

ENDOTARGET EU Project Nears Midway Point: Advancing Research on Rheumatic Diseases

The ENDOTARGET EU project, a 4-year EU initiative coordinated by Helsinki University Hospital, is approaching its halfway mark. Launched on January 1st, 2023, the consortium has worked diligently across nine interconnected work packages to investigate the link between gut microbiota, intestinal permeability, and systemic endotoxemia (SE). The aim is to uncover key factors that drive the transition from health to disease in rheumatic diseases (RDs) such as osteoarthritis (OA), rheumatoid arthritis (RA), and spondylarthritis (SpA).

After another six months of intensive work, the consortium reconvened virtually on October 7th to discuss the non-scientific work packages. This was followed by a hybrid meeting from October 11th to 12th in Stuttgart, Germany, hosted by project partner Steinbeis Europa Zentrum. During the gathering, consortium members engaged in in-depth discussions on the progress and challenges encountered across the various work packages.

Another project milestone in the past six months was the successful submission of the 1st periodic report to the European Commission 18 months after the project started.



Some glimpses into the current work of the ENDOTARGET project:

Population Cohort Analysis: The ENDOTARGET consortium has been conducting comprehensive population cohort analyses to explore novel biomarkers and lifestyle factors influencing the health-to-disease transition in RA, SpA, and OA. The project includes 12 cohorts, with five being used for population analysis: FINRISK Cohort, Estonian Biobank Cohort (EstBB), Northern Finland Birth Cohort (NFBC), Helsinki Businessmen Cohort (HBS), and the Portuguese Cohort. Recently, >15.000 samples from ENDOTARGET- cohorts were analysed for several endotoxemia-surrogate biomarkers, such as biomarkers lipopolysaccharide binding

protein (LBP) and soluble CD14. Moreover, the analysis of the intestinal permeability and inflammation biomarkers zonuline and intestinal type fatty acid binding protein (I-FABP) is currently ongoing.

Furthermore, ENDOTARGET has also established collaborations with the EU-HORIZON sister project GLYCANTRIGGER, testing the validity of glycans as biomarkers for Crohn's disease.

Focused cohorts & *in vitro* studies: This task is dedicated to investigating the role of SE and gut permeability in the pathogenesis of RA, SpA, and related inflammatory diseases. A key accomplishment here has been the extensive collection and analysis of clinical samples across multiple cohorts, including RA, SpA, and healthy controls. This will help to uncover how SE influences immune responses and contributes to the progression of inflammatory diseases. So far, efforts have focused on the collection of patient biopsy samples and the implementation of the necessary technologies and protocols. This work also includes the set-up and testing of a novel gut-on-a-chip system for investigating the impact of lipopolysaccharides (LPS), outer membrane vesicles, and extracellular vesicles on gut barrier permeability and functionality.

Mechanistic and Proof-of-Concept Studies: We have made progress in understanding the role of LPS in OA and RA by *in vitro* studies. Key findings include the molecular dynamics of LPS in the intra-articular joints and characterisation of novel LPS-binding mechanisms. Further *in vitro* and *in silico* studies are ongoing. Next to this, we have established preliminary animal models to study the systemic and local effects of LPS on OA progression.

Intervention Studies: ENDOTARGET is developing different intervention studies that evaluate distinct mechanisms that may interfere with gut microbiota, barrier integrity, and endotoxemia. The fecal transplant study in SpA is ongoing and will finish recruitment by the end of this year. The TASTY study that analyses the effect of the Mediterranean diet enriched with fermented foods on rheumatoid arthritis is actively recruiting patients.

Data Integration and Analysis: This task aims to integrate the results of the different studies and to use them for disease prediction modelling. In close collaboration with WPI, efforts were centred on extracting, standardising, and harmonising the obtained data to ensure consistency before analysis. While progress continues, most of the remaining tasks will be implemented in the coming years.

Dissemination & Communication Highlights:

- In October 2024, the ENDOTARGET EU Project partners Gonçalo Barreto (HUS) and Patrícia Costa Reis (iMM) were invited to the 2nd episode of the GlycanTrigger podcast to discuss the compelling topic: "How Gut Permeability Impacts Inflammatory and Autoimmune Diseases?". **Check this episode here:** [GlycanTrigger Podcast Series – Episode 2](#)
- On the 24th of October, the first ENDOTARGET webinar "Fecal Microbiota Transplantation as a treatment for microbiota dysbiosis associated conditions" took place with three interesting talks about FMT. **Watch the recordings here:** <https://endotargetproject.eu/communication-material/>

Upcoming Events:

Mark your calendars for the 12th of December (18:00 – 19:30 CET) for the 2nd ENDOTARGET webinar. We will give you interesting insights into the relationship between food, gut microbiome, and rheumatic diseases. Further, we will inform you about our currently running TASTY study.

→ Register here: <https://eveeno.com/319482806>

Scientific Publications:

Pazos-Pérez, A.; et al. **The Hepatokine RBP4 Links Metabolic Diseases to Articular Inflammation.** Antioxidants. 2024. [doi: 10.3390/antiox13010124](https://doi.org/10.3390/antiox13010124).

Guillán-Fresco, M.; et al. **Formononetin, a Beer Polyphenol with Catabolic Effects on Chondrocytes.** Nutrients. 2023. [doi: 10.3390/nu15132959](https://doi.org/10.3390/nu15132959)

Charneca, S.; et al. **Beyond Seasoning—The Role of Herbs and Spices in Rheumatic Diseases.** Nutrients. 2023. [doi: 10.3390/nu15122812](https://doi.org/10.3390/nu15122812)

Franco-Trepát, E.; et al. **β Boswellic Acid Blocks Articular Innate Immune Responses: An In Silico and In Vitro Approach to Traditional Medicine.** Antioxidants. 2023. [doi: 10.3390/antiox12020371](https://doi.org/10.3390/antiox12020371)

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