Better to Be an Agnostic than a Believer (at Least in Pulmonary Fibrosis)

Time flies: almost a decade ago the results of the INPULSIS (Safety and Efficacy of BIBF 1120 at High Dose in Idiopathic Pulmonary Fibrosis Patients) and ASCEND (Efficacy and Safety of Pirfenidone in Patients With Idiopathic Pulmonary Fibrosis) trials revolutionized the world of pulmonary fibrosis, leading to the worldwide approval of the first two antifibrotic drugs for the treatment of idiopathic pulmonary fibrosis (IPF) (1, 2). However, the gold rush of the scientific community to discover new, safe, and effective therapies for IPF has continued ever since. A next generation of molecules have been (or are currently being) tested in phase 2 randomized controlled trials in patients with IPF. Although some of these trials were either prematurely discontinued or produced negative results, recent years witnessed the completion (even in the context of the coronavirus disease [COVID-19] pandemic) of positive studies: the candidate antifibrotic drugs pamrevlumab, zinpentraxin alfa, BI 1015550, and PLN-74809 (3–6) provided encouraging results, leading to ongoing (or soon to start) large phase 3, confirmatory studies.

In this issue of the *Journal*, Ahangari and colleagues (pp. 1463–1479) present the results of an impressive amount of work to identify a potential antifibrotic molecule, saracatinib, a selective Src (Src protooncogene, nonreceptor tyrosine kinase) kinase inhibitor originally developed as anticancer drug, and to validate its efficacy in blocking fibrogenic processes across different *in vitro*, *in vivo*, and *ex vivo* models of pulmonary fibrosis (7). In the context of a drug repurposing strategy, the authors applied an innovative data-driven approach to explore potential connections among a set of 32 preselected compounds and more than 700 diseases via comparison of their transcriptomic signatures. This computational methodology led to the identification of a strong link between saracatinib and IPF. Saracatinib is a potent inhibitor of the Src-family tyrosine kinases, a group of intracellular kinases mediating several signaling pathways activated via transmembrane receptors and involved in a wide range of cellular processes. The signal clearly provided by the computational analysis has been further assessed using cultured normal human lung fibroblasts, two different murine models of pulmonary fibrosis (bleomycin induced and recombinant TGF-β [transforming growth factor-β] induced), and mouse precision-cut lung slice models. Decades of intense research unfortunately did not achieve the goal of a reliable preclinical model of IPF. Acknowledging this intrinsic limitation of the field, the use of multiple, imprecise, different experimental platforms may represent a surrogate approach for a nonexistent, ideally perfect animal model. In all preclinical models (*in vitro*, *in vivo* [animals] and *ex vivo* [animals, humans]) tested, saracatinib was able to attenuate the fibrogenic process compared with controls, apparently more effectively than nintedanib or pirfenidone, both assessed at clinically relevant doses. Finally, transcriptomic analyses were performed to show that saracatinib attenuated the expression of several genes altered by bleomycin and TGF-β in mouse models and by a profibrotic cytokine cocktail in human precision-cut lung slices. This massive set of experiments provided new insights into the mechanism of action of saracatinib, which acts via the inhibition of several profibrotic gene clusters alongside genes related to immune and inflammatory pathways.

Ahangari and colleagues should be heartily congratulated for adopting an innovative computational, biology-based approach to generate a robust working hypothesis for a compound already identified by previous clinical research. The history of pharmaceutical research in IPF is studded with clinical trials investigating drugs originally conceived for other indications; one of the best examples is probably nintedanib, initially developed to treat tumor angiogenesis through the multiple blockade of signaling pathways mediated by three proangiogenic tyrosine kinase receptors. Nintedanib is currently approved to treat both cancer and fibrosis, clearly showing that the same molecule can be safe and effective in diseases with (supposedly and partly) similar pathogenic mechanisms. This study also offers a modern perspective on how to optimize repurposing strategies, maximizing the chances of success while reducing research-related time and costs. In recent years, several candidate agents tested in phase 2 trials ultimately failed to demonstrate efficacy in patients with IPF, thus showing how positive proof-of-concept results do not automatically translate into a therapeutic success. This is probably due at least in part to the fact that existing models of pulmonary fibrosis cannot replicate the complexity of a disease whose multiple pathogenic pathways have not been fully elucidated yet. As such, the pleiotropic activities of the two approved therapies for IPF represents the most likely explanation for their efficacy. Moving toward a precision-based approach in the search for new antifibrotic agents, the data-driven methodology used by Ahangari and colleagues represents a significant step forward to fill the gaps of our incomplete knowledge of IPF mechanisms, using genome-wide transcriptional profiling to highlight the signaling pathways that are relevant in the profibrotic response. Although the effects of saracatinib were assessed mainly on TGF-β–dependent pathways in the *in vitro* and *in vivo* models, the analysis of transcriptomic data from murine and human precision-cut lung slices promisingly hinted at a diversified mechanism of action, including antiinflammatory and immunomodulatory activities. By the way, these latter effects should probably stimulate the design of a trial testing saracatinib in patients with nonidiopathic progressive pulmonary fibrosis (8).

The comparison of saracatinib with approved antifibrotic agents further corroborated the preclinical results, and the authors should be praised for this additional set of experiments, providing a further dimension to the comprehensive assessment of this candidate drug. On the other hand, it would be interesting to also

Originally Published in Press as DOI: 10.1164/rccm.202207-1437ED on August 26, 2022

assess the combination of saracatinib with either pirfenidone or nintedanib, as we know that it is likely that sooner or later, patients with IPF will be treated with a combination of different drugs. As with other candidate drugs, future trials of saracatinib will include patients with IPF on background antifibrotic therapy: any hint of a potential synergistic effect between standard of care and the investigational drug will facilitate enrollment.

Should the promising findings of saracatinib translate into a clinical benefit in human trials, safety data will remain of paramount relevance. Dose reductions and treatment discontinuations occur in a substantial proportion of patients treated with pirfenidone and nintedanib, suggesting the concept that the advantages of targeting a plethora of molecular pathways may come at the price of reduced tolerability. Existing evidence from oncological trials suggests that treatment with saracatinib is associated with gastrointestinal side effects (9), potentially in overlap with the tolerability profile of current antifibrotics. Assessing the safety and tolerability of saracatinib in human trials will be therefore of crucial importance, especially if the future of therapeutic management of patients with IPF will involve a combination of multiple therapies.

The lack of efficacy biomarkers represents an unmet need in the management of IPF patients, as functional deterioration still occurs despite treatment, and there are no validated tools to discriminate the extent to which the drug affects disease trajectory in the individual patient. As such, a further challenge to be addressed in the next phase of clinical testing of saracatinib will be to identify biomarkers of Src kinase activity and investigate their roles to assess response to treatment, as this could critically inform therapeutic strategies.

In conclusion, Ahangari and colleagues should certainly be applauded for providing a compelling example of comprehensive preclinical research in IPF, integrating a novel, *in silico* approach for drug repurposing, robust efficacy testing across several models of pulmonary fibrosis, and the provision of informative mechanistic insights through broad transcriptomic analyses. A phase 1b/2a clinical trial involving 100 subjects randomized to receive placebo or oral saracatinib 125 mg daily is ongoing (NCT 04598919); the publication of the present study in the *Journal* should provide further confidence and hope to both investigators and patients. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Giacomo Sgalla, M.D., Ph.D.
Luca Richeldi, M.D., Ph.D.
Fondazione Policlinico Universitario "A. Gemelli" IRCCS
Università Cattolica del Sacro Cuore
Rome, Italy

ORCID ID: 0000-0003-3130-9388 (G.S.).

References

1. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, *et al.* INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2071–2082.
2. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, *et al.* ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2083–2092.
3. Richeldi L, Azuma A, Cottin V, Hesslinger C, Stowasser S, Valenzuela C, *et al.* 1305-0013 Trial Investigators. Trial of a preferential phosphodiesterase 4B inhibitor for idiopathic pulmonary fibrosis. *N Engl J Med* 2022;386:2178–2187.
4. Raghu G, van den Blink B, Hamblin MJ, Brown AW, Golden JA, Ho LA, *et al.* Effect of recombinant human pentraxin 2 vs placebo on change in forced vital capacity in patients with idiopathic pulmonary fibrosis: a randomized clinical trial. *JAMA* 2018;319:2299–2307.
5. Richeldi L, Fernández Pérez ER, Costabel U, Albera C, Lederer DJ, Flaherty KR, *et al.* Pamrevlumab, an anti-connective tissue growth factor therapy, for idiopathic pulmonary fibrosis (PRAISE): a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2020;8:25–33.
6. Pliant Therapeutics. Pliant Therapeutics announces positive safety and efficacy data from phase 2a INTEGRIS-IPF clinical trial of PLN-74809 in patients with idiopathic pulmonary fibrosis. South San Francisco, CA: Pliant Therapeutics; 2022 [updated 2022 Jul 10; accessed 2022 Jul 29]. Available from: https://ir.pliantrx.com/news-releases/news-release-details/pliant-therapeutics-announces-positive-safety-and-efficacy-data.
7. Ahangari F, Becker C, Foster DG, Chioccioli M, Nelson M, Beke K, *et al.* Saracatinib, a selective Src kinase inhibitor, blocks fibrotic responses in preclinical models of pulmonary fibrosis. *Am J Respir Crit Care Med* 2022;206:1463–1479.
8. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, *et al.* Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2022;205:e18–e47.
9. Baselga J, Cervantes A, Martinelli E, Chirivella I, Hoekman K, Hurwitz HI, *et al.* Phase I safety, pharmacokinetics, and inhibition of SRC activity study of saracatinib in patients with solid tumors. *Clin Cancer Res* 2010; 16:4876–4883.