Where do we go from here? Clinical drug development in idiopathic pulmonary fibrosis

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Efficient IPF drug development is needed to ensure unmet medical need isn't overshadowed by scientific/financial risk http://ow.ly/K0aEv

Despite the recent success of the nintedanib and pirfenidone programmes [1, 2], idiopathic pulmonary fibrosis (IPF) remains a high-risk disease area for drug development. There are no adequate preclinical models in which to test potential compounds, and no established early clinical development pathway on which to make quick decisions regarding potential efficacy [3]. The historical approach in IPF of moving compounds directly from phase 1 safety and tolerability studies into large phase 2 studies with clinical end-points required major commitments from sponsors and research subjects. Now, with effective therapies reducing the frequency and responsiveness of clinical end-points, sponsors may decide that IPF is too costly a disease to invest in.

IPF needs a more efficient and informative early clinical development pathway. The innovative study by Wilkes *et al.* [4], published in this issue of the *European Respiratory Journal*, describing the phase 1 results of oral immunotherapy with type V collagen in patients with IPF illustrates one such approach. This study is worth careful consideration, both for the novelty of its potential therapy and for the approach it takes to three core study design issues.

Issue 1: which mechanism to target

Most therapies under clinical development for the treatment of IPF target collagen production, the most salient (but also the most terminal) event in IPF pathobiology [5]. Less attention has been given to upstream events, and for good reason as the aetiology of IPF appears complex and heterogeneous, and knowing where to focus one's efforts has been a major challenge.

There is a growing consensus that IPF represents a disease of alveolar epithelial cell dysfunction, and that this dysfunction leads to a profibrotic microenvironment in the lung [6]. There are many ways in which alveolar epithelial cell dysfunction may occur, including age-related senescence, genetic predisposition, inhalational exposure and autoimmunity. All of these areas represent potential upstream targets for novel therapeutics. Wilkes *et al.* [4] demonstrate that clinical research using cohorts of carefully phenotyped patients with accompanying biological samples can identify a plausible target, in this case autoimmunity against collagen V, with a potential therapeutic intervention. We need more of these types of programmes that use clinical and biological data from patients with IPF to identify potential aetiological pathways and test compounds that may modify them.

Issue 2: which patients to enrol

Cohort enrichment has been a hot topic in IPF clinical trial design. Most of the discussion has been about "prognostic" cohort enrichment, or the identification of patients more likely to experience an outcome of

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interest (*e.g.* decline in forced vital capacity (FVC)). Little attention has been given to "predictive" cohort enrichment, or the identification of patients more likely to respond to a specific therapy [7]. Predictive enrichment is central to the concept of precision (or stratified) medicine, an approach that promises more targeted and effective treatments for conditions like IPF that may encompass multiple distinct pathobiological subgroups [8].

Wilkes *et al.* [4] use a precision medicine approach to identify a sizable subgroup of IPF patients with elevated autoantibody levels to collagen V and hypothesise that therapy directed at modulating the immune response to collagen V will preferentially benefit these patients. Importantly, this early stage study provides no proof of this hypothesis, and there is a danger of false dichotomisation in precision medicine that deserves careful consideration. Nonetheless, predictive cohort enrichment has been transformative in developing therapies for other pulmonary diseases like lung cancer and cystic fibrosis, and it is worth further study in IPF. It may be particularly relevant when developing compounds focused on upstream targets, like autoimmunity against type V collagen, where heterogeneity in pathobiological pathways may be more clinically relevant.

Issue 3: which end-points to measure

While appropriate end-point selection for late stage efficacy trials in IPF has been widely discussed [9, 10], a more central challenge to clinical drug development has been finding efficient, informative end-points for early phase clinical trials. The default end-point has been change in FVC, but this is a relatively unresponsive end-point requiring hundreds of patients followed over many months to adequately power [11]. Molecular biomarkers promise smaller, faster and cheaper early phase trials by providing more rapidly responsive end-points, but widely accepted molecular biomarkers of IPF disease activity and/or progression remain unavailable [12].

Wilkes *et al.* [4] incorporate molecular biomarkers into their study, including matrix metalloproteinase 7, serum albumin, and anti-collagen V antibody-bound C1q, a mechanistic biomarker. The more effective oral immunotherapy with type V collagen is in reducing anti-collagen V antibody activity, the less C1q should be bound by anti-collagen V antibodies in the serum. Mechanism specific molecular biomarkers may prove most useful for early phase clinical drug development, as they directly reflect the impact of a compound on the biological process of interest. Indeed, it was the mechanistic marker anti-collagen V antibody-bound C1q that showed the most consistent results. Although not statistically significant, C1q binding appeared to be reduced by oral immunotherapy in a dose-dependent manner, and 24-week change in C1q binding appeared correlated with 24-week change in FVC [4].

Molecular biomarkers (in particular mechanistic molecular biomarkers) add an important dimension to the early clinical assessment of potential compounds and warrant consideration as primary end-points in phase 2 trials given their efficiency and responsiveness. Ultimately, sponsors will need to decide if early phase clinical trials designed around molecular biomarker end-points provide sufficient evidence of efficacy to justify investing in definitive phase 3 trials using clinical end-points.

The challenge for all of us moving forward is making IPF clinical drug development efficient enough so that the still substantial unmet medical need is not overshadowed by scientific and financial risk. There are many ways in which the IPF community can work with sponsors to improve clinical trial efficiency, which at their core will involve thoughtfully addressing the three study design issues posed in this editorial. If drug developers target relevant pathways and design trials around cohorts and end-points that enhance the likelihood of detecting a reliable signal in small sample sizes, potential compounds can be studied more quickly and cheaply and "go/no go" decisions can be made more intelligently. Wilkes *et al.* [4] have done the field a service by conducting a trial that identifies a promising new therapy using a forward-thinking study design, and it is hoped that future clinical drug development programmes in IPF will look to this study as a model.

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