Project no: **005223**

Project acronym: **EURAPS**

Project title:
Autoimmune polyendocrine syndrome type I –
a rare disorder of childhood as a model for autoimmunity

SPECIFIC TARGETED RESEARCH PROJECT
Thematic Priority: LIFE Sciences, Genomics and Biotechnology for Health

Publishable final activity report

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Partners and Group Leaders in EurAPS

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3. Royal College of Surgeons in Ireland, Ireland (terminated as a partner December 1, 2005)
4. University of Oxford, UK – Represented by **Vincenzo Cerundolo**
5. Australian National University, Australia – Represented by **Chris Goodnow**
6. University of Basel, Schweiz – Represented by **Georges Holländer and Ed Palmer**
7. Lund University, Sweden – Represented by **Rickard Holmdahl**
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EurAPS website

www.apeced.net

1. Project execution

The EU FP6 specific targeted research project EurAPS within the area of rare diseases was created by bringing together leading scientists in Europe, Australia and China to work on the best available biological model for autoimmune disease, Autoimmune Polyendocrine Syndrome type I (APS-1), a rare hereditary disorder. At the time when the EurAPS consortium commenced, all groundbreaking research within this area had been conducted in Europe, but as this model gained in popularity, significant competition from USA has evolved.

Autoimmune polyendocrine syndrome type 1 (APS-1) is a rare hereditary disorder with autoimmune manifestations affecting both endocrine and non-endocrine tissues. The disease, also named APECED (autoimmune polyendocrinopathy, candidiasis and ectodermal dystrophy), has been instrumental in unravelling mechanisms critically involved in the induction of tolerance. APS-1 is caused by mutations in the autoimmune regulator (AIRE) gene, a putative transcription factor primarily expressed in medullary thymic epithelial cells where negative selection is thought to occur, to some extent also in rare peripheral lymphocytes. This rare monogenic disease shares many features with more common autoimmune disorders with complex patterns of inheritance, such as type 1 diabetes, Hashimoto's thyroiditis, autoimmune premature ovarian failure and Addison's disease.

During the course of this 3 years project, a series of important research problems have been attacked in collaboration between partners with complementary expertise through a set of five different scientific work packages resulting in many publications in top ranking journals such as New England Journal of Medicine, PLoS Medicine and Proceedings of National Academy of Sciences.

EurAPS had a budget of € 6,5 million of with € 3,0 million was contributed by the EU. The project was coordinated by Uppsala University and included 17 academic partners including two from Australia and one from China.

Project objectives

The main objective is to utilize our unique position and pool of collected expertise in the biology of APS-1 and AIRE to create increased understanding of the molecular mechanisms underlying loss of tolerance in this disease and in autoimmune disorders in general and to develop new strategies for early and specific diagnosis of this monogenic autoimmune disease to identify patients with APS-1 before life-threatening conditions such as hypoparathyroidism with severe hypocalcemia or adrenal failure with Addisonian crisis occur and to enable early intervention in the disease process.

In order to achieve this objective the consortium has undertaken steps to:

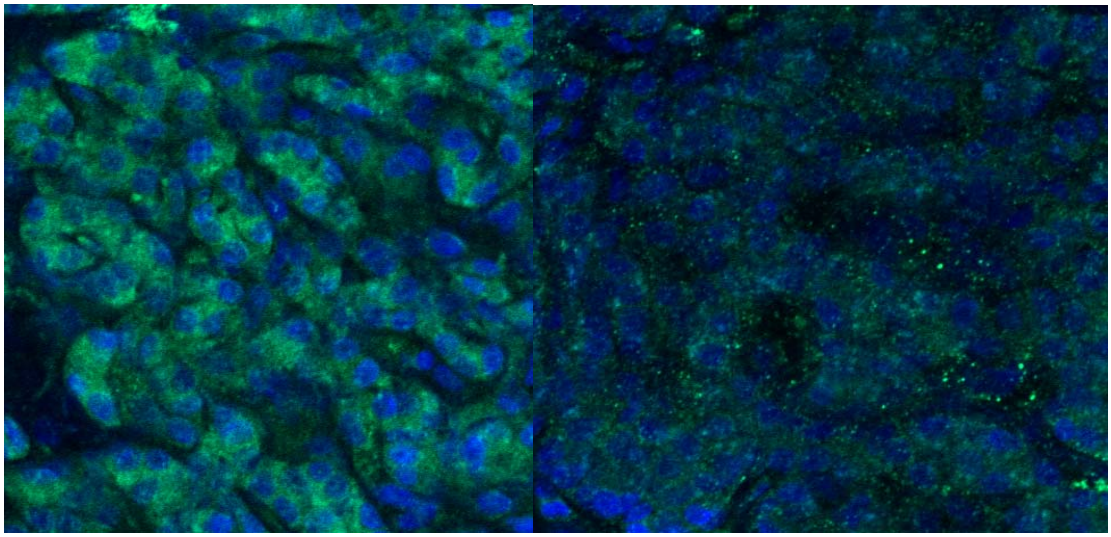
Work package 1: Establish a pan-European database and biobanks to facilitate standardized diagnostic and clinical practices for the care and monitoring of patients with APS 1.
Work package 2: Identify novel autoantigens and ameliorate the diagnostic procedures.
Work package 3: Establish new animal models of the disease and identify genes that modify the intensity and the course of the disease.
Work package 4: Determine the gene expression profiles of cells that express or do not express AIRE in order to identify pathways involved in the functions of the AIRE gene product in different cells.

Work package 5: Understand the propensity for the superficial mucocutaneous Candida infection that affect most APS I patients both at the T-cell level and at the level of innate immune system, i.e. involvement of Th-17 cells, presentation by dendritic cells or alteration of antimicrobial peptides.

Work performed and end results

WP 1: A biobank for DNA and sera has been established in Bergen, Norway. A web-site containing information for patients, clinicians, scientists and members of the consortium has been created (http://www.apeced.net). A consensus strategy for the treatment and clinical follow-up of APS-1 patients has been published (1).

WP 2: Autoimmune hypoparathyroidism is a hallmark of APS-1. The parathyroid autoantigen, NALP-5, was identified by a collaboration within the EurAPS consortium (2). This autoantigen provides better diagnostic opportunities and is the first well characterized autoantigen in the mouse model for APS-1, the Aire deficient mouse.



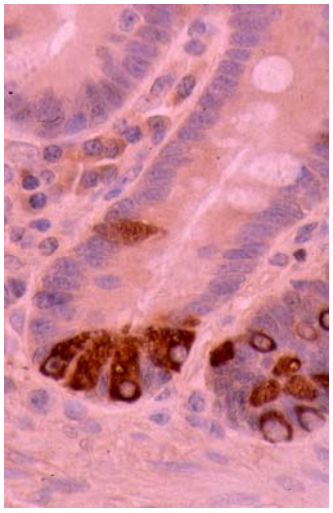
Staining of parathyroid cells with serum from an APS I patient with (left) and without (right) hypoparathyroidism

An important discovery made by the consortium is that almost all APS-1 patients develop autoantibodies to type 1 interferons (3). KCNRG was identified as a pulmonary autoantigen (4) and this discovery will enable early diagnosis of the rare but often fatal complication of pulmonary involvement in APS-1. A novel protein array technology to detect new autoantigens has been established. A mouse that expresses the recombinase Cre under transcriptional control of the Aire locus has been generated. This has provided evidence for a much wider function of Aire than previously anticipated.

WP 3: The breeding of Aire deficient mice on the C57BL/6 and C57BL/10 backgrounds has been completed (5) and breedings on other backgrounds susceptible for arthritis and experimental autoimmune encephalitis has recently finished. Also, breedings to study the interactions between Aire mutation and other autoimmune mutations have been started. The signaling pathway that initiates the negative selection of self-reactive thymocytes has been delineated.

WP 4: Expression array data have been collected from thymus and testis to identify genes that Aire directs (7). The promoter elements of the Aire gene have been characterized functionally and several interacting proteins identified. Futhermore, a novel AIRE interacting DNA-PK protein complex, which is able to phosphorylate AIRE protein, has been identified. Using NMR the three dimentional structure and interactions of the PHD-domains of AIRE with histones have been solved (8).

WP 5: An unexpected but highly interesting observation is that the mice model for APS I, the Aire deficient mouse does not develop Candidiasis. The reason for this species difference is unclear. The roles of Th-17 and dendritic cells have been analysed (manuscripts in preparation). Paneth cells involved in the innate immunity of the gastrointestinal tract have been identified as important targets for the immune attack in APS-1 (see Figure 2 below), but the autoantigens in Paneth cells remains to be identified.



Paneth cells in the small intestine stained with serum from a patient with Candidiasis and APS I

Impact of the EurAPS project

1. A higher awareness among clinicians to diagnose more patients with APS-1 earlier. Better and more uniform treatment modalities for APS-1 patients.

2. Importantly, as a model for autoimmune disorders, APS-1 will continue to provide a deeper insight into the mechanisms of tolerance induction and maintenance as well as autoimmunity in general (9). The identification of pathways important for the development of autoimmunity, will undoubtedly identify novel drug targets that may be instrumental in the development of new treatment modalities.

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2. Dissemination and use

The EU fp6 project EurAPS was designed to improve the diagnosis and treatment of patients with APS-1 and at the same time use this rare monogenic disorder as a model to understand autoimmunity in general using cellular assays and mouse models.

The success of the EurAPS project has had important consequences on our understanding of mechanisms for tolerance and autoimmunity at a molecular level and has also improved the diagnosis with the disease with the identification of several important novel autoantigens including type 1 interferons, NALP5 and KCNRG. As a result, a number of papers have already been published in high ranking scientific journals including New England Journal of Medicine, Immunity, PLoS Medicine and PNAS. In addition, reviews and book chapters aimed at a broader readership including clinicians have also been written. In May 2009 Journal of Internal Medicine, a journal aimed at clinicians, will publish four reviews written by members of the consortium to improve knowledge and awareness of the disease. In addition, work has been presented at several congresses and symposia, including meetings for rare diseases. A web-site has been set up intended for patients, clinicians and scientists. The exceptional collaboration with Australian scientists in an EU project has attracted a lot of attention in Australia to this project. Contacts have been taken with centres for rare diseases and with national societies for endocrinology in all EU member states.