

Summary of the 2009 Research Summit on the Immunology of Alopecia Areata

The National Alopecia Areata Foundation (NAAF) convened a Research Summit on the Immunology of Alopecia Areata (AA) in Denver Colorado on August 21, 2009. The purpose was to evaluate the state of immunology research in AA and to identify those areas of immunology research which should be supported by NAAF. To accomplish this, we invited major AA researchers working in genetics, immunology, neurobiology and clinical research. We also invited a diverse group of immunologists working in T cell biology, allergy, tolerance, autoimmunity, and translational research in autoimmunity who knew nothing about AA.



Background

Maria Hordinsky introduced the meeting attendees to AA a common autoimmune disease highly associated with atopy, controlled by genetics and the nervous system.

Amos Gilhar reviewed the classic animal model experiments that showed that AA is a CD4 and CD8 mediated diseases in which hair follicle melanocytes are the target, especially the antigens gp100, MART-1 and tyrosinase.

Jean Claude Bystryn showed that autoantibodies are common in human AA and in the C3H/HeJ model, and that the antibody specificities are quite different from the antibody specificities in human vitiligo.

Ralf Paus reviewed the data that supports the hypothesis that a major factor in AA pathogenesis is the breakdown of immune privilege (IP) in the hair follicle. He proposes a complex mechanism of IP and new drugs that might reverse the breakdown of IP in AA.

John Sundberg proposed that the C3H/HEJ mouse is the best model for adoptively transferrable reversible immune hair loss, which can be transferred by CD8+ cells. In this model, one can quantitatively measure the immune response that develops with time.

Angela Christiano presented a comprehensive and careful study of genetic associations in AA, material from the National Alopecia Areata Registry (NAAR). These exciting new results implicate T cells and NK cells and NK cell activating ligands. These new findings show upregulation of NK activating peptides in the connective tissue sheath around AA hair follicles.

Donald Leung explored the possible connections between atopy and AA, and raised some important questions about future research directions, especially the study of steroid resistance in AA treatment.

What we don't yet know:

1. NK, NKT, Treg, TH17 in AA patients, early middle and late
2. What are the antigens recognized by autoantibodies?
3. Are NK cells involved in induction or maintenance of disease?
4. Is the pathway to disease in the C3H/HEJ mouse the same as in patients with AA?
5. Genetic definition of disease subset
6. Role of barrier dysfunction in AA; relationship to atopy (determine disease severity or course? Induction or expansion?)

Discovery and New Technologies

Yehuda Shoenfeld discussed fundamental unmet needs in autoimmunity research, most of which are highly relevant to AA: The effects of vitamin D, infectious triggers of autoimmunity, the hygiene hypothesis, and molecular mimicry.

Phillipa Marrack believes that “the T cell is the center of the universe”, but concedes that in AA we should “look at autoantibodies and work backwards” to understand the antigen that triggers AA. Knowing the antigen helps us understand the mechanism of disease, how tolerance is broken, and may help treat disease.

Jeffrey Frelinger presented the proposition that we should knock out antigen-specific T cells to treat AA.

Anthony French presented the complex role of Natural Killer (NK) cells in innate and adaptive immunity. NK cells may either enhance or inhibit autoimmunity and so far their role in any autoimmune disease is only correlative.

Anne Bowcock presented an overview of psoriasis genetics and what we have and have not learned. Yosef Refaeli discussed the issues of IP, immune ignorance and immune tolerance. Based on the fact that the evidence for breakdown in IP in the hair follicle in AA is so far only correlative, he proposed a number of different experimental approaches to test the hypothesis in animal models of AA.

George Eisenbarth discussed modern approaches to the study of autoimmunity in diabetes, including studies of antibody specificity, use of biologics, induction of oral tolerance as treatment, development of anti-TCR antibodies, and use of NCI small molecule libraries to block the binding of antigen/TCR/or Antibody in autoimmune disease.

Stephen Miller presented the potential of treating autoimmune disease by re-establishing tolerance to self antigens that are the target of disease. He is applying this approach in organ transplantation and in the treatment of Multiple Sclerosis (MS); the concept is to induce the destruction of autoreactive T Cells early in disease.

Opportunities Discussed at the Summit

1. Genetic Targets
 - a. T cell, T reg, NK cells are all valid targets based on new genetic investigations
 - b. Epidermal differentiation targets (syntaxin)
2. Animal models
 - a. We need more! But what is the mechanism in man that we seek to emulate in mice?
 - b. Also - autoantigens in mice may be quite different
 - c. Need new engineered animals to study mechanism of disease.
 - d. Can we quantitatively measure hair regrowth in these models (a necessity for drug trials)?
3. Restoring immune privilege in the hair follicle
 - a. Why is there immune privilege in hair follicle?
 - b. Is loss of IP in the hair follicle in alopecia areata involved in disease mechanisms?
 - c. How do we restore immune privilege?
4. New immunologic targets
 - a. NK cells, TH17 cells
 - b. Infectious triggers
 - c. Characterize the autoantibodies!
5. New Therapeutic options
 - a. Induction of tolerance to HF proteins
 - b. Restoration of IP in the hair follicle on AA patients
 - c. Empiric use of biologics that affects various aspects of immune response

The immediate results:

1. Collaboration of Yehuda Shoenfeld with NAAR to screen sera for autoantibodies to infectious organisms.
2. Collaboration of Amos Gilhar, Yehuda Shoenfeld and Yosef Refaeli to bring cutting- edge immunology investigative techniques to the study of autoimmunity in AA patients and animal models. They met in September 2009 in Israel on this collaboration.
3. Recruitment of six major Immunology labs as potential sites for research fellowships for young AA researchers: Philippa Marrack, George Eisenbarth, Jeffrey Frelinger, Stephen Miller, Yosef Refaeli, Anthony French

The future directions established at the summit are as follows:

1. NAAF should serve as a "conciierge" to direct young scientists to potential labs for fellowship training: Marrack, Eisenbarth, Frelinger, Miller, Refaeli, or French
2. NAAF should release a Request for Proposals (RFP) to fund immunology proposals with several suggested areas of focus:
 - a. Detection of antibody specificities to targets in hair follicles.
 - b. Animal models to study immune privilege in the hair follicle in AA
 - c. Further genetic studies on the MHC in AA
 - d. Functional studies of Natural Killer (NK) cells in AA
 - e. Consider the use of new biologics and perform empiric clinical trials
3. Promote the NAAR as a source of material for these studies. Antibody and genetic studies can all be performed using registry material.