Personalised medicine in interstitial lung diseases

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ABSTRACT Interstitial lung diseases in general, and idiopathic pulmonary fibrosis in particular, are complex disorders with multiple pathogenetic pathways, various disease behaviour profiles and different responses to treatment, all facets that make personalised medicine a highly attractive concept. Personalised medicine is aimed at describing distinct disease subsets taking into account individual lifestyle, environmental exposures, genetic profiles and molecular pathways. The cornerstone of personalised medicine is the identification of biomarkers that can be used to inform diagnosis, prognosis and treatment stratification. At present, no data exist validating a personalised approach in individual diseases. However, the importance of the goal amply justifies the characterisation of genotype and pathway signatures with a view to refining prognostic evaluation and trial design, with the ultimate aim of selecting treatments according to profiles in individual patients.

Introduction

Interstitial lung diseases (ILDs) are a group of heterogeneous disorders, either idiopathic or associated with an overreaction of the immune system. Until recently, no effective therapy existed in patients with a progressive fibrotic phenotype, in part due to limited knowledge of pathogenesis. However, during the last decade, new concepts have developed on aetiological factors, pathogenetic mechanisms (inflammation versus active fibrosis) and genetic susceptibility. There has been an exponential increase in publications on the pathogenesis of ILDs and this applies especially to idiopathic pulmonary fibrosis (IPF), the most prevalent and progressive ILD. This period has seen the advent of antifibrotic therapies with proven treatment effects in IPF, which, among ILDs, continues to be the main focus of ongoing research.

Despite recent advances, there are many unanswered questions regarding the prediction of clinical behaviour and responsiveness to treatment in IPF. Initially, IPF was considered as a single disease with a...
characteristic pattern of disease behaviour. However, our understanding of the pathogenesis of IPF has evolved significantly [1]. The currently favoured model of disease is an epithelial-driven and fibroblast-activated process in which inflammation has an ancillary role that is not yet fully elucidated [2]. More specifically, accelerated parenchymal senescence determined by either telomere dysfunction or genetic defects, together with the concurrent noxious effect of smoking, severely compromise the regenerative potential of parenchymal epithelial stem cells, triggering a cascade of molecular signals and events (scarring, bronchiolar proliferation, abnormal remodelling) leading eventually to epithelial–mesenchymal transition and irreversible lung remodelling [3]. In the non-IPF group of ILDs, inflammation plays the key role, although the two pathogenetic processes have several molecular pathways in common.

The involvement of multiple pathogenetic pathways may account for the heterogeneity of the clinical behaviour of IPF. Some patients experience a slow decline, whereas others decline rapidly and die within a few months from the time of diagnosis. In another patient subset, there are episodes of acute deterioration (“acute exacerbations”) that are associated with a very high short-term mortality [4]. The accurate prediction of the course of IPF is one of the greatest challenges in this field, with major implications for the accurate design of clinical trials.

In 2014, two antifibrotic compounds were licensed for the treatment of IPF. Both pirfenidone and nintedanib slow the rate of progression of disease by 50%, as judged by serial forced vital capacity (FVC) trends [5, 6]. Both drugs are highly pleiotropic, acting on many disease pathways, and this may account for their efficacy across the broad group of IPF patients. By contrast, drugs targeting a single pathway have not proven to be efficacious. The possibility exists that nonpleiotropic agents are beneficial in a small subset of IPF patients, accounting for nonsignificant trends in some trials. However, if so, there is currently no means of identifying key patient subgroups that may respond to targeted therapies.

The desirability of matching individual treatments to the upregulation of key disease pathways in individuals, a need common to all ILDs, underpins growing interest in the concept of personalised medicine (also called precision or stratified medicine). Personalised medicine refers to the medical approach that emphasises the customisation of healthcare, with all decisions and practices tailored to individual patients [7], based on behavioural and environmental factors and genetic and molecular profiles. It is hoped that tailored therapy will improve treatment outcomes, reduce side-effects, prevent unnecessary exposure to ineffective therapies and save money through more efficient use of healthcare resources. The cornerstone of personalised medicine is the identification of biomarkers that can be used to inform diagnosis, prognosis, treatment stratification and/or therapeutic response.

Personalised medicine has already been successfully applied in the field of respiratory medicine. In asthma, the interleukin (IL)-5 monoclonal antibody mepolizumab is more efficacious in reducing severe asthma exacerbations in patients with elevated sputum eosinophils [8, 9]. Personalised medicine has had its greatest impact in oncology. In metastatic breast cancer, the expression of human epidermal growth factor receptor 2 (EGFR2) is associated with benefits from the EGFR2 monoclonal antibody trastuzumab [10]. In nonsmall cell lung cancer, tyrosine kinase inhibitors such as erlotinib, gefitinib and afatinib have increased efficacy in patients with mutations in EGFR [11, 12].

In this review, we summarise current data on behavioural and environmental factors as well as the most promising molecular and genetic biomarkers in ILDs, with specific focus on IPF, and we divide personalised medicine into predictive medicine and preventive/participatory medicine.

**Predictive medicine**

**Molecular biomarkers**

A plethora of molecular biomarkers has been identified (table 1), but we will only focus on the most studied markers. Measurement of those proteins can potentially distinguish separate populations of individuals who have activation of different disease pathways and distinct prognosis.

Elevated serum Krebs von den Lungen (KL)-6 levels have been identified in several ILDs, including IPF, nonspecific interstitial pneumonia (NSIP), hypersensitivity pneumonitis, connective tissue disease associated ILD (CTD-ILD), sarcoidosis and pulmonary alveolar proteinosis (PAP) [13–17]. A serum cut-off value of $\geq 1000$ U·mL$^{-1}$ was associated with poor prognosis in patients with ILD [14]. Baseline KL-6 is significantly higher in patients who developed acute exacerbation of IPF compared with patients with stable IPF [18] and baseline levels of KL-6 are predictive of acute exacerbations of IPF at a cut-off value of $\geq 1300$ U·mL$^{-1}$ after adjustment for disease severity [19]. Longitudinal analysis of serum KL-6 in a small cohort of patients with systemic sclerosis (SSc) showed that rapidly increasing levels of KL-6 were associated with new onset or progressive fibrosis and stable KL-6 levels were associated with stable disease [20]. In a group of CTD-ILD patients treated with cyclophosphamide, serum KL-6 levels decreased...
post-treatment, suggesting a decrease in disease activity despite stability in respiratory physiology [21]. 

Serum KL-6 levels depend on mucin-1 (MUC1) gene polymorphism, which explains the differences in levels between ethnicities [13, 22].

Increased serum surfactant protein (SP)-A and SP-D levels are a strong independent predictor of early mortality in IPF patients in two separate studies [27, 28]. A prediction model using both SP-A and SP-D was superior to a model with one marker alone in an IPF cohort [27]. In SSc-ILD, SP-D levels are more sensitive than SP-A in detecting ILD, as defined by high-resolution computed tomography [29]. SP-D levels correlate negatively with diffusing capacity of the lung for carbon monoxide (D\textsubscript{LCO}) and FVC [30]. Polymorphism in the SP-D gene (\textit{SFTPD}) affects the levels of SP-D [32].

Matrix metalloproteinase (MMP)-7 represents one of the most extensively studied biomarkers in the pathogenesis of IPF. Higher plasma MMP-7 levels correlate with disease severity as measured by FVC and D\textsubscript{LCO} [70], and predict survival in IPF [23]. Furthermore, MMP-7 is a marker of poor prognosis even after

**TABLE 1 Molecular biomarkers**

| Biomarker | Significance | [Ref.] |
|-----------|--------------|--------|
| **Alveolar epithelial cell dysfunction** | Correlation with disease severity (imaging and PFTs); increased levels suggest worse prognosis; higher levels in AE-IPF compared with stable IPF | [13–22] |
| KL-6 | | |
| SP-A, SP-D | Strong predictors of early mortality | [15–17, 20, 23–32] |
| CC16 | | |
| CK18 | | [35] |
| **Immune dysregulation and inflammation** | | |
| CCL18 | Predictor of increased mortality | [24, 36–38] |
| YKL-80 | Predictor of worse outcome | [39–45] |
| CXCL2, CXCL4, CXCL13 | Predictors of worse outcome | [46–51] |
| S100A8, S100A9, S100A12 | Predictors of increased mortality | [52, 53] |
| HSP70, HSP47 | Correlation with baseline PFTs; predictors of worse outcome; HSP47 higher in AE-IPF compared with stable IPF | [54, 55] |
| **Regulatory T-cells** | Association with progressive disease | [56, 57] |
| α-Defensins | Higher in AE-IPF compared with stable IPF | [58, 59] |
| IL-2, IL-12, IL-13, IL-16, IL-17, IL-23 | Correlation with disease activity and baseline PFTs | [60–69] |
| **Extracellular matrix remodelling and fibroproliferation** | | |
| MMP-3, MMP-7, MMP-9, MMP-12 | Correlation with disease severity; predictors of worse outcome | [23, 51, 53, 70–75] |
| LOXL2 | Association with risk of progression and higher mortality | [76] |
| Periostin | Correlation with physiological progression | [77, 78] |
| Fibrocytes | Correlation with PFTs; increased level associated with worse survival | [79–81] |
| Chitotriosidase | Correlation with disease activity in sarcoidosis (PFTs, chest radiography, serum angiotensin converting enzyme) | [82–86] |

KL: Krebs von den Lungen; SP: surfactant protein; CCL: C-C chemokine ligand; YKL-80: secreted chitinase-like protein; CXCL: C-X-C chemokine ligand; HSP: heat shock protein; IL: interleukin; MMP: matrix metalloproteinase; LOXL: lysyl oxidase-like; PFT: pulmonary function test; AE: acute exacerbation; IPF: idiopathic pulmonary fibrosis; ILD: interstitial lung disease.
adjustment for disease severity [53]. MMP-7 plasma levels in IPF have been associated with two single nucleotide polymorphisms in the gene’s promoter region, thus providing a potential genetic contribution to MMP-7 upregulation [53]. MMP-3 is highly upregulated in bronchiolised areas in IPF and peripheral blood MMP-3 levels are predictive of a more rapid decline, independently of disease severity [51]. Recently, analysis from the PROFILE study data has shown that concentrations of protein fragments generated by MMP activity are increased in the serum of IPF patients compared with healthy controls. The rate of change between baseline and 3 months of six neoepitopes was strongly predictive of overall survival, and the increased risk was proportional to the magnitude of change in neoepitope concentrations [71].

Periostin is an extracellular matrix and intracellular protein localised in fibroblasts, and upregulated in fibroblast foci in IPF. IL-13 leads to production of periostin by bronchial epithelial cells. Periostin promotes extracellular matrix deposition, mesenchymal cell proliferation and fibrosis. Lung tissue and serum periostin levels are elevated in IPF and correlate with physiological progression [77, 78].

Serum chitotriosidase is a true chitinase mainly expressed in differentiated and polarised macrophages, and deregulated in granulomatous and fibrotic ILDs. Several studies have shown that this biomarker is associated with disease activity in sarcoidosis as judged by radiographic stage, FVC, DLCO, presence or not of extrapulmonary disease, serum angiotensin converting enzyme and serum IL-2 [82–86]. Although no rigorous comparative analysis has been performed between sarcoidosis biomarkers, one study suggested that chitinase levels were more strongly associated than serum angiotensin converting enzyme levels with active sarcoidosis [86].

Genetic biomarkers
Genetic biomarkers are summarised in table 2.

In 2011, a single nucleotide polymorphism was identified in the promoter region of the mucin 5B (MUC5B) gene (rs35705950), on the short arm of chromosome 11, which was highly associated with both familial pulmonary fibrosis and sporadic IPF, with odds ratios of 6.3 and 8.3, respectively [87]. This genetic variant is present in 31–42% of patients with IPF [88–92]. The associations between MUC5B rs35705950 and short telomere length with extent of fibrosis, histopathological features of usual interstitial pneumonia and reduced survival in patients with chronic hypersensitivity pneumonitis were recently described [93]. No association has been found with SSC-ILD or sarcoidosis [89]. Increasing copies of the MUC5B promoter polymorphism were associated with progression of “interstitial lung abnormalities” (ILAs) [94]. The MUC5B variant is associated with better survival in two separate cohorts of IPF patients, independently of disease severity [97]. In sporadic IPF, survival was not influenced by MUC5B alleles; in familial pulmonary fibrosis, MUC5B minor allele predicted better survival [98] and was associated with a lower pulmonary bacterial burden and, in turn, a better survival [99].

A recent genome-wide association study reported the association of three Toll interacting protein (TOLLIP) gene single nucleotide polymorphisms with pulmonary fibrosis, implicating innate immunity processes in IPF pathogenesis. Interestingly, the minor allele rs5743890_G was protective against the development of IPF, but was associated with increased mortality [91]. A different single nucleotide polymorphism rs3750920 within TOLLIP was associated with a differential response to N-acetylcysteine (NAC) treatment in a retrospective analysis of subjects in the PANTHER trial. While NAC treatment was associated with a significant reduction in a composite end-point risk (defined as death, transplant, hospitalisation or ≥10% FVC decline) in patients with a rs3750920 TT genotype, a nonsignificant increase in end-point risk was seen in patients with a CC genotype [100].

### TABLE 2 Genetic biomarkers

| Gene | Chromosome | Mechanism | [Ref.] |
|------|------------|-----------|--------|
| MUC5B | 11p15 | Encodes glycoproteins in airway mucus | [87–99] |
| TOLLIP | 11p15 | Regulates innate immunity through Toll-like receptors (TLRs) | [91, 100] |
| TERT/TERC | 5p15.33/3q26 | Maintains telomere length | [101–108] |
| TLR3 | 4q25 | Regulates innate immunity | [109, 110] |
| SFTPC | 8p21 | Facilitates surfactant function and transport and innate defence | [111, 112] |
| ABCA3 | 16p13.3 | ATP-binding cassette involved in surfactant production | [113] |
| SFTPA2 | 10q22.3 | Facilitates surfactant function and transport and innate defence | [114] |
| CSF2RA and CSF2RB | Xp22.33, Yp11.2 and 22q12.3 | Reduce granulocyte–macrophage colony-stimulating factor receptor signalling | [115, 116] |
Mutations in both telomerase reverse transcriptase (TERT) and telomerase RNA component (TERC) have been reported in 8–15% of familial pulmonary fibrosis cases, creating a pathogenic link between short telomeres and pulmonary fibrosis [102–104]. Short telomeres are common in sporadic IPF, with ∼25% of patients demonstrating blood leukocyte telomere lengths below the 10th percentile [105]. Blood leukocyte telomere lengths were predictive of transplant-free survival in IPF, independent of conventional markers, but interestingly not in other ILDs [107], and independently associated with worse survival in another IPF cohort [108].

Recently, a specific variant in the Toll-like receptor-3 gene (L412F) was found to be associated with early mortality and accelerated lung function decline in IPF [110]. Mutations in the SP-C gene (SFTPc) are associated with early-onset NSIP, desquamative interstitial pneumonia and PAP [111]. In adults, they are mostly associated with a usual interstitial pneumonia pattern, but NSIP, desquamative interstitial pneumonia or organising pneumonia may also be observed [112]. Abnormalities that severely reduce granulocyte–macrophage colony-stimulating factor receptor signalling, including loss of heterozygosity and a function-altering point mutation in CSF2RA and homozygous CSF2RB mutations, have been identified as the cause of hereditary PAP [115, 116].

The so-called 8.1 ancestral haplotype (human leukocyte antigen (HLA) A*0101: Cw*0701: B*0801: DRB1*0301: DQA1*0501: DQB1*0201), which is common in Europeans, has been associated with the development of sarcoidosis. HLA-B8 and HLA-B7 seem to increase the risk of disease, and a common haplotype in Swedish patients HLA-A*03, B*07, DRB1*15 increases the risk of chronic disease [117]. The strongest associations have been reported with the HLA class II genes, where HLA-DRB1*01 and DRB1*04 are protective, but DRB1*03, DRB1*11, DRB1*12, DRB1*14 and DRB1*15 represent risk factors for sarcoidosis. Interestingly, in African-Americans, HLA-DQB1 and not DRB1 alleles were suggested to be primarily associated with sarcoidosis [118].

HLA genes have also been identified as the strongest genetic risk factor for SSc-ILD. HLA-DRB5*01:05 is a novel risk factor for developing ILD in patients with SSC, being significantly more frequent in SSc patients with ILD than in those without or in healthy controls [119].

Tumour necrosis factor (TNF)-α plays an important role in the pathogenesis of sarcoidosis. TNF-α inhibitors have shown promising results in the treatment of refractory sarcoidosis [120, 121]. The presence of the TNF-α-308A variant allele may identify patients with a favourable response to therapy [122, 123]. Sarcoidosis patients without the TNF-α-308A variant allele (GG genotype) had a three-fold higher response to TNF inhibitors [123].

Decreased peripheral blood mononuclear cell expression of genes involved in the “costimulatory signal during T-cell activation” pathway (including those for CD28, inducible T-cell costimulator (ICOS), lymphocyte-specific protein tyrosine kinase (LCK) and IL-2-inducible T-cell kinase (ITK)) was associated with a shorter transplant-free survival in an IPF cohort. The addition of the gene expression levels of these four genes increased the predictive capacity of a prognostic model compared with one containing solely clinical data (age, sex and FVC %) [124].

A gene set that included downregulation of genes involved in T-cell immune responses was predictive of poor prognosis in IPF, even after adjusting for the composite physiological index [125].

**Epigenetic biomarkers (microRNAs)**

There have been a number of epigenomic studies of microRNA (miRNA) profiles, mostly in IPF. Downregulated miRNAs in IPF lungs include let-7d, miR-29 and the miR-200 family, while upregulated miRNAs include miR-155, miR-21, miR-199 and miR-154 [126, 127].

A panel of miRNAs (miR-302c, miR-423, miR-210, miR-376c and miR-185) in lung biopsies from patients with IPF could differentiate rapid from slow progressors [128]. Selected miRNAs were validated in independent cohorts and appeared to differentiate slow versus rapid progressors. Compared with slow progressors, and in turn with controls, rapid progressors displayed higher circulating miR-21, miR199a-5p and miR-200c, and lower levels of miR-31, let-7a and let-7d [129]. miR-29 is involved in regulation of fibroblast activation. A beneficial effect of intravenously administered miR-29 in the mouse model of pulmonary fibrosis has been demonstrated [130]. miR-29a is strongly downregulated in SSC fibroblasts and skin sections compared with healthy controls [131]. Let-7d miRNA is consistently downregulated in IPF lungs and is believed to play a crucial role in inhibiting epithelial–mesenchymal differentiation [132]. Inhibition of the let-7d family resulted in upregulation of mesenchymal and downregulation of epithelial markers in alveolar epithelial cell lines [133].

**Preventive/participatory medicine**

The role of individual lifestyle in IPF and other ILDs has not been adequately studied. It is well known though that cigarette smoking is one of the most recognised risk factors for the development of IPF and...
smoking cessation campaigns should include this information. The role of diet and exercise could potentially contribute to disease development and progression, but further studies are required.

Factors originating from the external or internal environment also seem to contribute to the pathogenesis of IPF, but they have not been sufficiently explored. More recent work has focused on the interaction between the lung microbiome and the innate immune system, mostly in IPF, highlighting the role of host–environment interaction in disease pathogenesis.

BAL from IPF patients was characterised by a higher bacterial burden and a loss of bacterial species diversity compared with controls. Patients with the highest BAL bacterial burden had the worse survival, independent of disease severity, although no specific microbe was associated with the rate of progression [99]. Specific *Streptococcus* or *Staphylococcus* spp. were associated with more rapid disease progression in patients with IPF [134]. More recently, integrated analysis of the host transcriptome and microbial signatures in IPF patients demonstrated an apparent host response to the presence of an altered or more abundant microbiome. These responses remained elevated in longitudinal follow-up, suggesting that the bacterial communities of the lower airways may act as persistent stimuli for repetitive alveolar injury in IPF [135]. In a pilot study of patients with acute exacerbations of IPF and matched control patients with stable IPF, acute exacerbations of IPF were associated with an increased BAL bacterial burden compared with stable IPF. The bacterial communities of the stable IPF subjects were similar to those found in the airways of healthy individuals as well as subjects with asthma, chronic obstructive pulmonary disease and IPF. Following an acute exacerbation of IPF there was a notable change in the microbiota, with an increase in *Campylobacter* sp. and *Stenotrophomonas* sp., coupled with a significant decrease in *Veillonella* sp. The apparent translocation of bacteria usually confined to the gastrointestinal tract suggests a potential role for aspiration in the development of acute exacerbations [136]. These data suggest that the lung microbiome may serve as a preventive or therapeutic target as well as prognostic biomarker in IPF and potentially other ILD.

The unforeseeable and often rapidly progressive nature of IPF means that patients often have to deal with a number of challenges at different points during the disease course. Therefore, efficient communication between the healthcare professional and the patient is of major importance in helping the patient and their family cope and feel supported in the disease process. Another problem for IPF patients at the stages of diagnosis and treatment is education. Sufficient information should be provided regarding the prognosis and available treatments. Participatory medicine, a patient-centred approach, where the patient has the key role in decision making after sufficient education and communication, should be part of personalised medicine, and the focus of future work and research.

Implications of personalised pathways in appraising historical IPF data

At present, the only treatment data providing direct support for a personalised approach in IPF consist of the analyses showing a differential treatment effect according to *TOLLIP* genotype status [100]. It must be stressed that this study was underpowered and that the findings need to be confirmed. The findings have face and content validity, and can be viewed as establishing “proof of concept”. However, the stimulus to harnessing personalised medicine in IPF and other ILD comes primarily from data in other chronic lung diseases. For this reason, the main body of this review consists of a detailed compilation of candidate biomarkers that might lead to a personalised approach in future. Given these data, findings in historical studies can now be reappraised.

Several IPF treatment trials have been performed based on positive results in pre-clinical studies and early-phase clinical trials that suggested the possibility of benefit. Most did not fulfil expectations. However, increased awareness of personalised medicine has raised the question of whether negative findings reflected the necessarily indiscriminate recruitment of IPF patients, without reference to key pathway signatures.

In some trials a nonstatistically significant benefit on key outcome variables was observed in some patients, whereas there were important discrepancies between key end-points in others. For instance, in the BUILD-1 and -3 studies on bosentan in IPF a weak favourable effect was observed in a subset of patients with regard to progression-free survival [137, 138]. In a study of patients with fibrotic idiopathic interstitial pneumonia (mostly IPF), randomised to receive cotrimoxazole or placebo for 12 months, cotrimoxazole had no effect on individual parameters used clinically to assess efficacy in intention-to-treat analysis (FVC decline, *DlCO*, 6-min walk test or dyspnœa) [139]. After 12 months, however, there was an improvement in quality of life and a reduction in mortality. There are a number of possible explanations for marginal trends and discrepancies between end-points, including chance findings due to the multiplicity of analyses performed across the published literature. However, in both the above examples, it is possible that a subgroup of IPF patients might have been shown to benefit had it been possible to identify them and recruit an enriched cohort.
The first attempt to apply personalised medicine prospectively in an IPF treatment trial was unsuccessful. Lysyl oxidase-like 2 (LOXL2) is a regulator of collagen cross-linking. Higher serum levels in a subgroup of IPF patients were associated with rapidly progressive disease [76]. A recent phase II study of simtuzumab, an anti-LOXL2 monoclonal antibody, was terminated for lack of efficacy (with no difference in progression-free survival between treatment arms) [140]. However, the study design serves as a template for future attempts to apply personalised medicine to IPF interventions.

Variations between trial cohorts in the prevalence of key pathogenetic pathways may also explain the existence of major differences in treatment effects in different trials of the same therapeutic agent. In most trials, pirfenidone has had a major beneficial effect on serial FVC trends. In the one negative study, the placebo arm exhibited a FVC decline that was considerably lower than generally observed in other IPF placebo arms [141]. Again, it can be argued that the study may have been negative because of underrepresentation of patients with key pathways associated with progressive disease. This may be a greater problem in those trials with a numerical imbalance between treatment and placebo arms (e.g. a 2:1 recruitment strategy), with smaller placebo populations cohorts at greater risk of outlying findings.

This concept may also explain major divergences in the reported efficacy of antioxidant therapy in IPF. In the first positive IPF trial, prednisolone, azathioprine and NAC (compared with prednisolone, azathioprine and placebo) was associated with a beneficial effect on FVC and DLCO trends [142]. Although triple therapy was subsequently discredited due to an increased number of deaths and hospitalisations [143], no conclusion could be reached on pulmonary function trends because of the need for early cessation of the triple-therapy arm. Subsequently, the same investigators found no difference in FVC trends between the NAC monotherapy and placebo arms [144]. Although the study was, at first sight, definitively negative, subsequent analyses of the PANTHER cohort (discussed earlier) suggested that a major imbalance in outcomes existed according to TOLLIP status [100]. If this latter finding is confirmed, conflicting findings in historical studies of antioxidant therapy may be seen in a new light. In essence, an inability to apply personalised medicine may have resulted in misleading negative findings in a large IPF cohort, with an averaging of beneficial and adverse treatment effects.

The above examples illustrate the major difficulties that may arise in this complex therapeutic field, if interventions are not evaluated in relation to key pathogenetic pathways or if the wrong pathways are explored. In this regard, it is essential that pathways be chosen not only from pre-clinical data, but also from the validation of biomarker signals in key IPF subgroups. To this point, pathogenetic pathway identification has largely been driven by analyses of selected biomarkers across the whole spectrum of IPF, examined against pulmonary function trends (quantified as continuous variables) and survival (variably adjusted for baseline severity). A potentially fruitful complementary approach is to pre-define criteria for the rapidity of IPF disease progression and to determine which among a great many candidate pathways distinguish most accurately between rapid and slow progressors. For this purpose, the design of the PROFILE study can be seen as an important exemplar.

Another major opportunity lies in long-term studies of ILAs, the subject of several recent large cohort analyses. Much work remains to be done in refining the description of ILAs, which in different cohorts include varying proportions of nondependent ground-glass or reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing and traction bronchiectasis [94, 145–151]. There is a need for an international group to produce guidance to standardise future ILA studies in such a way as to allow underpowered findings in key subgroups to be amalgamated in a definitive evidence base. With reference to IPF, 80% of ILAs in the Framington cohort were found to be subpleural and reticular [94]. Importantly, ILAs and IPF have very similar demographic profiles and a common association with MUC5B rs35705950T positivity [145].

The major difficulty is that the prevalence of ILA in elderly cohorts of 5–7% greatly exceeds the prevalence of IPF. The opportunity lies in the identification of key pathogenetic pathways, operating in the subgroup who ultimately develop IPF [152]. In this regard, the higher plasma galectin-3 levels associated with the presence of ILAs, and with lower lung volumes and DLCO levels, provide proof of concept [153]. ILAs provide a unique opportunity to identify key biomarkers associated with progression to early IPF. In principle, this may allow pivotal upstream pathogenetic pathways to be isolated and to be studied selectively in future attempts to develop a personalised approach in established disease.

Conclusions
ILDs in general, and IPF in particular, are complex disorders with multiple pathogenetic pathways, various disease behaviour profiles and differential responses to treatment, all facets that make personalised medicine a highly attractive concept. At present, no data exist validating a personalised approach in individual diseases. However, the importance of the goal amply justifies the characterisation of genotype
and pathway signatures with a view to refining prognostic evaluation and trial design, with the ultimate aim of selecting treatments according to profiles in individual patients. Some historical trials may have been unsuccessful because interventions that were beneficial in some IPF patients were buried within whole-cohort analyses. It must be acknowledged, based on the very large body of nondefinitive data summarised in the current review, that the way ahead will be difficult. However, the successful application of targeted medicine in other chronic lung diseases should continue to inspire IPF researchers in attempting to transform the field.

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