The clinical phenotype and the outcome of Crohn’s disease (CD) and ulcerative colitis (UC), the opposite ends of chronic inflammatory bowel diseases (IBD), are heterogeneous and represent the result of a complex interplay of the gut microbiome with the immune system in genetically predisposed individuals. Disease management is much less heterogeneous as all patients are treated using non-specific anti-inflammatory agents, and only 30-50% achieve clinical and mucosal remission—the goal of therapy nowadays—therefore leaving large margins for improvement. The advances in knowledge about the factors triggering disease onset should be translated to approach the disease from a molecular angle. Key cellular pathways have emerged including bacterial recognition, autophagy, endoplasmic reticulum stress and intestinal barrier function. Functional/molecular characterization of these pathways in a given patient, correlation with meaningful clinical outcomes, and tailoring an individual therapeutic approach has never been attempted and will represent a breakthrough in the current paradigm of treating multifactorial inflammatory conditions. This project aims to functionally characterize patients with CD/UC for the major pathways by using integrated (epi)genetic, transcriptomic, immunologic, barrier integrity and metagenomic studies. From these readouts we will construct an index [the Crohn’s and Ulcerative Colitis Characterization and Intervention trial (CrUCCial) index], reflecting the proportional contribution of each of the pathogenic mechanisms in a given patient. We will next study the correlation of this index and its components to meaningful clinical outcomes and finally, the index will be tested in a pilot study of newly diagnosed patients in whom the disease will be targeted individually based on the components of the CrUCCial index. Our approach, from diagnosis over prognosis to therapy, will revolutionize the paradigm of disease management.
New light on inflammatory bowel disease

There is currently no cure for Crohn’s disease or ulcerative colitis, two closely related conditions which come under the wider umbrella of inflammatory bowel diseases, so treatment is focused primarily on managing the diseases. A number of treatments are available to help reduce the impact of IBD, including corticosteroids and immunosuppressive drugs. “They are anti-inflammatory agents, which reduce inflammation. Newer treatments are also available, where you block certain pro-inflammatory cytokines,” explains Professor Séverine Vermeire, the Principal Investigator of the CrUCCial project. These treatments are not always well-suited to the specific needs of the individual patient however, as IBD is highly complex and heterogenous in nature. “IBD is difficult to treat. Powerful drugs are available, but if you apply these drugs to 100 patients for example, then this will lead to clinical remission and complete healing of the bowel in only 30 percent of patients roughly,” says Professor Vermeire. “Furthermore, we don’t know - and still cannot predict - which patients will react to which drug.”

The work of the CrUCCial project, an EC-funded initiative based at Katholieke Universiteit Leuven (KU Leuven), holds clear importance in these terms. Professor Vermeire and her colleagues in the project aim to shed new light on the underlying factors behind the disease, which could eventually lead to improved, more precisely targeted treatment. “We would like to look at what is really triggering the disease in a particular patient. What goes wrong in that patient, in contrast to another? Can we treat the disease in a more functional way?” she says.

Inflammatory bowel diseases

The foundation of this work is a deeper understanding of the underlying causes behind IBD, which are rising in prevalence in many parts of the world, with around 0.3-0.4 percent of the population thought to be affected. While genetic background is an important factor in susceptibility to IBD, this cannot explain the rapid recent increase in the prevalence of these diseases, so Professor Vermeire says other factors must be considered. “The fact that we have not seen rising prevalence in sub-Saharan Africa or very rural areas of Latin America has led many people to think that this must have something to do with changes in lifestyle and diet,” she outlines. These are multi-factorial diseases, and the underlying causes behind each individual case may be different. “We want to first identify what has gone wrong with a patient, and then reflect that in treatment,” says Professor Vermeire. “So maybe you will want to block the inflammation, but if we can identify primary barrier defects in a patient, or disturbance in their recognition and defense against bacteria, there might also be other therapeutic considerations.”

Researchers are analysing and integrating data from over 4,500 patients, including data from blood samples, stool samples and biopsies, to gain a deeper understanding of the key cellular pathways involved in IBD. From these foundations, an index can then be developed reflecting the proportional contribution of each...
pathogenic mechanism in each patient, providing the basis for more tailored, individualised treatment; Professor Vermeire says this is complex work. “The difficulty is in analysing all of these different pathways together,” she explains. This work involves integrating data from different ‘omics studies, including genomics, proteomics, transcriptomics and metagenomics, each of which generates huge volumes of data. “We need to overlay all these ‘omics layers together, and this is the difficulty. So we have set up a kind of intermediate ‘omics layer,” says Professor Vermeire. “We’ve taken research that people have been working on over the last 15 years, and we’re trying to integrate all the knowledge that has been gathered and to bring it all together.”

Clinical outcomes

These diseases can also vary widely in severity, from relatively mild cases through to more serious situations, where a patient may require surgery. The CrUCCial index gives greater detail on the specific nature of each individual patient’s condition; researchers now aim to correlate this with data on clinical outcomes. “Now that we have data on clinical outcomes, we’re looking to see if we can draw links. Are the people that have problems in the composition of their microbiota the people that have more severe disease? Are these the people that have more disease in the small bowel?” says Professor Vermeire. This work could provide a more effective framework for the management of other multi-factorial diseases, aside from IBD. “There are many complex, multi-

We would like to look at what is really triggering inflammatory bowel disease in a particular patient. What goes wrong in that patient, in contrast to another? Can we treat the disease in a more functional way?

A number of important cellular pathways involved in IBD have been identified over the years, including bacterial recognition, autophagy, endoplasmic reticulum (ER) stress and intestinal barrier function. The project aims to build on this data and develop an index that reflects the proportional importance of each pathway in each patient. “We aim to rank patients, for example in terms of intestinal barrier function. If a patient is in the first quartile, that means they have a comparatively poor barrier function and may need treatment to strengthen it,” outlines Professor Vermeire. The project’s research could also hold relevance in terms of disease prevention. “If we identify a particular defect in a given individual that we think is a factor in disease, then maybe it would be worth testing their siblings to see if they also have that defect,” she continues. “That could be a first step towards prevention of the condition.”

Ulcerative colitis (UC)

Crohn’s disease (CD)