



ERS | *monograph*

Idiopathic Pulmonary Fibrosis

Edited by
Ulrich Costabel, Bruno Crestani
and Athol U. Wells

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Editor in Chief
Robert Bals

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Preface

Robert Bals

The field of ILD has gone through several years of change. Many old views on these diseases have been challenged and replaced by more convincing concepts. A good example is the change IPF therapy has undergone during recent years.

According to the US philosopher Thomas S. Kuhn (1922–1996), progress in science often undergoes paradigmatic shifts rather than continuous progress. In clinical medicine, however, many examples show that continuous progress results in improved diagnosis or therapy. The field of ILD and IPF is somehow a mixture of both paradigm shift and continuous progress. Ongoing research in recent decades provided insight into disease mechanisms and underscored the heterogeneity and complexity of these diseases. A chance paradigmatic shift in IPF therapy followed the “crisis” finding that classical therapy with immunosuppressants was more dangerous than beneficial. In parallel, novel drugs were approved after their efficacy has been demonstrated in clinical trials.



IPF is also a good example of a rare disease that needs special attention in the diagnostic process. However, if IPF is taken together with other ILDs, quite a high number of patients suffer from these conditions, meaning the whole disease area goes far beyond “rare” status. Interestingly, this field also gained much more attention when novel drugs became available; pharmaceutical advertisements in this field certainly increased.

The diagnosis and treatment of IPF is multidisciplinary, a fact that is well represented by the content and authors of this book. The book comprises chapters on molecular mechanisms, diagnosis, imaging, pathology and various aspects of therapy. It also reviews the fast developments in drug development. The critical use of data from clinical trials provides new ways to think about IPF and related diseases, and the shifted paradigms of recent years. The Guest Editors, Ulrich Costabel, Bruno Crestani and Athol U. Wells, have worked hard and very successfully to select these topics and to integrate these aspects

into a comprehensive book on the current knowledge about IPF and other ILDs.

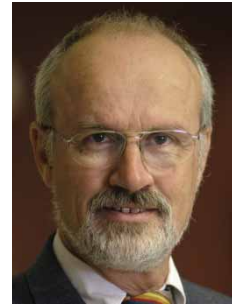
I thank the Guest Editors and all authors for their work on this excellent book. I hope the reader finds this book useful in their clinical practice.



Guest Editors

Ulrich Costabel

Ulrich Costabel is Professor of Medicine at the University of Duisburg-Essen (Essen, Germany) and Senior Consultant in Interstitial and Rare Lung Diseases at the Ruhrlandklinik (Essen, Germany). He was previously Chief of the Division of Pneumology and Allergology at the Ruhrlandklinik. He received his undergraduate training and his MD magna cum laude at the University of Freiburg (Freiburg, Germany). In 1992–1993, he spent a 6-month sabbatical with Professor Takateru Izumi at the Chest Disease Research Institute of the University of Kyoto in Japan (Kyoto, Japan).



Ulrich Costabel's research interests lie in clinical and immunological studies in ILDs, with a specific focus on clinical and research applications of BAL. In recent years, he has acted as principal investigator for major clinical trials in IPF. He is Past President of the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) and organised the World Congress on Sarcoidosis in Essen in 1997. He has been Chairman of the European BAL Group since 1998 and has co-organised several international conferences on BAL.

Ulrich Costabel has been actively involved with the European Respiratory Society (ERS) since its inception, having been Chair of the Occupational and Environmental Health Group and Secretary of the Occupation and Epidemiology Assembly, and later Chair of the Bronchoalveolar Lavage Group. From 2002–2005, he was Head of the Clinical Assembly and a member of the Executive Committee of the ERS and, in 2006, he was Chairman of the ERS Congress in Munich (Germany).

Since 1990 he has served on the Editorial Board of the *European Respiratory Journal (ERJ)*, from 1994–1999 as the Chief Editor. He was Editor of the German journal *Pneumologie* from 2001–2005, has co-edited the *ERS Monograph* on Sarcoidosis, and is currently on the board of *Sarcoidosis, Seminars in Respiratory and Critical Care Medicine* and *Current Opinion in Pulmonary Medicine*, among others. He is the recipient of several honours and awards, including the Sarcoidosis Research Prize presented by

the German Sarcoidosis Association and the World Sarcoidosis Person of the Year Award from the Irish Sarcoidosis Charity.

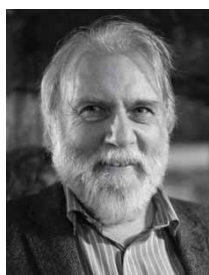
Bruno Crestani



Bruno Crestani is Head of the Pneumology Department at the Bichat Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP) in Paris (France). He is also a Professor of Pneumology at the Paris Diderot University School of Medicine (Paris, France). He is Director of the Lung Inflammation and Fibrosis research unit in INSERM 1152. In recent years, his team has focused on elucidating the pathophysiological mechanisms of IPF, including genetics.

Bruno Crestani is a founding member of the European IPF Network (eurIPFnet) and Head of the Fibrosis, Inflammation and REmodelling (DHU FIRE) university department at the Paris Diderot University School of Medicine. He is also an Associate Editor of the *European Respiratory Journal*.

Athol U. Wells



Athol U. Wells is a Professor of Respiratory Medicine, Senior Consultant and the Academic Lead of the Interstitial Lung Diseases Unit at the Royal Brompton Hospital (London, UK). He completed his undergraduate training at Otago University (Dunedin, New Zealand) where he was later awarded his MD with distinction. He trained as a post-graduate and later practised as a respiratory physician in New Zealand. From 1989 to 1994, he was a research fellow at the Royal Brompton Hospital. After returning to New Zealand for 5 years, he took up his current post at Royal Brompton Hospital in 1999.

Athol Wells has research interests in clinical and translational science with the unifying theme being studies of CT and PFT, both in staging disease and in the examination of disease behaviour (for clinical purposes and in studies of pathogenesis). He was a chair of the British Thoracic Society guidelines (BTS) for ILD, a co-chair in the recent (2013) American Thoracic Society (ATS)/European Respiratory Society (ERS) update of the classification of the IIPs, and a participant in a number of ATS/ERS expert groups. He created and developed the Disease Behaviour Classification, which was endorsed in the 2013 classification of the IIPs. He is the author/co-author of over 230 peer reviewed articles and over 100 editorials, chapters and review articles. He currently serves on the Editorial Board of the *American Journal of Respiratory and Critical Care Medicine*.

Athol Wells believes strongly in the need for an independent European voice in the field of ILD (to complement international consensus initiatives) and has led or co-led four European perspectives in recent years, including the current *ERS Monograph*. He is currently the Chair of European consensus statements on IPF and on lung disease associated with connective tissue disease.



Introduction

Ulrich Costabel¹, Bruno Crestani² and Athol U. Wells³

IPF is a serious, chronic, steadily progressive and ultimately fatal disease of unknown origin, occurring predominantly in the elderly male smoker or exsmoker. Survival is worse than in many malignancies. IPF is the most dreaded and also the most frequent of the IIPs. The morphological hallmark is the UIP pattern, either on HRCT or biopsy, but it is not specific for IPF. It is crucial to differentiate this distinct entity from other ILDs with different prognoses and treatment approaches, especially from chronic extrinsic allergic alveolitis, idiopathic fibrotic NSIP and interstitial pneumonias with autoimmune features.

Recent years have seen a number of advances and changes in our understanding of the pathogenesis, diagnosis and management of IPF. It became evident that diagnostic security could be sharpened by multidisciplinary discussion and that bronchoscopic lung cryobiopsy is probably as informative as surgical lung biopsy in this setting. Many patients do not undergo surgical lung biopsy because the procedure is too risky in patients with severe disease and marked comorbidities. A number of statements and guidelines have been published but the question of how to handle a patient with probable or possible IPF compared to definite IPF has never been addressed.

After decades of therapeutic disappointment, two antifibrotic drugs are now available, which have the potential to slow disease progression by preventing ~50% of the decline in FVC. In this context, early diagnosis, which requires the recognition of velcro-like crackles on auscultation in the elderly, deserves the highest attention in the new era of IPF as a treatable disorder. There are many open questions related to antifibrotic therapy: when should we start and stop treatment? Which drug should be used first? Will the future lie in sequential or combination therapy?

This *ERS Monograph* aims to broadly describe the new achievements associated with IPF. Beginning with epidemiology, genetics and pathogenesis, the key diagnostic issues and major contributors to diagnosis, such as imaging and histopathology/BAL, are covered. This is followed by a section on how to evaluate/stage the disease for prognosis and how to monitor progression, including a discussion on the potential value of biomarkers. Several chapters are devoted to complications and comorbidities and their impact on management, such as acute exacerbation, PH, lung cancer, emphysema, cardiovascular disease and GERD. The treatment chapters cover antifibrotic drug therapy, symptom control, rehabilitation,

¹Interstitial and Rare Lung Disease Unit, Ruhrlandklinik, University Hospital, University of Duisburg-Essen, Essen, Germany. ²Service de Pneumologie A, Centre de Compétences Maladies Rares Pulmonaires, Hôpital Bichat, APHP, INSERM, Unité 1152, Paris, France. ³Interstitial Lung Disease Unit, Royal Brompton Hospital, London, UK.

palliative care and transplantation. Finally, the book considers unmet patient needs, ongoing issues in clinical trials and perspectives for the future.

As editors we believe that this new *Monograph* is timely, given the numerous developments in this field. We hope that this book will be of interest to all those who are engaged as clinicians or researchers in this evolving topic of respiratory medicine.

List of abbreviations

| | |
|------------------------|--|
| 6MWD | 6 min walk distance |
| 6MWT | 6 min walk test |
| BAL | bronchoalveolar lavage |
| BALF | bronchoalveolar lavage fluid |
| COPD | chronic obstructive pulmonary disease |
| CPFE | combined pulmonary fibrosis and emphysema |
| CT | computed tomography |
| DLCO | diffusing capacity of the lung for carbon monoxide |
| FEV₁ | forced expiratory volume in 1 s |
| FVC | forced vital capacity |
| GAP | gender, age and physiology |
| GERD | gastro-oesophageal reflux disease |
| HRCT | high-resolution computed tomography |
| IIP | idiopathic interstitial pneumonia |
| ILD | interstitial lung disease |
| IPF | idiopathic pulmonary fibrosis |
| miRNA | micro RNAs |
| NAC | <i>N</i> -acetylcysteine |
| NSIP | nonspecific interstitial pneumonia |
| PFT | pulmonary function test |
| PH | pulmonary hypertension |
| QoL | quality of life |
| TGF | transforming growth factor |
| TLC | total lung capacity |
| UIP | usual interstitial pneumonia |
| VEGF | vascular endothelial growth factor |