Introduction to Innovations in the Immunology and Clinical Science of Alopecia Areata

Victoria D. Kalabokes[1], Wilma F. Bergfeld[1] and Angela M. Christiano[1]

Alopecia areata is an autoimmune skin disease resulting in the loss of hair on the scalp and elsewhere on the body. The disease most often occurs in childhood and affects males and females of all ages. The National Alopecia Areata Foundation conducts research summits every 2 years to review progress and create new directions in its funded and promoted research. The Foundation brings together scientists from all disciplines to get a broad and varied perspective. These summits are part of the Foundation's main strategic initiative, the Alopecia Areata Treatment Development Program to accelerate progress toward a viable alopecia areata treatment.

Journal of Investigative Dermatology Symposium Proceedings (2013) **16,** S1–S4; doi:10.1038/jidsymp.2013.1

This summit titled *From Basepairs to Bedside: Innovations in the Immunology and Clinical Science of Alopecia Areata* was held in Bethesda, Maryland, 29 and 30 November, 2012. It was convened to review recent progress in understanding the pathogenesis of alopecia areata and to chart the course for the future of translational research. It brought together an exciting group of scientists, immunologists, geneticists, veterinary scientists, medical experts, translational scientists, clinical dermatologists, and representatives of government agencies to discuss innate and acquired immunity, associated autoimmune diseases, their common immune pathways, and targeted immunological therapies.

At the Alopecia Areata Clinical Research Summit in October 2010, participating scientists had stressed the need to develop a translational platform. Essential to that platform were biomarker studies; new and established animal models; a uniform clinical trials protocol; incidence, prevalence, quality of life and other burden of disease studies; defined measurements and end points; further genetic and mechanistic studies; genetic and immunological pathway studies; and collaboration with the US Food and Drug Administration (FDA) to pave the way for approval of promising clinical trials. Advances have been made in all of these areas.

After listening to presentations at this 2012 Alopecia Areata Research Summit, the scientists in attendance expressed great satisfaction over the progress being made in providing the infrastructure needed for the many facets of progressing a drug through FDA approval.

ALOPECIA AREATA TREATMENT DEVELOPMENT PROGRAM

These alopecia areata research summits are part of the National Alopecia Areata Foundation's (NAAF) main strategic initiative, the Alopecia Areata Treatment Development Program (TDP). The first phase of the TDP, started in 2010 clarified and articulated its 7-year mission to accelerate progress toward a viable alopecia areata treatment. All of the accomplishments explained above have been part of this Program with NAAF acting as a concierge, leveraging all of our available research resources and clinical partnerships. Our strategic goal is to produce a safe, effective affordable treatment beneficial to the millions of people with alopecia areata. This summit was another strategic step on the structured and focused path toward that goal.

ALOPECIA AREATA RESEARCH GOALS FOR THE NEXT 2 YEARS ESTABLISHED AT THE SUMMIT

Genetics

- Execute combined association and linkage studies using 250 multiplex families from the Alopecia Areata Registry, Biobank, and Clinical Trials Network (formerly known as National Alopecia Areata Registry).
- Utilize functional genomics with deep sequencing.
- Develop a network plot.
- Determine the percentage of people with alopecia areata compared with the normal population with specified genes.
- Analyze shared variants among related diseases, including celiac disease, rheumatoid arthritis, and type 1 diabetes (five loci are shared between type 1 diabetes and alopecia areata).
- Increase the number of alopecia areata samples in the BioBank to 10,000.
- Determine whether there is a genetic basis for disease subsets, i.e., alopecia areata, alopecia totalis, and alopecia universalis.
- Analyze National Alopecia Areata Registry, Biobank, and Clinical Trials Network samples to determine whether

[1]*National Alopecia Areata Foundation, San Rafael, California, USA*

Correspondence: Victoria B. Kalabokes, National Alopecia Areata Foundation, 14 Mitchell Boulevard, San Rafael, California 94903, USA. E-mail: vicki@naaf.org

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 interleukin (IL)-15 pathway.
- Identify the protolerance T-cell receptor (TCR) signal; and then target it pharmacologically.
- Develop TCR 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 for clinical trials.
- Publish quality-of-life studies.
- Publish incidence and prevalence studies.
- Initiate additional 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.

Investigators interested in applying for grant funding to study any of these areas mentioned above should contact the National Alopecia Areata Foundation for research grant information.

The following talks were presented. Due to embargos for other publications, some talks were unable to be published in these proceedings. Presentations with asterisks (*) are included.

WELCOME FROM DR KATZ

We were excited to have Dr Stephen Katz, Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), 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.

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. This work greatly expands our understanding of the genetic architecture of this highly prevalent autoimmune disease.

Dr John Sundberg* presented the identification of three new inbred strains in addition to C3H/HeJ and A/J with naturally occurring alopecia areata in a large aging study, enabling genome-wide association mapping using large single-nucleotide polymorphism databases, revealing new insight into the complexity of this disease.

IMMUNOLOGY AND BIOLOGY OF ALOPECIA AREATA

In pursuing cytokines that might be critical to the activation of killer CD8 T cells, Dr Raphael Clynes and his team identified elevations of IL-15 in human alopecia areata skin and have pursued therapeutic approaches to block IL-15 signaling. These studies establish the pre-clinical rationale for pharmacological targeting of CD8 killer T cells in alopecia areata.

Dr Ralf Paus* discussed the clinical consequences of the hypothesis that alopecia areata is not a single disease entity but a stereotypic, clinically and histologically distinct hair follicle response pattern to various inflammatory insults associated with (e.g., interferon-γ (IFNγ)-induced) hair follicle immune privilege collapse.

Dr Thomas Waldmann* discussed two approaches to dysregulate IL-15 expression: targeting the IL-15 receptor or its JAK/STAT (Janus-activated kinase/signal transducer and activator of transcription factor) signaling pathway in mouse models of autoimmune diseases. Similar IL-15R or IL-15 signaling pathway direct approaches might be effective in alopecia areata.

Dr Adam Schrum* presented a new technological/analytical platform designed to allow network analysis of the protein–protein interactions (PPI) that compose T-cell signaling webs. Multiplex immunoprecipitation detected by flow cytometry is designed for high sensitivity and applicability to samples containing low numbers of T cells.

COMMON CAUSES: RELEVANCE OF ALOPECIA AREATA TO OTHER AUTOIMMUNE DISEASES

Using a mouse model of vitiligo, Dr John Harris and his team determined that IFNγ and the IFNγ-dependent chemokines CXCL9 (C-X-C motif chemokine ligand 9) 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 IFNγ, strongly imply a similar pathogenesis.

Dr Matthias von Herrath defended the position that a main problem in human T1D development and recurrence is autoimmunity, in spite of ample evidence of the involvement

of viruses and other environmental and genetic factors in type 1 diabetes pathogenesis.

To gain further insight into the genetic architecture of psoriasis, Dr James Elder* and his team conducted a meta-analysis of three genome-wide association studies and two independent data sets genotyped on the Immunochip (Illumina, San Diego, CA), involving 10,588 cases and 22,806 controls in total. They identified 15 new disease-susceptibility regions, increasing the number of psoriasis-associated loci to 36 for Caucasians. These 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

Dr Amos Gilhar* presented the development of an animal model for alopecia areata in which the clinical phenotype can quickly be induced within a previously healthy human organ *in vivo*.

Dr David Norris presented Dr Yosef Refaeli's new approach to generate chimeric mice bearing a human hematopoietic system.

Dr Julie Segre's research combines genomics, dermatology, microbiology, and immunology to explore cutaneous microbes in relation to healthy skin and dermatological disorders.

Dr Annemieke de Jong discussed the hypothesis that high-throughput TCR sequencing may provide patient-specific molecular tools for monitoring disease activity and response to therapy and provide insights in phenotype and function of pathogenic T cells in alopecia areata.

Dr Ali Jabbari presented an update on the Alopecia Areata Biomarker study aimed to develop a set of exploratory biomarkers that can later be validated and will be crucial for monitoring of improvement during clinical trials in alopecia areata.

Dr Amelia Wall Warner* discussed methods to capitalize on pharmacogenomic research to rapidly advance development of alopecia areata drug therapy.

Maureen McGettigan* presented alopecia areata from a patient's perspective.

Dr David Norris* began the second half of the meeting with a comprehensive review of several key topics discussed on the first day.

OVERVIEW OF CURRENT TREATMENTS

Dr Jerry Shapiro* presented an overview of the many therapeutic options that exist for alopecia areata, including topical, immunotherapeutic and systemic agents, and injections.

Dr Richard Strick* has been treating extensive cases of alopecia areata with 1-cholor-2, 4-dinitrobenzene for 35 years with considerable success and presented the protocol that has been used.

Dr Madeleine Duvic presented a case of a 35-year-old white male with a 1-year history of alopecia universalis in response to targretin gel treatment after beginning systemic steroids.

TREATMENT DEVELOPMENT PROGRAM

Richard Gelula* presented an overview of the Alopecia Areata Treatment Development Program, a multi-faceted initiative, a multi-pronged approach to develop safe and effective treatments for alopecia areata.

Dr Natasha Atanaskova Mesinkovska* presented her work in the development of a standardized alopecia areata research protocol to serve as a uniform template, outlining procedures for all future clinical trials.

Given the lack of reliable and accurate description of health-related quality-of-life (HRQoL) status in people with alopecia areata, Dr Tito Mendoza* and his team conducted a secondary analysis of the National Alopecia Areata Registry to better understand the HRQoL of people with alopecia areata. He presented his plan to develop a brief, concise, and validated patient-reported outcome tool to assess the impact of alopecia areata on the HRQol of people with the condition.

Dr Rochelle Torgerson presented her study to determine the incidence of alopecia areata among residents of Olmsted County, Minnesota, USA and a comparison of the results to those of a previous study conducted in the same geographic area.

ALOPECIA AREATA REGISTRY, BIOBANK, AND CLINICAL TRIALS NETWORK

Dr Madeleine Duvic* presented an update on the progress of the National Alopecia Areata Registry over the past 10 years and its emergence as a clinical trials network and biobank.

CASE REPORT PRESENTATIONS

Dr Wilma Bergfeld* discussed a young female child, aged 7 years, presented initially with chronic alopecia areata, which over 2 years progressed to alopecia areata universalis.

Dr Maria Hordinsky presented the case of a 36-year-old female who reported scalp pruritus with hair loss activity.

Dr John Harris reported two cases that represent a natural experiment in which separate autoimmune diseases interact within the skin, with very different results.

Dr Melissa Piliang* presented two young women with the combination of severe psoriasis, androgen excess, metabolic syndrome, thyroiditis, and alopecia areata.

Dr Robert Gensure* presented a patient with severe alopecia areata, multiple autoimmune diseases (chronic lymphocytic thyroidis, primary ovarian failure), and Down syndrome.

Dr Carolyn Goh* presented a case of alopecia universalis occurring shortly after treatment of chronic hepatitis C and discussed the implications this has in understanding the pathophysiology of alopecia areata.

Dr Lloyd King presented a study in which C3H/HeJ mice were treated with a laser comb FDA approved for human male pattern baldness.

CLINICAL POSTERS

Dr Robert Gensure* displayed a poster of his study testing the effects of a single dose of PTH-collagen binding domain (low or high dose) in an animal model for alopecia areata, the C3H/HeJ engrafted mouse.

Dr Vera Price* displayed a poster of two cases: one case revealed that a strongly positive pull test is not always alopecia

areata; and a second case revealed that alopecia areata is the only condition that can cause complete hair loss in 3 months without any previous symptoms or signs.

BUILDING OUR TRANSLATIONAL PLATFORM: LESSONS FROM PRE-CLINICAL AND CLINICAL STUDIES

Dr Thanh-Nga Tran* presented a summary of the latest technologies used to increase cutaneous delivery through the three different routes, delineating various chemical and physical methods as well as reviewing various drug delivery systems, including liposomes, microspheres, and nanoparticles.

Dr Massimo Gadina* discussed the advantages and disadvantages of selectively inhibiting JAKs tyrosine kinases for the treatment of autoimmune diseases.

Dr Sheila Kelly presented an overview of Abatacept (CTLA4–Ig), a novel fusion protein designed to modulate the T-cell costimulatory signal, in the treatment of autoimmune diseases.

Bimatoprost 0.03% solution is an FDA-approved prescription product indicated for the treatment of eyelash hypotrichosis. Dr Gurpreet Ahluwalia* presented a clinical study in which the product was investigated in a double-masked, randomized, and placebo controlled study in patients who had significant eyelash loss or hypotrichosis as a result of chemotherapy.

Dr Amy McMichael* described the use of a common treatment protocol with a specifically designed module to study the outcome of excimer laser treatment on moderate-to-severe scalp alopecia areata in adults.

MECHANISMS FOR FUNDING AND REGULATORY MATTERS

Dr Ricardo Cibotti presented NIAMS funding opportunities in functional genomics, ancillary studies of large clinical projects, and implementation of clinical trials with cooperative agreements.

Dr John McKew gave an overview of the new National Center for Advancing Translational Sciences and highlights of the translational research programs contained within.

Dr Heidi Marchand presented drug–development activities and average development times in the context of the FDA regulatory processes.

NEXT SUMMIT

The next Alopecia Areata Research Summit will be held on 4 and 5 December 2014 in Bethesda, Maryland as part of the Alopecia Areata Treatment Development Program. This next summit will review and strategically evaluate implications of findings from research driven by the goals outlined above. We expect some of the highlights to be: further demonstrating the disease burden of alopecia areata, including the medical, psychosocial, and financial impacts; clarifying the complexity of this heterogeneous disease with its wide range of genetic factors that may indicate different disease subsets and/or processes with potentially many treatment modalities; and further evaluating similarities to other autoimmune diseases and the potential applicability of their targets and treatments to alopecia areata. Hopefully, we will have promising treatments and targets to share with the autoimmune research community. The National Alopecia Areata Foundation has provided the support and leadership to enhance the understanding of alopecia areata. We look forward to future discoveries.

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

Funding for the Summit and publication of this article was provided by the National Alopecia Areata Foundation.