



INDUSTRY-ACADEMIA EXCHANGE TO FURTHER FXR-BASED THERAPEUTIC INTERVENTION AND NON-INVASIVE DIAGNOSIS IN INFLAMMATORY BOWEL DISEASE

The present training project proposal will bring together skills, experiences and (fundamental, translational and commercial) knowledge both from industry and academia, in the context of an innovative research project on novel diagnostic and therapeutic approaches for IBD and provides further education and training to a large group of researchers.

Inflammatory Bowel Disease (IBD) covers a group of disorders that are all characterized by chronic intestinal inflammation. IBD can seriously limit people's quality of life due to pain, vomiting, diarrhea, and other symptoms. Complications can be severe and in rare cases, IBD might even lead to mortality ¹. IBD affects approximately 0.2% of the human population with a higher prevalence in Europe. The main types of IBD are Crohn's Disease (CD) and Ulcerative Colitis (UC). The main difference between CD and UC is the *location* and *nature* of the inflammatory changes. CD can affect any part of the gastro-intestinal tract with a majority of cases involving the ileum. UC is confined to the colon, with occasional involvement of the ileum.

Current treatment options of patients with IBD are mainly aimed at suppressing the immune response, i.e. treatment of the symptoms rather than targeting the root cause of the affliction. However, although reasonably effective, treatment failures and significant side effects such as bone demineralization, growth retardation, diabetes, and hypertension often occur. This clearly stresses the need for novel treatment options in the treatment of IBD.

IBD appears to result from a deregulated mucosal immune system combined with a compromised intestinal epithelial barrier function in genetically predisposed individuals ². Several genes associated with IBD are involved in anti-bacterial defence (e.g. NOD2, *defensins*) and barrier function (e.g. myosin IXB, E-cadherin) ³⁻⁵. Another problem is that no specific, non-invasive test exists to monitor IBD disease activity. Currently, patients have to undergo endoscopy, which is a burden for the patient, but may also present complications, such as bleedings and infections.

The above illustrates that there is an urgent need for further multi-disciplinary research, in order to develop novel and improved IBD diagnostic and treatment options.

Recently, UMCU (project coordinator) demonstrated in collaboration with Intercept Pharmaceuticals (participant Advisory Board) that FXR has anti-inflammatory capacities in the intestine. This discovery opens the door for the development of a new class of drugs targeting the nuclear Farnesoid X Receptor (FXR) to ameliorate and resolve the chronically inflamed state underpinning IBD. This discovery was the trigger for scientific objectives of the current IAPP-project. However, without the training and exchange in this project it is not possible to go beyond this stage of scientific knowledge and have added clinical/medical value.

However, therapeutic drug discovery and development of diagnostics is a multi-disciplinary endeavour, requiring the input of diverse scientific fields in the area of chemistry, microbiology, cellular signal transduction and human (patho)-physiology. As a consequence, these developmental processes are greatly enhanced by a free flow of ideas and unfettered access to specialist knowledge.

With this project, we aim to initiate an exchange of scientists and researchers in order to further FXR-based therapeutic intervention and non-invasive diagnosis in Inflammatory Bowel Disease (IBD).



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The exchange not only benefits the drug- and diagnostic tool-developmental processes, but will also expose academic scientists to the practises at pharmaceutical companies, thereby providing them with valuable experience and training. Vice versa, researchers from companies are enabled to work in a scientific environment, refreshing their knowledge and broadening their scientific horizons, providing a boost to their creative capacities.

The present project proposal will bring together skills, experiences and (fundamental, translational and commercial) knowledge both from industry and academia, in the context of an innovative research project on novel diagnostic and therapeutic approaches for IBD and provides further education and training to a large group of researchers.

The **strategic objective** of this project is to strengthen existing collaborations and create new partnerships between the industrial and academic participants involved, in order to develop and share crucial knowledge that could lead to improved IBD diagnostics and treatment options. In the present project, we will aim for the following specific **objectives**:

1. To understand the molecular mechanisms of FXR-mediated inflammation inhibition. (WP2)
2. To develop microbiome-based non-invasive diagnostics for Crohn's patients. (WP3)
3. To develop selective anti-inflammatory FXR agonists. (WP4)
4. To deliver *in vivo* proof of principle of the novel diagnostic tools and FXR agonists. (WP5)

The **business objective** of the consortium involves a more efficient path to commercialization. In-depth knowledge of the non-invasive diagnostics and highly specific FXR agonists developed during the project will enable the industrial participants to effectively develop them into commercial products and speed-up the product development.