PA896 *ERS Congress 2026 | Session 12.04 — Rare ILD/DPLD | Abstract #62491*

GRI-0621 Phase 2a biomarker study in patients with IPF using gene expression, immune cell activity and collagen markers supports a repair phenotype with strong anti-fibrotic and pro-resolving effects

M. Hertz[1], J.C. Porter[2], H. Parfrey[3], P. Saunders[4], N. Chaudhuri[5], N. Hirani[6], A. Crawshaw[7], M. Gibbons[8], A. Menon[9], S. Schembri[10], V. Kumar[1], A. Agro[1],

[1]*GRI Bio, Inc., La Jolla, USA* · [2]*Royal Papworth Hospital, Cambridge, UK* · [3]*UCL Respiratory, University College London and University College London NHS Trust BRC, London UK* · [4]*Oxford University Hospitals Trust, Churchill Hospital, Oxford, UK* · [5]*University of Ulster, Londonderry, UK* · [6]*University of Edinburgh, Edinburgh, UK* · [7]*University Hospitals Birmingham, Queen Elizabeth Hospital, Birmingham, UK* · [8]*University of Exeter, Exeter, UK* · [9]*Medical University of South Carolina, Charlotte, USA* · [10]*Canberra General Repatriation Hospital, Garran, Australia*

Conflict of interest: *Dr. Hertz is employed by and holds a financial interest in GRI Bio, Inc* · **Acknowledgement:** *This work was supported by the National Institute for Health and Care Research (NIHR) Respiratory Translational Research Collaboration (TRC)* · **Trial registration:** *ClinicalTrials.gov NCT06331624*

Introduction: Idiopathic pulmonary fibrosis (IPF) is driven by epithelial injury, immune dysregulation and excess extracellular matrix (ECM) deposition. GRI-0621 is an oral retinoic acid receptor (RAR) β/γ-selective agonist repurposed from topical tazarotene that engages a receptor-selective transcriptional program coupling immune re-balancing to matrix catabolism and alveolar-epithelial repair, while sparing the RARα-driven mucocutaneous and metabolic toxicities that limited prior systemic retinoid programs.

Aims: To assess safety, translational biomarkers and exploratory lung function of GRI-0621, an oral RARβ/γ-selective agonist, in patients with IPF.

Methods: GRI-0621-IPF-02 (NCT06331624) was a Phase 2a, randomized, double-blind, placebo-controlled trial. Thirty-five patients with IPF were randomized 2:1 to oral GRI-0621 4.5 mg once daily (n=23) or placebo (n=12) for 12 weeks; 80% received background pirfenidone or nintedanib. Endpoints included adverse events, whole-blood RNA sequencing, a 12-marker serum ECM neo-epitope panel, 28-color spectral flow-cytometry, and forced vital capacity (FVC).

Results: GRI-0621 was well tolerated. Physiologically, the placebo-adjusted FVC change from baseline at Week 12 was +99 mL overall and +139 mL in the +SOC subset. Direction-consistent signals from ≥2 independent modalities supported each of the nine pre-specified mechanistic pillars (Tables 6–8).

The Nine Mechanistic Pillars

The Phase 2a evidence resolves into nine coherent mechanistic pillars. Figure 1 shows how a receptor-selective retinoid signal at RARβ (mesenchymal-epithelial) and RARγ (regenerating lung epithelium and AT2 progenitors) engages this nine-pillar cascade from the receptor level down to functional and patient-reported outcomes.

Figure 1. *Nine-pillar mechanism-of-action of oral RARβ/γ-selective agonism by GRI-0621 in IPF. Selective engagement of RARβ (mesenchymal-epithelial) and RARγ (regenerating lung epithelium, AT2 progenitors) — while sparing RARα-driven mucocutaneous and metabolic toxicity — initiates an integrated transcriptional program that resolves into nine coherent mechanistic pillars measured by four independent modalities.*

Table 1. Serum ECM Biomarkers Of Matrix Turnover

Expanded 12-biomarker panel (collagen formation and degradation neo-epitopes plus inflammation/turnover markers).

			All subjects (n=19 GRI / 9 PBO)[a]					+SOC subset (n=16 GRI / 6 PBO)[a]			
Biomarker	Fav. dir.	Type	GRI %CFB (mean ±SEM)	PBO %CFB (mean ±SEM)	PBO-adj Δ%CFB	HL Δ [95% CI]	GRI %CFB (mean ±SEM)	PBO %CFB (mean ±SEM)	PBO-adj Δ%CFB	HL Δ [95% CI]
PRO-C3	↓ (yes)	Formation	**+10.1**±4.9%	**+12.2**±5.8%	**−2.2%**	**−4.0** [−19.1,+10.5]	**+9.0**±5.3%	**+12.6**±8.3%	**−3.6%**	**−5.6** [−28.3,+17.5]
PRO-C6	↓ (yes)	Formation	**−4.1**±5.5%	**+8.2**±23.6%	**−12.3%**	**+0.0** [−20.6, +21.4]	**−5.9**±5.7%	**+25.8**±32.9%	**−31.7%**	**−7.7** [−42.2, +19.4]
PRO-C4	↑ (yes)	Formation	**+7.9**±2.6%	**+0.2**±4.4%	**+7.7%**	**+7.8** [−3.7, +17.5]	**+5.4**±2.5%	**+2.4**±5.0%	**+2.9%**	**+2.0** [−9.3, +15.0]
PRO-C5	↔	Formation	**+0.2**±3.5%	**−4.7**±6.8%	**+4.8%**	**+0.8** [−13.1, +21.5]	**−2.7**±3.2%	**−1.5**±7.5%	**−1.2%**	**−0.4** [−18.7, +20.0]
C1M	↑ (yes)	Degradation	**+33.4**±16.2%	**+50.5**±39.4%	**−17.1%**	**+1.4** [−63.2, +60.3]	**+25.5**±16.6%	**+20.8**±26.4%	**+4.7%**	**+0.7** [−69.1, +72.6]
C3M	↑ (yes)	Degradation	**−0.2**±2.5%	**−5.9**±7.6%	**+5.7%**	**+5.6** [−9.9, +23.3]	**−1.9**±2.8%	**−1.3**±9.5%	**−0.6%**	**+3.5** [−24.1, +21.0]
CTX-III	↑ (yes)	Degradation	**+6.8**±6.8%	**−2.8**±8.3%	**+9.6%**	**+3.6** [−7.3, +24.4]	**+11.7**±7.2%	**+5.7**±7.3%	**+6.0%**	**+1.4** [−7.3, +17.8]
C6M	↑ (yes)	Degradation	**+5.2**±2.5%	**−3.2**±7.2%	**+8.4%**	**+8.5** [−7.5, +23.4]	**+5.2**±2.4%	**−0.4**±8.1%	**+5.6%**	**+8.4** [−11.4, +24.6]
C4Ma3	↓ (yes)	Degradation	**+7.6**±3.8%	**+18.6**±9.7%	**−10.9%**	**−5.2** [−31.8, +13.0]	**+5.1**±4.1%	**+9.8**±9.3%	**−4.7%**	**−1.4** [−26.0, +17.1]
VICM	↓ (yes)	MØ activity	**+18.1**±11.2%	**+42.9**±28.0%	**−24.8%**	**−20.8** [−57.3, +31.3]	**+18.2**±13.2%	**+56.7**±40.4%	**−38.5%**	**−25.6** [−89.0, +39.7]
CPa9-HNE	↓ (yes)	Neutrophil activity	**−0.9**±3.7%	**+3.7**±5.4%	**−4.5%**	**−3.4** [−16.2, +10.5]	**−2.7**±4.2%	**+2.0**±5.4%	**−4.7%**	**−2.0** [−15.2, +11.6]
ELP-3	↓ (yes)	Lung injury	**−5.0**±2.7%	**−7.0**±6.7%	**+2.0%**	**−0.3** [−12.2, +13.0]	**−6.7**±2.9%	**−1.9**±5.5%	**−4.8%**	**−2.4** [−18.1, +10.4]

a n = evaluable subjects per arm. b PBO-adj Δ %CFB = GRI mean − PBO mean. c HL Δ = Hodges-Lehmann median difference (GRI − PBO); 95% CI = distribution-free Wilcoxon-Mann-Whitney interval. d Fav. dir. = direction of change considered biologically favorable (↑ = increase beneficial; ↓ = decrease beneficial; ↔ = stabilization beneficial).

Table 2. Collagen Synthesis-vs-Degradation Balance Ratios

Ratios of collagen formation neo-epitopes to their matched degradation neo-epitopes quantify net matrix balance shifts.

			All subjects (n=19 GRI / 9 PBO)[b]				+SOC subset (n=16 GRI / 6 PBO)[b]			
Ratio	Fav. dir.	Biological meaning	GRI %CFB (mean ±SEM)	PBO %CFB (mean ±SEM)	PBO-adj Δ%CFB	HL Δ [95% CI]	GRI %CFB (mean ±SEM)	PBO %CFB (mean ±SEM)	PBO-adj Δ%CFB	HL Δ [95% CI]
PRO-C3 / C3M	↓ (yes)	↑ degradation (fibrolysis)	**+11.1**±5.2%	**+24.7**±12.1%	**−13.6%**	**−10.5** [−22.7, +5.8]	**+11.8**±5.6%	**+15.6**±4.6%	**−3.8%**	**−12.0** [−20.5, +10.6]
PRO-C3 / CTX-III	↓ (yes)	↑ degradation (fibrolysis)	**+9.8**±8.0%	**+25.8**±18.2%	**−15.9%**	**−8.7** [−33.7, +16.0]	**+1.7**±6.3%	**+7.6**±7.3%	**−5.9%**	**−8.6** [−32.1, +16.1]
PRO-C6 / C6M	↓ (yes)	↑ degradation (fibrolysis)	**−7.5**±6.0%	**+6.5**±15.8%	**−14.0%**	**+0.0** [−33.6, +18.7]	**−9.9**±5.6%	**+20.9**±21.5%	**−30.9%**	**−21.4** [−58.0, +11.7]
PRO-C4 / C4Ma3	↑ (yes)	↑ formation (BM repair)	**+2.2**±4.0%	**−11.3**±6.9%	**+13.6%**	**+8.4** [−4.2, +26.4]	**+2.5**±4.7%	**−4.9**±5.3%	**+7.4%**	**+5.2** [−9.4, +22.0]

a %CFB of ratio = mean percent change from baseline of the (numerator / denominator) unitless ratio. b n = evaluable subjects per arm. c PBO-adj Δ %CFB = GRI mean − PBO mean. HL Δ = Hodges-Lehmann median difference (GRI − PBO); 95% CI = distribution-free Wilcoxon-Mann-Whitney interval. d Fav. dir. = beneficial for all four ratios. All four ratios are exploratory context-only endpoints — hypothesis-generating.

Table 3. Whole-Blood RNA-seq Anchor Genes Supporting The Nine Mechanistic Pillars

Curated anchor genes show coordinated, direction-consistent transcriptional change on GRI-0621.

Gene	Pillar	Dir.	|LogFC|[a]	p / FDR[b]	Biological role
ALDH1A2	Pharmacodynamic	↑	15.30	**0.011**	RAR pharmacodynamic target engagement (retinaldehyde dehydrogenase 2)
IL4	Immune re-balancing	↓	10.63	0.463	Th2 cytokine; corroborates flow CCR4↓ signal
IL13	Immune re-balancing	↓	3.09	0.857	Th2 cytokine; pro-fibrotic mediator
STAT6	Immune re-balancing	↓	1.54	0.095	TF M2/Th2 gene programs. STAT6-KO mice show attenuated fibrosis across models
CCR4	Immune re-balancing	↓	3.26	0.397	Th2/Treg homing receptor; concordant with protein flow signal
CCR8	Immune re-balancing	↓	6.67	0.182	Tissue-resident Treg/Th2 chemokine receptor. Blockade attenuates fibrosis in models
P2RY12	Reduced lung injury	↓	11.80	0.082	Tissue-resident macrophage receptor; active-disease anchor
FOLR2	Reduced lung injury	↓	6.76	0.082	Pro-fibrotic tissue-resident macrophage marker
PI3 (elafin)	Reduced lung injury	↑	19.19	**0.047**	Restrains neutrophil-elastase injury; connects to CPa9-HNE and ELP-3 serum biomarkers
E2F3	Myofibroblast inhibition	↓	3.70	**0.024**	Drives fibroblast differentiation into myofibroblasts
F2R	Myofibroblast inhibition	↓	2.14	**1e-4**	Activates of thrombotic injury fibrotic signaling cascade
TXNDC5	Myofibroblast inhibition	↓	2.97	**0.028**	Folds 7 stabilizes TGFBR1, augmenting TGF-β receptor signaling amplitude
SMAD7	Myofibroblast inhibition	↑	2.02	0.111	Inhibitory Smad; endogenous negative feedback on Smad2/3
ACTA2	Myofibroblast inhibition	↓	10.81	0.089	α-SMA; core myofibroblast contractile marker
ROCK2	Myofibroblast inhibition	↓	2.61	**0.035**	Rho-kinase 2; actin-cytoskeletal contractility
MYL12A	Myofibroblast inhibition	↓	2.25	**0.006**	Myosin regulatory light chain 12A; contractile machinery downstream of ROCK2
CCN3	Myofibroblast inhibition	↑	15.68	**0.047**	Anti-fibrotic matricellular protein; opposes CCN2/CTGF activity
PLOD1	Fibrolysis	↓	2.58	**0.042**	Hydroxylates lysyl on procollagen, a prerequisite for crosslink maturation and matrix rigidity. Elevated in IPF
COL6A3	Fibrolysis	↓	6.43	0.174	Largest type VI collagen α-chain elevated in fibrotic lung and co-localized with COL1/III
ADAMTS1	Fibrolysis	↓	15.13	**0.034**	Metalloproteinase; strongest fibrolysis transcript signal
MMP1	Fibrolysis	↓	18.32	0.095	Interstitial collagenase; connects to serum PRO-C3/C3M turnover
LAMA3	Basement-membrane repair	↑	11.73	0.115	Laminin α3; principal alveolar-epithelial BM protein, IPF-deficient
COL4A1/A2	Basement-membrane repair	↑	5.4 / 3.9	**0.053 / 0.058**	Type IV collagen α1/α2; transcript concordance with serum PRO-C4
COL17A1	Basement-membrane repair	↑	11.48	0.090	Type XVII collagen (BP180); hemidesmosome anchor restoring epithelial-BM adhesion
DLK1	Re-epithelialization (AT1/AT2)	↑	9.62	**0.003**	Notch-family transmembrane protein required for AT2→AT1 differentiation during repair
CAV1	Re-epithelialization (AT1/AT2)	↑	5.89	**0.015**	Caveolin-1; anti-fibrotic membrane-scaffolding protein reduced in IPF fibroblasts
NUPR1	Re-epithelialization (AT1/AT2)	↑	10.50	**0.043**	AT2 stress-resilience transcription factor (p8/COM1); reduced in IPF whole-lung baseline
CRB3	Re-epithelialization (AT1/AT2)	↑	7.62	**0.046**	Restored epithelial polarity
NAPSA	Re-epithelialization (AT1/AT2)	↑	8.84	0.075	Supports AT2 functional recovery; loss causes AT2 injury and fibrosis
ALDH1A2	Re-epithelialization (AT1/AT2)	↑	9.47	**0.011**	RALDH2, the rate-limiting enzyme for RA synthesis (impaired in IPF); supportive of AT2 identity and re-epithelialization.
FGF2	GI-protection	↑	5.83	**0.008**	AFT GI-toxicity mitigation; promotes epithelial repair in injured gut & counteracts AFT mucosal-vascular injury
FLT1	GI-protection	↑	4.28	**0.015**	AFT GI-toxicity mitigation; supports epithelial cell survival & counteracts AFT mucosal-vascular injury

a |LogFC| = absolute log fold-change, GRI-0621 vs. placebo, from the pillar evidence-summary transcriptomics. b Minimum FDR-adjusted p-value reported for that gene's strongest bucket contrast. c n = 19 GRI / 9 PBO evaluable for whole-cohort Phase 2a transcriptomics; per-bucket n are not separately itemized here. d TF = transcription factor; BM = basement membrane; ER = endoplasmic reticulum.

Seventy-two curated anchor genes were interrogated in whole-blood RNA-seq at baseline and Week 12. Eighteen transcripts reached FDR<0.05 with large-magnitude, direction-consistent change: **ALDH1A2** ↑ (retinaldehyde dehydrogenase 2; RAR pharmacodynamic target engagement); **ARG2** ↓; **PI3(elafin)** ↑; **E2F3** ↓; **F2R/PAR-1** ↓; **TXNDC5** ↓; **ROCK2** ↓; **MYL12A** ↓; **CCN3** ↑; **PLOD1** ↓; **ADAMTS1** ↓ (strongest fibrolysis transcript); **COL4A1/A2** ↑; **DLK1** ↑; **CAV1** ↑ (anti-fibrotic membrane scaffold, deficient in IPF fibroblasts); **NUPR1** ↑ (AT2 stress-resilience TF); and **CRB3** ↑ (apical epithelial polarity complex); **FGF2** ↑; **FLT1** ↑ .The transcript pattern is coherent across pillars.

28-color spectral flow cytometry

Twenty-eight-color spectral flow of paired PBMC and BAL profiled iNKT inactivation, immune trafficking and cytokine expression. Thirteen readouts reached p<0.05, including restored **iNKT Vα24Jα18 TCR MFI** ↑; coordinated **CCR4 MFI** ↓ down-regulation across six lineages — a Th2/Treg-homing collapse; **CXCR6 MFI** ↓ on Th17; BAL **interstitial & alveolar macrophage HLA-DR** ↑, consistent with a re-programmed antigen-presenting phenotype rather than immune suppression; **TGF-β** ↓. The flow panel provides the strongest inferential signal in the study and demonstrates **immune re-programming rather than immune suppression** (full data not shown).

Table 4. Cross-Modality Concordance — Immune Re-Balancing, Reduced Lung Injury, And Myofibroblast Inhibition Pillars

Direction-consistent findings across independent measurement modalities corroborate the immune re-balancing, reduced-lung-injury, and myofibroblast-inhibition pillars. Row groupings by pillar (1–3 of 9); individual effect sizes and CIs are in Tables 1–4. Continued in Tables 7–8.

Modality	Readout summary
1. Immune re-balancing	
Flow	IL-4 ↓, IL-13 ↓, IL-17A ↓, and IL-22 ↓, CCR4 & CXCR6 ↓; IFN-γ ↑; iNKT Vα24Jα18 TCR ↑ (MFI)
RNA-seq	IL4 ↓, IL13 ↓; STAT6/CCR4/CCR8 ↓ (Th2 module); FOLR2 ↓, MRC1 ↓, P2RY12 ↓ (M2 module)
2. Reduced lung injury	
Flow	HLA-DR MFI ↑ on interstitial and alveolar macrophage (re-programming, not suppression)
RNA-seq	AGER ↑, PTGES ↑, F2R ↓, ARG2 ↓, PI3 (elafin) ↑, NUPR1 ↑, TNFSF10 (TRAIL) ↓
Serum	CPa9-HNE ↓; ELP-3 ↓; VICM ↓
3. Myofibroblast inhibition	
Flow	TGF-β+ MFI ↓
RNA-seq	**TGF-β pathway**: **ADAMTS1** ↓, **F2R** ↓, **TXNDC5** ↓, LTBP1 ↓ (tethers latent TGFβ to ECM), TGFBR2 ↓ → SMAD6/7 ↑, **PMEPA1** ↑ (TGF-β negative feedback via SAMD) → FN1 ↓, CCN2 (CTGF) ↓, TGFB1 ↓ (TGF-β-induced matrix protein), MMP1 ↓ **ROCK2 pathway**: RHOA/B ↓ (upstream Rho GTPase activates ROCK) → **ROCK2** ↓, **MYL12A** ↓ → ACTA2 ↓, LIMK1 ↓ (activated by ROCK; cytoskeletal stiffening), CFL1 ↓ (inactivated by LIMK1; sustains myofibroblast contractility), TLN1/VCL ↓ (stabilized actin filaments; transmits contractile force to the ECM), MRTFA (co-activates SRF-driven contractile genes) ↓ → SRF ↓ (drives contractile gene program (ACTA2/MYL9/CNN1)
Serum	PRO-C3 / PRO-C6 ↓ (Type III & VI collagen synthesis)

Direction: ↑ = up-regulation / increase; ↓ = down-regulation / decrease; ** = no significant change. Individual effect sizes, statistics, and CIs are in the referenced Tables. Pillars 1–3 of 9; see Tables 7 and 8 for pillars 4–9.

Table 5. Cross-Modality Concordance — Fibrolysis, Basement-Membrane Repair, And Re-Epithelialization Pillars

Direction-consistent findings across independent measurement modalities corroborate the fibrolysis, basement-membrane repair, and re-epithelialization (AT1/AT2 alveolar repair) pillars. Row groupings by pillar (4–6 of 9); individual effect sizes and CIs are in Tables 1–3. Continued from Table 6; continued in Table 8.

Modality	Readout summary
4. Fibrolysis	
Serum	PRO-C3 / C6 ↓ (Type III & VI collagen formation / endotrophin); C3M, CTX-III, C6M turnover markers reported directionally
Serum (ratios)	PRO-C3/C3M ↓, PRO-C3/CTX-III ↓, PRO-C6/C6M ↓ (net synthesis/degradation shifts, fibrolysis-favoring)
RNA-seq	**TGF-β pathway**: **ADAMTS1** ↓, **F2R** ↓, **TXNDC5** ↓, LTBP1 ↓, TGFBR2 ↓ → SMAD6/7 ↑, **PMEPA1** ↑ → FN1 ↓, CCN2 ↓, TGFB1 ↓, MMP1 ↓ **ROCK2 pathway**: RHOA ↓, RHOB ↓ → **ROCK2** ↓, **MYL12A** ↓ → ACTA2 ↓, CFL1 ↓, LIMK1 ↓, TLN1 ↓, VCL ↓ → SRF ↓, MRTFA (MKL1) ↓
5. Basement-membrane repair	
Serum	PRO-C4 ↑ (Type IV BM synthesis); C4Ma3 ↓ (Type IV degradation)
Serum (ratio)	PRO-C4/C4Ma3 ↑ (net BM repair shift)
RNA-seq	**BM repair → AT2/AT1 repair**: **COL4A1/A2** ↑, LAMA3 ↑, COL17A1 ↑ → **CCN3** ↑ → **ALDH1A2** ↑, NAPSA ↑, SFTPB ↑ → **NUPR1** ↑, **CRB3** ↑ **CAV1** ↑, **DLK1** ↑, AGER ↑ (AT1), AQP5 ↑ (AT1)
6. Re-epithelialization (AT1/AT2 repair)	
RNA-seq	**BM repair → AT2/AT1 repair**: **COL4A1/A2** ↑, LAMA3 ↑, COL17A1 ↑ → **CCN3** ↑ → **ALDH1A2** ↑, NAPSA ↑, SFTPB ↑ → **NUPR1** ↑, **CRB3** ↑ **CAV1** ↑, **DLK1** ↑, AGER ↑ (AT1), AQP5 ↑ (AT1)
Clinical	FVC ↑ / dyspnea ↓ / cough ↓ as epithelial-repair-consistent functional read-outs

Table 6. Cross-Modality Concordance — FVC Stabilization, Antitussive, And GI-Protection Pillars

Direction-consistent findings across independent measurement modalities corroborate the FVC-stabilization, antitussive, and GI-protection pillars. Row groupings by pillar (7–9 of 9); individual effect sizes and CIs are in Tables 3–5. Continued from Table 7.

Modality	Readout summary
7. FVC stabilization	
Clinical	FVC responder rate ↑ (38.5% vs 20.0% overall; 50.0% vs 20.0% +SOC); Mean FVC ΔCFB ↑ (+99 mL overall PBO-adj; +139 mL +SOC PBO-adj); ≥10% FVC decline event rate ↓ (8% vs 20%)
PRO	Dyspnea ↓ (4% vs 17%, −76% relative)
8. Antitussive	
Clinical	Treatment-related cough ↓ (0% vs 25% within-study)
RNA-seq	**CAV1** ↑, TNFSF10 (TRAIL) ↓ (Epithelial-barrier) → HTR1B ↓, TAC3 ↓, CALCB ↓ (tunes C-fiber excitability)→ TRPA1 ↓, TRPV1 ↓ (peripheral sensory transduction channels; stimulus →nerve impulse on C-fibers)
9. GI-protection	
Clinical	Diarrhea ↓ (17% vs 33% within-study)
RNA-seq	**ARG2** ↓ (macrophage arginine metabolism; mucosal inflammatory tone), CCR4 ↓, MRC1 ↓ → **iNKT** inhibition; **FGF2** ↑, FGFR1/3 ↑, **FLT1** ↑ FLT4 ↑, PDGFA/B/C ↑, VEGFA ↑

Conclusion

In a 12-week Phase 2a study of oral tazarotene (GRI-0621) in IPF, no single serum ECM biomarker reached inferential significance at the individual-marker level — a limitation consistent with the small evaluable sample (n=19/9 all-subjects; n=16/6 on background SOC) and the high within-arm variance typical of exploratory Phase 2a panels. However, across four independent measurement modalities — serum neo-epitope biomarkers, whole-blood transcriptomics, 28-color spectral flow cytometry of paired PBMC and BAL, and physiological/patient-reported endpoints — all nine pre-specified mechanistic pillars showed directionally consistent, favorable signals from two or more modalities. GRI-0621 warrants evaluation in a 52-week study as the first oral RARβ/γ-selective agonist anti-fibrotic to demonstrate this breadth of modality-concordant mechanistic and clinical activity, particularly on top of background pirfenidone or nintedanib.