Hycult Biotech participates in study on infections in relation to chronic autoimmunity

EU project within Framework 7 : Assessing biomarkers for chronic autoimmunity

Project name: Infectious trigger of chronic autoimmunity
Project acronym: INTRICATE
Work programme topic: HEALTH 2010.2.4.5-2 Other chronic diseases

November 2010, Hycult Biotech (HB) has started participating in a European study on chronic autoimmunity. INTRICATE is a multidisciplinary European Consortium of scientists, clinical investigators and physicians collaborating in the fields of autoimmunity and infections. The current proposal is founded on the initiative of HEALTH.2010.2.4.5-2: Infection and dysbiosis as the triggers of the development of inflammatory processes in allergies and autoimmune diseases and its goals are to meet the challenge of unraveling the mechanisms and the role of bacterial infection in the initiation and development of human autoimmune disease. The processes involved are both diverse and complex and consequently our strategy will be to analyze them systematically using a „model disease“. We have selected ANCA associated systemic vasculitis (AASV) for this purpose because it is sufficiently well characterised clinically but still poses a major clinical problem. Our approach is to strategically dissect the molecular pathways that lead from chronic infection to autoimmunity by exploiting the opportunities provided by post-genomic research and translating them into clinically applicable approaches.

INTRICATE unites uniquely groups of scientists and clinical investigators who are at the forefront of immunological and biomedical research and have substantially contributed to the current knowledge of disease mechanisms, genetic aspects and clinical parameters of autoimmune and infectious diseases. All Partner of the consortium working in (clinical) immunology, autoimmunity, genetics, microbiology and bioinformatics not only bring to the consortium world class basic and applied biomedical research at the top of their respective fields. Eight principle investigators are clinically trained and are among the world leading clinical experts in immunological and rheumatology. Through direct patient contact and with their insight and sympathetic understanding of the patients suffering from these often fatal chronic diseases they have helped to change the way patients with AASV are treated today. This approach has led and will also ensure in the future that the results of the consortiums research will be truly „from bedside to bench – and back again“.

Summary of the project

The INTRICATE project is based on the premise that research into complex human disorders such as autoimmune disease must be undertaken primarily using samples and tissue taken from human subjects. Accordingly we will investigate the interaction between infection and autoimmunity in a “model” human disease: - Anti-neutrophil cytoplasmic antibody (ANCA) associated systemic vasculitis (AASV). AASV is ideally suited because it is known to be caused by autoantibodies of defined specificity and second because it is strongly linked to infection. INTRICATE will use mouse models but only to answer the specific question whether infection with clinically relevant bacteria induces autoimmune disease in transgenic mice that express the human autoantigen. Our concentration on human samples and “humanised” mouse models should mean that we will be able to translate the results swiftly into the clinic.
The INTRICATE project has four specific aims, namely to:

1. Use novel high-throughput antigen array technology and well-characterized patient cohorts to determine whether acute infection with specific microorganisms triggers the induction or re-activation of AASV; and to ascertain whether antibody responses to microbial proteins cross-react with native or epigenetically modified self-proteins
2. Elucidate the reasons why dysbiotic expansion of S. aureus in nasal sinuses and upper airways is linked to localised and systemic granulomatous vasculitis in AASV; and in particular to analyse the roles of microbial superantigens and the local adaptive immune response to them.

3. Analyse the mechanisms of molecular mimicry in transgenic mice expressing the human forms of LAMP-2, PR3 and MPO – the major targets of autoantibodies in AASV – by determining whether infection with bacteria that express molecular mimics induce AASV and, if so, to define under which circumstances they do so.
4. Characterise disease-associated genes identified in the European Vasculitis Genetics Consortium's genome wide association study (GWAS) of AASV and to examine their effect on gene expression and function; and to determine whether the genetic variants that predispose to AASV have been maintained in the gene pool because of a beneficial effect on resistance to infection.

Contribution Hycult Biotech
Hycult Biotech is a company specialized in biomarker assay development in innate immunity, inflammation and tissue damage with particular expertise in assays for neutrophil and complement proteins. In AASV, neutrophil proteins are directly linked to the inflammatory status. Within the INTRICATE project Hycult Biotech will contribute in Workpackage 1 and 2.
Within this project key molecular pathways involved in the onset of AASV will be identified and novel (auto)antigenic targets identified. This information will be used to mark disease specific molecules and mechanisms that may trigger an autoimmune response or lead to re-activation of remittent disease after infection. These will include assays for IgD specific ANCA (WP2) and complement components to measure complement activation in response to disease and compare it with complement pathways utilized during infection. This will provide the first robust investigation on the relation between complement activation, chronic infection and AASV. Overall, extensive research is warranted to gain more insight in the correlation between disease stage, the presence of ANCAs and complement activation in AASV. These novel biomarkers identified in AASV will be used by Hycult Biotech. These novel tools will be used initially for monitoring disease development and outcome of treatment in samples from patients with AASV only. In a second step, if the assays prove successful and indicate that the results could be used in autoimmune disease more generally, they will be made available for broader applications.

Updates on the INTRICATE project activities will be available on website http://www.intricate.eu/the-group/consortium/.

Contract number: 261382.

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