

# Master Thesis Proposal

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Lab/Institution: Proteomics of non-model organisms - ITQB

**TITLE: Discovery of anti-TNF  $\alpha$  agent's efficacy in ankylosing spondylitis patients using a proteomic approach**

Ankylosing Spondylitis (AS) is amongst the most common forms of inflammatory arthritis. It is characterized histopathologically by the presence of inflammation at the site of insertion of tendons or ligaments into bone, leading to new bone formation in affected joints.

Inflammatory back pain is a characteristic symptom and syndesmophyte formation with vertebrae fusion an x-ray hallmark of the disease. AS affect people around 20-30 years of age promoting physical function deterioration and work disability, with strong impact in quality of life.

The introduction of biologic therapies, such as anti TNF- $\alpha$  agents contributed for several benefits regarding clinical management and prognosis. Although most AS patients respond well to these therapies, partial response is still frequent. Current markers of response include younger age, HLA-B27 carriage and elevation of acute phase reactants. Whilst these are statistically significant biomarkers, it is clear that they don't have a relevant impact in terms of medical therapeutical decision. Identification of new and more discriminant biomarkers is an unmet need.

Under the framework of a multicenter national clinical study, AS patient's sera samples were collected from responders and non-responders to anti TNF- $\alpha$  blockers at several time-points during treatment. The levels of variation of serum proteins from the collected samples will be evaluated by a proteomic approach.

## **OBJECTIVES**

Identification of proteins for which the level of variation is tightly associated to the clinical response to anti TNF- $\alpha$  blockers. These proteins will be used as potential biomarkers for the prediction of therapy efficacy in daily clinical practice.

- To identify specific biomarkers for prediction of therapy efficacy to anti TNF- $\alpha$  treatment, differential proteomics will be performed with blood collected from responders and non-responders AS patients.
- Task 1: The immunodepleted protein extracts for each condition (responders and non-responders AS patients) will be obtained, quantified and digested with trypsin for LC-MS/MS analysis.
- Task 2: Tryptic digest mixtures will be analysed by high-resolution LC-MSMS. Proteins of each condition will be identified. A relative quantification of the levels of the identified proteins between the two conditions will be performed using adequate software.
- Task 3: Uni- and multivariate statistical analysis of the differential proteomic data followed by String network analysis will be used to select the more specific protein biomarkers, together with the known molecular mechanisms associated with AS.
- Task 4: The identified biomarker candidates will be validated by specific MS quantification (SRM).
- Task 5: Writing of master thesis

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10
Task 1										
Task 2										
Task 3										
Task 4										
Task 5										