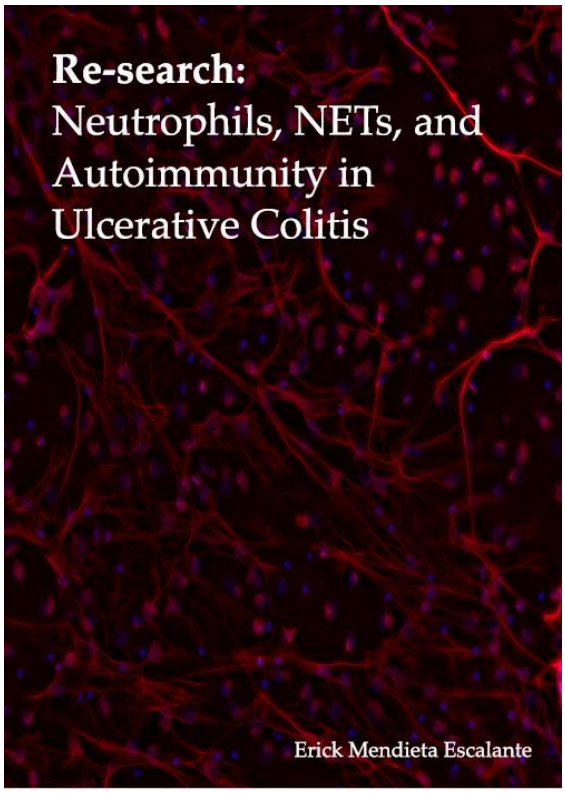

Samenvatting van het proefschrift

E. Mendieta Escalante
"Re-search: neutrophils, NETs, and Autoimmunity in Ulcerative Colitis"

Promotiedatum: 28 Januari 2026
Universiteit: Universiteit Groningen

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Ulcerative colitis (UC) affects millions worldwide, causing chronic intestinal inflammation with symptoms including bloody diarrhea and abdominal pain. Despite decades of research, the disease remains difficult to diagnose and treat, with its fundamental causes poorly understood. This doctoral research revisits a long-standing mystery in UC: atypical anti-neutrophil cytoplasmic antibodies (a-ANCAs), discovered in the 1990s but largely abandoned due to unclear targets and clinical significance.

This thesis reveals that a-ANCAs target neutrophil extracellular traps (NETs)-web-like structures released by immune cells to fight infections. By identifying these antibodies as anti-NET antibodies (ANETAs), this research establishes their role as predictors of severe disease outcomes in UC patients, providing the first clear clinical utility for these mysterious autoantibodies.

Taking into account that NETs can be induced by neutrophils with platelets, we study their ratio (NEUPLA ratio: neutrophil-to-platelet ratio) and we found that it can be a simple, cost-effective biomarker that clinicians can use to predict treatment response. Using only routine blood tests, this tool helps identify which patients will benefit from specific therapies, moving toward personalized medicine in UC management. Also, the presence of low-density neutrophils (LDN) in individuals and their relation to disease

activity could be related to the constant formation of NETs in UC. Additionally, this work investigates how mesalamine-one of UC's oldest treatments-works at the cellular level; we found that mesalamine timing matters: co-treatment with inflammatory triggers more effectively suppresses harmful NET formation than pre-treatment, offering practical insights for optimizing therapy.

By bridging fundamental immunology with clinical gastroenterology, this dissertation provides potential tools for UC diagnosis and treatment. The identification of ANETAs as disease severity predictors, the validation of NEUPLA as a practical biomarker, and the mechanistic insights into mesalamine action collectively advance our understanding of neutrophil-driven pathology in inflammatory bowel disease. These discoveries open pathways toward earlier intervention and more targeted therapeutic approaches for UC patients.