PROJECT

Supervisor:	Sara Massironi
Title:	Determinants of Delayed Response to Advanced Therapies in IBD: Insights from Extended Induction Strategies
Curriculum:	Clinical and Experimental Medicine
Link to the personal page of the University or relevant hospital site website:	https://www.unisr.it/docenti/m/massironi-sara

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Selective interleukin-23 inhibitors (IL-23i) have significantly improved outcomes in inflammatory bowel disease.[1-3] However, a substantial proportion of patients do not achieve response at the end of standard induction. Notably, nearly half of these patients subsequently respond following extended induction, suggesting the existence of a subgroup of "delayed responders"[4]. While clinical data support this phenomenon, its biological basis remains poorly understood. Biomarkers, including C-reactive protein and fecal calprotectin, do not adequately capture this heterogeneity, highlighting the need for tissue-level and immune profiling approaches.[4]

Rationale and hypothesis

IL-23i induce mucosal transcriptional changes marked by reduced expression of tissue injury, extracellular matrix remodeling, and inflammatory genes, with changes maintained over time in responders[5].

However, approximately 45% of patients exhibit discordance between clinical and transcriptional response at the end of induction[5], with some endoscopic non-responders showing transcriptomic profiles similar to responders.[6] This discrepancy may reflect temporal heterogeneity in response kinetics, where molecular changes precede overt clinical improvement, suggesting that single timepoint analyses may fail to capture the full dynamics of therapeutic response.[5,6]

We therefore hypothesize that a biologically distinct population of delayed responders exists, separate from early responders and true primary non-responders.[5,6,7,8]

Objectives and specific aims

(1) Given that overlapping transcriptomic profiles have been observed between clinical responders and non-responders[6], we aim to determine whether this can be resolved by identifying delayed responders as a distinct biological group. To this end, we will evaluate longitudinal mucosal transcriptional trajectories across early responders, delayed responders, and non-responders through transcriptomic profiling of intestinal biopsies.

(2) As single-cell RNA sequencing has demonstrated the ability to detect differences in the activation status of T cells between responders and non-responders in other IMIDs[9], and considering the central role of the immune compartment in the response to IL-23i[10], our aim is to resolve the cellular architecture and transcriptional programs underlying delayed response using single-cell RNA sequencing with CD45+ cell enrichment.

(3) Based on previous evidence showing that responder and non-responder patients display distinct IL-23–activated peripheral immune profiles[11], we aim to assess whether delayed responders exhibit a distinct or intermediate systemic immune phenotype through longitudinal peripheral blood analysis, including PBMC immunophenotyping and plasma cytokine profiling.

(4) To evaluate clinical, biochemical, endoscopic and long-term outcomes differences between early, delayed and non-responder.

Expected outcomes

The ultimate aim is to identify molecular predictors of delayed response to IL-23i and improve patient stratification.

Skills that the student should acquire (max. 600 characters including spaces):

- Collection of endoscopic biopsies in colonoscopy, blood, and processing of samples.
- Interpretation of transcriptomics data and familiarity with computational biology
- Competencies in molecular and cellular biology techniques
- Capability to critically discuss results
- Capability to write reports and the final manuscript, along with the final thesis
- Independence in coordinating experiments and clinical studies, under DoS's supervision

References (max. 15)

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6. Sudha Visvanathan, Patrick Baum, Azucena Salas, Richard Vinisko, Ramona Schmid, Kristie M Grebe, Justin W Davis, Kori Wallace, Wulf O Böcher, Steven J Padula, Jay S Fine, Julián Panés,

Selective IL-23 Inhibition by Risankizumab Modulates the Molecular Profile in the Colon and Ileum of Patients With Active Crohn's Disease: Results From a Randomised Phase II Biopsy Sub-study, Journal of Crohn's and Colitis, Volume 12, Issue 10, October 2018, Pages 1170–1179, https://doi.org/10.1093/ecco-jcc/jjy099

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