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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## REFERENCES

1 **Petty TL**. Benefits of and barriers to the widespread use of spirometry. *Curr Opin Pulm Med* 2005;**11**:115–20.
2 **Pauwels RA**, Buist AS, Calverley PM, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) workshop summary. *Am J Respir Crit Care Med* 2001;**163**:1256–76.
3 **Mannino DM**, Ford ES, Redd SC. Obstructive and restrictive lung disease and functional limitation: data from the Third National Health and Nutrition Examination. *J Intern Med* 2003;**254**:540–7.
4 **Celli BR**, Cote CG, Marin JM, *et al*. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;**350**:1005–12.
5 **Mannino DM**, Buist AS, Petty TL, *et al*. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. *Thorax* 2003;**58**:388–93.
6 **Mannino DM**, Aguayo SM, Petty TL, *et al*. Low lung function and incident lung cancer in the United States: data From the First National Health and Nutrition Examination Survey follow-up. *Arch Intern Med* 2003;**163**:1475–80.
7 **Eaton T**, Withy S, Garrett JE, *et al*. Spirometry in primary care practice: the importance of quality assurance and the impact of spirometry workshops. *Chest* 1999;**116**:416–23.
8 **Wilt TJ**, Niewoehner D, Kim C, *et al*. Use of spirometry for case finding, diagnosis, and management of chronic obstructive pulmonary disease (COPD). *Evid Rep Technol Assess (Summ)* 2005:1–7.
9 **Bednarek M**, Gorecka D, Wielgomas J, *et al*. Smokers with airway obstruction are more likely to quit smoking. *Thorax* 2006;**61**:869–73.
10 **Segnan N**, Ponti A, Battista RN, *et al*. A randomized trial of smoking cessation interventions in general practice in Italy. *Cancer Causes Control* 1991;**2**:239–46.
11 **Risser NL**, Belcher DW. Adding spirometry, carbon monoxide, and pulmonary symptom results to smoking cessation counseling: a randomized trial. *J Gen Intern Med* 1990;**5**:16–22.

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 lipopolysaccaride 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 effect[20] 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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## REFERENCES

1 **Millar A**. Anti-cytokine therapy in fibrosing alveolitis: where are we now? *Respir Res* 2000;**1**:3–5.
2 **Raghu G**, Brown KK, Bradford WZ, *et al*. A placebo-controlled trial of interferon gamma-1β in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2004;**350**:125–33.
3 **Azuma A**, Nukiwa T, Tsuboi E, *et al*. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2005;**171**:1040–7.
4 **Demedts M**, Behr J, Buhl R, *et al*. High-dose acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med* 2005;**353**:2229–42.
5 **Nakagome K**, Dohi M, Okunishi K, *et al*. In vivo IL-10 gene delivery attenuates bleomycin induced pulmonary fibrosis by inhibiting the production and activation of TGF-β in the lung. *Thorax* 2006;**61**:886–94.
6 **Gouwy M**, Struyf S, Proost P, *et al*. Synergy in cytokine and chemokine networks amplifies the inflammatory response. *Cytokine Growth Factor Rev* 2005;**16**:561–80.
7 **Armstrong L**, Jordan N, Millar A. Interleukin 10 (IL-10) regulation of tumour necrosis factor alpha (TNF-α) from human alveolar macrophages and peripheral blood monocytes. *Thorax* 1996;**51**:143–9.
8 **Moore KW**, de Waal MR, Coffman RL, *et al*. Interleukin-10 and the interleukin-10 receptor. *Annu Rev Immunol* 2001;**19**:683–765.
9 **Bingisser R**, Speich R, Zollinger A, *et al*. Interleukin-10 secretion by alveolar macrophages and monocytes in sarcoidosis. *Respiration* 2000;**67**:280–6.
10 **Lim S**, Caramori G, Tomita K, *et al*. Differential expression of IL-10 receptor by epithelial cells and alveolar macrophages. *Allergy* 2004;**59**:505–14.
11 **Armstrong L**, Millar AB. Relative production of tumour necrosis factor alpha and interleukin-10 in adult respiratory distress syndrome. *Thorax* 1997;**52**:442–6.
12 **Martinez JA**, King TE Jr, Brown K, *et al*. Increased expression of the interleukin-10 gene by alveolar macrophages in interstitial lung disease. *Am J Physiol* 1997;**273**(3 Pt 1):L676–83.
13 **Freeburn RW**, Armstrong L, Millar AB. Cultured alveolar macrophages from patients with idiopathic pulmonary fibrosis (IPF) show dysregulation of lipopolysaccharide-induced tumor necrosis factor-alpha (TNF-α) and interleukin-10 (IL-10) inductions. *Eur Cytokine Netw* 2005;**16**:5–16.
14 **Selman M**, Thannickal VJ, Pardo A, *et al*. Idiopathic pulmonary fibrosis: pathogenesis and therapeutic approaches. *Drugs* 2004;**64**:405–30.
15 **Bartram U**, Speer CP. The role of transforming growth factor beta in lung development and disease. *Chest* 2004;**125**:754–65.
16 **Broekelmann TJ**, Limper AH, Colby TV, *et al*. Transforming growth factor beta 1 is present at sites of extracellular matrix gene expression in human pulmonary fibrosis. *Proc Natl Acad Sci USA* 1991;**88**:6642–6.
17 **Taylor A**, Verhagen J, Blaser K, *et al*. Mechanisms of immune suppression by interleukin-10 and transforming growth factor-beta: the role of T regulatory cells. *Immunology* 2006;**117**:433–42.
18 **Giri SN**, Hyde DM, Hollinger MA. Effect of antibody to transforming growth factor beta on bleomycin induced accumulation of lung collagen in mice. *Thorax* 1993;**48**:959–66.
19 **Wang Q**, Wang Y, Hyde DM, *et al*. Reduction of bleomycin induced lung fibrosis by transforming growth factor beta soluble receptor in hamsters. *Thorax* 1999;**54**:805–12.
20 **Elliott MJ**, Maini RN, Feldmann M, *et al*. Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor alpha. *Arthritis Rheum* 1993;**36**:1681–90.
21 **Gomez-Reino JJ**, Carmona L, Valverde VR, *et al*. on behalf of the BIOBADASER Group. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may preolispose to significant increase in tuberculosis risk: a multicenter active surveillance report. *Arthritis Rheum* 2003;**48**:2122–7.
22 **Zimmer C**, Beiderlinden M, Peters J. Lethal acute respiratory distress syndrome during anti-TNF-alpha therapy for rheumatoid arthritis. *Clin Rheumatol* 2006;**25**:430–2.
23 **Kitani A**, Fuss I, Nakamura K, *et al*. Transforming growth factor (TGF)-beta$_1$-producing regulatory T cells induce Smad-mediated interleukin 10 secretion that facilitates coordinated immunoregulatory activity and amelioration of TGF-beta$_1$-mediated fibrosis. *J Exp Med* 2003;**198**:1179–88.