

Forging the Future: 2018 Alopecia Areata Research Summit Summary Report



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Alopecia areata (AA) is a common autoimmune skin disease resulting in the loss of hair on the scalp and elsewhere on the body that affects over 146 million people worldwide at some point in their lives. Founded in 1981, the National AA Foundation (NAAF) is a nonprofit organization that supports research to find a cure or acceptable treatment for AA, supports those with the disease, and educates the public about AA. NAAF conducts research summits every two years to review progress and create new directions in its funded and promoted research. This report from the seventh AA Research Summit, Forging the Future, held December 4–5, 2018 in New York City provides highlights of the research presented and future research priorities identified during targeted discussion sessions.

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INTRODUCTION

The seventh Alopecia Areata (AA) Research Summit, Forging the Future, provided a forum for expert researchers and clinicians from a variety of fields to present cutting-edge research, disseminate results from ongoing projects, and foster collaboration around the best ways to further advance AA research. The 113 Summit participants who gathered December 4 and 5, 2018, in New York City included 33 expert researchers within and outside the field of AA; 26 early career investigators; 34 biopharmaceutical industry representatives; 10 patient advocates; and 10 representatives from government and other organizations, including the National Institutes of Health (NIH) and International Dermatology Outcome Measures (IDEOM). Altogether, more than 35 academic institutions and research centers from the United States and eight countries across the globe were represented.

Our three outstanding co-chairs, Drs Jerry Shapiro, Natasha Mesinkovska, and Angela Christiano, organized two intensive days of scientific programming focused on the following: (i) the current state of AA research; (ii) clinical

research and outcome assessments; (iii) patient engagement in clinical development; (iv) new frontiers in basic science; and (v) epidemiology, health economics, and the burden of this disease. This report provides highlights of the research presented in each topic area and the future research priorities identified during targeted discussion sessions.

CURRENT STATE OF AA RESEARCH

Presentation highlights¹

Dr Natasha Mesinkovska, Chief Scientific Officer of the National AA Foundation (NAAF) and Director of Clinical Research at the University of California Irvine School of Medicine, summarized preceding research summits that laid the groundwork for the genetic and immunologic studies, research infrastructure, funding streams, and strategic partnerships resulting in the current investigative trajectory.

Dr Angela Christiano, from Columbia University Medical Center (New York, NY), presented an update on genetics and immunology studies that are central to understanding the underlying mechanisms of AA. Three new areas of research suggest that (i)

Jak2 inhibition is not required for efficacy in AA; (ii) Jak1/3 inhibitors may induce T-cell exhaustion as part of their mechanism of action; and (iii) the onset of AA may be associated with bidirectional dysbiosis in gut microbiota.

Dr Maria Hordinsky,* from the University of Minnesota Medical School (Minneapolis), provided an overview of current treatment practices for adult and pediatric patients with AA in the absence of Food and Drug Administration–approved therapies. Factors to consider when choosing a treatment include age; location of hair loss; disease extent and activity; associated medical problems; and patient and/or parent choice after a review of proposed treatment risks, benefits, and expectations. Current treatment of AA should include a conversation about current clinical research opportunities as well as the off-label use of oral or topical Jak inhibitors.

Dr Ralf Paus,* from the University of Miami (Florida) and the University of Manchester (United Kingdom), explored the hypothetical scenario that AA may not be a single disease, but a stereotypic response pattern that every

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healthy anagen hair follicle will show when IFN- γ immunologic damage triggers the pathobiology triad of immune collapse, hair follicle dystrophy, and premature catagen induction. He believes that a personalized medicine approach is needed to treat antigen-specific autoimmune AA as well as nonantigen-specific forms of the disease.

Dr Amos Gilhar,* from the Technion-Israel Institute of Technology (Haifa), reviewed the similarities and differences between the C3H/HeJ and humanized mouse models. The histologic features of the C3H/HeJ model are not always typical of human AA, so the humanized mouse model should also be used in preclinical testing of new candidate agents for AA.

CLINICAL RESEARCH AND OUTCOME ASSESSMENTS

Presentation highlights

Clinical research. Dr Brittany Craiglow,* a pediatric dermatologist from the Yale School of Medicine and Dermatology Physicians of Connecticut (Fairfield), reviewed several case reports and series on the use of topical and systemic Jak inhibitors for the treatment of AA in children aged 4–17 years, showing efficacy in at least 50% of patients. Multiple ongoing clinical trials evaluating Jak inhibitors for AA are now enrolling patients aged 12–17 years. Although more data is needed to further explore the safety and efficacy of Jak inhibitors in the pediatric population, their use may be considered for children with AA who are experiencing significant psychosocial impairment; such use should be preceded by a thorough discussion of the risks, benefits, and unknowns.

Dr Brett King, from the Yale School of Medicine (New Haven, Connecticut), evaluated the response of eyebrows and eyelashes in patients with AA treated with the Jak inhibitor tofacitinib (Xeljanz, Pfizer, New York, NY) from 2014 to 2018. Of 98 patients with total scalp hair loss, 86 had involvement of both eyebrows and eyelashes. Complete regrowth of all sites (scalp, eyebrows, and eyelashes) was achieved in 19 of 119 patients (16%), highlighting differences in hair follicle biology across different hair-bearing sites.

Dr Melissa Piliang, from the Cleveland Clinic Lerner College of Medicine (Ohio), shared results from a retrospective study

of 20 patients with alopecia universalis and alopecia totalis treated with 10–25 mg tofacitinib (Xeljanz, Pfizer) over an average of 13 months. A total of 11 patients (55%) experienced more than 50% hair regrowth, seven patients (35%) developed laboratory abnormalities, and six clinical adverse events were reported. Results indicate that tofacitinib is a viable long-term treatment option for severe AA, but further research is needed to understand the variation in efficacy among patients.

Dr Hind Almohanna,* from the University of Miami Miller School of Medicine (Florida), reviewed available data on the efficacy, safety, and mechanism of action of platelet-rich plasma (PRP) injections in treating AA. Although PRP is relatively safe and potentially effective, there are no standardized protocols or recommendations for the number of PRP sessions required to treat and maintain hair regrowth. Additional large-scale studies are needed to evaluate efficacy as a monotherapy or in association with other therapeutic modalities for AA.

Jessica Lin, from the University of California Irvine School of Medicine, presented a pilot study on the use of multiphoton microscopy (MPM) as an adjunct to histologic studies and a diagnostic tool for AA. Results showed MPM was able to visualize histologic features of AA and may be useful in noninvasive monitoring of disease progression in clinical practice.

Dr Emma Guttman-Yassky,* from the Icahn School of Medicine at Mount Sinai (New York, NY), presented data showing that AA is a highly inflammatory skin disease with increased T helper type 1, T helper type 2, and IL-23 cytokine circuits. Treatment with drugs aimed at specific cytokine inhibition may help uncover the pathogenic contribution of these pathways in AA.

Dr Mark Lebwohl, from the Icahn School of Medicine at Mount Sinai (New York, NY), showed how research related to psoriasis and atopic dermatitis models have been helpful in dissecting key immune pathways that play roles in the development of inflammatory skin disease. Following the same methodology and applying narrow-targeted therapeutics may help elucidate the role of each cytokine pathway in the development of AA.

Dr Maryanne Senna,* from Massachusetts General Hospital (Boston), presented three thought-provoking clinical case

reports on the art of treating patients with AA, and she highlighted the importance of using a personalized approach.

Dr Chloe Ekelem,* from the University of California Irvine School of Medicine, shared a series of case studies of three patients with AA treated with PRP over the course of 3 months using noninvasive optical coherence tomography (OCT) imaging to monitor response. The patient who also treated the scalp with a daily application of ice demonstrated the most significant regrowth. Results show that PRP may be effective in the treatment of patients with patchy AA with active lesions, OCT may be useful for monitoring disease progression in clinical practice, and cooling measures may have utility as an adjunct to therapeutic mainstays.

Dr Elena Peeva, from Pfizer (Cambridge, MA), reported results from an ongoing phase 2a, randomized, double-blind, multicenter study of an oral Jak3 inhibitor (PF-06651600) and an oral TYK2/Jak1 inhibitor (PF-06700841) in patients with moderate to severe AA. At 24 weeks, both Jak inhibitors demonstrated an improvement in hair regrowth on the scalp relative to baseline as measured by the Severity of Alopecia Tool (SALT) score (PF-06651600, 33.6%; PF-06700841, 49.5%). These results indicate that treatment with PF-06651600 or PF-06700841 was efficacious and well tolerated in patients with AA.

Dr James Cassella, from Concert Pharmaceuticals (Lexington, MA), reported interim results from an ongoing phase 2a, double-blind, randomized, placebo-controlled trial of an oral Jak1/Jak2 inhibitor (CTP-543) in patients with moderate to severe AA. At 24 weeks, treatment with 8 mg of CTP-543 significantly improved hair regrowth ($\geq 50\%$) in 47% of patients with AA with an acceptable safety profile.

Dr Ricardo Cibotti, Program Director of Immunobiology and Immune Diseases of Skin at the National Institute of Arthritis and Musculoskeletal and Skin Diseases (Bethesda, MD) (NIAMS), shared how AA is a rapidly expanding area of NIAMS research. The various funding opportunities to support clinical research were reviewed, including an R01 grant (the NIH's oldest grant mechanism), specifically focused on the pursuit of clinical observational studies to obtain data necessary for designing clinical trials such as disease symptoms, disease progression, comorbid conditions, and outcomes, and an R34 grant (a type of grant often

providing early support for research projects) to facilitate the necessary planning, design, and preparation of documentation before implementation of investigator-initiated clinical trials.

Future research priorities

- Develop consensus-driven, evidence-based guidelines for treatment, including statements on the definition of disease, severity subsets, diagnostic criteria, natural history, and paths for short- and/or long-term management for publication in a peer-reviewed journal.
- Study the differences in hair follicle biology and treatment effects across different hair-bearing sites, including eyebrows and eyelashes.
- Investigate response to therapy among different disease subgroups, including patients with new onset, patients with longstanding disease, and pediatric populations.

Clinical outcome assessments. Dr Elise Olsen, from Duke University Medical Center (Durham, NC), discussed the inherent challenges posed for clinical trials in AA, including the lack of standardized assessment methods and the necessity of taking into account the effect of extent, pattern, and duration of hair loss on regrowth. Dr Olsen provided an overview of assessment methods including the SALT, Lesional Density Score, and Alopecia Density and Extent scoring systems, as well as a potential global score.

Dr Justin Ko,* from Stanford University School of Medicine (California), presented the results of a study to understand the importance of eyebrows in the treatment goals of patients with AA. An online survey of 1,741 patients asked them to assess their satisfaction with various levels of response to treatment, as shown by edited photos depicting a range of eyebrows and scalp hair growth. Results showed that satisfaction with scalp and eyebrow regrowth is nonlinear. More participants were satisfied with complete eyebrows and no scalp hair (69%) than complete eyebrows and partial scalp hair (51%). Future studies may consider looking at eyebrow regrowth as a primary outcome in conjunction with scalp hair regrowth or potentially as a primary outcome alone.

Dory Kranz, Chief Executive Officer of NAAF, reported the progress of NAAF's

Patient-Reported Outcome Consortium to develop a single, consensus-defined patient-reported outcome instrument that can be shared across industry partners and other ongoing initiatives to incorporate the voices of patients in AA research.

Dr. Alice Gottlieb*, from International Dermatology Outcomes Measures and New York Medical College, presented the ongoing work of IDEOM, including the core domains for psoriasis and hidradenitis suppurativa and the development of global health care provider and patient-reported outcome measures for clinical practice across multiple dermatologic disorders. Potential areas of mutual interest with IDEOM and NAAF include fundraising; the development of outcome measures; and collaborations with researchers, industry, and government.

Dr Kathleen Wyrwich*, from Eli Lilly & Company (Indianapolis, IN), shared about the role of patients in the development of the AA Investigator Global Assessment (AA-IGA), a five-grade scale to measure clinically meaningful treatment response to AA treatment for patients with 50% or more scalp hair loss. When reviewed with patients and clinicians, the AA-IGAs were supported as a meaningful clinician-reported measure of scalp hair loss. The AA-IGA is available for others to use, with the goal of consistent measurement across AA research endeavors.

Future research priorities

- Define the relationship between hair regrowth and satisfaction with response and determine the threshold for meaningful response for scalp hair regrowth.
- Determine how patients want to be engaged in their health care and treatment decisions and the characteristics of meaningful shared decisions.
- Develop a training tool for the use of SALT that is available for clinical investigation and practice.
- Develop a core outcome set suitable across clinical trials in AA that represent both patients' and physicians' priorities. This will:
 - achieve agreement on what and how to measure (e.g., eyebrow and eyelash regrowth) and how best to use photos;
 - define a core set of domains (outcomes) to be measured with input from all stakeholders; and

- identify or develop measurements that are sufficiently validated and sufficiently assess these domains.

PATIENT ENGAGEMENT IN CLINICAL DEVELOPMENT

Presentation highlights

Patient perspective. Dustin Lee shared his perspectives on AA as a patient, a researcher in the immunology field, and an NAAF Health and Research Ambassador (HARA). HARA are a collaborative group of patients not only possessing the knowledge and first-hand experience of living with AA but also having expertise in a variety of subjects that intersect nicely with the pharmaceutical industry to result in valuable insights. Lee described the value of HARA engagement in meaningful dialogue with the industry to provide actionable feedback in a highly effective and impactful way to help direct treatment efforts toward the most desired end results for the patient community.

Industry perspectives. A panel of representatives from seven pharmaceutical companies (Aclaris Therapeutics, Bioniz Therapeutics, Concert Pharmaceuticals, Eli Lilly & Company, Legacy Healthcare, LEO Pharma, and Pfizer) was convened to discuss their programs for AA, how patient participation is useful, and where it is most needed.

All participants were passionate about their commitment to continuing patient engagement at every level to create greater efficiencies and better outcomes. A common theme of the discussion was centered on challenges posed by the United States healthcare system and ensuring that all patients have access to treatments once they are approved. Real-world evidence is needed to create data-driven insights into patient lifestyles, preferences, and decision-making processes to demonstrate the clinical and economic benefits of treatments, so that they are covered. The group agreed that collaboration is key to collecting, collating, and analyzing the right data to meet the needs of all stakeholders and help improve the lives of patients with AA.

Future research priorities

- Evaluate the decision-making process a patient goes through when considering benefit versus risk of treatment options, including clinical trials.

- Determine how patients weigh effectiveness against side effects and inconvenience when deciding whether to continue, change, or stop treatment.
- Predict which patients are likely to respond to which treatments.
- Address psychosocial and emotional impacts using terminology that does not increase stigma and acknowledges the severity of the disease. Provide an opportunity for dialogue and coordinate, draft, and submit the information to a peer-reviewed journal.
- Facilitate insights between patients and biopharmaceutical companies that patients want more than Jak inhibitors to be studied, and there is value in industry engagement bringing resources to AA research beyond the study of a particular treatment modality.

NEW FRONTIERS IN BASIC SCIENCE

Presentation highlights

Dr Elaine Fuchs, from the Howard Hughes Medical Institute and The Rockefeller University (New York, NY), shared new insights into how epidermal stem cells communicate during the cyclical bouts of hair growth and how the normal process of stem cell activation goes awry in AA. Regulatory T cells and dendritic cells are first responders when hair follicle stem cells sense a problem, and recent studies reveal that stem cells are likely to retain memory of their encounters with inflammatory cells, which could heighten subsequent responses. This is a unique type of immunologic memory that might prove to be an important target for new therapeutics.

Dr Maksim Plikus, from the University of California Irvine School of Medicine, presented a multiscale mathematical model developed to study mechanisms of collective hair follicle regeneration. Applied modeling reveals that skin behaves as a heterogeneous regenerative field, with areas of fast, slow, and very slow hair renewal, and the Wnt and BMP activator and/or inhibitor signaling pair modulates hair regeneration in all regions studied. This suggests that these two modulators provide a general molecular language for hair-to-hair growth coordination and can be potentially

augmented or suppressed by certain signals, leading to patterned hair growth pathologies.

Dr Eddy Wang, from Columbia University Medical Center (New York, NY), presented data showing that several keratinocyte- and melanocyte-derived antigen epitopes induced higher frequencies of T-cell activation in both human and mouse AA. New peptide prediction algorithms and fluorescent enzyme-linked immunospot assays allow the detection of activation of more specific T-cell types with high sensitivity. Integration of these findings with other complementary methods, such as TCR sequencing, may help identify disease-inciting T-cell populations and lead to new therapeutic targets. These recent advances in identifying the molecular targets of immune response in AA are the result of many years of basic immunology research now coming to fruition, moving us closer to the immunologists' dream of identifying and targeting the antigens and TCR clones that combine to drive the disease.

Dr Aziz Ghahary,* from the University of British Columbia (Vancouver, Canada), discussed his study to evaluate the inflammatory role of stage-specific embryonic antigen (SSEA)-expressing cells in AA. This study revealed a novel approach to generate AA in C3H/HeJ mice by dermal injection of splenocyte-derived SSEA-expressing cells, underscoring their potential role in driving inflammatory cascade and hair loss mechanisms.

Dr Lynn Petukhova,* from Columbia University (New York, NY), developed a novel analytic pipeline to identify mutations that contribute to AA etiology. Exome studies of rare variants in patients and family members indicate that 12 genes from five genomic regions contribute to the hair follicle extracellular matrix, suggesting a crucial point of communication between the hair follicle and the immune system. Additional research could lead to the identification of a new biological point of intervention for inhibiting aberrant immune-mediated destruction of the hair follicle.

Future research priorities

- Microbiome studies to identify mechanisms of microbiome-

associated induction and development of AA.

- Examination of immune-mediated mechanisms—and the roles of regulatory T cells, NK cells, $\gamma\delta$ T cells, B cells, dendritic cells, chemokines, autoimmune regulators, monocytes, and mast cells—for early intervention, prevention, and restoration of immune privilege.
- Genetic architecture studies to identify biomarkers, molecular subtypes, and new therapeutically targetable pathways.
- Epigenetic studies of environmental factors that interact with gene expression.
- Identification of TCR antigens and/or epitopes driving the disease.
- Investigations of the mechanisms of hair follicle biology, hair cycling, and pigmentation in AA.

EPIDEMIOLOGY, HEALTH ECONOMICS, AND BURDEN OF DISEASE

Presentation highlights

Yamuna Rajoo, from RMIT University (Melbourne, Australia), presented a cross-sectional study to examine the associations between physical activity (PA), mental health, and QOL in 148 patients with AA. Most of the participants surveyed (91, or 61.5%) did not meet minimal PA levels according to Australia's 2014 PA and Sedentary Behavior Guidelines. Results indicate that increasing PA levels in patients with AA may reduce symptoms of depression, anxiety, and stress and improve mental wellbeing.

Dr Amit Garg, from the Donald and Barbara Zucker School of Medicine (New Hyde Park, NY), shared examples from big data analyses in hidradenitis suppurativa to highlight the application of big data in making important observations on disease burden, disease course, comorbid associations, disease outcomes, and treatment outcomes. Big data has the potential to harness both power and granularity to advance knowledge of AA.

Dr Arash Mostaghimi,* from Brigham & Women's Hospital (Boston, MA), presented a cross-sectional study of 45,016 patients to establish the current point prevalence of AA among the general population in the United States. Participants screening positive for AA using the Alopecia Assessment Tool

completed SALT to determine severity, and those with self-reported AA were invited to upload photographs for adjudication by three clinicians. Self-reported AA point prevalence was 1.14% overall, 1.24% among adults, and 0.24% among adolescents. Based on photographs from 104 adults, clinician-adjudicated prevalence was 0.21% overall.

Dr Jean-Phillip Okhovat,* from Massachusetts General Hospital and Harvard Medical School (Boston), presented a study of patients with AA focused on their willingness to pay (WTP) out of pocket (in US dollars) for a cure or control of their condition. A total of 40 patients recruited from the dermatology clinic of UCLA completed the AA Symptom Impact Scale and a WTP questionnaire and were assessed by a dermatologist to calculate their SALT score. Results indicate that 33% of patients with AA were willing to pay \geq \$5,000 for a permanent cure, and their median WTP as a percentage of monthly income was 10–20%—a figure that is comparable with that of patients with atopic dermatitis and psoriasis.

Dr Amy McMichael,* from Wake Forest Baptist Medical Center (Winston Salem, NC), discussed ways to recruit, engage, educate, and study those of diverse backgrounds in AA trials. Strengthening ties to the community of affected patients at individual sites through increased cultural competency and commitment can overcome other barriers that potential study participants may consider. Identifying and prioritizing our research gaps for underrepresented groups in AA will help redefine a successful approach to more diverse studies.

Future research priorities

- Study the cumulative life-course impacts of AA and associated comorbidities on patients' lives over time.
- Determine factors that influence differences in value to patients within

populations, including differences in perspectives and priorities between patients, caregivers, and physicians.

- Address the underrepresentation of real-world patient subsets in clinical studies.
- Identify practice gaps between a patient's and a provider's views of what is important and what works for patients.

CONCLUDING REMARKS

This two-day Summit created new connections, increased dialogue, and galvanized a diverse group of stakeholders to work together to advance research for patients with AA and their families. The meeting underscored the rapid progress that has occurred since 2016, with Jak inhibitors being used widely with impressive effect, numerous biopharmaceutical companies pursuing new generations of systemic and topical treatments for AA, and expanding partnerships aimed at directing treatment efforts toward the most desired patient-centered outcomes.

AA research summits are part of NAAF's main strategic initiative, the AA Treatment Development Program. Many of the research accomplishments highlighted above have been part of the Treatment Development Program, with NAAF either providing direct funding or acting as a concierge, leveraging our available research resources and clinical partnerships. The strategic goal of NAAF is to hasten discovery, approval of, and access to safe, effective, affordable, easy-to-use treatments beneficial to the millions of people with AA. This Summit celebrated another milestone on the focused path toward achieving that goal. Many of the research priorities proposed and discussed are projects that are in progress. NAAF has and will continue to provide support and leadership toward accomplishing these future research priorities to help bring effective therapies for AA to market and enhance our

understanding of this disease. We look forward to future discoveries. Please contact us if you can help in any way or are interested in applying for funding to study any of the future research priorities outlined in this article.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

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