Monitoring Innate Immunity in Arthritis and Mucosal Inflammation (MIAMI)

Research Areas

- Biomarker Research
  - Diagnostic
- Basic Research

At a Glance

- Status: Active Consortium
- Year Launched: 2013
- Initiating Organization: European Commission Seventh Framework Programme (FP7)
- Initiator Type: Government
- Location: Europe

Abstract

The Monitoring Innate Immunity in Arthritis and Mucosal Inflammation (MIAMI) consortium will deliver improved and/or novel methodology for early diagnosis of disease in people at risk, who do not exhibit clinically relevant conventional indicators (yet). MIAMI will establish a list of biomarkers indicating onset and course of inflammation and will devise potential strategies for therapeutic intervention, including identification of cellular and molecular targets for treatment of the disease. With the help of small to medium-sized enterprises that have a strong research and development commitment to biomarkers and personalized medicine solutions, assays will be developed that go beyond academic research formats. The aim is to develop proprietary point-of-care tests for easy and unrestricted use in the clinic or at the bedside, and to validate them. Multiplex assays or lateral-flow immunoassays can be developed for simultaneous detection of a variety of proteins and evaluated in a prospective setting. Novel targets such as microRNA will be addressed in innovative assay formats and validated prospectively. Finally, pilot data on the applicability of the identified biomarker targets to be used in cutting-edge molecular imaging approaches will be provided. The latter holds great potential for further innovations going beyond the scope of in vitro biomarker determination. MIAMI will follow a translational concept: It will analyze the mechanisms of disease initiation and progression with a special focus on innate immune activation that connects the joint and the gut as well as the skin. This
basic research, involving experimental models of the disease in the murine system, will be linked to clinical studies in which MIAMI will use markers of innate immune activation for patient identification and stratification. MIAMI seeks to maximize the opportunity for success by combining this translation of its molecular insights into clinical practice with a biomarker discovery effort to identify novel markers that will enable monitoring of disease activity, which is a prerequisite for individualized therapeutic strategies. Biomarkers that indicate the extension of disease will be addressed. Finally, MIAMI intends to explore how it may further translate its findings into novel technologies including imaging tools, for which the translation process will be bidirectional. Therefore, validated markers will be investigated initially by molecular imaging in mice with the longer-term goal of achieving a biomarker imaging strategy in humans.

Mission

MIAMI’s scientific focus, which is directed toward achieving better diagnostic tools and novel targets for pharmaceutical therapies to significantly improve patient care in seronegative arthritis, can be summarized into four main objectives:

Objective 1: Mechanisms of initiation and progression of the disease

MIAMI will analyze the expression of S100-DAMPs in arthritis and mucosal inflammation, using synovial fluid and articular and intestinal biopsy tissue (to be completed at month 24). Special attention will be given to compare their role in systemic immune activation (by analyzing S100-DAMPs on human monocyte-macrophage functions) with their role at sites of inflammation (gut or/and joint compartments).

MIAMI will investigate S100-DAMPs as bystanders, amplifiers, or as disease-driving forces in cellular assays and mouse models of experimental arthritis and colitis (mouse models, see Work Pages (WP) 1 and 2). MIAMI will analyze the proinflammatory function of S100-DAMPs in arthritis and mucosal inflammation (to be completed at month 36).

Objective 2: The potential of biomarkers for patient identification and stratification

DAMPs will be used as biomarkers for an early identification of patients (e.g., systemic JIA) or groups at special risk (e.g., mucosal or articular inflammation in relatives of patients with SpA, inflammatory
bowl disease (IBD), or psoriasis), to be completed at month 36.

MIAMI will optimize the performance of different assays for S100A8/A9 and S100A12 regarding disease-specific cut-offs in the different forms of seronegative arthritis and bowel disease. In addition, and as a strong translational link to objective 1, MIAMI will develop a quantitative assay for murine S100A8/A9 and in this way will establish (in murine models of arthritis) the first reliable biomarker to monitor disease activity.

For a major technical innovation, MIAMI will translate its findings from objective 1 into clinical application by addressing specific targets (monomers of S100A8 and S100A9, complex forms, other S100-DAMPS); specific formats (semi-quantitative bedside tests, stool assays, blood, synovial fluid, imaging); or specific indications (screening of risk populations, detection of organ-involvement, prediction of response and outcome, confirmation of disease remission). Novel point-of-care tests will be developed and validated (e.g., lateral-flow immunoassays). This represents a horizontal task (across WPs) to analyze/validate the results from other objectives (to be completed at month 36).

Objective 3: Identification of novel disease markers for monitoring activity

MIAMI will use a comprehensive and coordinated approach to identify promising new biomarkers (to be completed at month 24), using advanced protein expression profiling technology by label-free LC-MS/MS (proteomics), multiplex cytokine and chemokine assays (cytokinomics), and screening of micro-RNA profiles (transcriptomics). This will provide a unique and distinctive advantage of being able to integrate the results of different discovery (molecular profiling) strategies.

MIAMI will use samples from existing cohorts and biobanks to analyze the identified biomarker panels as tools to improve outcome measures in chronic joint and gut disease. After providing proof-of-principle, prospective clinical studies implementing stratified therapeutic approaches based upon biomarkers will be designed longitudinally (existing experience at UCMU and WWU for JIA, WWU for IBD, UGent for SpA, and UCD for PsA).

MIAMI will monitor therapy and search for subclinical inflammation in patients during disease remission. By defining clinically valuable cut-offs for definition of immunological remission, MIAMI will provide therapy-stop-rules, with the aim of developing commercial assays (to be completed at month 36).

Objective 4: Monitoring local disease activity and extension
Starting from preliminary data, molecular imaging using S100-DAMPs will first be established in animal models. MIAMI will image-track macrophages to inflamed joints in mouse models of seronegative arthritis or to the inflamed intestine in experimental colitis. MIAMI will combine imaging of S100-DAMPs with specific fluorescent antibodies and enzyme (metalloproteinases) activity using fluorescent probes and correlate that to joint destruction in seronegative arthritis (to be completed at month 36).

Comparison with data from humans will be analyzed by also correlating to imaging results and immunohistochemical analyses in biopsy specimens (synovia, gut, skin). These studies will provide insights on how targets that can be detected by molecular imaging correlate to the site and extent of inflammation in vivo (to be completed at month 36).

To foster translational activities, MIAMI will develop new means to image inflammation by using existing small molecules binding to S100-DAMPs, which are approved for use in humans (to be completed at month 36).

Financing

MIAMI is funded by the European Union Seventh Framework Programme.

Links/Social Media Feed

Homepage http://www.miamiproject.eu/

Points of Contact

Klinik für Pädiatrische Rheumatologie und Immunologie
Dirk Föll
Röntgenstr. 21 • 48149 Münster
phone: +49 251 83-58178
fax: +49 251 83-58104
Sponsors & Partners

Biogazelle
Buhlmann
European Research Services GmbH
Gent University
Radboud University Medical Center Nijmegen
University College Dublin
University Medical Centre Utrecht
University of Muenster

Updated: 04/15/2016