

Scientists Are Amazed at Progress of Alopecia Areata Treatment Development Program at Research Summit

From Basepairs to Bedside: Innovations in the Immunology & Clinical Science of Alopecia Areata

After listening to presentations at the 2012 Alopecia Areata Research Summit, the scientists in attendance expressed great satisfaction over the progress being made. The summit, titled *From Basepairs to Bedside: Innovations in the Immunology & Clinical Science of Alopecia Areata* and held in Bethesda, Maryland, at the end of November, was convened to review recent progress in understanding the pathogenesis of alopecia areata and to chart the course for the future of translational research.

At the Alopecia Areata Clinical Research Summit in October 2010 guest scientists had stressed the need for us to develop a translational platform. Essential to that platform were biomarker studies; new and established animal models; a uniform protocol; incidence and prevalence studies; quality of life studies; burden of disease studies; defined endpoints; defined hair measurement; more genetic and mechanistic studies; genetic and immunological pathway studies; and collaboration with the U.S. Food and Drug Administration. Advances have been made in all of these areas.

BACKGROUND ON ALOPECIA AREATA

Dr. Maria Hordinsky introduced meeting participants to alopecia areata, a complex genetic, immune-mediated disease that targets anagen hair follicles. Dr. Hordinsky reviewed the clinical presentations of alopecia areata, the pathophysiology of this disease, and the treatment challenges. Dr. David Norris summarized the outcomes resulting from the past three summits and assessed the current state of alopecia areata research initiatives, clinical trials, and the National Alopecia Areata Registry. These two doctors successfully set the stage for the discussion of new findings in alopecia areata research in genetics and immunology.

GENETICS OF ALOPECIA AREATA

Dr. Angela Christiano discussed the progress she has made in genetics research since the last summit. A joint analysis performed with an independent genome-wide association

study (GWAS) of 1,435 cases and 2,032 controls resulted in the validation of previous GWAS targets and the identification of new associated genes. Some of these associated genes are unique to the hair follicle in alopecia areata. Dr. Christiano discussed targeting the interferon signature in the treatment of alopecia areata. She also discussed the genetic relationship between alopecia areata and other autoimmune diseases, including the minimal overlap with psoriasis or vitiligo. This work greatly expands our understanding of the genetic architecture of this highly prevalent autoimmune disease.

We were excited to hear Dr. Stephen Katz, Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, welcome participants. Dr. Katz stated that one of the fastest growing areas of investment by the National Institutes of Health is hair investigator-initiated research.

Dr. David Norris will be preparing a scientific summary of the presentations, and it should be completed soon after publication of this newsletter. Later this year the Proceedings of the Summit will be published in the *Journal of Investigative Dermatology*. The participants will be finalizing the goals that are to be met over the two years leading up to the next Alopecia Areata Research Summit in the fall of 2014. (These draft goals are provided because they were not yet finalized when this NAAF newsletter went to press.)



GOALS FOR THE NEXT TWO YEARS

Genetics

- Execute combined association and linkage studies using 250 multiplex families from the National Alopecia Areata Registry.
- Utilize functional genomics with deep sequencing.
- Develop a network plot.
- Analyze shared variants with related diseases, including celiac disease, rheumatoid arthritis, and type 1 diabetes (5 loci are shared between type 1 diabetes and alopecia areata).
- Develop a biobank.
- Determine the percentage of people with alopecia areata compared to the normal population with these genes.
- Determine if there is a genetic basis for disease subsets, i.e., alopecia areata patchy, alopecia areata totalis, and alopecia areata universalis.
- Increase alopecia areata samples to 10,000.
- Analyze National Alopecia Areata Registry samples to determine if alopecia areata is a composite of several different disease processes and the possibility that there are actually many treatment modalities.

Immunology

- Study how to restore immune privilege.
- Analyze the potential of targeting the IL-15 pathway.
- Identify the protolerance TCR signal; then target it pharmacologically.
- Develop T cell–receptor sequencing.
- Complete biomarker studies.

Animal Models

- Identify and develop mouse and humanized mouse models.
- Validate these models.
- Determine which model will be the best to replicate alopecia areata.

Clinical

- Finalize and validate the Alopecia Areata Uniform Protocol.
- Publish quality of life studies.
- Publish incidence and prevalence studies.
- Initiate burden of disease studies.
- Use pharmacogenomics to predict which patient populations will respond and which will get side effects.
- Determine the attractive pathways for targeted therapy.
- Continue collaborations with industry and government agencies to facilitate the regulatory path for alopecia areata treatments.

Editor's Note: Register on the NAAF website to receive research progress updates between our print newsletters.

Additional Summit Presentations

GENETICS OF ALOPECIA AREATA

John P. Sundberg, DVM, PhD

Alopecia Areata: Updates on Genetics from the Mouse Perspective
Identification of three new inbred strains with naturally occurring alopecia areata in a large aging study enables genome-wide association mapping, revealing new insight into the complexity of this disease.

IMMUNOLOGY & BIOLOGY OF ALOPECIA AREATA

Raphael Clynes, MD, PhD

Identity of Cytotoxic T Cells in Alopecia Areata and Therapeutic Strategies

In pursuing cytokines that might be critical to the activation of killer CD8 T cells, elevations of IL-15 in human alopecia areata skin were identified resulting in the pursuit of therapeutic approaches to block IL-15 signaling.

Ralf Paus, MD

Immune Privilege in Alopecia Areata

The speculation that alopecia areata is not a single disease entity, but a stereotypic, clinically and histologically distinct HF response pattern to various inflammatory insults associated with HF IP collapse and clinical consequences of this novel hypothesis.

Thomas A. Waldmann, MD

IL-15 in the Life and Death of Lymphocytes: Implications for the Pathogenesis and Treatment of Autoimmune Disorders

A collaborative trial using Hu-Mik-Beta-1 (anti-IL-2/IL-15R beta, CD122) and including patients with refractory celiac disease, a disorder with a high propensity for the development of CD8 EATL, implying that similar IL-15R or IL-15 signaling pathway direct approaches may be effective in alopecia areata.

Adam G. Schrum, PhD

Toward T Cell Protein-Protein Interaction Signatures in Human and Mouse Alopecia Areata

A new technological/analytical platform designed to allow network analysis of the protein-protein interactions (PPI) that compose T cell–signaling webs and Multiplex Immunoprecipitation detected by Flow Cytometry (MIF) designed for high sensitivity and applicability to samples containing low numbers of T cells.

COMMON CAUSES: RELEVANCE OF ALOPECIA AREATA TO OTHER AUTOIMMUNE DISEASES

John E. Harris, MD, PhD

IFN γ -Dependent Chemokines Are Critical for Autoimmunity in Vitiligo: Implications for Alopecia Areata

IFN γ and the IFN γ -dependent chemokines CXCL9 and CXCL10 are critical for the development and maintenance of vitiligo. The similarities between vitiligo and alopecia areata, including a dependence on CD8 $^{+}$ T cells and expression of IFN γ , imply a similar pathogenesis.

Matthias von Herrath, MD

Translational Research in Type 1 Diabetes

Argument that a main problem in human T1D development and recurrence is autoimmunity, in spite of ample evidence on the involvement of viruses and other environmental and genetic factors in type 1 diabetes pathogenesis.

James T. Elder, MD, PhD

Advances in Psoriasis Genetics

Overview of meta-analysis of three genome-wide association studies (GWAS) and two independent datasets genotyped on the immunochip to gain further insight into the genetic architecture of psoriasis. Results portend a better understanding of shared and distinctive genetic determinants of immune-mediated inflammatory disorders and emphasize the importance of the skin in innate and acquired host defense.

EMERGING TECHNOLOGIES

Amos Gilhar, MD

Alopecia Areata Induction in a Healthy Human Organ

Development of an animal model in which the clinical phenotype can quickly be induced within a previously healthy human organ in vivo.

David Norris, MD for Yosef Refaeli, PhD

Development, Characterization & Preclinical Evaluation of a Human Xenograft Mouse Model for Alopecia Areata

Development of humanized chimaeric mice to address the major limitation of using xenograft models to study alopecia areata—the lack of an immune component in the human skin microenvironment.

Julie Segre, PhD

Skin Microbiome in Health & Disease

Overview of research combining genomics, dermatology, microbiology, and immunology to explore cutaneous microbes in relation to healthy skin and dermatologic disorders.

Annemieke de Jong, PhD

High Throughput T Cell Receptor β Chain Sequencing for the Identification & Monitoring of Pathogenic T Cells in Alopecia Areata

Identification of pathogenic T-cell clones in lesional skin allows the extent to which T cells circulate through the blood to be assessed and the possible correlation with disease severity to be evaluated.

Ali Jabbari, MD, PhD

Update on Alopecia Areata Biomarker Study

Investigations to identify biomarkers in the skin and blood of patients with alopecia areata in order to develop a set of exploratory biomarkers that can be validated and utilized for monitoring improvement during clinical trials.

Amelia Wall Warner, PharmD, RPh

Pharmacogenomics in Clinical Trials & Drug Development

Methods to capitalize on pharmacogenomic research, enabling the pharmaceutical industry to understand variability of patient responses to drugs during clinical drug development and post-marketing surveillance, to rapidly advance development of alopecia areata drug therapy.

REVIEW OF FIRST DAY

David Norris, MD

Introduction & Review of Immunological and Genetic Components of Alopecia Areata

The second half of the meeting began with a comprehensive review of several key topics discussed on the first day.



Drs. Amos Gilhar (Israel) and Ralf Paus (Germany)

OVERVIEW OF CURRENT TREATMENTS

Jerry Shapiro, MD, FRCP

Current Treatments for Alopecia Areata

An overview of the many therapeutic options that exist for alopecia areata including topical, immunotherapeutic, and systemic agents and injections.

Richard A. Strick, MD

Case Report: DNCB Use in Treating Severe Alopecia Areata

Results from a patient group treated with DNCB and the argument that DNCB has been underutilized as a therapy for alopecia areata.

Madeleine Duvic, MD

Case Report: Phase I/III Randomized Bilateral Half-head Comparison of Topical Bexarotene 1% Gel for Alopecia Areata

Response of 35-year-old white male with a one-year history of alopecia universalis to targretin gel treatment after beginning systemic steroids.

TREATMENT DEVELOPMENT PROGRAM

Richard Gelula, MSW

Overview of Treatment Development Program

A multipronged approach to develop safe and effective treatments for alopecia areata, including basic science to determine the genetic basis and immunological triggers, testing available treatments, population studies, and initiatives to prepare for FDA evaluation.

Natasha Atanaskova Mesinkovska, MD, PhD

Alopecia Areata: One Protocol for All?

Development of a standardized alopecia areata research protocol to serve as a uniform template outlining procedures for all future clinical trials.

Tito R. Mendoza, PhD, MS, MEd

Health-Related Quality of Life in Alopecia Areata Patients & the Development of the Alopecia Areata Symptom Impact Scale

A secondary analysis of the National Alopecia Areata Registry to better understand the health-related quality of life (HRQoL) of patients with alopecia areata and development of a concise, validated patient-reported outcome tool to assess the impact of alopecia areata on the HRQoL of patients with the condition.

Rochelle R. Torgerson, MD, PhD

Incidence of Alopecia Areata in Olmsted County, Minnesota, 1990–2009

Determination of the incidence of alopecia areata among residents of Olmsted County, Minnesota, and comparison of results to those of a previous study conducted in the same geographic area.

ALOPECIA AREATA REGISTRY & CLINICAL TRIALS NETWORK

Madeleine Duvic, MD

Registry Update

The commencement of active patient recruitment and research uncovering alopecia areata immunogenetic mechanisms.

CASE REPORT PRESENTATIONS

Wilma F. Bergfeld, MD, FAAD

Case Report: Growth Hormone Deficiency in a Patient with Alopecia Areata Universalis and Celiac Disease

Postulation that growth hormone, celiac disease, and alopecia areata are autoimmune conditions and are closely related.



Co-Chairs Drs. Wilma Bergfeld and Angela Christiano



Drs. Amy McMichael and Angela Kyei



Drs. David Norris and John Harris

Maria Hordinsky, MD

Case Report: Altered Scalp Sensation in Patients with Alopecia Areata
C-fiber activation is altered in the affected scalp of patchy alopecia areata patients, confirming that not only is neuropeptide expression abnormal in alopecia areata but also peripheral nerve function.

John E. Harris, MD, PhD

Case Report: Two Patients, Four Inflammatory Responses, and the Lessons Learned about Autoimmune Pathogenesis

Two cases represent a natural experiment in which separate autoimmune diseases interact within the skin, with very different results.

Melissa Piliang, MD, FAAD

Case Report: Alopecia Universalis, Androgen Excess and Psoriasis
Presentation of two young women with the combination of severe disabling psoriasis, PCOS, thyroiditis, and alopecia areata.

Robert Gensure, MD, PhD

Case Report: Clinical Response to Combined Therapy of Cyclosporine and Prednisone

Excellent clinical response observed from the combined therapy of cyclosporine and prednisone in a 13-year-old female with chronic lymphocytic thyroiditis, primary ovarian failure, and down's syndrome.

Carolyn Goh, MD

Case Report: Sudden Onset Alopecia Areata Universalis after Discontinuation of Telaprevir, Peginterferon Alfa-2a and Ribavirin Therapy for Chronic Hepatitis C

Interferon-alfa treatment, with and without ribavirin, is linked to the exacerbation or onset of several autoimmune conditions as well as hair loss related to patchy alopecia areata, telogen effluvium, and injection site alopecia.

Lloyd E. King, MD, PhD

Case Report: Lack of Response to Laser Comb in Spontaneous and Graft-Induced Alopecia Areata in C3H/HeJ Mice

Results from the treatment of C3H/HeJ mice with a laser comb the FDA has approved for human male pattern baldness.

BUILDING OUR TRANSLATIONAL PLATFORM: LESSONS FROM PRECLINICAL & CLINICAL STUDIES

Thanh-Nga T. Tran, MD, PhD

Cutaneous Drug Delivery: An Update

An overview of the new trends and developments in cutaneous drug delivery, a proven and attractive option for treating a variety of dermatologic conditions.

Massimo Gadina, PhD

Jak Kinases: An Ideal Target for the Treatment of Autoimmune Diseases

Targeting the Type I and Type II families of cytokine receptors or their signaling pathways as a proposed means of treating immune-related disorders was discussed, as well as the advantages and disadvantages of selectively inhibiting JAKs tyrosine kinases for the treatment of autoimmune diseases.

Sheila Kelly, MD

Abatacept from Bristol-Myers Squibb

An overview of Abatacept (CTLA4-Ig), a novel fusion protein designed to modulate the T cell co-stimulatory signal.

Gurpreet Ahluwalia, PhD

Bimatoprost Stimulates Eyelash Growth in Patients with Chemotherapy Induced Eyelash Loss

A daily application of bimatoprost solution 0.03% over a one-year period is determined to be safe and well-tolerated in subjects with idiopathic or chemotherapy-induced hypotrichosis, and provides statistically significant and clinically meaningful benefits.

Amy J. McMichael, MD

Excimer Laser in Alopecia Areata Protocol and Module

Initiation of a protocol to assess the efficacy and safety of the 308-nm Excimer laser in the treatment of scalp alopecia areata, as well as the comparison of treatment outcomes.

MECHANISMS FOR FUNDING & REGULATORY MATTERS

Ricardo R. Cibotti, PhD

NIAMS Funding Opportunities in Immune-Mediated Skin Diseases

An overview of the Immunobiology and Immune Diseases of Skin Program and opportunities for funding studies focusing on the role of the skin microbiome on all immune-mediated skin diseases.

John C. McKew, PhD

Translational Resources within NCATS

An overview of the new center and highlights of the translational research programs contained within.

Heidi C. Marchand, PharmD

FDA & Regulatory Advocacy

Summary of necessary scientific benchmarks that enhance and improve the development of potential therapeutic products to meet the FDA's regulatory requirements. ■

I Was “Blown Away” by Alopecia Areata Research Summit and Advances

*Bob Flint, Member of NAAF Board of Directors
Houston, Texas*

I had the pleasure of attending NAAF’s Alopecia Areata Research Summit in Bethesda, Maryland in late November, and I thought I’d share a few of my learnings and observations there. But, first, let me give you an executive summary: I was blown away! And I was filled with the belief that we are truly getting much closer to finding a cure or effective treatment for alopecia areata

As a quick introduction, I am a member of the NAAF Board of Directors but have no medical or scientific background. I was a lay attendee at the meeting, so much that what was said was way over my head! But here are a few of the many highlights I picked up at the meeting:

- The speed and depth of advances in understanding the genetics of our disease has really increased.
- Two clinical trials are currently underway for alopecia areata treatments, with others in the wings.
- There is increased understanding of alopecia areata’s relationship to other autoimmune diseases, and it seems likely that approved treatments for these other diseases may be effective on alopecia areata.
- There are new discoveries from the alopecia areata mouse model.
- Representatives from the National Institutes of Health (NIH) say that that the basic science developed by our doctors, researchers, and scientists have earned increased emphasis from NIH on hair research and funding.
- Representatives from the Food and Drug Administration (FDA) discussed and offered guidance on efficiently and quickly taking potential treatments through clinical trials, FDA approval and into the marketplace.
- The necessary systems for FDA approval of potential treatments are essentially complete, including a new study of the incidence of alopecia areata in the population (indicating an incidence of 2.1%), a quality of life impact study, and standardized procedures and protocols for clinical trials and studies.

- The 58 people in attendance at the summit represented
 - 17 U.S. states and 5 countries
 - 30 leading research universities and hospital institutions (Mayo Clinic, Harvard Medical School, Johns Hopkins, Columbia University, Georgetown University, UCLA, Cleveland Clinic, Duke University, University of Texas, and many more)
 - The Food and Drug Administration and the National Institutes of Health
 - Three pharmaceutical companies
 - 40 leading doctors, scientists and researchers from key disciplines (dermatology, immunology, genetics, endocrinology and veterinarian medicine)
- And, perhaps most important, were the collaborative discussions, the idea generation, the networking, the “ah ha” moments, the energy in the room, and the new leads that were generated throughout the two-day meeting as ideas were exchanged and discussed among the top alopecia areata doctors and scientists in the world.



As I said, I was blown away! I left the meeting feeling the speed of advances in alopecia areata research and treatment has really taken off and we are on the cusp of much more rapid advances. Thanks, NAAF, for making all of this happen and reinforcing my conviction that we will defeat alopecia areata—and soon! ■

Basic Immunology and Hair Biology: An Introduction



To begin to understand the relationship between immunity and hair biology, and what NAAF is doing in the Treatment Development Program, it can be helpful to know a few words and their definitions.

The term **autoimmune** refers to the body's development of intolerance to the antigens on its own cells. *Autoantigens* are antigens that stimulate the production of *autoantibodies*, which attack the body's own cells.

Many cells are responsible for the body's immune responses, including **T cells**. These cells have distinct roles in the immune system and communicate with other immune cells by cytokines. **Cytokines** are chemicals made by cells that act on other cells to stimulate or inhibit their function, and cytokines that stimulate growth are called "growth factors." **Interleukins** (IL) are a group of cytokines that play an important role in the immune system; they modulate inflammation and immunity by regulating the growth, mobility, and differentiation of lymphoid and other cells. **Janus kinases** (JAKs) are cytokine receptors that convert chemical signals via their signaling pathways.

Research has established the basis of autoimmunity in alopecia areata but very little information exists on the hair follicle autoantigen(s) involved in the course of the disease. Alopecia areata primarily affects the hair follicle as it enters the prolonged growth phase called **anagen**. Alopecia areata attacks growing hair follicles (those in the anagen phase) that engage in the active production of melanin. These observations have encouraged the assumption that hair follicle melanocyte-associated and/or anagen-associated autoantigens play a key role in the development of alopecia areata.

A major focus of research related to autoimmunity in alopecia areata involves discovering the **specificity** of the immune response or the specific target that the immune response is attacking. The specificity of the immune response is determined by either antibodies or T cell receptors. The T cell receptor is located on the surface of T cells that migrate through the body seeking antigens to attack. In alopecia areata, specific T cells attack antigens in the hair follicle.

Natural killer (NK) cells are an important element of the immune system as they are capable of killing tumor cells and cells

infected by viruses. NK cells express a large number of cell surface receptors that deliver either activating or inhibitory signals. Human NKG2D is an orphan receptor that is expressed on NK cells and many T cells. NKG2D functions as a ligand, a binding molecule, for cell surface proteins. Common pathways in some autoimmune diseases (such as rheumatoid arthritis, celiac disease, and type 1 diabetes) involve NK ligands in target organs. In alopecia areata, research has discovered an over-expression in the hair follicle of the ULBP3 gene, which encodes the NKG2D ligand, activating an autoimmune response. Alopecia areata is often likened to a "swarm of bees" in the form of specific killer T cells (CD8) that are attracted to the hair follicle by NKG2D ligands.

It is well recognized in the research community that the normal hair follicle is one of the few tissues in the human body that enjoys a state of immune privilege protecting it from autoimmune attack. Normal hair follicles are cloaked from immune recognition. The collapse of this immune privilege is what allows the swarm of killer T cells leading to alopecia areata.

Interleukin-15 (IL-15), which is required for the growth and sustenance of the natural killer T cells (CD8) that surround the growing end of the hair follicle during active disease, has been identified as a highly promising therapeutic target in alopecia areata. It can be addressed along the IL-15 signaling pathway by using Janus kinase inhibitors (JAK).

New treatment opportunities based on these research findings, which implicate T cell and NK cell activation pathways, are leading to new approaches in future clinical trials of alopecia areata. Future treatment approaches for alopecia areata include use of drugs that:

- Block the NKG2D ligand and NKG2D receptor interaction
- Halt activated T cells
- Modify the inflammatory cytokines network

Many drugs currently being used or being evaluated for other autoimmune diseases that work through these mechanisms might prove to be very effective for alopecia areata. ■