

**MEK/ERK INHIBITORS:  
A PROOF-OF-CONCEPT STUDY IN LUNG FIBROSIS**

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**ABSTRACT**

**There is no therapy for chronic fibroproliferative diseases, in spite of the fact that current health statistics suggest that these (which include cardiovascular disease, pulmonary fibrosis, diabetic nephropathy, liver cirrhosis and systemic sclerosis) have been estimated to cause approximately 45% of the deaths in the developed world. Recently, many studies have shown that mitogen activated protein kinases (MAPKs) are activated in response to fibrogenic agents and contribute to the formation and function of the myofibroblast, the critical cell type responsible for excessive scarring. A recent report (Madala SK, Schmidt S, Davidson C, Ikegami M, Wert S, Hardie WD. Am J Respir Cell Mol Biol. 2011 Oct 20. [Epub ahead of print]) has provided a proof-of-concept study showing that the specific MEK inhibitor ARRY-142886 (ARRY) can both suppress the progression of fibrosis and reverse an animal model of lung fibrosis. Thus MEK inhibition could be a valuable method to treat lung fibrosis.**

TGF $\beta$  induces fibrogenic responses through the canonical Alk5/Smad3/4 pathway; yet, the MAPK cascade, including the ras/MEK/ERK pathway are also involved (Leask 2010; Chen et al., 2005). In particular, TGF $\beta$  induces (for example) CCN2, matrix contraction

and collagen expression (Leask et al., 2003; Chen et al., 2005, 2008, 2011; Wang et al., 2006; Samuel et al., 2010). Moreover, the compound iloprost, which has some antifibrotic ability in vivo and in vitro blocks TGF $\beta$ -induced ERK activation (Stratton et al., 2001, 2002; Zhu et al., 2010; Stratton and Newton, 2010). The transcription factors that act downstream of ERK appear to be ets-1 and Smad 1 (Pannu et al., 2007; van Beek et al., 2006; Mott et al., 2011).

Recent evidence has shown that ERK activation is increased in the bleomycin model of lung fibrosis and PD98059 blocks the fibrosis observed (Galuppo et al., 2011). Moreover, in a separate model of fibrosis, in which TGF $\alpha$  is overexpressed by lung epithelia using a doxycycline-dependent system, ERK is also activated; a novel MER inhibitor ARRY-142886 (ARRY) was both able to prevent the onset of fibrosis as well as to reverse established fibrosis (Madala et al., 2011), including TGF $\alpha$ -induced lung cell proliferation and matrix gene production.

It is interesting to note that TGF $\beta$ -induced CCN2 expression depends on ERK (Stratton et al., 2002; Leask et al., 2003). Moreover, CCN2-dependent fibrosis also relies on ERK (Ponticos et al., 2009; Sonnylal et al., 2010; Nakerakanti et al., 2011). Although the following specific hypothesis was not evaluated in the recent studies using ERK inhibitors, it is plausible that ERK inhibition may prevent fibrosis by blocking the action of CCN2 in vivo.

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