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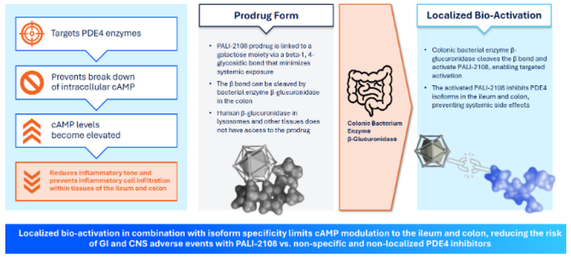
Development of a Mechanistically Anchored PDE4/cAMP Transcriptomic Biomarker to Predict Response to PALI-2108 in Ulcerative Colitis

Joerg Heyer PhD[1]; Swaraj Basu; and Mitch Jones MD, PhD[1]
[1]Palisade Bio, Denver, CO; [2]Strand Life Science, San Francisco, CA

INTRODUCTION AND AIM

Therapeutic response in ulcerative colitis (UC) remains heterogeneous, with limited biomarkers to guide patient selection. Phosphodiesterase-4 (PDE4) inhibition modulates intracellular cAMP signaling and downstream inflammatory pathways but is limited by systemic tolerability, including GI adverse effects that can exacerbate underlying disease symptoms. PALI-2108 is a once-daily oral prodrug designed for targeted lower GI tract delivery, where it is locally bioactivated in the ileum and colon. The active moiety is then absorbed and distributed systemically, allowing for both local and systemic pharmacologic effects. We **aimed** to develop a transcriptomic biomarker integrating disease biology and PDE4 mechanistic activity to predict therapeutic response.



Localized bio-activation in combination with isoform specificity limits cAMP modulation to the ileum and colon, reducing the risk of GI and CNS adverse events with PALI-2108 vs. non-specific and non-localized PDE4 inhibitors

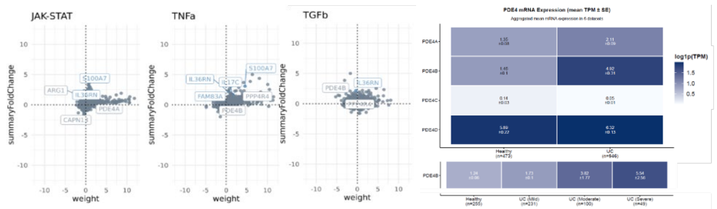


Figure 1:
(left) Volcano Plots of RNAseq biomarker data demonstrate enriched PDE4 expression in multiple inflammatory and fibrotic pathways in UC and CD patient tissue biopsy samples.

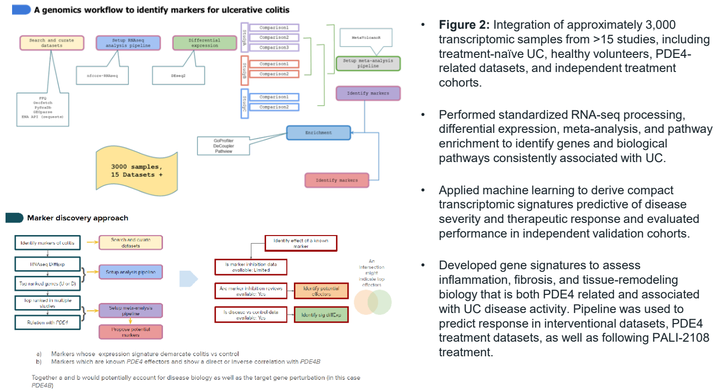
(right) Overexpression of PDE4A, B, and D mRNA and correlation between disease activity and PDE4B expression. This has been independently confirmed at the protein level (Li et al. 2020).

METHODS

A multi-stage biomarker framework was applied using publicly available and proprietary RNA sequencing datasets (see **Figure 2**). The publicly available discovery cohort included n=1751 (UC (N=1338); controls (N=413)). Differential expression analyses compared case vs control, inflammatory vs non-inflammatory, and severe vs mild disease states. Genes selection was based on differential expression ($P \leq 0.05$, $|\log FC| \geq 0.6$), reproducibility, and biological relevance. A random-effects meta-analysis was used to identify robust markers, enhanced using correlation of known PDE4 effectors with PDE4B expression and seven PDE4 inhibition datasets. Final gene signatures were achieved by integrating PDE4B-correlated effectors with meta-analysis-derived markers. Machine learning-based weighted scoring classified responder phenotypes, with a composite disease activity score (Pscore-Nscore), where Pscore reflects upregulated PDE4B-associated genes and Nscore reflects inverse/downregulated genes.

RESULTS

Integrative Transcriptomic Meta-Analysis Workflow for Biomarker Discovery and Fibrosis Pathway Assessment in UC and PDE4 Inhibition Studies



- **Figure 2:** Integration of approximately 3,000 transcriptomic samples from >15 studies, including treatment-naïve UC, healthy volunteers, PDE4-related datasets, and independent treatment cohorts.
- Performed standardized RNA-seq processing, differential expression, meta-analysis, and pathway enrichment to identify genes and biological pathways consistently associated with UC.
- Applied machine learning to derive compact transcriptomic signatures predictive of disease severity and therapeutic response and evaluated performance in independent validation cohorts.
- Developed gene signatures to assess inflammation, fibrosis, and tissue-remodeling biology that is both PDE4 related and associated with UC disease activity. Pipeline was used to predict response in interventional datasets, PDE4 treatment datasets, as well as following PALI-2108 treatment.

Transcriptomic Biomarker Signatures Demonstrate Superior Separation Using Biomarker Score Compared to Selecting Based on PDE4 Expression Alone

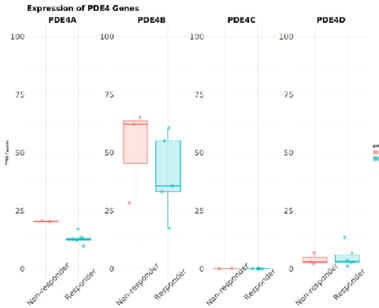


Figure 4: Expression data for PDE4 genes in Responders and Non-responders showing Transcripts Per Million (TPM).

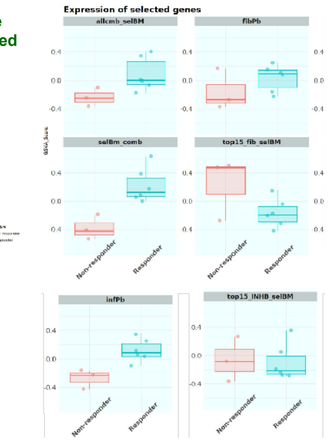


Figure 5: Group expression score data for groups of high performing biomarkers associated with inflammation and fibrosis and under evaluation as part of a Disease Activity Score (DAS) index for PDE4 related genes and those correlated with UC and CD disease activity

Transcriptomic Biomarker Signature Demonstrates Predictive Performance for Treatment Response in UC Patients

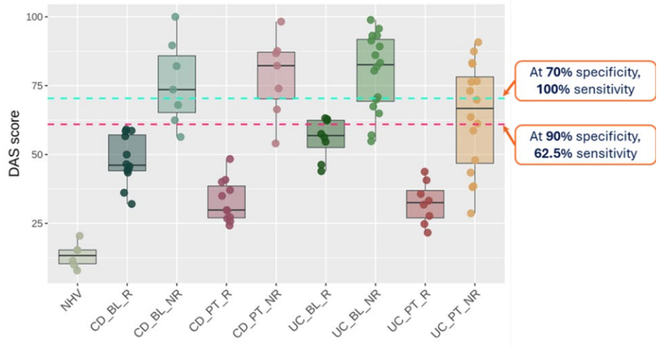


Figure 3. The model demonstrated an AUC of approximately 0.67. Optimized gene sets achieved 100% sensitivity at 70% specificity (blue dashed line) and 62.5% sensitivity at 90% specificity (red dashed line), representing candidate thresholds for responder classification using the DAS RNA-seq assay. AUC, area under the curve; BL, baseline; CD, Crohn's disease; DAS, disease activity score; NHV, normal healthy volunteers; NR, non-responders; PT, post-treatment; R, responders; UC, ulcerative colitis.

SUMMARY

We developed a mechanistically anchored transcriptomic biomarker integrating disease biology and PDE4/cAMP pathway activity to predict therapeutic response in UC.

PALI-2108's targeted lower-GI prodrug activation, combined with systemic distribution of the active compound, provides a differentiated pharmacologic profile enabling both local and systemic modulation of disease pathways.

This biomarker framework identifies patients likely to benefit from PDE4 modulation, improving response prediction and capturing inflammatory and fibrotic biology.

Prospective validation is ongoing to support clinical implementation to improve response rates and reduce unnecessary drug exposure in UC.

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