify the important growth factors that drive the development of the myofibroblast, we can attenuate scar formation. Some treatments have been developed that have a beneficial effect on the blood vessels and are effective in impacting upon inflammation – though there is more to do in these areas as the beneficial effects are often modest and the drugs have toxicities and side-effects – but to date, there are no effective treatments for scarring and fibrosis.

Can you describe how the Centre uses biobanking in its fibrosis research?

We collect samples from patients with these complex diseases and use them in two main

approaches. One is genetics. With our large patient cohorts, we take blood samples and examine gene polymorphisms that associate with the disease and its subsets. For example, we study patient groups with lung fibrosis and ask what genes are linked to those patients using whole genome analysis. We then look for different genes in those patients compared to ones with SSc who do not have lung fibrosis.

A second area is biomarkers. We look at biomarkers in the serum and plasma by performing large proteomic screens and assessing the entire protein complement of the biological fluids. We then find the proteins expressed there and compare those with serum samples from a control cohort. We can examine the differences between these cohorts and identify biomarkers – or proteins – in the serum and hypothesise if a patient might fall into a certain disease subset.

As a member of the UCL Knowledge Transfer and Enterprise Board for the Faculty of Medical Sciences, how do you work to translate innovative research into commercial enterprise?

Bridging research and the transfer of laboratory work into effective clinical applications is a challenge. Working closely with clinical colleagues is important, and in terms of Knowledge Transfer and Enterprise Board, I try to facilitate interactions between academia and industry. My goal is to provide the optimum opportunity for the best knowledge of the disease process to be joined with the best target or drug that might have an impact on the disease. I believe these partnerships will result in a greater chance of successfully enhancing the transition from research into application. There will always be a risk in projects, but through collaboration and gaining insight into the disease process, and by partnering with industry where cutting-edge technologies and unrivalled drug discovery expertise exist, along with critical experience in clinical trials and successfully bringing drugs to market, we believe these risks are substantially lowered.



Chris Denton,
Professor of
Experimental
Rheumatology

In which direction will you take your research in the future?

We will focus mainly on fibrosis and SSc, and on translating or transferring our basic biomedical research findings into treatments. Over the last 10 years, we have been able to improve our understanding of the disease process occurring within SSc. We also have a good idea of what are likely to be the key cell and molecular targets driving tissue remodelling and fibrosis. We now have several targets (growth factors, kinase inhibitors and transcription factors) that are in patents, and we are moving forward in new clinical trials.

How do you see biomedical research progressing in the years to come?

It is an exciting time for biomedical research. Technologies are available that can help us understand the disease process in very precise detail. Once we identify important mediators, it will be possible to develop new research tools, such as antibodies, inhibitors and model systems, with which to study pathogenesis. Moreover, antagonists and biologics are often already available, so once a target is identified, significant translational potential exists.

Additionally, biomedical research is likely to intersect more frequently with personalised medicine. This is a key research domain at UCL, because it is important to know if drugs given to patients might have a disease-modifying effect. At the Centre, we are working to stratify patients into different groups based on their history of disease. This way, we can tailor treatments to some extent. If you take pulmonary arterial hypertension, for example, we are now able to identify patients by a series of clinical tests and biomarkers. Once we have identified individuals eligible for certain treatment programmes, we can work towards targeting the problems involved in pulmonary arterial hypertension.

Fighting fibrosis

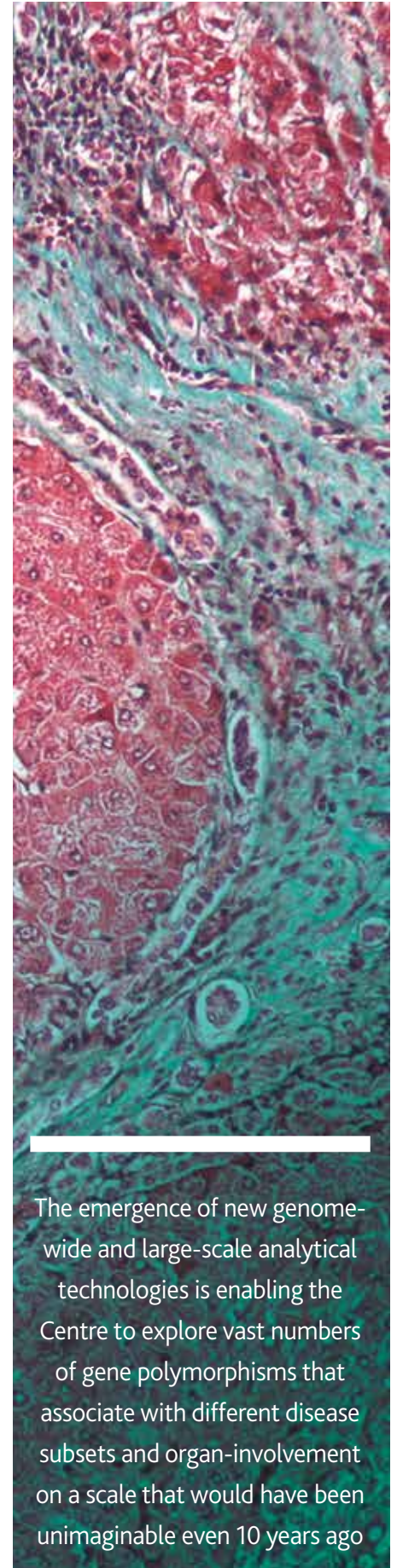
Scientists in the Centre for Rheumatology and Connective Tissue Diseases at **University College London** are examining the mechanisms that spur fibrosis, with the goal of treating and even preventing diseases, such as scleroderma, that display scarring as a major component

THOUGH IT MAKES up every bit of fat, bone and cartilage in the body, when it works properly, connective tissue often goes unnoticed. However, when tissue misbehaves, it can wreak havoc on an individual's everyday life, causing great pain, discomfort and even leading to death. Furthermore, while the number of connective tissue diseases is high – there are over 200 – there is a lack of effective treatments. In London, there is a research centre aiming to expand this knowledge base and improve the lives of the millions of people worldwide who live with connective tissue diseases. Research led by Professor David Abraham at the Centre for Rheumatology and Connective Tissue Diseases at University College London (UCL), UK, is working to understand the molecular and cell biology of connective tissue diseases, including the genetic and molecular mechanisms underlying tissue scarring and replacement fibrosis.

FOCUSING ON FIBROSIS

The lens through which the Centre examines connective tissue disease is that of fibrosis – the unrestrained thickening and scarring of tissue. Fibrosis is a common feature to this spectrum of diseases, which affects 80-100 million people across Europe, the US and Japan. In general, the body's ability to produce scar tissue is a good thing, especially when an individual sustains an injury, such as a burn or a cut. To mount a healing response, the body activates fibroblast cells, which are present in all soft connective tissues. "The fibroblast cell undergoes a fundamental change in its differentiation. It becomes a synthetic and contractile cell – the myofibroblast. This cell secretes a complex protein glue called the extracellular matrix (ECM) and coordinates repair of the wound," Abraham explains.

Once the myofibroblast cells repair the tissue, they are supposed to shut off and disappear through apoptosis. However, in fibrotic disorders, this shutdown process goes awry, and the myofibroblasts continue to secrete ECM into the



The emergence of new genome-wide and large-scale analytical technologies is enabling the Centre to explore vast numbers of gene polymorphisms that associate with different disease subsets and organ-involvement on a scale that would have been unimaginable even 10 years ago

wound. Over time, this scar tissue builds up to the point that it overwhelms the affected organs' architecture, compromising its function. This is a dangerous turn of events, especially in diseases such as pulmonary fibrosis and liver cirrhosis, as the organs can stop working altogether. In fact, it has been estimated that fibrosis plays a major role in nearly 50 per cent of deaths in the Western world.

A SPOTLIGHT ON SCLERODERMA

While fibrosis can develop after an injury, it has also been known to occur due to environmental, genetic and immunological responses. This is likely the case for scleroderma (SSc), a multi-system spectrum of rare chronic autoimmune diseases that cause swelling and pain in muscles and joints, as well as the tightening and hardening of skin and connective tissue. It is extremely fatal and, in the past, scientists have often called it incurable.

SSc can take two forms. In limited cutaneous SSc, skin fibrosis is restricted to particular sections of the body – mainly the extremities – and is often characterised with vascular manifestations. However, nearly 40 per cent of SSc patients have diffuse cutaneous SSc, in which fibrosis rapidly progresses to the skin, lungs and other internal organs. For patients, receiving a diagnosis of either disease is deadly news, as estimates from a recent UK cohort show that patients with limited and diffuse cutaneous SSc having survival rates of 57 per cent and 50 per cent, respectively.

While the number of individuals who suffer specifically from SSc is relatively small – 75,000-100,000 individuals in the US suffer from it – scientists at UCL are paying special attention to this condition because it is distinct from most fibrotic disorders. Nearly every patient with the disease experiences Raynaud's phenomenon, a condition that affects the blood supply to certain parts of the body, usually the fingers and toes, as an early symptom. Additionally, SSc often displays other forms of small-vessel vasculopathy, as well as inflammation and autoimmunity, before the interstitial and vascular fibrosis starts in the skin, lungs and organs. This disease progression is

Royal Free Campus.



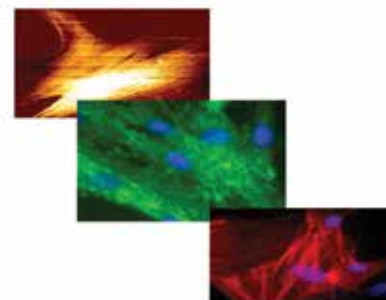
significant because it means that immune cells and vascular dysfunction might play significant roles in activating the genetic programme responsible for fibrosis. Therefore, the UCL scientists can use these characteristics as natural biomarkers to indicate the severity of SSc and create targeted treatments.

Excitingly, these biomarkers are not only useful for patients who have SSc. As fibrosis is present in many human diseases – and since many are immunologically driven and all forms of fibrosis are believed to progress through the same common stages – SSc's biomarkers may be applicable to a large variety of fibrotic disorders. "Several biomarkers such as an Interleukin-6 (and other cytokines), brain natriuretic peptide and some chemokines are currently showing promise as markers in fibrotic disease along with specific ECM proteins, their degradation products and ECM modifying enzymes derived from the scar tissue," Abraham expands.

CREATING TREATMENTS

In addition to clinical services, the Centre completes many important clinical trials. Current treatments for SSc – and for fibrotic diseases in general – are aimed at slowing its progression and managing its complication through lifestyle modification and pharmacological intervention. Unfortunately, at most these actions only have a small impact on the disease pathogenesis. This is a reality that Abraham and his team are working to change: "We are driven by the desire to transfer our basic and applied scientific research into meaningful therapies".

To achieve this remit, the Centre mainly focuses its research efforts on three models – *in vitro*, animal models and tissue slices. These integrate gene candidates and biomarkers so the team can test potential therapeutics. "Although much information has been gleaned from *in vitro* systems concerning SSc's complexity, it is impossible to mimic *in vitro*, highlighting the need for *in vivo* models," Abraham states. Therefore, complex multi-cell systems and animal models have been especially important to his and the Centre's work. Since patients with SSc can experience different combinations of its four key features – vasculopathy, inflammation, autoimmunity and fibrosis – the UCL scientists are using three different types of animal model to examine specific aspects. "These range from naturally-occurring models of fibrosis to models that can assess fibrosis in different target organs. We have also developed new models that use genetic modification with gene knock-out and knock-in technologies and with multiple gene approaches. This is an essential component of biomedical research as preclinical models assess the influence of new therapies *in vivo*," Abraham enthuses.



The myofibroblast: visualised by atomic force microscopy (top panel) and by immunofluorescence, vinculin (green) and alpha smooth muscle actin (red).

Since a major manifestation in SSc is skin fibrosis, damaged tissue is relatively accessible to obtain pre- and post-treatment. In the clinical trial world, this is an enviable ability because it enables researchers to analyse gene and protein signatures much earlier in the process. Through this, the clinical team in the Centre for Rheumatology and Connective Tissue Diseases is able to assess the presence of their trial's various drug targets and examine their therapeutic potential quickly and easily.

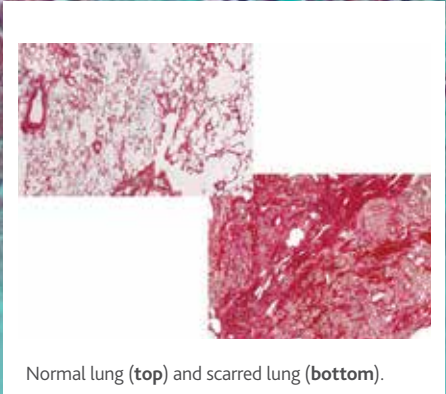
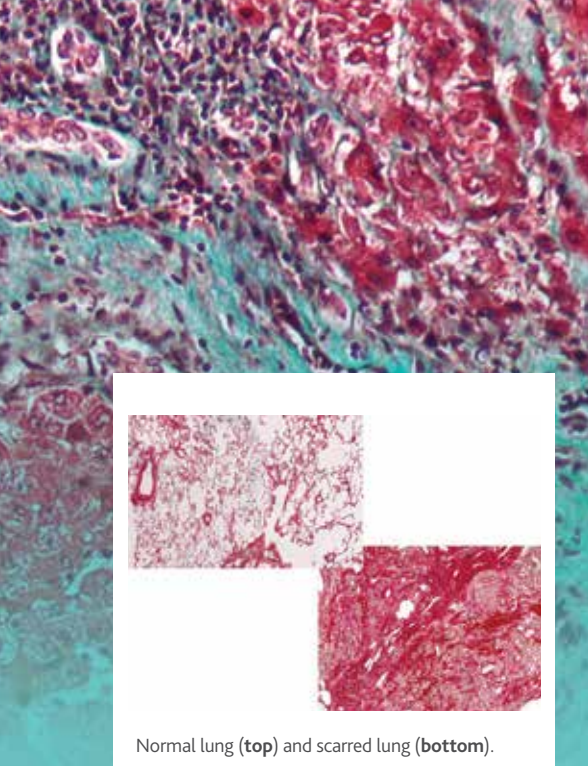
Key to this work is Professor Chris Denton, who is the clinical leader of the Centre. Denton and Abraham work intimately together to ensure that the translational research the group undertakes – from concepts in the lab through to clinical trials and treating patients – is seamless. "It's important that we have this collaboration between scientists and clinicians. A team-based approach with basic scientists understanding the disease process and clinicians at the interface of taking studies into clinical trials will mean better treatment for patients," Abraham explains.

IMPROVING TRIALS

While much information has been gleaned about SSc from the phase I, II and III clinical trials performed by the Centre through the years, Abraham is taking steps to improve the effectiveness of future trials. For example, his team is focusing on using more evidence-based approaches. In these, the scientists are targeting the pathways and molecules involved in the disease process, with the goal of creating treatments that apply specifically to them. They are also in the process of conducting research, trials and studies that rely on patient stratification, which occur in clearly defined groups so that individuals have comparable phenotypes. Patient stratification will also enable the team to carry out the trials and studies over a much shorter timeframe.

END GOALS AND FUTURE TARGETS

A debate is raging among scientists in the field concerning the future of fibrosis research.



Normal lung (top) and scarred lung (bottom).

FLARRE

Professor David Abraham is the Steering Committee Chair for the UCL Consortium for Inflammation, Tissue Repair, Scarring and Fibrotic Diseases. He explains how the Consortium collaborates to promote the breadth of basic, translational and clinical research on fibrotic diseases

The Consortium for Inflammation, Tissue Repair, Scarring and Fibrotic Diseases (FLARRE) is a powerhouse of scientists and industry members all dedicated to aspects of fibrosis research. It grew out of my University College London (UCL) Enterprise role as a way to assemble basic, biomedical and clinician researchers from across UCL with interests in FLARRE. It also acts to raise awareness of the depth and breadth of research being carried out, and highlight entrepreneurial or commercial potential.

Essentially, I want to develop and promote a UCL cluster of expertise in FLARRE and highlight multidisciplinary skills that would promote synergy across the university, and to increase collaboration within it. Additionally, I aim for FLARRE to identify and promote the young people at UCL – PhD students and emerging Principal Investigators alike – as these are the people with all the new and outside-the-box ideas that will push the field forward.

An important aspect of the Consortium is to augment commercial engagement, develop interaction with industry and pharma, and 'open-up' FLARRE for business. In terms of fibrosis, there are experts across UCL for almost all 'forms' and target organs, so UCL is a 'one-stop-shop' where industry can help across a wide range of fibrotic diseases. More importantly, perhaps, is the fact that we can provide expertise in disease areas to find new targets, validate existing targets, and access and use of pre-clinical models and human samples to gain confidence in targets, pathways and concepts. Moreover, UCL has partner hospitals and many of the patient groups required for clinical trials can be made available via our clinical colleagues.

The Consortium has several other important goals; for example, we want to enter into and enhance international academic collaborations, such as the fibrosis collaboration we have started with Yale University, USA. We also endeavour to act in the interest of patients, by facilitating translation of innovative research into commercial enterprise, and to champion drug repositioning through the exploration of therapeutic switching and drug re-tasking.

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INTELLIGENCE

SCAR TISSUE, TISSUE SCARRING DISEASE AND FIBROSIS: CHALLENGES AT THE FRONTIER OF RESEARCH TO ENABLE THERAPEUTIC ADVANCE

OBJECTIVES

To develop proven effective antifibrotic therapies to treat underlying fibrotic disease.

KEY COLLABORATORS

Professor unless otherwise stated

UK: **Christopher Denton**; **Massimo Pinzani**; **Rachel Chambers**; **Lucie Clapp**; **Derek Gilroy**; **Dr Marilena Loizidou**, University College London (UCL) • **John Dart**, Moorefields Eye Hospital • **George Bou-Gharios**, University of Liverpool • **Robert Brown**, Royal National Orthopaedic Hospital • **Adrian Hobbs**, Queen Mary University of London/William Harvey Institute • **Claudia Kemper**, King's College London • **Chris Jackson**, University of Bristol • **Tim Mohun**, Medical Research Council (MRC) - National Institute of Medical Research/Crick • **Dr Allan Lawrie**, University of Sheffield • **James Leiper**, Imperial College London • **Athol Wells**, Royal Brompton Hospital • **Andrew Pitsillides**, Royal Veterinary College

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