Repositioning compounds from cancer drug discovery to IPF: PI3K inhibition

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Idiopathic pulmonary fibrosis (IPF) is a fatal interstitial lung disease that presents with a 5-year survival of 20–30%, hence with a mortality rate as high as many aggressive cancer types.[1] According to a current analysis by the British Lung Foundation, the incidence of IPF in the UK has long been underestimated (https://www.blf.org.uk/). In addition, a recent systematic review shows that IPF incidence rates have increased worldwide.[2] Two recently approved treatments for IPF, pirfenidone and nintedanib, have been shown to decelerate lung function decline in IPF, but do not halt disease progression or cure the disease.[3 4] Hence, there is a clear need for novel therapeutic strategies, which manifests in (at time of writing) 46 registered interventional clinical studies for IPF (http://clinicaltrials.gov) and a continued quest for novel drug targets by the scientific community, fuelled by an increased understanding of IPF pathogenesis.[5] Considering the substantial pathological heterogeneity of IPF and the multitude of dysregulated signalling pathways,[6] it is likely that a successful cure of IPF will involve not a single, but several active agents, specifically targeting different pathomechanistic aspects of IPF.

With de novo drug development being an expensive and time-consuming process, it seems highly sensible to examine whether effective treatment for other disease entities with significant pathomechanistic overlap with IPF is suitable for IPF therapy as well. Notably, repositioning of drugs can shorten drug development time by >50% as phases like chemical optimisation, safety assessment or pharmacokinetic (PK) profiling can be bypassed.[7] In this context, several recent studies and reviews have highlighted similarities between IPF and cancer, including genetic and epigenetic changes, activation of migration and invasion, altered responses to growth stimuli or suppressors, an inflammatory component and dysregulated signalling pathways.[8–11] Notably, nintedanib was originally developed for anticancer treatment and has proven effectiveness in several oncology clinical trials prior to its approval for IPF therapy, clearly supporting this concept.[12] Wouldn't it be reasonable, therefore, to evaluate potential overlaps between cancer and IPF and choose novel approaches for therapeutic intervention based on such similarities?

Mercer *et al*[13] propose the novel antitumour agent GSK2126458, a pan-class I phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) inhibitor, as a therapeutic agent for IPF. Following activation via tyrosine kinases and/or G protein-coupled receptors, PI3Ks generate the lipid second messenger phosphatidylinositol-3,4,5-trisphosphate ($PtdIns(3,4,5)P_3$), which coordinates localisation of multiple signalling molecules with a Pleckstrin homology domain, most importantly Akt, at the plasma membrane.[14] The oncogene *PIK3CA*, which encodes p110α, one of the four class I PI3K catalytic subunit isoforms, and the tumour suppressor gene *PTEN* (encoding the major $PtdIns(3,4,5)P_3$ phosphatase) are among the most frequently mutated genes in cancer. Accordingly, activation of PI3K represents a central node in oncogenic signalling, which has prompted extensive studies on targeting the PI3K signalling pathway for cancer therapy.[15] The mTOR, part of the two multiprotein complexes TORC1 and TORC2, constitutes a major player in the PI3K pathway, acting both upstream and downstream of Akt.[15] Recent reports have provided evidence that PI3K signalling is also activated in IPF and that its inhibition attenuates transforming growth factor-β-induced fibroblast proliferation and differentiation to myofibroblasts in vitro[16 17] as well as pulmonary fibrosis in vivo.[18]

In this context, the authors set out to evaluate the scientific rationale for PI3K/mTOR inhibition in IPF and test the efficiency of GSK2126458 in cells and precision-cut lung tissues from patients with IPF. Since PK data from a phase I trial of GSK2126458 in subjects with solid tumours or lymphoma (NCT00972686) were surfacing, the authors carried out a comprehensive set of in vitro inhibition studies in IPF fibroblasts, carefully determining IC50 values for Akt phosphorylation and proliferation. The integration of these two data sets, the PK data from the ongoing trial and the gathered in vitro data using the described functional readouts, is a major strength of this study as it allowed the authors to deduce a dosing framework, which should ensure safe and effective target engagement in the lungs of patients with IPF. Hereby, Mercer *et al*[13] not only paved the way for an IPF proof-of-mechanism study (NCT01725139), but provided a generally valid roadmap for how to evaluate the potential of drug repositioning at the early clinical trial stage, and the authors should be lauded for this effort.

To date, access to lung tissue from patients with IPF is becoming increasingly limited, and as such, monitoring drug pharmacodynamics and treatment efficacy during IPF clinical trials will be a continuous challenge. In this context, the authors suggest the use of cells obtained by bronchoalveolar lavage, which mostly consist of alveolar macrophages, as a relatively easily accessible pharmacodynamic biosensor.[13] Even if (myo-)fibroblasts and bronchial/alveolar epithelial cells, and not macrophages, represented the main target cell type for IPF pathogenetic research approaches in the past, this appears as a compelling way to assess whether a drug reached the target tissue and affected resident lung cells.

There are four class I PI3K isoforms termed PI3Kα, PI3Kβ, PI3Kγ and PI3Kδ, which are heterodimers consisting of a catalytic subunit (p110α, p110β, p110γ or p110δ) and a regulatory subunit. Targeting all four class I PI3K isoforms in addition to mTOR, GSK2126458 displays relatively broad target specificity. Clearly, this provides both advantages and disadvantages compared with a single-target approach. On the one hand, compounds with broad substrate specificity frequently require higher doses and are more likely to produce unpredictable off-target effects.[14] Also, from a mechanistic point of view, the use of this inhibitor makes it impossible to dissect the relative contribution of class I PI3K isoforms or mTOR inhibition to the observed effects. On the other hand, it has been reported that class I PI3Ks show considerable functional redundancy, at least in haematopoietic cells, which argues for the use of pan-class I PI3K inhibitors in the context of haematopoietic malignancies.[19] Also, many patients exhibit IPF and lung cancer and,

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irrespective of disease-specific isoform involvement, in these cases a pan-class I PI3K inhibitor might kill two birds with one stone.[20] Furthermore, the PI3K-Akt-mTOR pathway encompasses a sophisticated negative feedback system emphasising the potential need to hit more than one node in the network. To date, however, no evidence for functional redundancy of PI3K enzymes in IPF has been reported. In contrast, Conte *et al*[16 17] have provided evidence that the isoform p110γ plays a central role in fibroblast proliferation and myofibroblast differentiation in IPF. Also, although inhibition of mTOR has been shown to counteract profibrotic gene expression and protect from pulmonary fibrosis,[21 22] results from clinical trials have provided evidence that mTOR inhibition might actually induce interstitial lung disease.[23] Hence, the current data do not unequivocally justify the application of a pan-class I PI3K/mTOR inhibitor in isolated IPF, but offer hope that it will help in select cases.

In conclusion, in light of an unabated need for novel IPF treatment options and the recently accumulated evidence for remarkable similarities between lung cancer and IPF pathogenesis, Mercer *et al* put forward an intriguing novel concept for future drug repositioning from early-stage clinical cancer trials for IPF. Undoubtedly, more studies are warranted to decipher the relative contribution of the different PI3K isoforms and mTOR to IPF pathogenesis, address the possibility of isoform-specific targeting of PI3K for IPF treatment and critically examine the efficacy of mTOR inhibition versus its adverse pulmonary effects.

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Staab-Weijnitz CA, Eickelberg O. *Thorax* 2016;**71**:675–676.

Published Online First 15 June 2016

▶ http://dx.doi.org/10.1136/thoraxjnl-2015-207429

Thorax 2016;**71**:675–676.
doi:10.1136/thoraxjnl-2016-208680

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