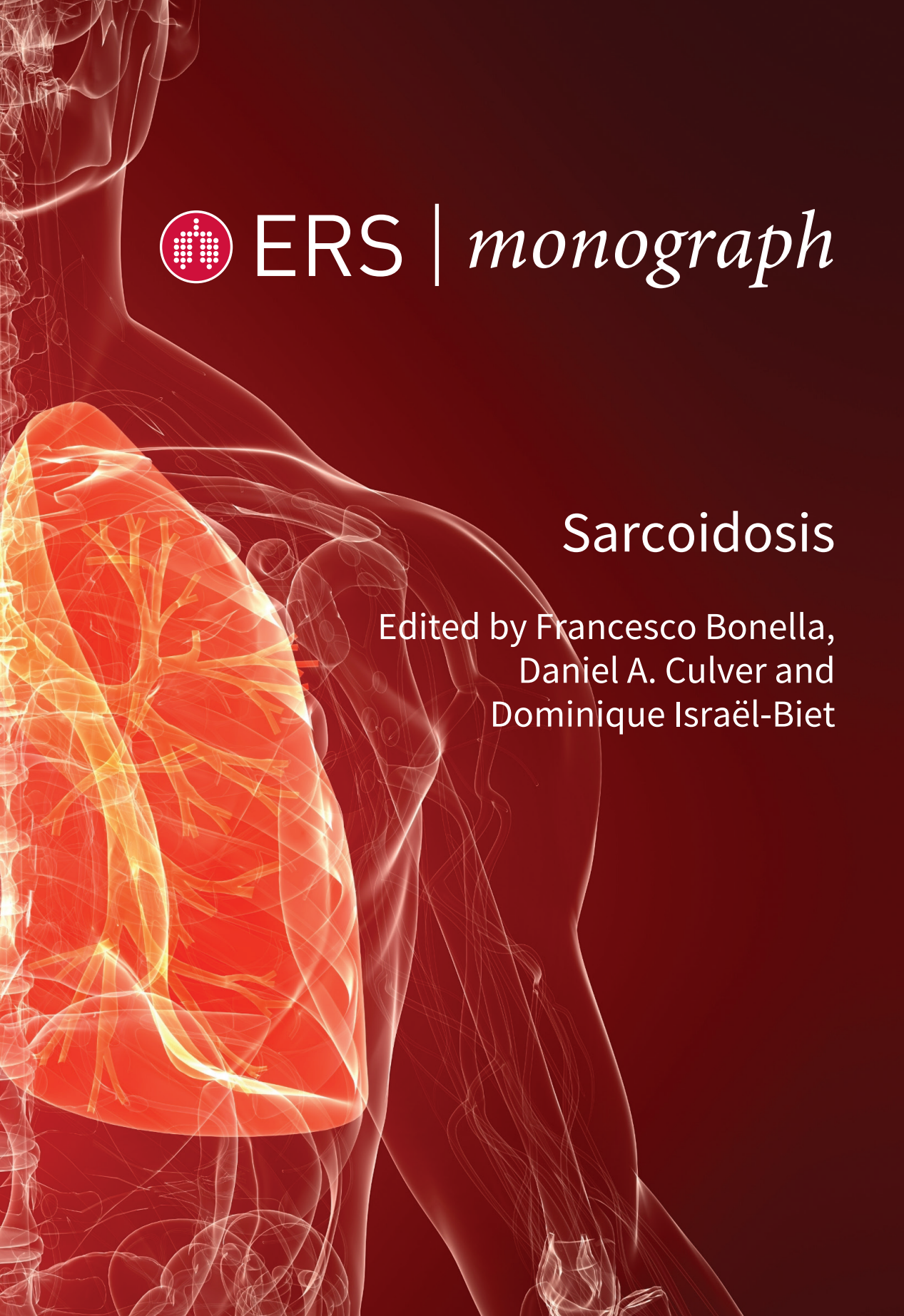
ERS | monograph
Sarcoidosis
Edited by Francesco Bonella,
Daniel A. Culver and
Dominique Israël-Biet

Sarcoidosis

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Editor in Chief
John R. Hurst

This book is one in a series of *ERS Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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Preface

John R. Hurst

It's a pleasure to introduce this latest edition of the *ERS Monograph*, which addresses that most enigmatic of conditions: sarcoidosis. With myriad clinical manifestations, and multi-system involvement, there is a need for all clinicians – generalists and specialists alike – to have a working knowledge of the condition. This collection goes beyond a simple working knowledge, however, and I'd like to thank Guest Editors Francesco Bonella, Dominique Israël-Biet and Daniel A. Culver for commissioning and collating a comprehensive and excellent collection of state-of-the-art reviews, which provide a critical update on all aspects of sarcoidosis. The field is moving rapidly with new developments in both basic science and clinical practice, and therefore the collection is timely. I would also like to recognise the work of the individual chapter authors and reviewers for delivering this collection at a difficult time and, as always, the *Monograph* would not be possible without the dedicated support of the excellent ERS Publications Office. I learnt a lot about sarcoidosis reading these reviews, and I recommend them to you too.

Disclosures: J.R. Hurst reports receiving grants, personal fees and non-financial support from pharmaceutical companies that make medicines to treat respiratory disease. This includes reimbursement for educational activities and advisory work, and support to attend meetings.

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Guest Editors

Francesco Bonella

Francesco Bonella is Associate Professor of Medicine and Head of the Division for Interstitial and Rare Lung Disease, Department of Pneumology, at the Ruhrlandklinik University Hospital (Essen, Germany). He received his undergraduate training and his MD from the University of Verona (Verona, Italy), and completed his PhD in ILD at the University of Essen under the guidance of Professor Ulrich Costabel.

His research interests include sarcoidosis, IPF, autoimmune ILD, and pulmonary alveolar proteinosis, with a special focus on biomarkers, genetic predisposition and the application of BAL. He has acted as an investigator for major clinical trials in IPF, sarcoidosis and pulmonary alveolar proteinosis.

Francesco founded EuPAPNet, the European Network for pulmonary alveolar proteinosis, and is a member of the Steering Committee of ERN-LUNG: the European Reference Network on rare respiratory diseases. He has been actively involved in the European Respiratory Society (ERS) since 2014 and was Chair of the Rare DPLD/ILD Group. Francesco is involved in a range of patient advocacy initiatives and chaired the Scientific Advisory Board of the European Idiopathic Pulmonary Fibrosis and Related Disorders Federation (EUIPFF) in 2013–2019. He has been an Executive Committee member of the World Association for Sarcoidosis and Other Granulomatous Disorders (WASOG) since 2016.

Francesco is the recipient of several honours and awards, including the Sarcoidosis Research Prize presented by the German Sarcoidosis Association. He is a member of the editorial boards of the *European Respiratory Journal* and *Chest*, and is Associate Editor of *Respirology*.

Daniel A. Culver

Daniel A. Culver is the Chair of the Department of Pulmonary Medicine in the Respiratory Institute at Cleveland Clinic (Cleveland, OH, USA) and the President of WASOG.

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Daniel completed his undergraduate studies at The Ohio State University (Columbus, OH, USA) and received his medical degree from the Heritage College of Osteopathic Medicine at Ohio University (Athens, OH, USA). After completing post-graduate training in the Cleveland Clinic Health System, he joined the Departments of Pulmonary and Critical Care in the Respiratory Institute, as well as Inflammation and Immunity in the Lerner Research Institute.

Dominique Israël-Biet

Dominique Israël-Biet is Professor Emeritus of pulmonary medicine of the Université de Paris (Paris, France).

Dominique graduated from the Faculté de Médecine Cochin-Port Royal, Université Paris V René Descartes (Paris), and obtained a PhD in Immunology at the Institut Pasteur (Paris).

She was trained in pulmonary medicine under the guidance of Professor Jacques Chrétien. As Associate Professor of Clinical Immunology then Professor of Pulmonary Medicine, she worked in the Department of Lung Diseases at the University hospital Laënnec (Paris), which Professor Chrétien directed, and was responsible for both the clinical sector and the BAL laboratory. She then moved to the University Georges Pompidou hospital (Paris), and became the Head of the Center for Rare Pulmonary Diseases.

Dominique's research interests mainly focus on sarcoidosis and ILDs and she has actively participated as an investigator in clinical trials in these fields.

Dominique was a member of the ERS Task Force on Bronchoalveolar Lavage and the ERS Task Force on The Treatment of Sarcoidosis.

She is actively involved in WASOG. As an elected member of its Executive Committee since 2011, she co-organised the WASOG International Conference in Paris in 2013 with Professor Dominique Valeyre. She is currently the General Secretary of WASOG.

Dominique is on the Editorial Board of *Respiratory Medicine* and is the author of a number of original papers, reviews and textbook chapters.

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Introduction

Francesco Bonella [1], Daniel A. Culver[2] and Dominique Israël-Biet[3]

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This book includes the voices of clinicians, basic scientists and patients to better illustrate the most recent advances in research and care of sarcoidosis, a many-faceted disease with complex pathogenesis and various clinical manifestations https://bit.ly/32cyVUo

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Sarcoidosis is a systemic, multi-pathway disease and a clinical chameleon. Recent reports indicate that the prevalence of sarcoidosis is rising and the mortality in patients suffering from chronic sarcoidosis is increasing [1]. The high variability of manifestations, from asymptomatic to life-threatening, depends on organ involvement and disease activity, which still lacks a clear definition. About half of patients experience a chronic course. The consequences on quality of life and wellbeing can be devastating, especially if patients are not promptly referred to sarcoidosis specialists. To date, there are few approved treatments for sarcoidosis, mostly based on expert opinion, and the majority of investigational drugs have failed in clinical development. Although enormous advances have been made in the understanding of the disease pathogenesis and in the development of new diagnostic tools and management strategies, the burden of sarcoidosis, both socially and economically, is still considerable and the unmet needs persist.

It has been 17 years since the first *ERS Monograph* on Sarcoidosis, edited by Marjolein Drent and Ulrich Costabel, was published [2]. This *Monograph* is therefore timely and our main aim is to provide the reader with a comprehensive overview of the most recent advances in sarcoidosis.

We begin the book by illustrating the newest data on epidemiology [3] and cover the evidence for pathobiology of granuloma formation, including aetiological agents [4], the link between genotypes and phenotypes, and the genetic mutations occurring in familiar forms [5].

We then move on to discuss phenotyping, specific organ manifestations [6–9] and general diagnostic pathways [10], from conventional radiographic features to the use of novel modalities (*e.g.* PET scan) for diagnosis and assessment of disease activity [11]. We will also provide an update on the usefulness of circulating and imaging biomarkers for assessing disease severity and treatment response [12].

Traditional as well as innovative treatment strategies will be discussed, providing insight into unique aspects of therapy that differ between various organs. In two chapters focusing on when

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and how to treat sarcoidosis, the principles of treatment and stepwise algorithms will be critically appraised [13, 14]. The pipeline drugs on the horizon and ongoing clinical trials will be presented in a dedicated chapter [14].

Another novel and major element is represented by highlighting the patient's perspective. Besides a chapter exploring non-organ-related symptoms like fatigue and cognitive impairment [15], which all belong to the clinical picture of sarcoidosis, a chapter covering the effects of the disease on quality of life and an overview of tools used to assess quality of life is presented separately [16].

We have tried to include the voices of clinicians, basic scientists and patients to provide a better insight into this many-faceted insidious disorder. We believe that readers around the world will find this book helpful.

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fees from Boehringer Ingelheim and Mallinkrodt; support for attending meetings/travel from Roche; and fees for participation in a data safety monitoring board or advisory board from Boehringer Ingelheim, Xentria and Roivant. D.A. Culver is the President of the World Association for Sarcoidosis and Other Granulomatous Disorders. D. Israël-Biet reports receiving: consulting fees from Boehringer Ingelheim; honoraria for educational events from Boehringer Ingelheim and Roche; payments from Galapagos as a member of an adjudication committee; and support for attending meetings and/or travel from Boehringer Ingelheim.

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List of abbreviations

^{18}F-FDG	^{18}F-fluorodeoxyglucose
ACE	angiotensin-converting enzyme
BAL	bronchoalveolar lavage
CT	computed tomography
D_{LCO}	diffusing capacity of the lung for carbon monoxide
EBUS	endobronchial ultrasound
EBUS-TBNA	EBUS transbronchial needle aspiration
EUS	endoscopic ultrasound
EUS-FNA	EUS-guided fine-needle aspiration
FEV_1	forced expiratory volume in 1 s
FVC	forced vital capacity
HLA	human leukocyte antigen
HRCT	high-resolution CT
IFN	interferon
IL	interleukin
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
MMF	mycophenolate mofetil
MRI	magnetic resonance imaging
mTOR	mechanistic target of rapamycin
MTX	methotrexate
PET	positron emission tomography
TGF	transforming growth factor
Th1	T-helper cell type 1
TNF	tumour necrosis factor