Overview of AA and Research Progress: What Have We Learned and Where Are We Headed?

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During its 25th anniversary year, the National Alopecia Areata Foundation undertook a project to completely re-evaluate their research program and to help focus and direct future directions of alopecia areata research to better meet the goals of people with alopecia areata (AA) and the scientists working to discover mechanisms of disease and better treatments for AA. This project was embodied in four research summits in 2008, 2009, 2010, and 2012, as part of the Foundation's main strategic initiative, the Alopecia Areata Treatment Development Program to accelerate progress toward a viable alopecia areata treatment. The first summit was an evaluation of the progress of AA research in a global sense, with an emphasis on how to use the research programs to bring better treatments to patients. The second summit focused on immunology and how to better understand the autoimmune nature of AA. The third summit focused on developing a clinical research network that could most effectively bring new treatments to patients. The fourth summit consolidated the considerable evidence of the mechanisms of AA, and how these mechanisms could be targeted by modern therapies, many of which were being used effectively in other autoimmune diseases. These four summits laid the foundation for the fifth summit in the series: *From Targets to Treatments: Bridging Autoimmune Research to Advance Understanding of Alopecia Areata*.

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Alopecia areata (AA) is a complex genetic, immune-mediated disease that targets anagen hair follicles (Alkhalifah *et al.*, 2010; Gilhar *et al.*, 2012). The disease is characterized by round or oval patches of hair loss, which may assume a variety of patterns: loss of all scalp hair (alopecia totalis), loss of all body hair (alopecia universalis), or extensive loss on the occipital and parietal scalp (ophiasis pattern hair loss). Nail abnormalities may precede, follow, or occur concurrently with hair loss activity. About 50–80% have sporadic or patchy alopecia areata patchy while alopecia areata totalis and alopecia areata universalis are much more rare. The diseases associated with alopecia areata in studies around the world include vitiligo, hypo- and hyperthyroidism, and atopy. Males and females of all ages can be affected, though onset is often found in childhood, and there is no known racial, ethnic, or gender preponderance. A recent study found a cumulative lifetime incidence of 2.1% that translates into 6.5 million people in the United States and 145 million worldwide who have, had, or will develop alopecia areata at some point in their lives (Mirzoyev *et al.*, 2014). Alopecia areata can have devastating effects on an affected person's quality of life and people with the disease are searching for an effective treatment or cure. Currently there are no treatments with Food and Drug Administration (FDA)-approval for this indication, and a recent Cochrane review notes that there are no treatments that have been shown to induce long-term benefit in alopecia areata (Delamere *et al.*, 2008). They concluded, ''There is a desperate need for large well conducted studies that evaluate long-term effects of therapies on quality of life.''

During its 25th anniversary year, the National Alopecia Areata Foundation undertook a project to completely re-evaluate their research program and to help focus and direct future directions of alopecia areata research to better meet the goals of people with AA and the scientists working to discover mechanisms of disease and better treatments for AA. This project was embodied in four research summits in 2008, 2009, 2010, and 2012, as part of the Foundation's main strategic initiative, the Alopecia Areata Treatment Development Program to accelerate progress toward a viable alopecia areata treatment. The first summit was an evaluation of the progress of AA research in a global sense, with an emphasis on how to use the research programs to bring better treatments to patients. The second summit focused on immunology and how to better understand the autoimmune nature of AA. Several projects were proposed to identify specific targets of the immune response in AA, and to develop animal

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models to study these mechanisms in detail. A parallel objective was to identify drugs used in other autoimmune diseases to treat AA.

The third summit was initiated in response to the demand of new treatments by AA patients, and focused on developing a clinical research network that could most effectively bring new treatments to patients. This summit launched a number of important initiatives to develop and fund a clinical investigations network in AA, based on the framework of the Alopecia Areata Registry:

1. Develop a uniform AA clinical research platform that stratifies extent and duration, has a crossover component, and an unambiguous end point.
2. Mine the National Alopecia Areata Registry data and publish quality-of-life data on AA.
3. Identify biomarkers from previous AA studies.
4. Develop a translational clinical research platform with biomarkers (Skin, serum, whole blood, RNA, and DNA).
5. Develop a plan to approach multiple pharmaceutical companies to use drugs in development of already approved for other diseases in AA.
6. Develop a strategy to assist individual investigators in submitting grants to NIAMS to support clinical pilot and feasibility studies.

The fourth summit consolidated the considerable evidence of the mechanisms of AA, and how these mechanisms could be targeted by modern therapies, many of which were being used effectively in other autoimmune diseases. We learned that:

1. Both innate and acquired immunity are involved in AA.
2. Both genetic and functional immunologic studies have identified complex immunologic networks in both human- and animal-model AA. NKG2D ligands, interleukin (IL)-15, CTLA-4, and Jak signaling have emerged as attractive targets for treatment of AA using modern biologic and pharmacologic approaches.
3. Modulation of immune privilege continues to be an intriguing target to modulate AA induction and progression.
4. The specificity of the immune response in AA is still unknown. Pigmented anagen hair follicles appear to be the target. Whether antigen-specific activated T cells or antibodies are required for AA is not yet known.

The fourth summit focused on identifying attractive targets for treatment of AA using modern biologic and pharmacologic approaches and developing a robust clinical research platform to facilitate the testing of a number of new drugs being effectively used in other autoimmune diseases. The summit provided a number of recommendations for future research to achieve the goal of finding safe, effective affordable FDA-approved treatment for alopecia areata.

Genetics

1. 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).
2. Utilize functional genomics with deep sequencing.
3. Develop a network plot of pathways activated in alopecia areata.
4. Determine the percentage of people with alopecia areata compared with the normal population with specified genes.
5. 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).
6. Increase the number of alopecia areata samples in the BioBank to 10,000.
7. Determine if there is a genetic basis for disease subsets, i.e., alopecia areata, alopecia totalis, and alopecia universalis.
8. Analyze National Alopecia Areata Registry, Biobank and Clinical Trials Network samples to determine whether alopecia areata is a composite of several different disease processes and the possibility that there are actually many treatment modalities.

Immunology

1. Study how to restore immune privilege.
2. Analyze the potential of targeting the IL-15 pathway.
3. Identify the protolerance TCR signal; then target it pharmacologically.
4. Develop TCR sequencing.
5. Complete biomarker studies.

Animal models

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

Clinical

1. Finalize and validate the Alopecia Areata Uniform Protocol for clinical trials.
2. Publish quality-of-life studies.
3. Publish incidence and prevalence studies.
4. Initiate additional burden of disease studies.
5. Use pharmacogenomics to predict which patient populations will respond and which will get side effects.
6. Determine the attractive pathways for targeted therapy.

The recent advancements and discoveries in AA research through the efforts of NAAF and four highly successful research summits laid the groundwork for the fifth summit in the series: *From Targets to Treatments: Bridging Autoimmune Research to Advance Understanding of Alopecia Areata*. This meeting, held in December 2014, represented the successful collaborative efforts of the AA research community with research advances into the cause and mechanisms of AA and early-stage clinical trials of drugs targeting autoimmune pathways showing promising hair regrowth.

CONFLICT OF INTEREST
The author states no conflict of interest.

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REFERENCES

Alkhalifah A, Alsantali A, Wang E *et al.* (2010) Alopecia areata update: part I. Clinical picture, histopathology, and pathogenesis. *J Am Acad Dermatol* 62:177–88

Delamere FM, Sladden MM, Dobbins HM *et al.* (2008) Interventions for alopecia areata. *Cochrane Database Syst Rev* 2:CD004413

Gilhar A, Etzioni A, Paus R (2012) Alopecia areata. *N Engl J Med* 366:1515–25

Mirzoyev SA, Schrum AG, Davis MD *et al.* (2014) Lifetime incidence risk of alopecia areata estimated at 2.1% by Rochester Epidemiology Project, 1990-2009. *J Invest Dermatol* 134:1141–2