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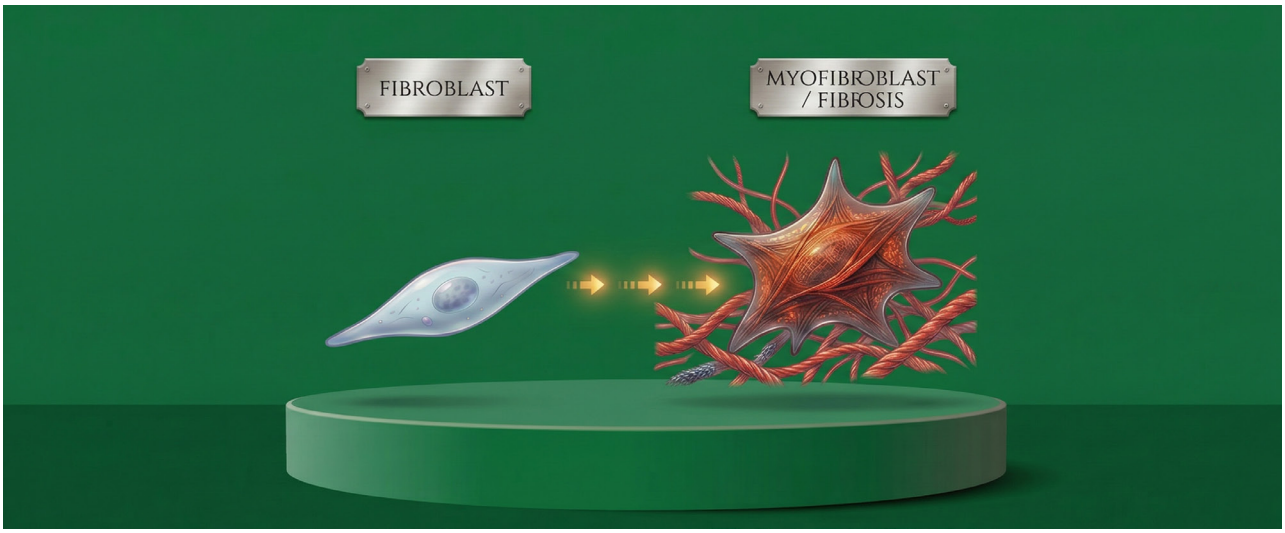
A pulmonary fibrosis proof-of-concept wave puts antifibrotic progress within reach

BY LAUREN MARTZ, EXECUTIVE DIRECTOR, BIOPHARMA INTELLIGENCE



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Halting fibrosis has been one of drug development's most persistent challenges, but the science is reaching a tipping point. Drug developers are starting to strike a workable balance between broad-acting approaches that carry toxicity risk and more selective strategies that may sacrifice potency, and patients with a rare form of lung fibrosis may be among the first to benefit.

With at least 20 therapies in Phase II testing for idiopathic pulmonary fibrosis (IPF) — most with first-in-class potential — the next two years are poised to deliver proof-of-concept readouts that help identify the signaling pathways most central to fibrosis progression and guide development strategy.

Breakthroughs in IPF could also inform development of therapeutics for a long list of other diseases driven by fibrotic pathology.

One reason that tackling fibrosis has been so challenging is that the pathology is intertwined with normal wound healing, which needs to remain functional. Fibrotic scars form when wound-healing responses become dysregulated and excessive.

> **"THERE IS THIS IDEA THAT THE SCIENCE HAS CAUGHT UP WITH INVESTOR INTEREST."**
> MARC HERTZ, GRI BIO

A second reason is the complex, redundant signaling network that drives scar formation after epithelial injury. Intervening upstream often proves toxic because the targets are essential to normal cell function, while finding effective downstream intervention points is difficult because multiple inputs can drive fibroblast expansion and activation.

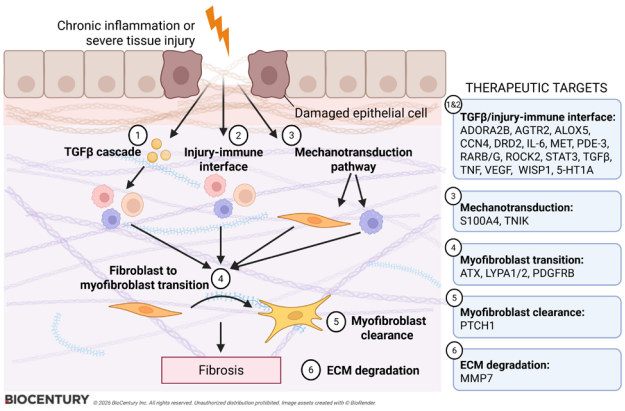
Compounding the challenge is the long-standing dogma that fibrosis isn't reversible. Though that belief is now being reconsidered, the current treatment goal is to slow or stop progression. Because patients often present with symptoms only after extensive tissue damage affects organ function, long and costly trials are required to demonstrate that a therapy slows disease progression.

None of the three approved IPF therapies halts disease progression, let alone reverses fibrosis, leaving an unresolved major unmet need.

Pirfenidone and nitedanib, both approved in 2014, have broad yet incomplete antifibrotic activity. They act by blocking kinases upregulated throughout the pro-fibrotic molecular pathways. FDA's December approval of Jascayd nerandomilast from Boehringer Ingelheim GmbH ushered in the first new IPF therapy in over a decade, and though it works by a clearer, more targeted mechanism, PDE-4B inhibition, it still slows rather than stops progression.

"There's still a lot to be desired in the marketplace for patients, because the therapies are really only slowing the lung decline down," Mediair Therapeutics Inc. CSO Paul Yaworsky told BioCentury. "There's this incredible need, but I would say it's balanced with the incredible potential of the current pipelines right now." Mediar's lead program, WISP1-targeting MTX-463, is among the advancing Phase II wave in IPF.

These latest programs are testing the hypothesis that selectively targeting the pathways that trigger fibrosis after epithelial injury, drive fibroblast differentiation into matrix-depositing myofibroblasts and related subtypes, sustain myofibroblast activity, or amplify pro-fibrotic signaling cycles can halt the process in a tolerable way.



IPF's inflection point

The current interest in IPF development is thanks, in part, to the success of Jascayd and the two therapies that came before it. Those programs defined a viable development pathway and set endpoint standards in the indication, making it accessible to smaller biotechs.

"It's probably not that unique to fibrosis, but there is this idea that the science has caught up with investor interest and the identification of meaningful markets. There's enough investor support to allow little companies like Gri to actually pursue these things," said Marc Hertz, president and CEO of Gri Bio Inc. (NASDAQ:GRI).

Gri is one of many companies that are now taking on fibrosis through IPF as a starting point; its candidate GRI-0621, is a dual agonist of RARβ/γ. In addition to an established clinical and regulatory pathway, relatively consistent disease biology across patients has made this form of pulmonary fibrosis attractive.

Other priority fibrotic diseases include metabolic-associated steatohepatitis (MASH), which can progress to liver fibrosis, and systemic sclerosis (SSc), but both indications present barriers for smaller companies. In MASH, unpredictable regulatory requirements have led some biotechs to initially pursue proof of concept elsewhere. In systemic sclerosis, disease heterogeneity has been the challenge, as it makes demonstrating clinical benefit more challenging.

Hertz said MASH looked unusually uncertain at the time Gri was choosing indications, pointing to the regulatory experience of Intercept Pharmaceuticals, since acquired by Alfasigma S.p.A., as a signal that the goalposts were unclear. "There was enough uncertainty around what FDA actually wanted to see for registration of a product in that space that as a small company, it was a huge risk to take on," he said, adding "the kind of studies and the resources needed to get a strong signal in MASH would just be a stretch."

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JONAS HALLÉN, CALLUNA

Calluna Pharma Inc., via its Arxx Therapeutics subsidiary, is an example of a company that pivoted away from systemic sclerosis. Its lead therapy, CAL101, is an S100A4 inhibitor now in Phase II for IPF.

"What initially attracted us to SSc was that you can actually biopsy the skin," making it possible to understand the effect of the molecule in a small number of patients in early development, CMO Jonas Hallén told BioCentury. "In SSc, however, if you look at the regulatory endpoints, the subjective skin score endpoint has not been able to support any approvals because of the variability and the heterogeneous nature of how skin disease evolves in these patients."

He noted that SSc approvals have been based on pulmonary function tests, as they have for IPF. "If you look at the interstitial lung disease component of SSc, it's more heterogeneous and more variable in terms of how the disease progresses, whereas

IPF is more deterministic and predictable," he added. Because IPF is an orphan indication in which drugs had already been approved, "we felt we could get some really strong signals out of a relatively obtainable study," Hallén said.

Though IPF has become a common starting point for anti-fibrotic mechanisms, many of the companies interviewed by BioCentury hope to expand their therapeutic mechanisms into other fibrotic diseases.

"We thought anything we learned in IPF would obviously be applicable for IPF, but likely for other fibrotic indications as well," said Hertz. "If we continue to be successful in IPF, jumping over to liver fibrosis" could be a workable next move.

Mechanistic, translational and clinical barriers

Though new products with new mechanisms have been pouring into the IPF landscape, encouraged by scientific and regulatory developments, there are still barriers to overcome at each stage of the development process.

Homing in on the right targets and pathways has been a challenge because epithelial injury sets off a complex series of signaling pathways that lead to fibroblast activation, myofibroblast generation and ultimately the deposition of fibrotic matrix components. Intervening upstream in the pathway is associated with a narrow therapeutic index, while intervening downstream risks failing to identify and block all of the critical nodes required to halt the process.

"Targeting just one pathway will easily be bypassed or compensated by other pathways. Broad tropic mechanisms will be slightly effective but hampered by a narrow therapeutic index and lots of tolerability issues," said Hallén.

Early therapeutic mechanisms centered on TGFβ, which sits at the top of the cytokine signaling pathway and acts as the non-canonical driver of fibrosis, but blocking the broadly acting fibrotic factor proved toxic.

As research has moved away from the broad antifibrotics in search of targeted approaches, translational challenges have also been a barrier.

"Animal models of the disease are horrible. I think at this point, something like 700 molecules have been effective in the bleomycin mouse model, and only a couple have gotten approved," John Hood, co-founder and CEO of Endeavor BioMedicines Inc. told BioCentury.

He said it was data from human samples that pointed to core development pathways pathologically upregulated in fibrotic lung tissue, including the hedgehog pathway targeted by the company's lead molecule taladegib.

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Gri relied on preclinical data compiled from a suite of fibrotic models across different organ systems to help predict clinical efficacy. "What we relied on was trying to use other models that, if not more predictive, at least give us breadth that gives us some comfort. We did the shotgun approach here, with every model of acute or chronic fibrosis in different tissues that we could reasonably get set up on our own or through collaborators," Hertz said.

Mediar relied on preclinical data from human-derived models and tissues. "What we and others have had to do is add human systems, where possible, to increase our confidence that a first-in-class antifibrotic will actually work," CEO Rahul Ballal told BioCentury, citing "precision-cut lung slices" and human organoids in 96-well plates.

Many biopharmas believe they've found the right target, and upcoming Phase II readouts should be informative; however, IPF is an indication where positive Phase II results have often failed to translate to Phase III success. Most recently, bexotegrast from Pliant Therapeutics Inc. (NASDAQ:PLRX), one of the leading targeted therapies in the IPF pipeline, failed its Phase III trial due to liver toxicity.

The current wave of companies advancing toward proof of concept is using lessons from prior programs to inform Phase II and III trial design. Collectively, they are applying at least three strategies.

First, some believe longer, larger Phase II trials could be key to identifying toxicities before Phase III. "What we've seen is that 12-week studies are not able to pick up on potential safety signals" that take time to develop, Hallén said, noting that for some programs, "safety is emerging as a concern after maybe four or five months." He said 24 weeks was the sweet spot for Calluna's Phase II program.

Hertz added that getting the most out of a Phase II trial is critical to inform Phase III designs. "Any time you're doing a clinical study, you want to learn as much as you can. Spend the extra money to do the extra translational substudy or collect the samples." He acknowledged this can risk "overburdening" patients. "You don't want to do that, especially for IPF patients, but at the same time, data should drive all these decisions."

The second is abandoning programs that haven't shown positive results in other fibrotic settings. "If a drug or a pathway has failed in other fibrotic indications, maybe it's a stretch to think it's going to work in IPF," Hertz said. "Some of it, I think, is putting too much emphasis on what they've seen preclinically or early on and ignoring failures" by themselves or others going after the same target.

The third is focusing on causal biology. "I think what's limited success in the past is that there haven't been really good agents that went after the cause of disease," Hood said.

Mechanisms facing the Phase II test

Despite the challenges, more than 20 companies are now advancing programs through Phase II. The resulting data will test whether IPF has intervention points that are both biologically central to fibrosis and therapeutically tractable, and will help define which mechanisms meet that bar.

IPF therapies in Phase II

Company	Product	Molecular target	Modality
1. TGFb cascade			
Gri	Tazarotene	RARG; RARB	Small molecule
Redx	Zelasudil	ROCK2*	Small molecule
Tide, Graviton	GV101	ROCK2*	Small molecule
Tvardi	TTI-101	STAT3	Small molecule
2. Injury-immune interface			
Kyorin	Tipelukast	PDE-3; ALOX5	Small molecule
Mediar, Eli Lilly	MTX-463	CCN4; WISP1	Antibody
Palobiofarma	PBF-1129	ADORA2B	Small molecule
Reviva	Brilaroxazine	DRD2; 5-HT1A	Small molecule
Taiho	TAS-115	MET; VEGF	Small molecule
Vicore	Buloxibutid	AGTR2	Small molecule
3. Mechanotransduction			
Calluna	CAL101	S100A4	Antibody
Insilico	INS018_055	TNIK	Small molecule
Insilico	Rentosertib	TNIK	Small molecule
4. Myofibroblast transition			
Boehringer	BI 1819479	LYPLA2; APT1	Small molecule
Ligachem, BridgeBio	BBT-877, LCB17-0877	ATX	Small molecule
Raynovent	ZSP1603	PDGFRB	Small molecule
5. Myofibroblast clearance			
Endeavor	Taladegib	PTCH1	Small molecule
6. ECM degradation			
Arrowhead, Sarepta	ARO-MMP7	MMP7	siRNA
Optimized traditional antifibrotics			
Avalyn	Aerodone inhaled pirfenidone	Undisclosed	Small molecule
Celea	Deupirfenidone	TNF; IL-6; TGFB	Small molecule
Roche	AK3280	Undisclosed	Small molecule

Source: Press releases, company websites • Categorization is based on BioCentury's assessment of the best match; some mechanisms span multiple categories

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The therapeutic mechanisms being tested in the Phase II class include intervening at the epithelial injury-immune interface, when injury recruits inflammatory cells and sets off an inflammatory cascade, and blocking different cytokines and fibrotic growth factors in the canonical TGFβ pathway. Other interventions include blocking activation and differentiation of fibroblasts into fibrosis-depositing phenotypes, promoting the clearance of fibrotic myofibroblasts, and cleaning up the fibrotic ECM that has been deposited.

Calluna is targeting an amplifier of TGFβ signaling in fibrosis without directly inhibiting the centrally acting cytokine, by blocking S100A4.

S100A4 is released into the extracellular space by multiple cells, where it alerts the tissue to danger and sets in motion a range of downstream pathways that are involved in driving inflammatory and fibrotic responses, Hallén said. "By removing S100A4, you remove the amplification loop and so you have the potential to impact a number of pathways simultaneously, but you're not shutting them down completely."

Others aim to block signaling through the LPA1 receptor, which is expressed on fibroblasts and acts downstream of TGFβ signaling. It's thought to be a central signaling node for the activation of fibroblasts and their transition to myofibroblasts. Companies intervening at that point will get an early read on the mechanism's efficacy. Bristol Myers Squibb Co. (NYSE:BMY) is testing potential first-in-class LPAR1 antagonist admilparant in Phase III studies for IPF and progressive pulmonary fibrosis (PPF). Admilparant is one of very few novel mechanisms in Phase III testing, and its IPF study should read out in the fourth quarter.

Cristian Massacesi, CMO and head of development at BMS, told BioCentury that the Phase III trial enrolled some patients who will receive admilparant only and others who will receive admilparant on top of standard of care. "We are ensuring the Phase III is mirroring the population and the assumptions that we had in Phase II. This is to be the best way to hopefully have the same outcome."

Mediar is pursuing the target WISP1, a protein downstream of TGFβ signaling that is secreted by lung epithelial cells and by fibroblasts, specifically in the more advanced stages of fibrosis. WISP1 is involved in the transition of fibroblasts to myofibroblasts, and the company believes the target's upregulation in advanced disease, when intervention usually takes place, will create differentiation. The protein also has potential as a serum biomarker for defining disease severity and correlating it with therapeutic response.

"I think one of the things that's really exquisite about the WISP1 biology is that it is not an early driver of disease. It's not involved in that early inflammation step," said Yaworsky. Instead, the company believes WISP1 acts in three parts of IPF pathology: promoting differentiation into myofibroblasts, affecting alveolar cell biology and modulating immune responses, he said.

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JOHN HOOD, ENDEAVOR BIOMEDICINES

ROCK2, which is activated by pro-fibrotic mediators in the lung including TGFβ, is a candidate target being pursued by Graviton Biosciences Corp.

Rui Wu, EVP, head of research and preclinical and chief CMC officer at Graviton, told BioCentury that the target has support from human genomic analyses.

"When the tissue is injured, then we see activation of RhoA-ROCK. So those proteins are upregulated and affecting fibroblast formation," she said. "If you have haploinsufficient ROCK1 or ROCK2, you see those immune responses and fibrosis responses are dampened significantly, so that's part of the genetic evidence."

She added that ROCK2 is involved in other profibrotic mechanisms, including a second fibrotic feedback loop. It increases actin polymerization and cytoskeleton tension, which promotes a focal adhesion and ultimately activation of TGFβ.

Rather than specifically targeting the formation of myofibroblasts, Endeavor is aiming to promote the cells' apoptosis through hedgehog pathway inhibition. In lung fibrosis, part of the problem is that the myofibroblasts that become active stay active and resist apoptosis. By inhibiting the hedgehog pathway, Hood said the active myofibroblasts can be cleared.

"Ultimately, if the myofibroblasts are the bad actors, you don't just want to stop the accumulation of them. You would rather clear them and get rid of them," said Hood. He believes that mechanism is the reason the company's Phase IIa data, including imaging analyses and evidence of an improvement in lung function on the forced vital capacity test, suggest reversal of fibrosis may be occurring.

Graviton is another company that noted an improvement in lung function in its Phase II study, but CMO Amy Melsaether cautioned that there's often an early improvement in lung function that corrects over time. "A lot of the early Phase II trials are 12 or 16 weeks and you see an initial bump in forced viral capacity, but that will come down over time." She said that in the Phase II trial, "we saw an increase in forced viral capacity at 24 weeks, which is pretty unusual against placebo."

Other mechanisms in proof-of-concept studies include a TNIK inhibitor from Insilico Medicines Inc. (HKEX:3696) and a STAT3 inhibitor from Tvardi Therapeutics Inc. (NASDAQ:TVRD).

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NEWSROOM
news@biocentury.com

SAN CARLOS, CA
+1 650-595-5333; Fax: +1 650-595-5589

CHICAGO
+1 312-755-0798; Fax: +1 650-595-5589

WASHINGTON, DC
+1 202-462-9582; Fax: +1 202-667-2922

UNITED KINGDOM
+44 (0)1865-512184; Fax: +1 650-595-5589