A BIOINFORMATIC APPROACH TO PALI-2108 TREATMENT IN ULCERATIVE COLITIS REVEALS THE POTENTIAL FOR ANTI-FIBROTIC EFFICACY WITH LOCAL PDE4 INHIBITION IN INTESTINAL FIBROSIS

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Joerg Heyer PhD[1], Akshaya Kanthimathinathan[2], Aastha Tripathi[2], Sampuran Chakraborty[2], Swaraj Basu PhD[2], Florian Rieder MD[3], Mitchell Jones MD, PhD[1]
1) Palisade Bio, Carlsbad, CA, 2) Strand Life Sciences, San Francisco, CA, 3) Cleveland Clinic, Cleaveland, OH

Introduction

Intestinal fibrosis is a complex pathological condition that is associated with chronic inflammation, including ulcerative colitis (UC) or Crohn's Disease (CD). UC is characterized by ulcerations, diarrhea, hematochezia, abdominal pain, and emaciation. The pathogenesis of UC involves a multifactorial interplay between dysregulated mucosal immunity, compromised epithelial integrity, and genetic susceptibility. These interactions foster a pro-inflammatory environment, leading to the recruitment and activation of various immune cells, including macrophages, dendritic cells, and T lymphocytes, which contribute to tissue damage and fibrosis over time. Fibrosis, the excessive deposition of extracellular matrix components, is a hallmark of chronic UC and can significantly impair intestinal function, complicating the disease course and limiting therapeutic options.

Recent advances in understanding the molecular mechanisms underlying UC have highlighted the potential role of phosphodiesterase-4 (PDE4), an enzyme that regulates cyclic adenosine monophosphate (cAMP) levels. Inhibition of PDE4 has been shown to modulate immune responses and mitigate inflammation. Specifically, PDE4 inhibition leads to suppression of pro-inflammatory cytokines and chemokines production, thereby modulating immune cell activation and infiltration. PDE4 inhibitors, such as apremilast, have been approved for the treatment of inflammatory conditions, including psoriasis and bronchial disorders. However, the therapeutic potential of PDE4 inhibition in UC and CD, particularly in preventing or reversing intestinal fibrosis, remains under exploration.

Methods

To identify potential responders to PDE4 inhibition, we developed an algorithm targeting cAMP-regulated genes using RNAseq data from 3,000 UC and CD patient samples, proprietary and in-house animal model data. All samples were processed through a Nextflow RNAseq pipeline and the data were analyzed for correlation and interactions with PDE4. Meta-analysis was conducted using MetaVolcanoR. A ML model selected biomarkers, assigned weighted scores, and multinomial logistic regression to classified disease states. The weighted sum expression was then used to classify responders versus non-responders (in a public microarray dataset, TNFa inhibitor therapy) : SUM=∑wi·gi, where wi is the weight for gene i, and gi is its expression level.

Results

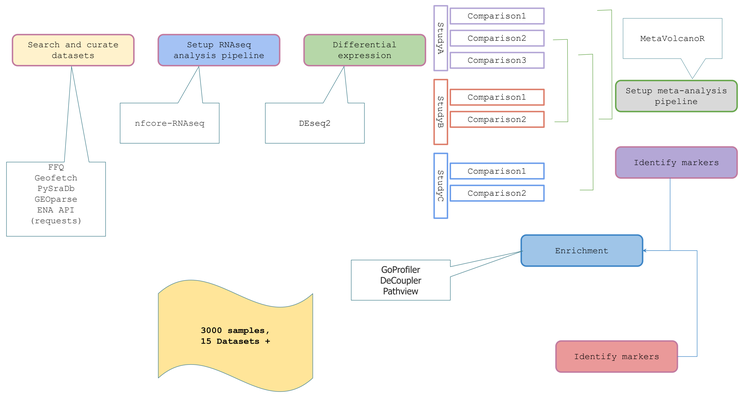
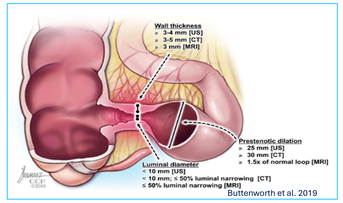
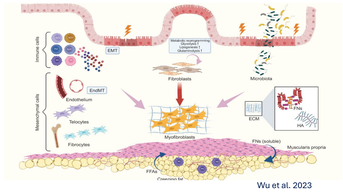


Figure 2. A genomics workflow to identify markers for ulcerative colitis



- Symptoms Associated with Fibrosis:
  - CD: Strictures and obstructive symptoms.
  - UC: Urgency and motility abnormalities.
- Significant Unmet Need Particularly in Crohn's Disease
  - In CD, the majority (>50%) of patients experience fibrosis, presenting as strictures and obstructive symptoms, at least once in their lifetime.
  - Often necessitates surgical interventions.



- Extra Cellular Matrix (ECM) Deposition and Scar Formation:
  - Physiological process for tissue repair.
  - Excessive ECM causes tissue stiffness and functional impairment.
  - Intestinal fibrosis is present even without stricture formation.
- Mesenchymal Cells Important Driver of Fibrosis:
  - Increased MC number in intestinal fibrosis.
  - Heterogeneous population: Fibroblasts, myofibroblasts, smooth muscle cells (SMC).
  - Function: provide the scaffold where cells reside, shaping tissue structure.

Figure 1 . Stenosis in Crohn's Disease and ulcerative Colitis

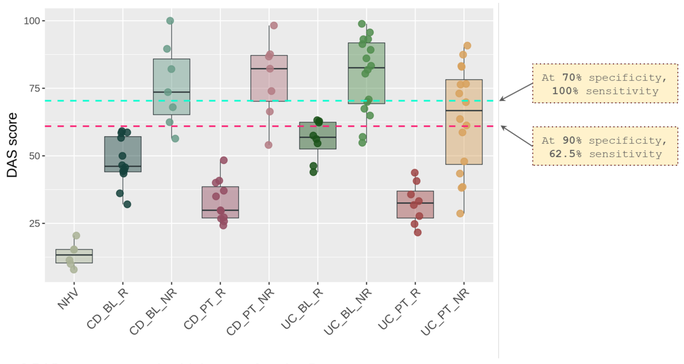


Figure 3 DAS score approach with best performing 5 genes

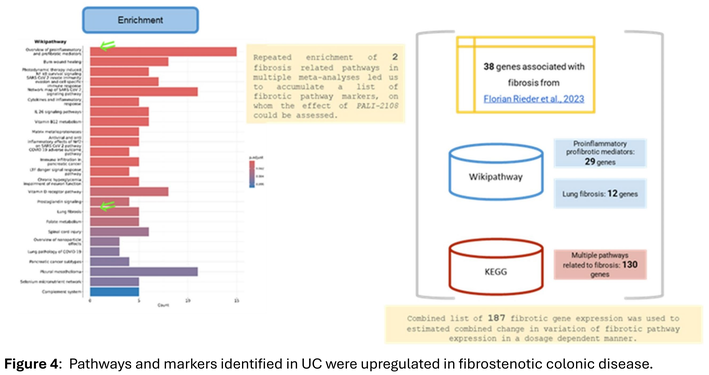


Figure 4: Pathways and markers identified in UC were upregulated in fibrostenotic colonic disease.

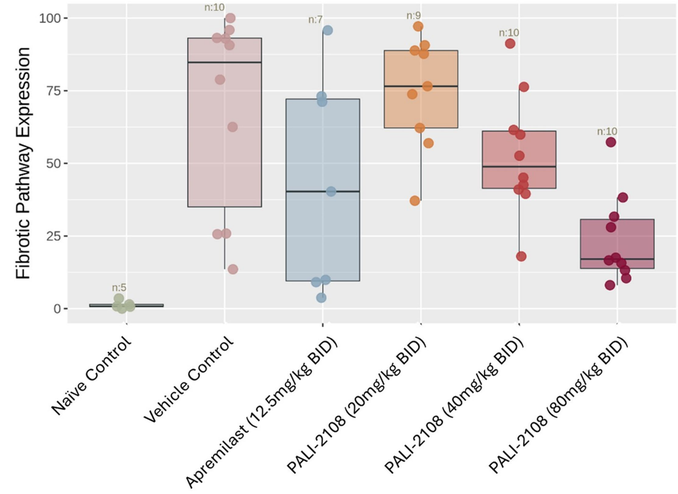


Figure 5: DAS score approach with best performing 5 genes

Methods

PALI-2108 is a novel, promising therapy for Inflammatory Bowel conditions such as ulcerative colitis (UC) and Fibrostenotic Crohn's Disease. Its localized bioactivation, expanded lower GI-Tract therapeutic window, extended-release characteristics, and potent PDE4 inhibition result in improved efficacy compared to other PDE4 inhibitors. PALI-2108 is currently under evaluation in a Phase 1 study, with a favorable safety profile observed in ascending single-and multiple ascending-dose cohorts.

Our findings suggest that cAMP-regulated drivers of inflammation are activated in both UC and fibrostenotic Crohn's Disease. Therapy leading to a reduction of cAMP regulated inflammation and stenosis could offer new treatment options for patients in Ulcerative Colitis and Fibro-Stenotic Crohn's Disease. PALI-2108's potential to engage antifibrotic pathways may provide a novel therapy to treat patients which currently lack treatment options.

Better-tolerated oral PDE4 inhibitors remain an unmet need in IBD. PALI-2108, a lower GI-Tract activated PDE4 inhibitor with high bioavailability, effectively reduces colitis symptoms in the DSS mouse model without CNS toxicity associated with systemic exposure. This suggests it could be a novel alternative for UC patients. Safety and tolerability of PDE4 inhibitors are closely linked to peak drug concentrations (Cmax). The proposed BID dosing during induction minimizes Cmax, while the extended-release characteristics allow for effective QD dosing during maintenance. The pharmacokinetic modeling suggests a favorable therapeutic window, with PALI-2108 achieving higher tissue-to-plasma drug ratios and enhanced tissue inhibition compared to other PDE4 inhibitors.PALI-2108 has now entered a Phase 1 study to assess its tolerability in healthy volunteers and UC patients and studies in Fibrostenotic Crohn's Disease are planned.