Building and Crossing the Translational Bridge: 2016 Alopecia Areata Research Summit Highlights

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Alopecia areata (AA) is a common autoimmune skin disease that results in the loss of hair on the scalp and elsewhere on the body and affects over 146 million people worldwide at some point in their lives. Founded in 1981, the National Alopecia Areata Foundation 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. 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 AA research summits are part of the Foundation's main strategic initiative, the AA Treatment Development Program, to enhance the understanding of AA and accelerate progress toward a viable treatment.

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INTRODUCTION

The sixth Alopecia Areata Research Summit since 2008, "Building and Crossing the Translational Bridge," brought together leading experts from a host of fields and organizations to discuss current research progress and identify new opportunities to move effective therapeutics for alopecia areata (AA) from discovery to market. The excitement about the numerous AA therapies in development and future clinical trials was palpable. The 120 Summit participants who gathered on November 14 and 15, 2016, in New York City included almost equal representation from expert AA researchers (26), young investigators with an interest in AA (26), experts in related fields (24), and biopharmaceutical industry representatives (24). We also benefited from participation by nine patient stakeholders and eight representatives from governmental and other organizations, including three Institutes within the National Institutes of Health, the U.S. Food and Drug Administration (FDA), the Patient-Centered Outcomes Research Institute, Advancing Innovations in Dermatology, and the National Health Council. All told, more than 40 academic institutions and research centers from the United States and eight countries across the globe were represented.

Our three exceptional co-chairs, Angela Christiano, John Harris, and Maria Hordinsky, worked together to develop a dynamic program focused on (i) the current state of AA research; (ii) clinical trials, epidemiology, and assessment tools; (iii) emerging research technologies and therapeutic targets; (iv) autoimmune and immunological aspects of AA and related conditions; (v) genetics and the hair follicle microenvironment; and (vi) advancing treatments to patient care.

MEETING SUMMARY

Current state of AA research

***Presentation highlights*.** William Ju, President of Advancing Innovations in Dermatology (Mendham, NJ), discussed ways to support the emerging AA product development ecosystem. He highlighted the role of catalysts in bringing together experts from both the technical and financial arenas to define unmet medical needs, understand disease pathophysiology, and develop outcome assessment tools.

Maria Hordinsky*, from the University of Minnesota Medical School (Minneapolis, MN), provided an overview of current treatment practices for adult and pediatric patients with AA in the absence of FDA-approved therapies; emerging treatment options; and the need for placebo-controlled trials to determine the risks, benefits, and durability of new therapeutic agents such as JAK inhibitors.

David Norris*, from the University of Colorado School of Medicine (Aurora, CO), summarized the preceding six research summits, which laid the groundwork for the genetic and immunological studies, clinical trial tools (outcome measures, biomarkers, the Core Uniform Protocol), and funding streams resulting in the current state of AA research.

Angela Christiano, from Columbia University Medical Center (New York, NY), presented an update on the preclinical studies that paved the way for early clinical investigation in patients.

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Abbreviations: AA, alopecia areata; FDA, U.S. Food and Drug Administration; NAAF, National Alopecia Areata Foundation; TCR, T-cell receptor

* Presentations with asterisks are published in these symposium proceedings.

These include genome-wide association studies and gene expression studies that uncovered biomarker signatures that can be used to follow response to treatment, immunological studies focusing on the role of $CD8^+$ T cells in mediating disease, and the use of JAK inhibitors to prevent and treat AA in the C3H/HeJ mouse model.

Ralf Paus*, from the University of Manchester (Manchester, UK), provided an overview of immune privilege concepts and how they relate to AA, including the physiological role of γΔ T cells in the immune cascade in AA. He communicated that identifying autoantigens and elucidating the roles of immune cell types are critical for restoring peripheral privilege in AA.

Madeleine Duvic, from the University of Texas MD Anderson Cancer Center (Houston, TX) shared the accomplishments and current enrollment status of the AA Registry, Biobank, and Clinical Trials Network (Registry), the largest collection of AA data and biological samples in the world available to investigators studying the disease and pharmaceutical companies developing treatments.

Future research priorities

- Use 23andMe (Mountain View, CA) or similar genotyping databases to study additional AA patient cohorts and potentially double the number of identified risk alleles for deep sequencing analysis.
- Perform whole exome and targeted genomic sequencing for risk variants in AA.
- Study the microbiota correlated with AA and identify mechanism(s) of microbiome-associated induction and development of AA.
- Investigate the role of endoplasmic reticulum stress and unfolded protein responses in AA.
- Study the role of autophagy and pigmentation in the pathogenesis and progression of AA.

CLINICAL TRIALS, EPIDEMIOLOGY, AND ASSESSMENT TOOLS

Presentation highlights

Study design and outcome measures. Elise Olsen, from Duke University Medical Center (Durham, NC), presented the Alopecia Density and Extent Score (i.e., ALODEX), a new visual aid for assessing hair loss in AA that can track absolute hair loss and small changes in density that may otherwise go undetected with the Severity of Alopecia Tool score.

Leslie Castelo-Soccio*, from the University of Pennsylvania School of Medicine (Philadelphia, PA), discussed using computer vision to quantify pediatric AA using a photo library of more than 800 images to develop a new algorithm. The algorithm provides a Severity of Alopecia Tool score but can also offer other quantitative and visual information. The goal is to develop an app for the use of patients and providers.

Tito Mendoza*, from the University of Texas MD Anderson Cancer Center (Houston, TX), presented the AA Symptom Index Scale (i.e., AASIS), a 13-item questionnaire that uses a 0-to-10 scale. He provided an update on the iterative process of psychometric validation and future directions, which include qualitative interviews and cognitive debriefings.

Amy Paller, from Northwestern University Feinberg School of Medicine (Chicago, IL), discussed important factors to consider when conducting pediatric clinical trials including challenges of recruitment, parental consent, institutional review board approval, scheduling, cooperation, and outcome measures.

Epidemiology. Joel Gelfand, from the University of Pennsylvania Perelman School of Medicine (Philadelphia, PA), shared epidemiology considerations in clinical trial design, including the development of an analysis plan with defined exposure, outcomes, and confounding factors to minimize selection and information bias.

Jordan Thompson*, a research fellow at Brown University Warren Alpert Medical School (Providence, RI), presented a cross-sectional analysis from the Nurses' Health Study and Nurses' Health Study II showing increased odds of AA based on self-reported diagnosis and race in black and Hispanic women.

Clinical trials with JAK inhibitors. Julian Mackay-Wiggan, from Columbia University Medical Center (New York, NY), reported results with biomarker analysis using gene expression from pilot trials at Columbia University to test the efficacy of ruxolitinib, a JAK 1/2 inhibitor (Jakafi, Incyte, Wilmington, DE), tofacitinib, a pan-JAK 3 inhibitor (Xeljanz, Pfizer, New York, NY), and abatacept, CTLA4-Ig (Orencia, Bristol-Myers Squibb, New York, NY) to treat AA. Seventy-five percent of patients with moderate to severe AA had significant hair regrowth after treatment with Jakafi, and similarly, approximately 65% experienced hair regrowth after treatment with Xeljanz (Mackay-Wiggan J, Jabbari A, Nguyen N, Clark C, Ulerio G, Furniss M, et al. Oral ruxolitinib induces hair regrowth in patients with moderate-to-severe alopecia areata. JCI Insight 2016;1(15):e89790). One patient out of 15 responded to treatment with Orencia, suggesting that it may not be broadly effective across AA patients but could be highly effective in subpopulations with genetic susceptibility at the CTLA4 locus.

Wilma Bergfeld, from Cleveland Clinic (Cleveland, OH), presented results from a retrospective study to test the efficacy of Xeljanz in severe recalcitrant AA. Seven of 13 patients (54%) received therapy for more than 3 months and experienced hair regrowth.

Justin Ko, from Stanford University School of Medicine (Redwood City, CA), shared results from a Stanford/Yale case series of 66 patients with moderate to severe AA treated with Xeljanz. After 3 months of treatment, one third of patients experienced more than 50% hair regrowth (Ibrahim, O, Bayart CB, Hogan S, Piliang M, and Bergfeld WF. Treatment of alopecia areata with tofacitinib. JAMA Dermatol 2017;153:600−2).

Brett King*, from Yale School of Medicine (New Haven, CT), reported results of off-label use of Xeljanz alone or with pulsed prednisone to treat 90 adults and 13 adolescents with severe AA. Approximately 60% of adults and 75% of teenagers experienced hair regrowth. (Kennedy CM, Ko JM, Craiglow BG, Li S, Shankar G, Urban JR, et al. Safety and efficacy of the JAK inhibitor tofacitinib citrate in patients with alopecia areata. JCI Insight 2016;1:e89776).

Elise Olsen, from Duke University Medical Center (Durham, NC), presented promising results from a study evaluating ruxolitinib (INCB018424) 1.5% phosphate topical cream in 12 patients with moderate to severe AA. Six of 12 patients experienced 50% hair regrowth at the end of 24 weeks, encouraging further development of topical JAK inhibitors.

Alice Gottlieb, from New York Medical College (Valhalla, NY), shared lessons and cautions from studies of topical JAK inhibitors in psoriasis and recommended that future trials develop early formulation data, assess systemic exposure with penetration enhancers using subtotal inunction studies, and consider future stratification of patients based on molecular subtypes.