simple intervention can improve cessation in other populations.

Does spirometric screening work? For this group of men from Poland, the answer—with regard to increasing smoking cessation—appears to be a qualified yes. Those of us interested in decreasing the most preventable cause of death and disease in the developed world now have a road map to help us design studies for implementation in our own populations.

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IL-10 and IPF

IL-10: another therapeutic target in idiopathic pulmonary fibrosis?

A B Millar

The need for appropriately designed clinical trials in IPF

These are exciting and hopeful times for those involved in the treatment of idiopathic pulmonary fibrosis (IPF). Despite the ever expanding wealth of cellular and molecular biology, translation into clinical trials for IPF has been limited.¹ However, in the last 2 years results on three potential therapeutic agents have been published, albeit with limited benefit, with others imminent.^{2–4} The study by Nakagome *et al*⁵ in this issue of *Thorax* gives further support to the concept of interleukin (IL)-10 as an additional biological therapeutic agent.

In the last 20 years the ability of the scientific community to analyse the biological interactions between cells has led to an information explosion. This has been exemplified by the analysis of cytokine (and growth factor) networks.⁶ Typically, the initial identification of a protein is followed by its receptor(s), its inhibition or induction by lipopolysaccharide and dexamethasone, and then a cascade of publications on interactions with other biologically active proteins. Unfortunately for the lung biologist, despite its relative inaccessibility, the unique role of the lung makes the requirement for cell and

organ specificity even more crucial than in other tissues when dissecting these networks. This is exemplified by the constitutional secretion of the anti-inflammatory IL-10 by human lung alveolar macrophages, contrasting with tissue macrophages from other organ sites.⁷

In vitro or ex vivo studies of individual cytokines and growth factors lead to the identification of molecules with potential useful biological activity. In the case of IL-10, it was identified as an anti-inflammatory agent.⁸ In the context of the lung, IL-10 has been shown to be expressed by alveolar macrophages constitutionally and stimulated by lipopolysaccharide, both directly and indirectly by tumour necrosis factor (TNF)—effectively controlling inflammation in a homeostatic feedback loop. Its role in inflammation has been explored in a number of inflammatory conditions including sarcoidosis, asthma, and acute respiratory distress syndrome (ARDS).^{9–11} Similar studies in IPF have been limited and conflicting.^{12–13} This may be related to the change in view of IPF from a condition with an inflammatory basis to that of “dysregulated repair” based on the epidermo-mesenchymal unit.¹⁴

The latter view of IPF has led to a much greater focus on fibroblast function and fibrogenic cytokines, in particular transforming growth factor (TGF)- β . This cytokine has been shown to induce fibroblast proliferation, chemotaxis, and collagen production.¹⁵ In the context of IPF, it is mainly produced by the alveolar macrophages and expressed in fibroblastic foci.¹⁶ There is a paucity of studies on the potential interaction between IL-10 and TGF- β , but some recent work has suggested potential interactions.¹⁷ All such studies are limited by the isolation of cells from the tissue milieu, albeit facilitating clear cut answers. The evaluation of animal models of disease provides an alternative method of investigation.

Nakagome *et al*⁵ have used the bleomycin mouse model for their work, recognising its limitations—in particular the observation that fibrosis can resolve with withdrawal of bleomycin, in contrast to the human condition. A significant number of potential biological treatments have previously been shown to ameliorate fibrosis in this model, including TGF inhibition.^{18–19} However, in such studies the agent has been given either prior to or synchronously with the inducing agent. In the well controlled study by Nakagome *et al* the administration of IL-10 2 weeks after induction led to amelioration of fibrosis. This is a crucial finding for a condition such as IPF in which presentation is invariably that of established disease. The authors used an intravenously delivered IL-10 plasmid which resulted in increased systemic production of IL-10 perfusing all organs and was shown to be increased in the lung. The use of genetically modified animals has been a further step forward for this type of

work, and undoubtedly the next step will be to use a model with lung specific inducible IL-10 production.

The paucity of treatments for IPF means that there is a pressing need for identification of therapeutic targets and translational studies. Some agents have come through the process and, for both patients and those involved in their care, this gives hope. It seems that there is increased interest within the pharmaceutical industry which is welcome. However, the prolonged administration of a potent anti-inflammatory agent such as IL-10 would need to be carefully considered in pulmonary disease, as exemplified by TNF inhibition. TNF inhibition has been used in rheumatoid arthritis with excellent effect²⁰ but, nevertheless, it has been associated with both a risk of infection and inflammatory pneumonitis within the lung.^{21 22} The precise mechanisms responsible for these events remain unclear, but may well reflect disruption of the lung's tightly controlled homeostatic host defence mechanisms. The anti-fibrogenic effect of IL-10 may reflect the fact that tissue repair occurs both as part of maintenance and in response to injury.²³

Whatever the outcome for IL-10, translation into clinical trials of treatment is the ultimate goal. The recent tranche of such trials shows the readiness of patients to be involved. It remains the responsibility of the wider community to ensure that they fulfil their purpose by appropriate design.

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