

Regulation of Fibroblast Biology in Ileum and Rectum by Guselkumab in Crohn's Disease:

Post-hoc Analysis of GALAXI Ph3 Program

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Background

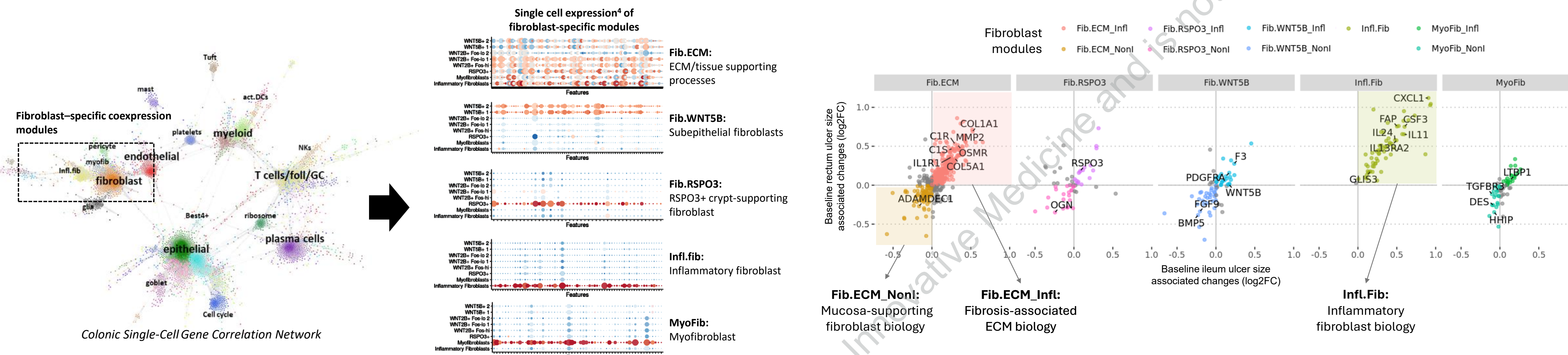
- Fibroblasts contribute to inflammatory signaling and fibrosis in Crohn's disease (CD).
- GALAXI Phase 3 established guselkumab (GUS) efficacy and superiority to ustekinumab (UST) in endoscopic endpoints at WK48.¹
- Bulk transcriptomics previously differentiated GUS from UST.²

Objectives

- Evaluate the effects of GUS and UST on fibroblast-associated changes using single-cell gene coexpression patterns to deconvolute bulk transcriptomics.

Methods

- GALAXI Phase 3 design, randomized 2:2:2:1:
GUS 200 mg IV → 200 mg SC q4w
GUS 200 mg IV → 100 mg q8w
UST 6 mg/kg IV → 90 mg SC
Placebo
- Ileum and rectum patient biopsies from Week (WK) 0, WK12 and WK48 timepoints underwent bulk RNA-seq and single-cell module deconvolution using published modules.^{2,3,4}
 - 33% of ileum samples were from participants with any ileal stenosis (SES-CD narrowing > 0) at baseline
- Differential analysis of fibroblast modules over time per treatment per segment was performed using linear mixed effects models in representative subject samples² (i.e., molecularly inflamed samples from segments with SES-CD>0 at baseline)



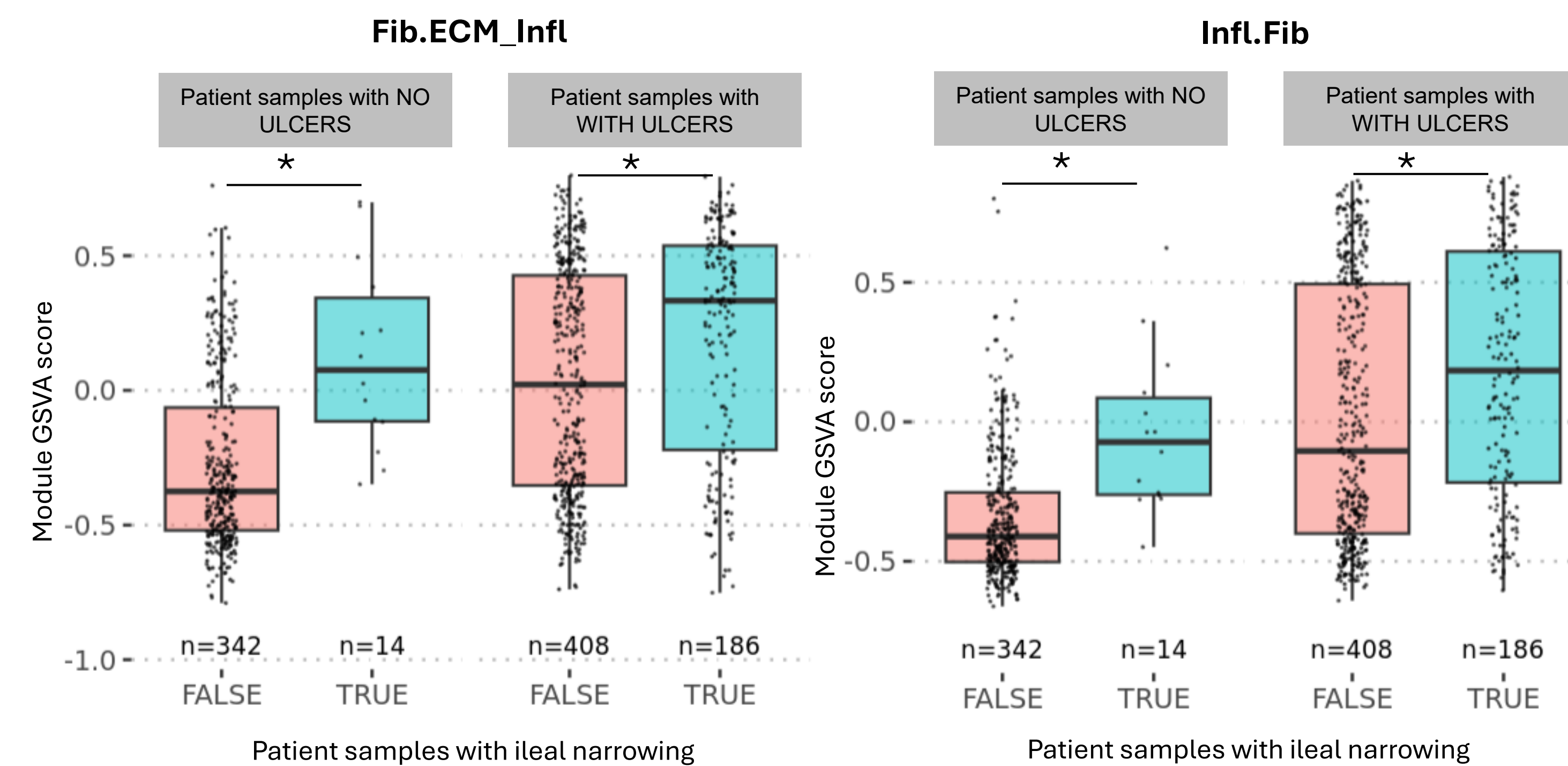
Leveraging single cell coexpression patterns for deconvolution of bulk transcriptomics. Single cell coexpression networks establish fibroblast-derived gene modules to facilitate deconvolution of bulk transcriptomics (left). Disease-based tailoring of fibroblast modules accounts for association of fibroblast genes with ulcer size in ileum and rectum in Crohn's disease (right).

Results

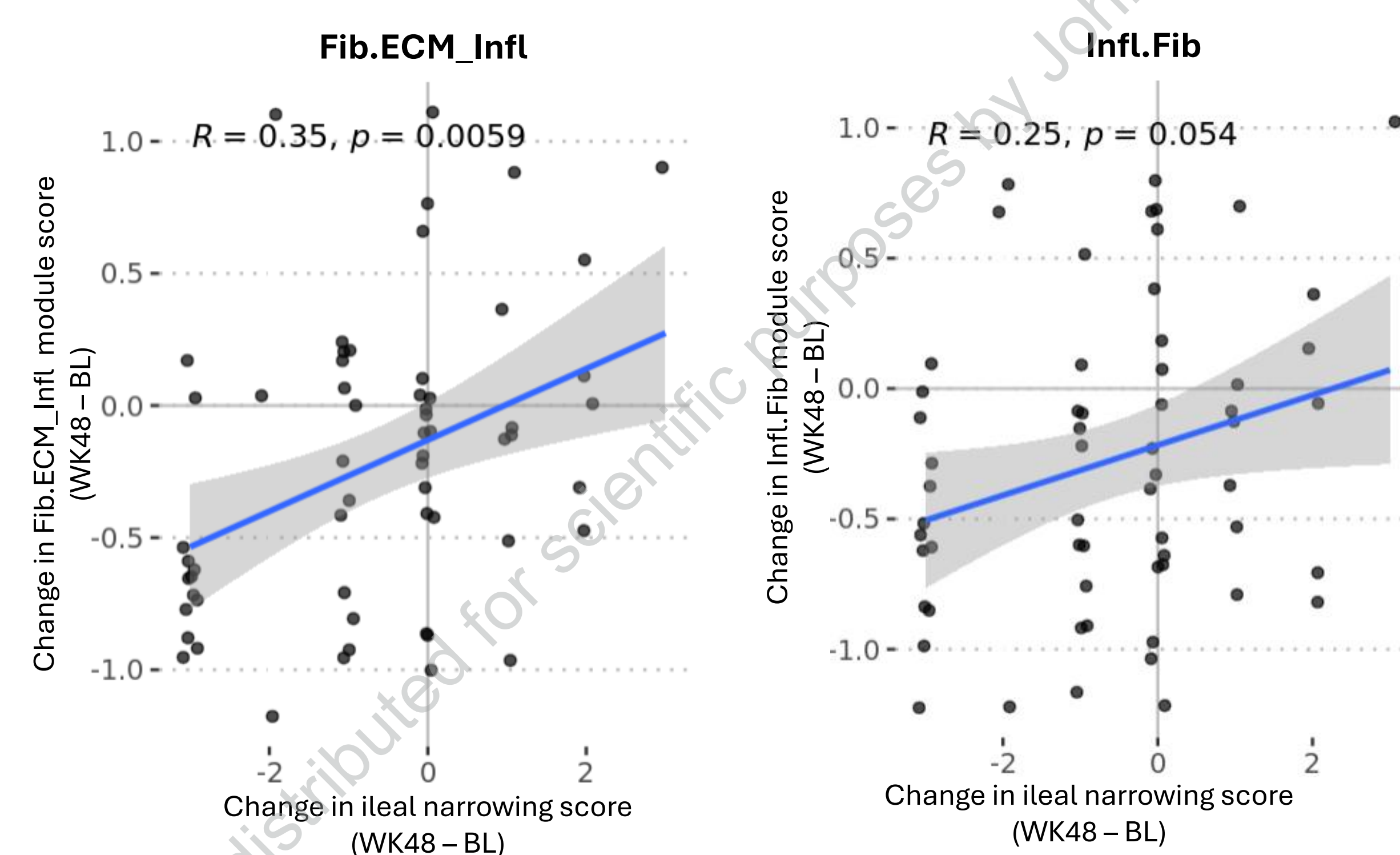
Both inflammatory and fibrosis-related biology are present in ileal biopsies with active narrowing, independent of ulceration

Reductions in inflammatory and fibrosis-related gene modules are correlated to paired changes in narrowing in the ileum

Regulation of inflammatory and mucosa-supporting fibroblast biology at WK12 with GUS is followed by significant reduction in fibrosis-related biology by WK48 in ileum and rectum



Note: Analysis performed in total set of ileum biopsies



Note: Analysis performed in subset of ileum biopsies from patients with active narrowing (SES-CD narrowing > 0) at baseline



Note: Analysis performed in total set of ileum and rectum biopsies

Key Takeaways

- Fibroblast gene modules capture ulcer- and ileal narrowing-associated biology in CD mucosal pinch biopsies
- Reductions in inflammatory fibroblast and fibrosis-related modules correlate with improved ileal narrowing at WK48
- Selective inhibition of the IL-23p19 subunit with GUS demonstrated greater reversal of disease associated fibroblast biology in the ileum and rectum compared with IL-12/23p40 subunit blockade with UST