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EDITORIAL

The European IPF Network: towards better care for a dreadful disease

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Idiopathic pulmonary fibrosis (IPF) is one of the most aggressive forms of diffuse parenchymal lung disease (DPLD) and probably affects up to 340,000 people in Europe and North America [1]. Despite extensive research over the past 25 yrs, considerable investment in controlled clinical trials, and significant progress in defining appropriate outcome measures and surrogates of disease progression, IPF remains a progressive and invariably fatal disease with a mean survival of ~3 yrs from diagnosis.

With the exception of pirfenidone [2], which is now on the way of being approved in Europe, and N-acetylcysteine [3], which has shown some signs of therapeutic efficacy in IPF, no other investigational agents, including bosentan [4], imatinib [5] and interferon-γ [6], have proven to be beneficial in phase III studies performed over the last decade. IPF, therefore, remains a dismal disease for which new effective therapeutic approaches are urgently needed. Despite this, we would argue that there is much cause to be optimistic in terms of the current climate for scientists and clinicians striving to develop novel therapeutic strategies for this devastating disease. The last 5 yrs or so have seen major advances, including the definition of novel paradigms of disease pathogenesis and the discovery of novel biomarkers. Pharmaceutical interest and investment from both academia and industry are at unprecedented levels. We must, however, be careful to heed the lessons we have learned from our past experience.

WHY HAVE SO MANY TRIALS IN IPF FAILED AND WHY HAVE THERE BEEN NO MAJOR BREAKTHROUGHS IN THE TREATMENT OF IPF?

There are many possible answers to these important questions. First, we need to deconstruct the way IPF has been approached in terms of controlled clinical trials. Most of the trials conducted to date were based on an ''opportunistic approach'', using drugs or investigational compounds developed for other disease indications rather than agents which emerged from a systematic programme for the development of novel drugs, aimed specifically at IPF and other DPLDs. Had the mechanism of action of drugs already developed for other indications been relevant to IPF pathogenesis, such an approach might have led to rapid success, with the costs for establishing a new therapy for IPF much reduced compared with the development of completely new agents. However, in the face of many failed trials, IPF researchers working in both academia and industry are now faced with the realisation that this approach is unlikely to yield a much needed new therapy for this disease.

For many years, the arduous task of deciphering the pathogenic mechanisms of IPF with the view of identifying novel targets for therapeutic intervention was confined to academic groups working somewhat in isolation. This situation has now changed considerably over the last 3 yrs with the establishment of IPF research networks in both the USA and in the European Union (EU), coupled with unprecedented resources being diverted to pre-clinical IPF research and development by a number of major pharmaceutical and biotech companies.

Another potential reason for the relative lack of progress in developing novel strategies may lie in the inherent challenges of IPF in terms of both the nature of the disease and our understanding of IPF pathogenesis. We may also have given too much credence to poorly predictive models and flawed paradigms of the disease. A point in case for the latter is epithelial necrosis. This phenomenon was first described in an original paper by MYERS and KATZENSTEIN [7] in 1988, but it took the IPF research community far more than a decade to accept the concept that IPF may be an epithelium-driven disease. In terms of animal models, we are now increasingly aware that studies performed in the commonly used bleomcyin model need to be interpreted with caution. It is now clear that concepts developed in mice may not be valid in humans and that drugs that work in the bleomycin model will not necessarily work in IPF [8]. There is no doubt that animal models have yielded novel insights into potentially relevant pathogenic mechanisms and will continue to do so. Translating these findings to the clinic will, however, require careful pre-clinical study design (*i.e.* based on therapeutic rather than prophylactic dosing) and, most importantly, validation of the potential relevance of findings using patient-derived biomaterial, tissues and cells. Due to the fact that we are dealing with a relatively rare disease, access to patient material from large patient cohorts and biobanks remains a major challenge for IPF researchers. Access to larger collections of IPF-related materials, especially lung tissue from well defined IPF subjects is currently limited to the biggest sites, or in the frame of consortia, such as the American Lung Tissue Research Consortium.

A final potential reason for the relative lack of progress in IPF treatment, at least in Europe, is the obvious lack of strong

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patient advocacy groups that help to better and systematically define patient needs and bring awareness of the disease at both government and societal levels. At the time of diagnosis, most IPF subjects may already be too sick to engage with of such honorary offices. The Coalition for Pulmonary Fibrosis in the USA may serve as an example for an alternative approach. Here, IPF medical experts allied themselves with patients to build up an advocacy group.

WHAT ARE POSSIBLE SOLUTIONS TO THIS DILEMMA?

In the USA, the National Insitutes of Health have provided substantial funding for the US IPFnet (www.ipfnet.org), the aim of which is primarily to conduct clinical trials [9]. Such an approach needs to be commended, and there is no doubt that the US IPFnet will perform pivotal studies, and greatly expand and influence our knowledge and clinical management of IPF. As the number of sites is restricted, the US IPFnet cannot expand, but is currently seeking to set up closer communication and cooperation with other IPF clinical experts. Although the primary remit of this network is not aimed at conducting basic research, many of the clinicians involved in IPFnet are from sites with strong basic research activities, thus enabling transfer of novel findings from bench to bedside.

Based on funding through the 7th Framework Programme, the EU is currently supporting the European IPF Network (eurIPFnet) with a slightly different concept (www.pulmonary-fibrosis.net) [10]. The eurIPFnet is primarily a translational network, with the remit of deciphering the natural course and molecular pathogenic mechanisms of IPF in order to develop future novel therapeutic strategies. Apart from the basic and translational research, over the last few months, the eurIPFnet has implemented a European-wide, internet-based patient registry (eurIPFreg) and biobank (eurIPFbank) of IPF and other idiopathic interstitial pneumonias (IIPs), allowing a precise description of the natural course and its dependence on environmental factors and respiratory comorbidities, as well as enabling access to IPF biomaterials for investigators involved in IPF research. Since the opening of the registry 1 yr ago, 300 IPF subjects have already been entered into the registry.

The eurIPFreg is a truly internet-based and highly secure registry, which has been granted full ethics committee approval in Germany, France, Italy and the UK, and fulfills all aspects of data safety. Patient and physician questionnaires include all relevant and encrypted information on patient history and all important medical data, the registry and biobank also allows upload and storage of high-resolution computed tomography scans, biomaterials, and internet-based and secure access to fully digitalised histological slides. Each new case entered into the registry undergoes diagnosis verification by an external, independent, interdisciplinary expert panel.

We feel that the eurIPFreg could be the nucleus of a new wave of translational research activity in Europe, which would greatly be enhanced by the inclusion of other European respiratory/IPF centres. Apart from entering cases and biomaterials, the eurIPFreg also welcomes initiatives from participating colleagues to define and submit their own projects within the frame of the eurIPFreg. In addition and most importantly, the eurIPFreg may also serve as a platform for patient recruitment into clinical trials. We strongly believe that the eurIPFreg has the real potential to change the landscape in IPF and other IIPs. By partnering across Europe on the basis of well-defined conditions of collaboration, by interacting with clinicians and basic researchers in the network and in virtual and real conferences, and by aligning our research strategies in a coordinated and complementary fashion, we are hopeful that we will be successful in truly making a difference to the lives of those that need our help most: our patients.

To register your interest please visit our homepage (www.pulmonary-fibrosis.net/index.php?option=com_fabrik&view=form&fabrik=4&random=0&Itemid=18) or contact us directly *via* info@pulmonary-fibrosis.net

STATEMENT OF INTEREST

None declared.

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