PROJECT

Supervisor:	Silvio Danese
Title:	Integrating molecular profiling and mechanobiology to guide dilation of asymptomatic strictures in Crohn's disease
Curriculum:	Clinical and Experimental Medicine
Link to the personal page of the University or relevant hospital site website:	https://www.unisr.it/docenti/d/danese-silvio

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

Background/gap of knowledge

Fibrostenosing Crohn's disease (CD) is a progressive phenotype characterized by bowel wall fibrosis and luminal narrowing, often leading to obstructive symptoms. Strictures may be primary or postoperative, both with high recurrence and surgical risk [1],[2]. Endoscopic balloon dilation (EBD) is effective for short strictures [3] but rarely used in asymptomatic patients, leaving biologically active "silent" lesions at risk of progression [4], [5]. No molecular markers currently identify which asymptomatic strictures could benefit from early EBD.

Rationale and hypothesis

Fibrostenotic CD lesions are not biologically inert [5]. Mechanical stress and matrix stiffness drive fibrosis by promoting fibroblast activation, extracellular matrix (ECM) deposition, and tissue remodeling, creating a self-perpetuating, inflammation-independent fibrotic loop [6]. Mechanical stretch and luminal distension further upregulate profibrotic mediators enhancing collagen deposition and smooth muscle hypertrophy, while reduction of mechanical tension can reduced fibrosis, indicating that mechanotransduction is pathogenic but potentially reversible [7].
These lesions exhibit distinct transcriptomic and circulating biomarker profiles enriched for stromal activation, ECM remodeling, and mechanotransduction, reflecting biologically diverse, mechano-responsive phenotypes [8], [9], [10], [11]. Active, remodeling-prone signatures may predict sustained benefit from EBD and reduced reintervention. Additionally, EBD may transiently modulate mechano-dependent fibrotic pathways, although this has not yet been demonstrated in humans with CD [7].

Objectives and specific aims

1. To determine whether the baseline biological signature of fibrostenotic strictures predicts clinical benefit from early EBD in asymptomatic CD patients.

1a. Based on evidence that transcriptomic profiles reveals fibroblast heterogeneity with most stricture-selective changes in the mucosa/submucosa [12], we will characterize baseline bulk transcriptomic profiles on stricture fresh biopsies.

1b. Given that collagen markers correlate with histological fibrosis and chronic inflammation [9], we will assess baseline circulating biomarkers associated with CD stenosis.

1c. We will evaluate the association between baseline biological signature (transcriptomic profiles and circulating biomarker) and treatment strategy (EBD vs observation) on 1-year outcomes (maintenance of asymptomatic status, need for repeat EBD or surgery)

2. To assess the effect of EBD in transcriptomic profiles and circulating biomarkers.

Based on evidence that mechanical stress drives fibrosis via fibroblast activation and ECM remodeling, while its release can attenuate profibrotic signaling [6], [7], we will perform bulk transcriptomic profiles on post-EBD stricture fresh biopsies (2-4 weeks) and circulating biomarkers at 3, 6 and 12 months.

Expected outcomes

The integration of molecular data could guide precision endoscopic therapy, enable proactive management, and reduce morbidity and surgical risk in fibrostenosing CD.

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

Competencies in molecular and cellular biology techniques: RNA extraction, and analysis of circulating biomarkers

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)

[1] Chan WPW, Mourad F, Leong RW. Crohn's disease associated strictures. J Gastroenterol Hepatol 2018;33:998–1008. https://doi.org/10.1111/jgh.14119.

[2] Click B, Merchea A, Colibaseanu DT, Regueiro M, Farraye FA, Stocchi L. Ileocolic Resection for Crohn Disease: The Influence of Different Surgical Techniques on Perioperative Outcomes, Recurrence Rates, and Endoscopic Surveillance. Inflamm Bowel Dis 2022;28:289–98. https://doi.org/10.1093/ibd/izab081.

[3] Bettenworth D, Baker ME, Fletcher JG, Jairath V, Lu C, Bemelman W, et al. A global consensus on the definitions, diagnosis and management of fibrostenosing small bowel Crohn's disease in clinical practice. Nat Rev Gastroenterol Hepatol 2024;21:572–84. https://doi.org/10.1038/s41575-024-00935-y.

[4] Lichtenstein GR, Loftus EV, Afzali A, Long MD, Barnes EL, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol 2025;120:1225–64. https://doi.org/10.14309/ajg.0000000000003465.

[5] Wang X, Huang L, Lin S, Shen X, Zheng Q, Zhang R, et al. Magnetic resonance cell size imaging reveals intestinal fibrosis to predict intestinal disease progression in patients with Crohn's disease. J Crohns Colitis 2025;19:jjaf119. https://doi.org/10.1093/ecco-jcc/jjaf119.

[6] Johnson LA, Rodansky ES, Sauder KL, Horowitz JC, Mih JD, Tschumperlin DJ, et al. Matrix stiffness corresponding to strictured bowel induces a fibrogenic response in human colonic fibroblasts. Inflamm Bowel Dis 2013;19:891–903. https://doi.org/10.1097/MIB.0b013e3182813297.

[7] Lin Y-M, Zhang K, Geesala R, Lipson KE, Qiu S, Powell DW, et al. Mechanical stress-induced connective tissue growth factor plays a critical role in intestinal fibrosis in Crohn's-like colitis. Am J Physiol Gastrointest Liver Physiol 2024;327:G295–305. https://doi.org/10.1152/ajpgi.00123.2024.

[8] Acharjee A, Shivaji U, Santacroce G, Akiror S, Jeffery L, Varnai C, et al. Novel Transcriptomic Signatures in Fibrostenotic Crohn's Disease: Dysregulated Pathways, Promising Biomarkers, and Putative Therapeutic Targets. Inflamm Bowel Dis 2025;31:1502–13. https://doi.org/10.1093/ibd/izaf021.

[9] Poulsen A, Alexdóttir MS, Riis LB, Ovesen PD, Rasmussen J, Wewer MD, et al. Serum biomarkers of collagen remodeling are associated with intestinal fibrosis and differentiate stenotic from luminal Crohn's disease patients: a pre- and post-resection longitudinal study. J Crohns Colitis 2025;19:jjaf085. https://doi.org/10.1093/ecco-jcc/jjaf085.

[10] Kong L, Subramanian S, Segerstolpe Å, Tran V, Shih AR, Carter GT, et al. Single-cell and spatial transcriptomics of stricturing Crohn's disease highlights a fibrosis-associated network. Nat Genet 2025;57:1742–53. https://doi.org/10.1038/s41588-025-02225-y.

[11] Bauer-Rowe KE, Pham B, Griffin M, Liang NE, Kim A, Lu JM, et al. Creeping fat-derived mechanosensitive fibroblasts drive intestinal fibrosis in Crohn's disease strictures. Cell 2025;188:6536-6553.e26. https://doi.org/10.1016/j.cell.2025.08.029.

[12] Mukherjee PK, Nguyen QT, Li J, Zhao S, Christensen SM, West GA, et al. Stricturing Crohn's Disease Single-Cell RNA Sequencing Reveals Fibroblast Heterogeneity and Intercellular Interactions. Gastroenterology 2023;165:1180–96. https://doi.org/10.1053/j.gastro.2023.07.014.