AROGICAL AREATA RESEARCH SUMMIT

Building & Crossing the Translational Bridge

PRE-READING MATERIALS

Monday, November 14 – Tuesday, November 15, 2016
New York Academy of Medicine, New York City, USA

SUMMIT CO-CHAIRS

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HOSTED BY

National Alopecia Areata Foundation

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BUILDING AN ECOSYSTEM TO ENABLE, ENCOURAGE AND SUPPORT NEW PRODUCTS FOR ALOPECIA AREATA

William Ju
Advancing Innovation in Dermatology, Inc.

Advancing Innovation in Dermatology (AID) is a non-profit organization with a mission to help grow an ecosystem for creating and bringing to market an increased number of innovative and scientifically-based products that substantially improve dermatologic health. To that end, AID hosts two annual conferences, which are the Dermatology Innovation Forum and the Dermatology Summit.

The Dermatology Innovation Forum is held in association with the American Academy of Dermatology’s Annual Meeting. The Forum’s primary focus is to educate participants about inspiring innovations that can provide a basis for the next generation of important dermatology products and services. The conference brings together leaders in the field, including physicians, researchers, inventors, investors, strategic corporate partners, service providers, government regulators, patient advocates, and other stakeholders. The meeting also provides networking opportunities in which attendees can communicate with, learn from, and collaborate with each other. The innovations presented are typically from the research stage through early clinical testing.

By providing mechanisms for bringing together a broad range of stakeholders that share common interests in product innovation, AID envisions that the dermatology community can significantly increase the number of impactful therapies for skin diseases such as alopecia areata. This flow of new products and services can help ensure that dermatology remains a vibrant field in healthcare that will continually have better solutions to address the needs of its patients.

CURRENT TREATMENTS FOR ALOPECIA AREATA

Maria K. Hordinsky
University of Minnesota Medical School

In the absence of an approved treatment by the Federal Drug Administration, choosing a treatment for alopecia areata (AA) in children and adults takes into consideration several factors including age of the patient, location of the loss, disease extent, presence of other medical problems and if indicated, assessment of the hair cycle and inflammation in a scalp biopsy as well as patient/parent choice after a review of proposed treatment risks, benefits and expectations. A typical clinic visit in 2016 also includes a discussion of ongoing and future clinical research opportunities. Despite the absence of information from large clinical trials with evolving therapies such as with the use of Janus kinase inhibitors and in particular oral tofacitinib, patients and some physicians are eager to try this therapy with the support of industry patient assistance programs or in some cases, insurance coverage.

A number of treatments can induce hair growth in AA but few have been tested in randomized controlled trials and there are few published data on long-term outcomes. A proportion of pediatric and adult patients do respond well to currently available treatments, in particular high potent topical steroids in pediatric AA, local injection of corticosteroids into lesions of patchy AA and immunomodulation with sensitizers such as diphenylcyclopropenone. Patients though need to be reminded that this autoimmune disease may recur and if this happens, disease extent is unpredictable and our most used tool to halt disease activity is the use of topical, intralesional, oral or even intravenous corticosteroids. In contrast, there are patients with long standing recalcitrant extensive AA who have tried and failed treatments or have elected not to treat their AA who view the emerging treatments and opportunities for clinical trial participation with interest and hope. Last but not least, the treatment of the patient with AA should also include a discussion of clinical subtypes, confirmation of which one the patient has, the genetics of AA and an awareness and discussion of the psychosocial impact of this disease on the patient, family members and significant others.

CURRENT STATE OF RESEARCH AND SUMMARY OF PRECEDING SUMMITS

David A. Norris
University of Colorado School of Medicine

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 five research summits in 2008, 2009, 2010, 2012 and 2014 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. The fifth summit focused on using our advancing knowledge of the mechanisms of AA to develop new therapies. This year’s summit, “Building and Crossing the Translational Bridge” will demonstrate how the translational research program in AA has been created and is succeeding.

UPDATE ON GENETICS AND IMMUNOLOGY OF ALOPECIA AREATA

Angela M. Christiano
Columbia University Medical Center

In recent years, GWAS studies in Alopecia Areata (AA) have provided new insights into disease immunopathogenesis, with at least 14 susceptibility loci identified to date. Combined with synergistic approaches such as gene expression profiling, these combined large-scale efforts have lead to a definition of the genetic and genomic landscape of AA that is unprecedented in the field. Emerging approaches such as epigenetic analysis, miRNA studies, TCR sequencing, and copy number variants, among others, continue to drive the field forward using the latest and most innovative technologies. New studies are also underway to begin to define the effects of the microbiome on the development of AA, in efforts to dissect the environmental influences and triggers. Systems biology approaches have begun to define master regulators (transcription factors) that govern much of the immune response in AA and give us new potential targets for therapy. We will review the latest findings in the genetics and immunology of AA, and efforts in functional genomics (linking the genetic findings to functional perturbations in the hair follicle and immune cells), as well as take a look forward to the next 5 years and what might be on the horizon as the analysis of single cells and gene editing becomes a reality.

REVISITING THE ROLE OF IMMUNE PRIVILEGE IN ALOPECIA AREATA PATHOBIOLOGY

Ralf Paus
University of Manchester

Defined tissue compartments of the hair follicle (HF), namely the anagen hair bulb and the stem cell-harboring bulge zone, enjoy a relative state of immune privilege (IP). Under physiological circumstances, this IP protects them from autoaggressive inflammatory hair diseases like alopecia areata (AA = bulb IP collapse) or lichen planopilaris (=bulge IP collapse). HF IP rests on two major pillars: the downregulation of MHC class I molecules, probably in order to sequester HF-associated autoantigens from immune recognition by CD8+ T cells, and the creation of an immunoinhibitory signaling milieu by locally generated IP guardians such as alpha-MSH, TGFβ2, and IGF-1. However, it is now clear that this basic system is complemented by multiple other (predominantly immunoinhibitory) mechanisms. These include, for example, the downregulation of NKG2D-activating stimuli such as MICA by the HF epithelium, immunoinhibitory functions of perifollicular mast cells as well as VIP and SP secretion by perifollicular nerve endings, and intrafollicular cortisol production. Most recently, we have identified a previously unappreciated role for immunosurveillance γδT cell receptor+ lymphocytes that recognize distressed HFIs and can induce human HF IP collapse, premature HF regression (catagen), HF damage – the hallmarks of AA. Abnormalities in this unexpectedly complex IP system of the HF, whose full complexity we likely have only grazed upon so far, render a given individual susceptible to...
developing AA and are one key prerequisite for AA to develop and progress. Therefore, the protection and restoration of HF IP remains the most fundamental prophylactic and therapeutic challenge in AA management. It is logical to assume that both will be achieved most effectively and most long-lastingly by targeting IP at multiple different levels simultaneously, rather than by targeting a single pathway or cell type.

**CLINICAL TRIAL DESIGN & OUTCOME MEASURES**

**SALT II: A NEW VISUAL AID FOR ASSESSING HAIR LOSS IN ALOPECIA AREATA**
Elise A. Olsen, Doug Canfield, Amy Michael, Ken Washenik, Janet Roberts, Valerie Callender, George Cotsarelis, Wilma Bergfeld, Marsha Hordinsky

The validated assessment methodology for hair loss in alopecia areata is currently limited to the use of the Severity of Alopecia (SALT) visual aid and methods published in 1999 and 2004 by a NAAF workgroup. This method depends on the investigator visually moving all remaining hair in each quadrant (top, back and sides) of the scalp and summing the total scalp hair loss to determine the SALT score. It does not allow for changes in small but important changes in hair density in existing areas of hair loss and does not allow tracking of hair loss present at baseline vs new areas that may occur during a study. The SALT II visual aid and the electronic capture of data allows for determination of both scalp area involved with hair loss, density of hair loss in as small as 1% areas of the scalp, and generation of total scalp hair loss or SALT score. The results of two validation meetings on this new methodology held recently at Duke University will be presented.

**USING COMPUTER VISION TO QUANTITATE PEDIATRIC ALOPECIA AREATA**
Elena Barandina, Leslie Castelo-Soccio
Children's Hospital of Philadelphia; University of Pennsylvania Perlman School of Medicine

The goal of the study was to create standardized and automated image quantification of alopecia areata in pediatric patients. To do so we created a 4 view photo database with 100 pediatric patients with alopecia areata and then use sophisticated vision analysis to identify and automate areas of alopecia, low density hair and normal hair. This image analysis is the first step in identifying visual indicators of disease progression and improvement.

**UPDATES ON THE USE OF THE ALOPECIA AREATA SYMPTOM IMPACT SCALE**
Tito R. Mendoza, Joyce Osei, Quilling Shi, Madeleine Ducic
The University of Texas MD Anderson Cancer Center

Alopecia areata (AA) is an autoimmune disease that causes hair to fall out. Although the disease can be objectively characterized, the condition has significant ramifications on the participant's well-being. We previously reported the preliminary psychometric properties of the Alopecia Areata Symptom Impact Scale (AASS), a disease specific measure asking participants about their symptoms (symptom subscale) and how these symptoms interfere with their daily functioning (interference subscale). The goal of this study is to provide a psychometric update for the AASS. A total of 452 participants with AA were administered the AASS using a variety of methods. Scalp hair loss was the most severely rated symptom followed by body or eye lashes hair loss, feeling anxious or worried, irritated skin, feeling sad, itch or painful skin and tingling or numbness of the scalp. In terms of interference with daily functioning, enjoyment of life was rated the most severe followed by quality of life, interaction with others, daily activities, sexual relationships and work. Factor analysis showed that the symptom subscale can be further decomposed into hair loss symptom and other symptoms. Cronbach coefficient alpha for the hair loss symptoms, other symptoms and interference subscales were 0.83, 0.77 and 0.93, respectively. The Spearman rank correlations of the other symptoms and interference subscales of the AASS were in the moderate range (-0.42 to -0.59) with the overall ratings of physical, mental and emotional well-being. In contrast, the Spearman rank correlations of the AASS hair loss symptom subscale with the overall ratings of physical, mental and emotional well-being were very low at -0.09, -0.06 and -0.07, respectively. Cognitive debriefing results showed that 97% of participants find the AASS items easy to understand and the response options easy to use. About 17% of participants indicated that they have other symptoms that bother them but were not asked. The most commonly cited symptoms were losing fingernails and sweating. Qualitative interviews of participants with AA are warranted to further our understanding of the symptoms of AA and their impact. Other desirable psychometric properties such as test-retest reliability, clinically meaningful difference and sensitivity to change are also needed.

**PEDIATRIC CLINICAL TRIAL DESIGN**
Amy S. Paller
Northwestern University Feinberg School of Medicine

In considering the conduct of a clinical trial in children, many complicating factors must be taken into consideration that are not as important in clinical trials in adults. These include: a) more time required per visit overall; b) greater recruitment challenge, giving concern about risk vs. benefit, difficulty with scheduling visits because of conflicts and constraints, concerns about patient discomfort (e.g., venipuncture and biopsy), and more intense requirements by the IRB; c) issues with cooperation, especially in younger children; d) more complex consenting process; e) limited outcome measures that are validated in pediatric patients, especially younger patients; and f) faster questionnaire fatigue. These issues all must be considered in setting up pediatric trials to optimize recruitment and retention.

**CLINICAL TRIALS, EPIDEMIOLOGY AND BIOSTATISTICS IN SKIN DISEASE**
Joel M. Gelfand
University of Pennsylvania Perelman School of Medicine

The use of observational epidemiology methods in medicine dates back to Hippocrates and Galen. More recently clinical epidemiology and its methods have developed into the basic science underlying much of public health, preventative medicine, and individual patient care decisions. For example, epidemiological studies have been essential for identifying exposure and disease relationships such as smoking and lung cancer, ultraviolet radiation and melanoma, eflazumab and progressive multi-focal leukoencephalopathy, and many other examples with tremendous public health implications. Clinical trials are often considered the gold standard of evidence based medicine and their widespread implementation has revolutionized treatment of psoriasis, atopic dermatitis, acne, and multiple other diseases. In this brief talk we will discuss observational and experimental methodological approaches, as well as their strengths and limitations, for conducting patient oriented research.
UPDATE ON CLINICAL RESEARCH IN ALOPECIA AREATA

Julian Mackay-Wiggan
Columbia University Medical Center

Alopecia areata (AA) is a common autoimmune disease with a lifetime risk of 1.7%. Current treatments including corticosteroids and other immunomodulators are not FDA-approved for AA and have demonstrated variable efficacy. In 2010, the first genome wide association study in AA revealed several susceptibility loci shared with other autoimmune diseases and in key pathways that regulate adaptive and innate immunity. This evidence, in conjunction with gene expression profiling, supported a critical role for the interferon-gamma (IFNγ) pathway, whose expression levels are markedly upregulated in AA. Since the IFNγ pathway is regulated in part by Janus kinases (JAKs), we first conducted pre-clinical studies to ask whether immunosuppression with JAK inhibitors could induce hair regrowth in the C3H/HeJ grafted mouse model of AA. We found that both systemic as well as topical treatment with ruxolitinib (JAK1/2 inhibitor) reversed established disease. We therefore initiated open label, proof-of-concept clinical trials for the treatment of moderate to severe AA (30-100% scalp hair loss) in humans, using oral ruxolitinib 20mg twice per day and tofacitinib 5mg to 10mg twice. We enrolled 12 patients in each study for 3-18 months of treatment followed by 3-6 months follow up off drug. Both studies showed remarkable response to therapy. Gene expression profiling was used on scalp biopsy mRNA to monitor the response to treatment. With rare exceptions, safety parameters including complete blood count and differential, liver function and lipids remained within normal limits and no serious adverse effects have been reported. These results indicate the potential benefit of JAK inhibitors in the treatment of alopecia areata.

CLEVELAND CLINIC’S ALOPECIA AREATA TOFACITINIB TREATMENT RESULTS, A RETROSPECTIVE THERAPEUTIC STUDY

Wilima F. Bergfeld, Melissa Piliang, Omer Ibrahim, Cheryl H. Bayart
Cleveland Clinic

13 patients with severe recalcitrant alopecia areata (universalis-totalis types; 72-93% loss), with mean duration of 18 years, were treated with oral tofacitinib using a standardized treatment regime of initial of 5 mg twice a day (10 mg/day) with 54% regrowth in 44% (7 patients) within an average of 4.2 months (range 1-9 months). Several patients needed an escalation of from tofacitinib 10 mg/day to 30 mg/day (average dose 16.7 mg/day) to achieve a treatment response. The average hair growth response was 4.2 months (range 1-9 months). Regrowth ranged from 2-90% with a mean regrowth of 29% (<0.006, CI: 10.4-47.76). 4 patients (33.3%) achieved a regrowth of at least 29.0%, 6 patients (50%) had less than 50% regrowth and 3 patients (16.7%) showed no growth.

No major adverse events were noted, however one patient had a drug rash and peripheral edema within two weeks of tofacitinib treatment which resulted in discontinuation of therapy, while 2 patients with liver enzymes elevations and one patient with lipid abnormalities were managed by a reduced tofacitinib dosing.

10 of thirteen patients have remained on therapy with 54% regrowth, in 44% of cases. Durability appeared limited to the continuation of treatment. Two patients who lost insurance coverage had complete loss regrown hair in 2 months. 36% of patient’s noted increase in body hair and one patient had a reversal of onychodystrophy and dystrophy after 6 months of therapy and 59% scalp hair regrowth at one year.

In summary, in the Cleveland Clinic’s alopecia areata tofacitinib retrospective study, tofacitinib appears to be a viable treatment for severe alopecia areata with variation in efficacy and dosing. For future studies, we recommend that a study duration of at least one year to assess efficacy, safety and durability.

SAFETY AND EFFICACY OF ORAL TOFACITINIB CITRATE IN SEVERE ALOPECIA AREATA — RESULTS FROM THE STANFORD/YAILEY TRIAL

Stanford University School of Medicine; Yale University School of Medicine; Columbia University

Alopecia areata (AA) is an autoimmune disease characterized by hair loss mediated by CD8+ T cells. Presently there are no reliably effective therapies for AA. Based on recent developments in the understanding of the pathomechanism of AA, JAK inhibitors appear to be a therapeutic option; however, their safety and efficacy for the treatment of AA has not been systematically examined.

LESSONS FROM CLINICAL STUDIES WITH JAK INHIBITORS

This was a 2-center, open-label, single-arm trial using the JAK 1/3 inhibitor, tofacitinib citrate, for AA with > 50% scalp hair loss, alopecia totals (AT) and alopecia universalis (AU). Tofacitinib 5mg twice daily was given for 3 months. Endpoints included regrowth of scalp hair assessed by the Severity of Alopeia Tool (SALT), duration of hair growth after completion of therapy and disease transcriptome.

Of 66 subjects treated, 32% experienced greater improvement in SALT score. AA and ophiasis subtypes were more responsive than AT and AU. Shorter duration of disease and histological peribulbar inflammation on pre-treatment scalp biopsies were associated with improvement in SALT score. Drug cessation resulted in disease relapse in 8.5 weeks. Adverse events were limited to grade I/II infections. Previously published ALADIN score did not adequately segregate responders and non-responders: the Alopeia Areata Responsiveness to JAK-STAT Inhibitors (AARSIN) score was developed to understand transcriptome changes associated with treatment response.

At the dose and duration studied, Tofacitinib is an effective and safe treatment for severe, recalcitrant alopecia areata, though did not result in a durable response and reveals unexpected molecular complexity within the disease. (ClinicalTrials.gov NCT02197455 and NCT02312882)

TOFACITINIB FOR THE TREATMENT OF ALOPECIA AREATA AND VARIANTS IN ADULTS AND ADOLESCENTS

Lucy Y. Liu, Britzany G. Craiglow, Feng Dai, Brett A. King
Yale University School of Medicine

Alopecia areata (AA) is a common autoimmune disorder and until recently effective therapy for severe AA was elusive. Short-term treatment with tofacitinib has shown efficacy for AA in adult patients but long-term data are lacking in both adults and the pediatric age group. We sought to evaluate the safety and efficacy of the Janus kinase 1/3 inhibitor, tofacitinib, in both a large series of adult patients and a small series of adolescent patients (ages 12-17) over an extended period of time.

Ninety adult patients and 13 adolescent patients were evaluated separately. In the adult series, 65 potential responders to therapy, defined as those with either AT or AU with duration of current episode of disease of 10 years or less and or severe AA, 77% achieved a clinical response, with 58% of patients achieving greater than 50% change in SALT score over 4 to 18 months of treatment. In the adolescent series, 9 patients experienced significant hair regrowth. Median percent change in SALT score was 93% (1%-100%; mean 61%) at an average of 6.5 months of treatment. Tofacitinib was well tolerated, and there were no serious adverse events. Tofacitinib should be considered for the treatment of severe AA, AT, and AU in adults and adolescents.

TOPICAL JAK INHIBITORS IN PSORIASIS

Alice Bendix Gottlieb
New York Medical College

Effective and safe topicals for long term use are needed for many dermatologic disorders and for psoriasis in particular. JAK inhibition is an attractive target because of its effect on multiple pathways of the immune response and because of the availability of multiple agents for clinical trials. This presentation will review the available data for topical JAK inhibition in psoriasis.

Topical tofacitinib (JAK 1, 3 inhibitor) was tested in a phase 2a randomized, vehicle-controlled, parallel cohort study in 71 mild to moderate psoriasis vulgaris patients. Statistically significant, modest decreases on target plaque severity and itch severity were observed after 4 weeks of treatment. No significant safety issues were noted, however systemic absorption was observed.

Topical INC0184 (JAK 1, 2 inhibitor) was tested in a small, phase 2 randomized, vehicle controlled, bilateral comparator study of patients with mild to moderate psoriasis vulgaris. Statistically significant, modest decreases target plaque severity scoring and itch severity were observed after 4 weeks of treatment. No significant safety issues were noted. In a separate, subtotal inunction study, skin biopsies of clinical responders showed decreased gene expression of Th-1 and Th-17 dependent genes.

Although the first two studies were published, further drug development with these JAK inhibitors has not been reported. Innovative formulations and studies need to be done with JAK inhibitors not only for psoriasis but for atopic dermatitis, alopecia areata, vitiligo, cutaneous lupus, dermatomyositis, contact dermatitis and other dermatologic disorders.
**ALOPECIA AREATA REVERSAL BY INTERLEUKIN-7 RECEPTOR BLOCKADE VIA UPREGULATION OF THE PD-1 SIGNALING PATHWAY**

Dai Z, Cerise J, Petukhova I, Chen J, de Jong A, Jabbari A, Clynes R, Christianso AM
Columbia University College of Physicians and Surgeons

Allopecia areata (AA) is an autoimmune disease driven by effector cytolytic T cells (CTLS) that infiltrate the hair follicle. Interleukin 7 (IL-7) is an important factor in T cell survival and regulation of function, and IL-7 and its receptor IL-7Rα are involved in several T cell-dependent autoimmune processes. We detected over-expression of IL-7 and IL-7Rα in both human and mouse AA skin. We further demonstrate the critical role of IL-7 in AA, evidenced by 1) hair follicle infiltrating T cells are IL-7Rα positive, 2) administration of exogenous IL-7 accelerated the onset of AA, and 3) blockade of IL-7 signaling by administrating anti-IL-7Rα mAb ameliorated ongoing AA and reversed established AA. The mechanism of IL-7Rα blockade is not simply to reduce the number of activated effector T cells, but also appears to involve upregulation of PD-1 and signaling with its ligand PD-L1, which is reported to induce long-term tolerance in the NOD mouse model. We observed that PD-Ls, PD-L1, and PD-L2 were all upregulated in skin from both humans and mice with AA. The expression of PD-1 was also seen on some hair follicle infiltrating T cells. We found that anti-IL-7Rα treatment induced PD-1 expression on alopeic effector T cells. Although PD ligand expression is increased in hair follicles in C3H/HeJ mice, AA hair loss still developed, suggesting a defective role of this signaling pathway in blocking disease progression. We and others showed that IL-7 inhibits the expression of PD-1 on mouse T cells. Based on our data, we postulate that increased availability of IL-7 in AA lesional skin, in addition to supporting T cell survival, may also contribute to the downregulation of PD-1 for proactive immunity in AA. By blocking IL-7, we anticipate that this will increase PD-1 expression on effector T cells, and importantly, also restore the inhibitory function of PD-1. This work broadens our understanding of the pathogenic role of IL-7/IL7R pathway in AA and invites evaluation of therapeutic interventions to block the IL-7/IL7R pathway as a potential new treatment for human AA.

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**SUMMARY ABSTRACTS**

**EMERGING TECHNOLOGIES & TARGETS**

**BIOMARKERS FOR ALOPECIA AREATA AND DEPLOYMENT INTO CLINICAL TRIALS**

Ali Jabbari
Columbia University Medical Center

Allopecia areata (AA) is an autoimmune disease with a range of presentations of hair loss that typically involve spontaneously resolving patches on the scalp or may lead to total body hair loss. Long-term treatments for AA, especially the more severe forms, are currently lacking. Broad immunosuppressants are sometimes used for treatment purposes, which often suffer from worrisome side effects without substantial benefit. There is therefore a need for targeted treatments in AA and a framework to objectively and precisely evaluate the efficacy of proposed treatments.

Recent work by our group and others have identified cellular and molecular drivers in AA pathogenesis. Cytotoxic CD8 T cells, in particular, have been identified as the critical cellular effectors of disease. In addition, interferon (IFN)-gamma, a pro-inflammatory soluble cytokine, was established to be essential for disease initiation. These participants, among a growing set of others, represent potential targets for drug development and could potentially serve as biomarkers that may be used for predictive or prognostic purposes.

Based on several lines of evidence including our prior genomic and gene expression studies in human AA and murine AA models, JAK inhibitors were selected as a drug class with potential efficacy in AA. We have previously reported the development of a set of biomarkers based on gene expression signatures in the skin that differed among patients with mild and severe forms of AA. The Allopecia Areata Disease Activity Index (ALADIN), is a multidimensional biomarker tool comprised of the expression of sets of genes that correspond to cytotoxic T lymphocyte (CTL), interferon (IFN), and hair keratin (KRT) signatures. Here, report on the utility of the ALADIN biomarker to track disease status and potentially predict disease response early in the course of treatment in two open label clinical trials assessing the JAK inhibitors ruxolitinib and tofacitinib in patients with moderate to severe AA.

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**NON-CONVENTIONAL T-CELLS IN THE PATHOGENESIS OF ALOPECIA AREATA**

Amos Gilhar
Technion Israel Institute

Allopecia areata (AA) is now widely accepted as a CD8/NKG2D T cell-dependent, antigen- and organ-specific autoimmune disease that selectively attacks growing hair follicles (HFs). However, NKG2D+ cells represent a rather mixed collection of cells, which produce large amounts of IFN-γ. These cells include CD8+ T lymphocytes, NKT cells, NK cells, γδ TCR+ lymphocytes and type 1 innate lymphocytes (ILC1). Some of the subpopulations, such as regulatory NK cells, FOXP3+ Tregs, FOXP3+ NKT, FOXP3+ γδ T cells and subgroup of CD8+ cells can promote autoimmunity, while others may suppress it. A novel subgroup of regulatory iNKT cells producing IL-10 (named NKT10 cells) is activated by the synthetic glycolipid molecule, α-galactosylceramide (αGalCer).

The aim of the present study was to address whether non-conventional T cells are involved in the pathogenesis of AA. Triple immunofluorescence microscopy showed the existence of several different subsets of non-conventional lymphocytes (iNKT, γδ T cells, ILC1, ILC2) around the HFs in lesional areas of AA patients, raising the possibility that these cells may be additional players in the pathogenesis of the disease. While there were no ILCs in healthy, there was a significantly increased number of ILC1 in AA compared to ILC2 (p<0.05). However, a significantly increased number of pure NK cells was observed in AA versus the number of ILC1 (p<0.05).

In addition we utilized the humanized AA mouse model to demonstrate the effects of iNKT10 cells. Administering αGalCer to autologous, IL-2 activated immune cells expressing high levels of NKG2D prior to their injection into the hair-bearing human scalp skin xenotransplants, prevented the development of AA –like phenotype. Furthermore, injections of αGalCer to xenotransplant-grafted mice once a week following the administration of the autologous immune cells prevented alopecia in the treated human scalp skin grafts. In contrast, the protective effect of αGalCer was inhibited by adding iNKT cell blocking antibodies or depletion of iNKT cell from the culture of IL-2 activated immune cells/αGalCer before the injections. The therapeutic effect was evidenced by hair regrowth in experimentally induced AA lesions in the scalp skin xenografts grafts following treatment with either αGalCer or IL-10.

These findings identify new potential therapeutic targets in AA management.

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**HAIR FOLLICLE REGENERATION AND PATHOPHYSIOLOGY: LESSONS FROM LIVE IMAGING**

Panteleimon Rompolas
University of Pennsylvania Perelman School of Medicine

The hair follicle is an incredibly complex, yet efficient organ with regenerative capacity that can be impaired by disease or aging. Understanding the biological basis of hair regeneration will lead to better therapeutic approaches to address hair loss. Using live imaging to visualize stem cell behavior in an undisturbed hair follicle niche, in live mice, we previously established that proliferation is temporally and spatially regulated during the initial stages of hair growth. In addition, we addressed the functional requirement of critical niche components and showed that hair regeneration cannot proceed in the absence of the Dermal Papilla. In order to establish stem cell activity and contribution at a single cell level in vivo we leveraged our ability to visualize the niche at high resolution and re-watch the same hair follicles in regular intervals over a full regeneration cycle. Using this approach, we utilized gene-specific fluorescent reporters to label single cells in various epithelial compartments and trace their lineages from their original location within the niche and throughout the different stages of hair growth, as the regeneration program unfolds. Furthermore, using laser-induced cell ablation we tested the functional requirement of various epithelial stem cell compartments for hair regeneration and examined the interplay between different resident stem cell populations in homeostasis and injury repair. Injuring the epithelial component of the hair follicle does not impair hair regeneration as long as the integrity of the interaction with the Dermal Papilla is maintained. Under these conditions non-hair epidermal progenitors can become functional hair follicle stem cells following injury.
HYPE OR HOPE? DATA REVIEW OF MICRO-NEEDLING AND PLATELET RICH PLASMA THERAPY

Jerry Shapiro, Kristen Lo Sico, Lauren Strazzulla, Lorena Pavia de Avila
New York University School of Medicine

Since 1970's Platelet Rich Plasma (PRP) has been used for tissue repair and homeostasis. It is an autologous concentration of platelets in plasma. It is a rich source for growth factors which may enhance angiogenesis, cell proliferation and cell differentiation. Platelet derived growth factor (PDGF), transforming growth factor (TGF-b), and vascular endothelial growth factor (VEGF). Insulin growth factor is found in plasma. PDGF induces and maintains anagen phase in mouse hair cycling, and is involved in both epidermis-follicle interaction and dermal mesenchymal interaction required for hair canal formation and growth of dermal mesenchyme.

VEGF is a major mediator of hair growth and cycling by improved follicle revascularization. IGF-1 act on keratinocytes and prevent catagen like status. PRP has been found to increase proliferation of epidermal and hair follicle bulge cells revealed by an increase in Ki-67, a marker for cell proliferation. There are series of reports comparing PRP, triamcinolone acetonide, and placebo. Some studies showed equal efficacy to triamcinolone acetonide injections while a study on 45 patients showed increased efficacy of PRP compared to corticosteroid injections. A case report using combined treatments of cortisone and PRP showed better results than cortisone injections only in a split scalp study on one patient. At NYU we are undergoing clinical trials with androgenetic alopecia (clinical trials.gov). Eventually we will proceed with alopecia areata. Results may vary due to the kits used and frequency of injections for hair regrowth and maintenance.

Microneedling is being studied at NYU for androgenetic alopecia (clinical trials.gov) in a split scalp study using minoxidil on one side and microneedling with Skin Pen II and minoxidil on the other side. Twenty male patients are being recruited. Results still pending. Mechanism of action is believed to be via signaling between mesenchymal-derived dermal papilla cells and multipotent stem cells in the follicular bulge. It is believed there is a telogen to anagen transition of upregulation of Wnt, beta catenin, and Shh. Breach of stratum corneum allows for more drug delivery. There is data of efficacy on androgenetic alopecia. No studies yet on alopecia areata.

SCIENTIFIC POSTERS

001 - ANDROGEN EXCESS IN ALOPECIA AREATA, AN UNEXPECTED FINDING

G Cheyana Ranaasinghe, Wilma F Bergfeld, Melissa P Piliang
Cleveland Clinic

Studies on the pathophysiology and comorbidities associated with alopecia areata (AA) are limited. The purpose of this study was to determine the prevalence of androgen excess in AA and its subtypes, in relation to demographics and comorbidities. Medical records of 1,587 patchy AA, alopecia totalis (AT), alopecia universalis (AU), and ophiasis patients seen in the Department of Dermatology at the Cleveland Clinic Foundation in Ohio between 2005 and 2015 were reviewed. Out of this cohort, 226 patients met the inclusion criteria. There is evidence that patients with AA had significantly greater prevalence of androgen excess than the general population (p<0.001). Androgen excess was identified in 42.5% (n=96) of the 226 patients with AA and all subtypes (p<0.001). The androgen excess group was significantly more likely to present with adult acne, hirsutism, PCOS, and/or ovarian cysts (p<0.001). It is important to note that AT and AU patients did not exhibit hirsutism, due to the nature of these subtypes. This study was limited by being retrospective. Our study demonstrated that AA is associated with androgen excess.

002 - PARATHYROID HORMONE-RELATED PEPTIDE AND THE HAIR CYCLE

Robert Gensere
Tufts Medical Center; The Floating Hospital for Children; BiologicsMD

Alopecia is a very common condition with a variety of causes, including androgenic stimulation (male-pattern hair loss, polycystic ovarian syndrome), drug-induced (chemotherapy alopecia), and autoimmune disorders (alopecia areata/alopcaica totalis and universalis). Hair loss can cause psychological stress, and the lack of effective therapies can cause patients to pursue off-label use of potentially hazardous treatments. Parathyroid hormone-related peptide (PTHrP) is a hair cycle regulator which provides a promising target for development of alopecia therapies. While early studies focused on using PTHrP antagonists to prolong the anagen phase by reducing anagen->catagen transitions, more recent studies suggest that PTHrP agonists can initiate the anagen phase by increasing levels of beta-catenin in hair follicles. Skin targeted PTHrP analogs have been shown to increase hair growth in animal models of chemotherapy alopecia and alopecia areata. The treatments result in increased number of hair follicles and resolve the dystrophic changes seen in these conditions. There is an associated increase in beta-catenin levels, which suggests that PTHrP agonists act through activation of the Wnt signaling pathway. Specifically, the activated PTHrP receptor activates the G-protein Gs-alfa, which increases levels of cyclic AMP and activates protein kinase A. Protein kinase A phosphorylates beta-catenin, reducing its degradation and promoting nuclear translocation. While there are no animal models for androgenic alopecia, the mechanism of action for this disorder, which is depletion of beta-catenin through binding to the androgen receptor-ligand complex, suggests that a therapy which increases beta-catenin levels would be effective. These findings suggest a promising target for drug development for many forms of alopecia.

003 - TREATMENT FUTILITY, PATIENT-PROVIDER COMMUNICATION AND DISEASE ACCEPTANCE IN SEVERE ALOPECIA AREATA

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2Duke University Medical Center

For many Severe Alopecia Areata (SAA) patients, treatment options are exhausted. At this point, we hypothesize that patients experience Treatment Futility (TF), defined as sensing that continued treatment will not result in meaningful hair regrowth. When this occurs, we believe the role of the provider is to discuss treatment discontinuation as an option and promote acceptance and healing.

Study purpose is to explore the prevalence of TF in SAA patients; extent TF conversations occur between patients and doctors and the facilitators and barriers to conversation occurrence; patients’ perceived quality of TF conversations and how patients’ satisfaction with TF conversations relate to condition acceptance. Elucidate how doctors report addressing psychosocial issues during appointments and how patients would like their doctors to respond.

IRB-approved e-surveys; 305 SAA patients, 119 providers, recruited through the Alopecia Areata Registry, Biobank and Clinical Trials Network and public list of 2010-2011 Society of Pediatric Dermatology conference attendees, respectively. 90 % of SAA patients report TF, but only 2/3 report discussing TF with their doctor. When TF conversations occur, 81% of patients indicate they initiated. Providers who seek patient input, demonstrate empathy, inquire about patient coping and spend more time in direct patient contact increase patients’ willingness to express TF concerns. Patients’ satisfaction with the quality of the TF conversation is not related to who initiates the conversation (doctor or patient) but does predict patients’ condition acceptance. When TF conversations occur, providers report 80% of patients respond positively. An incongruence exists between patients and doctors in terms of social support: patients desire emotional social support from their doctor (e.g. inquiring about patient coping), while doctors tend to rely on providing informational social support (e.g. NAAF referral, Locks of Love).

Given current treatment efficacy, TF should be expected in SAA patients. Providers psychologically available to patients during clinic appointments increase patients’ willingness to express TF concerns. Doctors providing patient-centered care and emotional social support may help SAA patients reach healing through condition acceptance.

004 - A PROMISING SAFE BOTANICAL CUTANEOUS SOLUTION FOR THE TREATMENT OF SCALP AA IN PEDIATRIC POPULATION

Harti Saad, Guichard Alexandre, Cauwenbergh Geert, Liu JiaWei
Legacy Healthcare SA

AA is a chronic immunologically mediated inflammatory condition associated with abnormal hair follicular cells apoptosis. Previous studies demonstrated that improvement in AA coincided with upregulation of the anti-apoptotic protein Bcl-2 and an elevated level of Ki-67+ cells was also observed in improved AA patients.

To study the Product (a cutaneous solution containing four herbal extracts) safety and potential efficacy in normalization of hair follicular cells apoptosis and reduction of follicular inflammation.
The safety and efficacy of the Product were studied in in vitro and clinical trials in male and female volunteers presenting androgenetic alopecia (AGA). The Product allowed the restoration of androgen/telogen ratio via normalization of hair follicular cells apoptosis, reduction of scalp inflammation and increase of collagen content and its remodeling. Human scalp biopsy analysis showed that the anti-apoptotic protein Bcl-2 was normalized from a lower towards a higher level comparable to that observed in healthy volunteers. The improved cell survival capacity was verified by the detection of increased expression of the cell proliferation marker, Ki-67.

No side effect was reported in all studies.

The anti-inflammatory function was shown in an in vitro test, via the reduction of pro-inflammatory molecules (E-selectin, ICAM-1 and IL-8) in TNF α-treated Human Umbilical Vein Endothelial Cells.

These results on AGA (safety, efficacy and the proposed mechanism of action) provide support for the concept that the Product may be expected to safely improve the AA condition, especially in the pediatric population, by acting simultaneously on three aspects, i.e. hair follicular cell survival, scalp inflammation, collagen content and remodeling in the scalp.

Based on the above studies, European Medicines Agency has granted us to conduct a double-blind randomized controlled multi-center study in pediatric AA population, based on NAAF Core protocol.

005 - THE PSYCHOLOGICAL IMPACTS OF ALOPECIA AREATA: SEMI-STRUCTURED INTERVIEWS WITH DERMATOLOGISTS

Salman T. Hussain1, Carl Y. Peterson2, Elizabeth Carpeneter-Song1, Paul J. Barr1, Jeremiah R. Brown1, Arash Mostaghimi2, Kathie P. Huang1

1The Dartmouth Institute for Health Policy & Clinical Practice; 2National Cancer Institute, National Institutes of Health; 3Dartmouth College; 4Brigham and Women’s Hospital; 5Harvard Medical School

Although alopecia areata results in cosmetic complications, there is a significant gap in understanding and addressing its psychosocial complications including anxiety, depression, and isolation. Even though alopecia does not have physically harmful effects, the gap in understanding its psychosocial complications may understate its true burden. It is unclear whether dermatologists are aware of and discuss the psychological impacts of this disease with their patients. Semi-structured interviews were conducted with 17 dermatologists at two academic medical centers and various private practices to assess the extent to which dermatologists discuss and manage the psychological impacts of alopecia areata. Data were analyzed to identify themes, which were then compared and contrasted across the interview transcripts.

Dermatologists are generally aware of the psychological impacts of alopecia areata, but face numerous challenges in meeting the psychological needs of their patients. Short visit times, payment incentives, and feeling ill-equipped to discuss the emotional side of conditions they treat all discourage dermatologists from discussing how the condition is making their patients feel. A shared compilation of resources for managing the psychological impacts of alopecia is needed. Dermatology training should also focus on mental health and how it can relate to dermatologic conditions, as well as on the development of consolation and counseling skills, to better equip dermatologists to meet the needs of their patients. Payment incentives should be revised so that dermatologists are incentivized for providing counseling services to patients. Alopecia areata has no cure and has substantial psychosocial needs of their patients.

Since current treatments are not satisfactory to the majority of patients, additional research into how to boost patients’ resiliency and help them cope better with their disease is needed. Research into how to boost patients’ resiliency and help them cope better with their disease is needed.

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006 - A STUDY OF INCB018424 PHOSPHATE TOPICAL CREAM IN SUBJECTS WITH ALOPECIA AREATA - OPEN-LABEL TREATMENT PERIOD

Janet DuBois1, Steven Kemper2, Janet Roberts3, Suzanne Bruce4, Richard Leff5, Kang Sun6, Elise Olsen7

1DermResearch Inc; 2Associated Skin Care Specialists; 3Northwest Dermatology & Research Center; 4Suzanne Bruce & Associates; 5Incyte Corporation; 6Duke University Medical Center

Inflammatory cytokines that signal through Janus kinase (JAK)-signal transducers and activators of the transcription pathway have been implicated in alopecia areata (AA), suggesting JAK inhibition may be an effective treatment approach. INCB018424 is a potent inhibitor of JAK1/JAK2 with low systemic absorption when applied topically. This study evaluates the efficacy and safety of INCB018424 phosphate topical cream in subjects with AA. Part A (reported here) is open-label and Part B is double-blind, randomized, and placebo-controlled (NCT02553330). Subjects between 18-70 years old with terminal scalp hair loss of 25% < 50% as determined by the Severity of Alopecia Tool (SALT) with a current episode for ≥12 months or 50–100% for ≥6 months, were eligible. Subjects received topical INCB018424 1.5% cream BID for 24 weeks. The primary endpoint was the proportion of subjects achieving ≥50% improvement from baseline in SALT score (SALT50) at any visit with SALT90 a secondary endpoint.

All twelve subjects enrolled in Part A completed treatment through week 24. Mean (range) age of subjects was 48 (25-67) years; 75% were female and 92% were white. Mean time since onset of AA was 12.8 years, 33% had a current episode duration of >5 years, and 75% had prior therapy for AA. The mean (SD) SALT score at baseline was 56.2 (21.0) and the mean reduction from baseline at week 24 was –26.7% (72.0). SALT50 was achieved in 0% at week 4, 25% at week 12, and 50% at week 24. Two (17%) subjects achieved SALT90 by week 24. Nine subjects had one or more adverse events (AEs); no specific AE occurred in more than 1 subject and no AE resulted in discontinuation from the study. Non-serious treatment-related AEs (follitucilis, vulvovaginal mycotic infection, dry skin/pruritus, skin exfoliation) were reported in 3 subjects. Two subjects had serious AEs (one with non-cardiac chest pain, sepsis, pulmonary mass [each Grade 3], and one with worsening of a generalized anxiety disorder).

INCB018424 demonstrated efficacy and was well tolerated in this open-label study. The safety and efficacy of INCB018424 will be further evaluated in Part B, the largest double-blind, randomized, placebo-controlled trial in AA to date.

007 - A SUB-NETWORK OF SIGNALING PROTEIN COMPLEXES IN AA MAY PROVIDE NEW MOLECULAR CANDIDATES FOR PHARMACOLOGIC TARGETING

Stephen E.P. Smith, Steven C. Neier, Tessa R. Davis, Gabriel F. Scallies, Carolyn N. Wieland, Rochelle R. Torgerson, Diana Gil, Claudia Neuhaus, Adam G. Schrum

Mayo Clinic College of Medicine

Current understanding is limited regarding the autoantigens, T cell antigen receptors (TCR), and biochemical signals that drive Alopecia Areata (AA). To observe the network activity of TCR signaling proteins in AA, we applied a novel matrix analysis (called “PISCES”) to primary T cells from patient scalp skin from 4-mm punch-biopsies. Visualization of the signaling network suggested overall agreement between control patient and AA patient T cells, with many of the same protein complexes being induced in response to stimulation. Despite this similarity, network analysis of the protein complexes was able to discriminate between control and AA patient groups, which indicated that there was an underlying disease-associated difference in signaling activity. To better understand this difference, basal T cell signaling complexes were analyzed separately from exogenous stimulation-induced complexes. In the basal condition, we found significant enrichment of signaling complexes in AA patients over controls, consistent with autoreactive TCR involvement in human AA. Among protein complexes from exogenously stimulated cells, a sub-network was observed that significantly correlated with disease status. Preliminary bioinformatics analysis led to prioritization of a hypothesis in which control patients favor ZAP70 departure from TCR to nucleate a complex with LAT, GRB2/SOS1, PLCg, and PKC-theta, leading to ERK activation, differentiation, and clonal expansion. In contrast, AA-disease patients balance activity toward a complex where ZAP70 bridges TCR/CD3 with LAT, GADS, and other SPL76-associated interactors to favor signaling pathways that maximize cell-cell adhesion. In summary, network signatures of signaling protein complexes were shown to (i) distinguish AA patient and control groups, (ii) detect autoreactive T cell signaling in AA, and (iii) identify a candidate disease-associated sub-network for which pharmacologic strategies could be designed.

008 - GAPS IN THE DERMATOLOGIC LITERATURE REGARDING ALOPECIA AREATA AMONG AFRICAN AMERICANS

Ajay Kailas1, Chauncey Caldwell1, James A. Solomon1, 2, 3

1University of Central Florida College of Medicine; 2University of Colorado; 3Ameriderm Research Group; 4University of Illinois

Hair and scalp disorders are among the 5 most common dermatologic diagnoses in the African American population. The structure of African American hair differs from that of Caucasian hair in that there tend to be more sebaceous glands, decreased water content, a flattened elliptical shaped hair shaft and decreased anchoring elastic fibers in the former. In addition, there exist distinct cultural hair care practices which are quite common among African Americans including use of chemical relaxers, plait, corn rolls, less frequent washing and wearing weaves/wigs. The combination of these hair care practices plus innate structural differences in African American hair often predispose to a variety of hair and scalp disorders. For example, chemical relaxers have been associated with central centrifugal cicatricial alopecia (CCCA) and trichonhrosis nodosa while tight braiding or pulling styles have been linked with
traction alopecia. Though other alopecias are discussed in the dermatological literature, the data regarding alopecia areata in African Americans is sparse. Yet, alopecia areata has been reported to occur equally among races. This identifies a gap in the literature regarding alopecia areata among African-Americans. Speculations may be made as to why this gap exist. One likely assumption is that many of these patients are misdiagnosed. Common hair loss conditions thought prevalent in African Americans such as traction alopecia, CCCA, tinea capitis or discoid lupus may be overly presumed leaving alopecia areata underdiagnosed. Another presumption is that the lack of literature regarding the prevalence of alopecia areata in the African American community may lead to decreased awareness and presentation to a dermatologist by this population. A final possibility is that cultural practices such as weaves, wigs, and hairpieces are commonly used in African American culture even in those without hair loss. This cultural practice can often mask the prevalence of alopecia areata in the African American community. Overall, more studies are needed to help clarifying why this gap exist. Further exploration of this topic will help providers to adequately identify and treat African American patients who may be suffering from alopecia areata.

009 - PREVALENCE OF ALOPECIA AREATA DIFFERS BY RACE IN TWO LARGE COHORTS
Jordan M. Thompson, Min Kyung Park, Tricia Li, Abrar A. Qureshi, Eunyoung Cho
1Warren Alpert Medical School, Brown University; 2Brigham and Women’s Hospital and Harvard Medical School; 3Brown School of Public Health

The clinical epidemiology of alopecia areata is largely unexplored and, therefore, we sought to investigate the association between self-reported race and prevalence of disease in two large cohorts of women. We conducted a cross-sectional analysis from the Nurses’ Health Study (NHS) and Nurses’ Health Study II (NHSII). Participants were surveyed biennially in regards to medical history and lifestyle factors, and responded in 2012 (NHS) and 2011 (NHSII) to the question of previous physician-diagnosed alopecia areata. Using logistic-regression analysis, we determined odds ratios (OR) for alopecia areata by self-reported race. We calculated ORs in an age-adjusted model and multivariate model adjusting for age, smoking status, alcohol intake, body mass index, physical activity, UV-B flux at residence, post-menopausal hormone use, and history of immune-mediated disease (e.g. psoriasis, systemic lupus), cardiovascular disease, hypertension, high cholesterol, or diabetes. Among 57,317 women from the NHS and 94,030 women from the NHSII, we identified 373 and 792 cases of alopecia areata, respectively. In the NHS, the multivariate-adjusted OR was 2.16 (95% CI 1.10-4.23) among black women as compared to white women. In NHSII, the multivariate-adjusted OR was 5.17 (3.54-7.55) in black women as compared to white. In addition, Hispanic women as compared to white had a multivariate-adjusted OR of 3.16 (95% CI 0.77-12.99) in NHSII. In this study we found increased odds of alopecia areata based on self-reported race, in black and Hispanic women. Potential limitations of this study include a reporting bias where respondents may mistake other forms of hair loss for alopecia areata, such as traction alopecia, androgenetic alopecia, or alopecia related to systemic lupus, conditions which might themselves explain variability by race. Further studies are needed to explore the mechanism of this disparity related to alopecia areata.

KEYNOTES

IDENTIFYING A SMALL MOLECULE BLOCKING ANTIGEN PRESENTATION IN AUTOIMMUNE THYROIDITIS
Yaron Tomer
Albert Einstein College of Medicine Montefiore Medical Center

The term autoimmune thyroid diseases (AITD) refers to a group of autoimmune diseases manifesting by the presence of T-cells and autoantibodies targeting the thyroid gland. The major AITD include Graves’ disease (GD) and Hashimoto’s thyroiditis (HT). While the clinical manifestations are different, GD manifesting by thyrotoxicosis and HT manifesting by hypothyroidism, their pathogenesis involves shared immunogenetic mechanisms. AITD are caused by an interaction between environmental and genetic triggers. Although the exact pathogenesis and causative interaction between environment and genes are unknown, family and population studies confirm the genetic inheritability of GD and HT. AITD susceptibility genes can be characterized as either thyroid specific (Tg, TSHR) or immune-modulating (HLA-DR, CTLA-4, PTPN22, CD40, FOXP3, CD25). Most of the genes predisposing to AITD participate in the immunological synapse which is the interface between antigen presenting cells and T cells created during antigen presentation. Among the immunological synapse genes HLA-DR containing arginine at position 74 of the beta chain gives the strongest risk. Understanding the importance of the immunological synapse in the etiology of AITD have paved the way to blocking antigen presentation as a novel therapeutic approach to AITD.

WHAT TREATMENT MEANS TO ME: A PATIENT’S PERSPECTIVE
Angela Rodgers
Contra Costa Regional Medical Center

In society, physical health is prioritized more than emotional health. In his Ted Talk, psychologist Guy Winch, Ph.D. explains the negative impact that this societal belief has on individuals and communities. If physically healthy individuals struggle with mental health, imagine the impact that mental health can have on those with chronic disease. Alopecia areata (AA) is a chronic unpredictable autoimmune disease that can completely alter one’s physical appearance. It can manifest at any age, in any gender, under various circumstances, within any ethnic community. It can worsen rapidly resulting in little time to adjust to a new reflection. It can also resolve quickly and then for some rapidly lead to a recurrence of hair loss. This erratic change in one’s life and the lives of those involved can lead to significant emotional distress. The presence of this problem for many with skin conditions is well documented in dermatology journals worldwide. However, the discussion of available support resources and referral to mental health services does not appear to be routine. One source of emotional distress for those with AA is the search for a therapy. Currently, there is no cure or FDA approved treatment for AA. It is common for those with AA to hear the statement “It’s only hair,” but this is not true. The lack of accessible, safe, and affordable treatments available for AA combined with the feeling of AA not being “a serious disease” can be very detrimental to those living with the daily struggles of a chronic skin disease like AA.

As a National Alopecia Areata Foundation (NAAF) support group leader, prior NAAF Health and Research Ambassador (HARA), resident physician, and a woman diagnosed with aa over 20 years ago, I will take you on a journey of the evidence-based mental health burden of aa as well as the real reasons why a breakthrough treatment would be meaningful to the entire aa community.

RULES OF ENGAGEMENT IN DRUG DEVELOPMENT: ACTIVATING THE PATIENT VOICE
Eleanor M. Perfetto
National Health Council

Recent advances in patient engagement in research, including patients’ and advocates’ roles in patient focused-drug development (PFDD) and patient-reported outcomes (PROs) will be discussed. Examples of how patients are building capacity to engage, the contributions they have made, and how they are activating for the future will be provided.

ELUSIVE ALOPECIA AREATA AUTO-ANTIGENS

Keisuke (Chris) Nagao
National Cancer Institute, National Institutes of Health

The skin is not only an important physical barrier, but also is the outermost immunological interface of the body, it harbors a variety of leukocytes and we believe that there exist skin-specific mechanisms that either support or suppress immunity. Hair follicles are unique to mammalian skin, and we found in the recent years that it is an immunologically active structure, that it responds to physical stress to recruit certain leukocyte subsets to sites of minor trauma. Better understanding of the roles that hair follicles play during immune regulation in the skin should help us gain further insight into the pathomechanisms of inflammatory diseases such as alopecia areata. This talk will focus on recent findings that we have made in the cross-talks that occur between the hair follicle and the immune system.
IDENTIFICATION OF ANTIGENIC MIMOTOPES RECOGNIZED BY AA-SPECIFIC HUMAN CD8+ T CELLS IN SITU

M Bertolino, S Altendorf, Y Uchida, DA Belov, Q Zhou, A Rossi, K Dormirai, R Paus

The most common autoimmune hair loss disorder, alopecia areata (AA), is an organ-restricted, CD8+ T-cell-dependent autoimmune disease that attacks hair follicles (HF) which have lost their immune privilege. However, the MHC class I-presented (auto-)antigens(s), that are likely expressed in the proximal hair bulb of lesional HF in AA patients, and the T-cell receptor (TCR) repertoire of the primary autoreactive CD8+ T-cells remain unknown. Therefore, all currently available AA therapies are purely symptomatic, rather than curative. To address this challenge, we have adopted the strategy to analyze the TCR repertoire by systematically screening the TCR alpha- and beta-chains of intra- and peri-lesional CD8+ T-cells as a basis for subsequently identifying the pathogenic (auto-)antigen(s). Therefore, we have isolated disease-specific, intra- and peri-lesional CD8+ T-cells from AA skin by laser microdissection in order to determine their TCR clonotype in situ. This is the only method which allows one to distinguish peri- from intra-lesional infiltrating CD8+ T-cells while simultaneously identifying their paired alpha- and beta-chains.

Up to now, we have been able to characterize several TCR beta-chains of such autoreactive CD8+ T-cells, namely Vbeta7, 12, and 27, and the corresponding alpha-chains, specifically Valpha4, 10, and 13 (including CDR regions) from the skin of AA patients, whose HLA type was characterized. In selected, but not all, investigated AA patients, these transcriptional data were confirmed by immunohistology, using the few commercially available beta-chain antibodies, which detected corresponding beta-chain TCR proteins.

So far, our protein level in situ results point to Vbeta12 as the most widely expressed beta chain in AA lesions, followed by Vbeta13. However, since the most expanded CD8+ T-cell TCR clonotypes vary greatly from patient to patient, we are currently expanding the number of CD8+ T-cells investigated in situ from each examined AA patient. Once disease-specific TCRs have been identified, even if the corresponding (auto-)antigens have not been characterized yet, this can serve as a basis for TCR-specific lymphocyte elimination immunotherapy in AA, and may also provide prognostic biomarkers.

IDENTIFYING PATHOGENIC T CELL RECEPTOR SEQUENCES IN ALOPECIA AREATA

Annemieke de Jong

Columbia University

The central role of T cells in the process of hair follicle destruction in Alopecia Areata (AA) has led us to take a closer look at the dynamics of T cell clones in the pathogenic process. Because each T cell harbors a distinct receptor that has been generated by gene recombination, the specific T cell receptor (TCR) can be used as a unique identifier by which a given T cell clone can be detected and monitored. High throughput T cell receptor (TCR) sequencing has enabled us to perform a detailed quantitative analysis of the T cell repertoire during the course of AA, and has provided insights in the pathogenesis that would not have been possible with conventional methods of T cell receptor analysis. Our previous study of high throughput TCR β chain sequencing in the mouse model of AA revealed clear evidence for antigenic drive in this model, and showed that pathogenic T cells reside in the scalp and peripheral blood T cell subsets of AAP and AU patients. In contrast to the TCR repertoire of lesional skin in mice that overlapped primarily with NKG2D+CD8+ T cells, the lesional TCR repertoire in human AA overlapped largely with the CD4+ T cell repertoire as well as the CD8+ population, supporting a role for CD4+ T cells in disease. This finding is consistent with our genome-wide meta-analysis of AA, which revealed HLA-DR as a key etiologic driver in AA. Lesional CD8+ T cells were detected at similar frequencies in both NKG2Dlow and NKG2Dhigh T cell fractions, suggesting that in human AA, markers other than high NKG2D levels are needed to define the pathogenic CD8+ T cells. Lastly, we detected T cell clones with near-identical TCR β chains among most expanded T cell clones in lesional skin, supporting the notion that human AA is also driven by antigen recognition.

LARGE SCALE EPIPOTE IDENTIFICATION SCREEN AND ITS POTENTIAL APPLICATION TO THE STUDY OF ALOPECIA AREATA

Alessandro Sette

La Jolla Institute for Allergy and Immunology

In our laboratory we have been developing various methods that combine proteomic and genomic screens with epitope prediction for CD4 and CD8 T cells, to identify specific epitope and associated antigens from a variety of different disease applications. The feasibility of these approaches was validated in different experimental systems. In the case of allergic responses the transcriptome of complex allergens such as pollen or house dust mites was probed by 2D gels and sera from allergic patients and both Ig G and Ig E reactive were studied. Epitope predictions allowed identifying new allergens and epitopes recognized by allergist disease patients. In the case of tuberculosis, genome wide screen of several thousand microbial ORF was also achieved, leading to a high-resolution map of human reactivity. The same approach has been more recently used to map reactives from other bacteria (such as bordetella pertussis), and autoantigens. We are currently devising strategies to apply this technological framework to the study of alopecia areata.

SIMILARITIES BETWEEN TYPE 1 DIABETES AND ALOPECIA AREATA

Teresa P. DiLorenzo

Albert Einstein College of Medicine

Type 1 diabetes is an organ-specific autoimmune disease that results from a failure to establish and maintain immunologic self-tolerance to a number of pancreatic beta cell antigens, including insulin. Alopecia areata is also an organ-specific autoimmune disease, and it shares a number of striking similarities with type 1 diabetes. Careful consideration of these may forward the clinical and research goals of both fields and will be reviewed during this presentation. These similarities include the “patchy” nature of disease, a comparable prevalence rate and lack of gender bias, and an increasing incidence of disease. Several of the genes associated with alopecia areata are expressed in immune cells and are also associated with type 1 diabetes. Indeed, relatives of patients with alopecia areata have been reported to exhibit an increased incidence of type 1 diabetes. Autoimmune thyroid disease, vitiligo, and psoriasis are associated with relatives of patients having either alopecia areata or type 1 diabetes. While in both type 1 diabetes and alopecia areata, many of the disease-associated genes have immunologic functions, others are expressed in the target organ, i.e., pancreatic beta cells in type 1 diabetes and the hair follicle in alopecia areata. Finally, CD8 T cells are required for pathogenesis in rodent models of both diseases and they have been localized to the inflammatory lesions in patients. Given the striking similarities between type 1 diabetes and alopecia areata, collaboration between the fields should yield abundant benefits.

IMMUNOLOGY OF THE SKIN

T CELLS, DENDRITIC CELLS, AUTOIMMUNITY AND THE HAIR FOLLICLE

Daniel H. Kaplan

University of Pittsburgh

Resident memory T cells (TRM) are a recently appreciated subset of memory T cells that reside in the skin and are required for optimal protection against many previously encountered pathogens. These cells also likely participate in a number of cutaneous autoimmune diseases including vitiligo and alopecia areata. Many of the signals responsible for the recruitment and differentiation of TRM cells in the skin have recently been elucidated. Our work focuses on the factors that maintain long-term residence of TRM and dendritic cells in the epidermis of mice. Working first with Langerhans cells (LC), the only subset of epidermal resident dendritic cells, we found that the loss of TGF β 1 signaling within the LC was required for their migration out of the skin and into skin draining lymph nodes. Loss of TGF β 1 signaling was required both for steady-state and inflammation induced LC migration. Notably, the key regulated step was the obligate activation of TGF β 1 by the integrins αv β 6 and αv β 8 that are expressed by keratinocytes. Genetic or antibody mediated blockade of these integrins resulted in loss of LC from the epidermis. TRM also require TGF β 1 signaling for epidermal residence and can be depleted by inhibiting αv β 6 and αv β 8 function. These findings highlight the important function of keratinocytes in determining the epidermal occupancy of dendritic cells and TRM and provide a potential therapeutic target to deplete these cells in disease states.
REGULATORY T CELLS IN SKIN FACILITATE HAIR FOLLICLE STEM CELL DIFFERENTIATION

Niwa Ali, Tiffany C. Scharschmidt, Keyon Taravati, Madeleine R. Tan, Michael D. Rosenblum
University of San Francisco California

The maintenance of tissue homeostasis is critically dependent on the self-renewal and differentiation capacity of epithelial stem cells (SCs). How extrinsic signals, including tissue resident immune cells, govern SC behavior is largely unknown. We have previously observed that regulatory T cells (Tregs) in skin preferentially localize to hair follicles (HFs), which house a major subset of skin SCs (HFSCs). HF regeneration is critically dependent on HFSCs. Here, we mechanistically dissect the role of Tregs in HFSC biology. We found that Treg abundance and activation state in skin precisely correlate with the synchronous HF cycle. Lineage-specific cell depletion revealed that Tregs are required for HF regeneration. Tregs preferentially localize to the bulge region of HFs and facilitate HF cycling by directly augmenting HFSC proliferation and differentiation. Transcriptional and phenotypic profiling of Tregs and HFSCs revealed that Tregs in skin preferentially express high levels of the Notch ligand family member, Jag1, and the Notch signaling pathway was significantly enhanced in HFSCs when Tregs were present. In functional experiments, expression of Jag1 in Tregs was required for HFSC function and efficient HF regeneration. Taken together, our work functionally dissects the role of Tregs in HF biology and establishes a mechanistic link between tissue resident immune cells and epithelial SCs. These findings have clinical implications in human diseases of HFs, such as Alopecia Areata (AA), where Tregs are thought to play a role in disease pathogenesis.

MAKING AND BREAKING TOLERANCE: NEW INSIGHT INTO SKIN DENDRITIC CELL FUNCTION

Niroshana Anandasabapathy
Harvard Skin Disease Research Center; Brigham and Women’s Hospital

The skin is considered a primary defense barrier, yet immune cells in the skin must appropriately discriminate pathogens from self-antigens—such as those released by the rapid cycling of the hair follicle and epithelia. The dendritic cell (DC) is specialized immune sentinel that directs T cells to tolerance or immunity to self and non-self-antigens. We have identified distinct properties promoting self-tolerance in DCs originating in tissues such as skin. We find during inflammation skin migratory DCs may direct T cells to tolerance, counter-regulating and controlling immunity. These cells are uniquely genetically programed in humans and in mouse to dampen immunity with a high expression of shared tolerance genes, including some genes such as PD-L1 that have been successfully targeted in the clinic. We hypothesize homeostatic maintenance of self-tolerance by skin DCs is a critical step to prevent autoimmune disease and describe new therapeutic targets and pathways promoting this activity.

COMMENSAL BACTERIA CONTROL PLASMACYTOID DENDRITIC CELL RECRUITMENT AND ACTIVATION INTO INFLAMED SKIN

Jeremy Di Donzilo, Michel Gilliet
University Hospital of Lausanne, Switzerland

Plasmacytoid dendritic cell (pDC) infiltration of the skin and their activation to produce type I IFN appear to be involved in the initiation of skin inflammation in many disorders including alopecia areata. To understand the mechanisms underlying this process we used a skin wounding model based repetitive tape stripping of mice skin. In this model, pDC rapidly infiltrate skin and are activated to produce type I IFNs, which promotes inflammation in wounded skin. We found that this process is driven by neutrophils that release the chemokine CXCL10. Neutrophil-derived CXCL10 recruited pDC into the skin and was sufficient to activate pDC by forming complexes with extracellular DNA leading to activation of TLR9. Interestingly, skin microbiota played an essential role in this process. On one hand, the microbiota induced CXCL10 expression in neutrophils infiltrating the skin. On the other hand, the microbiota was a direct target of the antimicrobial activity of CXCL10, which killed the bacteria and formed immunogenic complexes with their DNA. In fact, in the context of skin injury, the principal constituent of immunogenic CXCL10 complexes was microbial DNA and not host-derived DNA. Accordingly, high levels of type I IFNs induced in human skin blisters was abrogated by local antibiotic treatment. Thus, skin microbiota plays a central role in initiating inflammation in the skin by recruiting and activating pDC.

NUTRITIONAL FACTORS POTENTIALLY INFLUENCING HAIR GROWTH AND ALOPECIA

George Cotsarelis
Perelman School of Medicine, University of Pennsylvania

The hair follicle matrix keratinocytes in the bulb are some of the most rapidly proliferating cells in the body. Their maintenance and proliferation are essential for continuous hair growth and maintenance of anagen. Disruption of hair follicle growth by nutritional deficiencies can cause telogen effluvium, which may trigger alopecia areata. Low iron stores have been associated with both telogen effluvium and alopecia areata. Knockout mice with mutant genes related to iron metabolism serve as a model for alopecia caused by iron deficiency. The vitamin D receptor and retinoic acid receptor pathways have also been implicated in maintaining normal hair follicle cycling. Proposed mechanisms for the effect of nutritional deficiencies on hair growth and alopecia will be discussed.

MESENCHYMAL NICHE CONTROL OF HAIR FOLLICLE FORMATION, GROWTH AND REGENERATION

Michael Rendl
Icahn School of Medicine at Mount Sinai

The activity of many genes implicated in the control of skin homeostasis are regulated by miRNAs, which represent a new regulatory layer controlling an execution of lineage-specific differentiation programs. For example, prominent expressions of miR-31 and miR-214 in anagen hair follicle are required for a fine tuning of the activities of WNT and BMP signaling pathways and contribute to the control of the hair follicle size. Previous studies demonstrated that miRNAs control the inflammatory response acting as important post-transcriptional regulators of the inflammation-related mediators. Indeed, miRNAs contribute to the development of the varied pathological conditions, including autoimmune diseases. However, how miRNAs are involved in the mediating signaling induced by pro-inflammatory cytokines and control inflammation, hair follicle apoptosis and hair loss in alopecia areata-affected skin are largely unknown.

To investigate the role for miRNA in alopecia areata, the global miRNA profiling was performed in alopecia areata affected skin in C3H/HeJ mouse skin versus corresponding control. We observed very high levels of miR-486 and miR-451 in non-affected anagen skin, being prominently expressed in the follicular epithelium, while both miR-486 and miR-451 are markedly downregulated in the skin affected by alopecia areata. Such expression pattern was confirmed in the human skin. Intradermal delivery of miR-486 and miR-451 mimics into C3H/HeJ mouse affected by alopecia areata prevented pre-mature emergence of the hair follicles into catagen phase. Dramatically reduced expression of major histocompatibility complex (MHCI, MHCI) antigens were detected in the skin and hair follicles treated with miR-486 and miR-451 mimics compared to control mice. These treatments were also resulted in a reduction of numbers of macrophages, and in decrease in CD4+ and CD8+ lymphocytes in the peri- and intra-follicular skin compartments. Because miR-486 and miR-451 are implicated in the regulation of the genes that control inflammation and apoptosis, we will continue unravelling the role of miR-486 and miR-451 in the control of hair follicle immune privilege by protecting the hair follicle from the cytotoxicity induced by pro-inflammatory cytokines.

GENES, THE HAIR FOLLICLE & THE MICROENVIRONMENT

THE ROLE OF MICRORNAS IN ALOPECIA AREATA

David Bradley1, Andrey A Sharov2, John Sundberg2, Natalia V Botchkareva1
1University of Bradford, University of Bradford; 2Boston University; 3The Jackson Laboratory

Plasmacytoid dendritic cell and immune cell dysregulation have shown to contribute to the development and progression of alopecia areata. In an age of increasing emphasis on the role of human microbiome in disease, we have previously observed that regulatory T cells (Tregs) in skin preferentially localize to hair follicles and epithelia. The dendritic cell (DC) is a specialized immune sentinel that directs T cells to tolerance or immunity to self and non-self-antigens. We have identified distinct properties promoting self-tolerance in DCs originating in tissues such as skin. We find during inflammation skin migratory DCs may direct T cells to tolerance, counter-regulating and controlling immunity. These cells are uniquely genetically programed in humans and in mouse to dampen immunity with a high expression of shared tolerance genes, including some genes such as PD-L1 that have been successfully targeted in the clinic. We hypothesize homeostatic maintenance of self-tolerance by skin DCs is a critical step to prevent autoimmune disease and describe new therapeutic targets and pathways promoting this activity.
COMMENSAL MICROBES AND HAIR FOLLICLE MORPHOGENESIS COORDINATELY DRIVE TREG MIGRATION INTO NEONATAL SKIN
Tiffany C. Scharschmidt1, Kimberly S. Vasquez1, Mariela L. Pauli1, Elizabeth G. Leitner1, Hong-An Truong1, Margaret M. Lowe1, Robert Sanchez Rodriguez2, Niwa Ali1, Zoltan G. Laszik1, Justin L. Sonnenburg3, Sarah E. Miller2, Michael D. Rosenblum1
1University of California, San Francisco; 2Stanford University School of Medicine; 3Perelman School of Medicine, University of Pennsylvania

We have previously reported that a wave of regulatory T cells (Tregs) into neonatal skin is responsible for establishing tolerance to skin commensal microbes. However, mechanisms mediating the abrupt accumulation of this population remain undefined. Here we show that neonatal Tregs localize to hair follicles upon skin entry and are reduced in mice in which hair follicles fail to develop. Hair follicles are a primary reservoir for skin commensal microbes, and mice born in germ-free conditions had reduced Tregs in neonatal skin. Using an unbiased discovery approach, we identified Ccl2o as a hair follicle-derived and microbiota-dependent skin chemokine expressed early in life. In addition, Ccr6, the receptor for Ccl2o, was preferentially and highly expressed by newborn skin Tregs. In functional experiments, Ccl2o was preferentially capable of driving migration of neonatal Tregs in vitro. Likewise, Ccr6 on Tregs facilitated their migration to neonatal skin in vivo. Taken together, our results support a model whereby colonization of developing hair follicles by commensal microbes helps to augment expression of Ccl2o by hair follicle keratinocytes, thereby promoting migration of Ccr6+ Treg cells into neonatal skin. Thus, hair follicle morphogenesis and colonization by commensals work in concert to create the skin Treg niche early in life, during the critical time period in which tolerance to commensal microbes is established.

ADVANCING RNA CHEMISTRY TOWARDS MODULATION OF GENE EXPRESSION IN SKIN
Anastasia Khvorova
University of Massachusetts Medical School

Oligonucleotide therapeutics is a new class of drugs that demonstrate robust efficacy in clinic. Characteristics like long duration of effect (months with a single administration), specificity, and the ability to modulate the expression of all genes make this technology transformative in the development of human therapeutics. Recent advances in chemistry allow for efficient delivery and modulation of gene expression in skin, both locally and systemically. The potential of this technology for the treatment of alopecia will be discussed.

COMORBIDITIES PRESENT IN THE ALOPECIA AREATA REGISTRY, BIOBANK & CLINICAL TRIALS NETWORK
Lynn Petukhova
Columbia University Medical Center

Comorbidities are medical conditions that tend to occur together and may provide etiological insight, suggest novel therapeutic strategies, and help patients and family members understand risk of other health conditions. Epidemiological studies have established clustering of autoimmune diseases within patients and families, and previous studies in alopecia areata have examined comorbidities in small cohorts of patients identified through records from hospitals or outpatient clinics. In this study, we evaluated the distribution of autoimmune comorbidities among patients in the Alopecia Areata Registry, Biobank & Clinical Trials Network conducting the largest study to date, analyzing data on 11,125 individuals from 9,271 families. Seventeen percent of AA patients report having one or more autoimmune/inflammatory comorbidities. Interestingly, 17% of unaffected relatives of AA patients report having one or more autoimmune diseases other than AA. Only 9% of unaffected unrelated controls report having an autoimmune disease. The most common comorbidities among AA patients are atopy and diseases of the thyroid. We are in the process of validating this data by deploying a new survey to patients.

UNDERSTANDING THE COMMONALITIES ACROSS AUTOIMMUNE DISEASES
John E. Harris
University of Massachusetts Medical School

Vitiligo and alopecia areata are both common, T cell-driven autoimmune diseases of the skin. Recognizing similarities and differences between these diseases will promote a more complete understanding of their pathogenesis, as well as the development of new treatments. We previously reported that IFN-γ and the IFN-γ-dependent chemokine CCL10 are highly expressed in human vitiligo, and are required for both the progression and maintenance of depigmentation in a mouse model. A similar expression profile was reported in human and mouse alopecia areata as well, prompting the use of Jak inhibitors to block cytokine signaling in preclinical mouse testing as well as clinical studies in patients. Case reports have suggested similar efficacy of Jak inhibitors in vitiligo patients as well. We propose that neutralizing antibodies and small-molecule inhibitors that interfere with the IFN-γ–chemokine axis provide an opportunity for developing new treatments for both vitiligo and alopecia areata. I will briefly discuss recent findings about the role of the IFN-γ–CCL10 pathway in vitiligo, as well as emerging treatment strategies.

NEURONAL TYPE 2 CYTOKINE SIGNALING CRITICALLY REGULATES CHRONIC ITCH IN THE SETTING OF ATOPIC DERMATITIS
Landon K. Oete1, Madison R. Mack1, Timothy M. Whelan1, Amy Z. Xu1, Haikia Niu1, Changsong Guo1, Jing Feng1, Jiale Luo1, Hengteng Hui1, Steve Davidson2, Qin Liu1, Brian S. Kim1
1Washington University School of Medicine; 2Howard Hughes Medical Institute; 3University of Cincinnati College of Medicine

Chronic itch is the central and most debilitating symptom of the inflammatory skin disorder atopic dermatitis (AD). It is widely appreciated that the pathogenesis of AD is largely driven by the proinflammatory type 2 cytokines interleukin (IL)-4 and IL-13. However, despite our increasing understanding of the immunologic basis of skin inflammation, the cellular and molecular mechanisms that mediate chronic itch remain poorly understood. We show for the first time that both murine and human sensory ganglia express type 2 cytokine receptors and IL-4 and IL-13 directly activate itch-sensory neurons. Strikingly, we found that type 2 cytokine signaling through IL-4Rα is necessary for the development of chronic itch in the setting of AD-like disease. These findings strongly support the hypothesis that IL-4Rα signaling is a critical therapeutic target for the treatment of AD-associated itch. Additionally, these studies highlight a novel mechanism by which emerging therapeutics such as dupilumab (an anti-IL-4Rα monoclonal antibody) may function to limit itch in patients. Future treatments may be further improved by targeting neuronal IL-4Rα signaling within the nervous system.

CYTOKINE TARGETED THERAPEUTICS: LESSONS FROM ATOPIC DERMATITIS AND OTHER INFLAMMATORY SKIN DISEASES
Emma Guttmann-Yassky
Icahn School of Medicine at the Mount Sinai Medical Center

Alopecia areata (AA) is a common, T-cell mediated, hair-centered skin disease that lacks efficacious, long-term therapies for extensive disease. Systemic immune suppressants are usually used, despite their nonspecific actions, often associated with substantial side effects. Although, the Th1 pathway was suggested as pivotal in the disease, recent studies suggest that Th2, Th9, phosphodiesterase (PDE) 4, and IL-23 axes might contribute to AA pathogenesis. AA was shown to share some phenotypic similarities with atopic dermatitis (AD), a highly prevalent inflammatory skin disease. In line with clinical associations between the conditions, personal or familial history of atopy, and AD in particular, is the highest risk factor of AA development, and AA patients with concomitant AD have a higher risk for severe AA.

The therapeutic revolution for AA is now beginning, with multiple possible therapeutic targets being explored, both broad and specific. These include small molecules with more widespread cellular effects (JAK and PDE4 inhibitors), and specific IL-23, IL-17 and Th2 (IL-13) antagonists that are currently tested in clinical trials. Despite their reported efficacy in early studies, JAK inhibitors are broad-targeting and cannot elucidate the pathogenic axes involved in AA. As in psoriasis and AD, targeting specific immune pathways will help elucidate primary disease pathogenesis for AA. Such approach will eventually dissect the molecular circuits characterizing AA, and help therapeutic development for AA. We are now beginning a new treatment paradigm for AA, with introduction of possibly safer, and/or more efficacious drugs, in contrast to the limited treatment options that have been previously available. Ongoing and future clinical trials utilizing narrow-targeted therapeutics will be able to better elucidate the role of each cytokine pathway in creating the AA disease phenotype.
CHALLENGES & OPPORTUNITIES: ADVANCING DRUGS TO PATIENT CARE

TOPICAL AND MICRONEEDLE DRUG DELIVERY AIMED AT THE HAIR FOLLICLE AND DEEPER DERMIS
Ramezani T, Zheng Z, Michniaik-Kohn BB
Rutgers-The State University of New Jersey

A platform technology has been developed based on amphiphilic biocompatible ABA triblock copolymers that self-assemble to form polymeric nanomicelles (TyroSpheres) and can be used as a carrier system for enhancing topical delivery of lipophilic actives and their stability in the formulation. Our goal was to investigate the applicability of TyroSpheres for follicular drug delivery and develop an aqueous-based gel formulation of drug-TyroSpheres for the treatment of acne.

Our model anti-acne drug was adapalene, a third generation retinoid with log P of 8.2. Adapalene-TyroSphere formulations were characterized for particle size, binding efficiency, drug loading, drug release, sebum partitioning, crystallinity, and follicular delivery. Gel formulations of adapalene-TyroSpheres were also prepared using different thickening agents and analyzed for content uniformity, rheometry, particle agglomeration and skin irritation. A preclinical acne animal model was employed to test the efficacy of the adapalene treatment via TyroSpheres and compare it with the commercial product. Using TyroSpheres we were able to develop an alcohol-free aqueous-based formulation of adapalene, which is potentially less irritant than the commercial product (Differin® gel). Small particle size in addition to good partitioning of adapalene in human sebum contributed to targeted delivery of adapalene-TyroSpheres to the pilosebaceous unit, where acne originates.

For drug delivery to the deeper dermis (as opposed to the hair follicle), the microneedle approach will be discussed. The current microneedle arrays have a fixed small area for delivery but have the advantage of being painless, flexible in how drugs are delivered and by-pass the main barrier to skin delivery, the stratum corneum.

INFLAMMATORY BIOMARKERS: INTERROGATING BIOLOGY AND INFORMING CLINICAL TRIALS
Raphael Clynes
Columbia University Medical Center; Bristol Meyers Squibb

Alopecia areata is a common autoimmune disease characterized histopathologically by T cells surrounding and attacking the anagen hair follicle. Yet there is significant disease heterogeneity with wide variation in age of onset, severity at presentation, patterns of progression, treatment response and remission. Identification of informative biomarkers predictive of an individual’s clinical course and potential for response to specific therapies would effectively guide clinical management, increasing the success rate of treatment while minimizing unnecessary exposure in patients unlikely to respond. In other diseases, “actionable” biomarkers have been helpful in identifying patients with “high risk” disease or as more attractive candidates for targeted therapies. For autoimmune diseases and cancer, introduction of transcriptional profiling of tissues is aiding in the diagnostic evaluation and in guiding therapy. In dermatologic autoimmune states diagnostic evaluations have historically included histopathology and serology (autoantibodies), but transcriptional profiling studies of lesional tissues are increasingly advancing our understanding of disease subtypes and therapeutically targetable pathways. In most patients with alopecia areata, lesional transcriptional profiles are dominated by cytotoxic lymphocyte and IFN response signatures. Early clinical data indicates that these signatures may be helpful in stratifying patients with “active” inflammatory signatures that are likely to be reversed by JAKi anti-inflammatory regimens. Moreover, as an informative pharmacodynamic signal on treatment, these biomarkers may be helpful in guiding dosing and scheduling of therapy, to optimize response and durability while minimizing duration of systemic exposure.

REPURPOSING DRUGS FOR ALOPECIA AREATA: THE VYTORIN EXPERIENCE
Antonella Tosti
University of Miami

Statins are powerful immunomodulators and first report of use of statins in the treatment of alopecia areata dates back to 2007. Since then efficacy of statins has been confirmed by another case report and a small uncontrolled study from our Institution.

The purpose of our study was to review the literature and report personal experience on treatment with statins in alopecia areata.

Our study indicated that the association simvastatin/ezetimibe might prevent relapses in patients with clinical remission as we found statistically significant association between being on therapy and stable remission of the disease. The study included patient with moderate to severe patchy alopecia areata. Other authors however have recently reported failure of treatment with simvastatin/ezetimibe in alopecia totalis/universals.

Since statin’s immunological mechanism of action is more directed in preventing interferon-γ signaling and lymphocyte activation, these drugs are possibly more indicated for acute alopecia areata than for stable chronic disease.

REGULATORY MATTERS & FUNDING OPPORTUNITIES

PATIENT-FOCUSED DRUG DEVELOPMENT INITIATIVE
Dory Kranz
National Alopecia Areata Foundation

FDA committed to a new initiative called Patient-Focused Drug Development (PFDD) with the goal of obtaining the patient perspective on certain disease areas during the five year period of the fifth authorization of the Prescription Drug User Fee Act. The goal of PFDD initiative is to obtain patient perspectives on certain disease areas in order to provide context for the FDA’s review of applications for new drugs in these disease areas.

In 2015, thanks to the tireless efforts of the National Alopecia Areata Foundation (NAAF) patient community, FDA selected alopecia areata (AA) for a PFDD meeting during FY2016—2017 to bring the patient voice into the regulatory benefit-risk assessment and help innovative new drugs receive approval. Although AA takes a tremendous physical, emotional, and social toll on affected individuals, there are currently no FDA approved treatments for AA and no standardized and generally accepted patient-centered outcome instruments to account for the effect of AA on quality of life (QoL). Current instruments were developed prior to FDA’s 2009 PRO Guidance and lack inclusion of concepts deemed important to patients with AA.

With research accelerating in AA and the PFDD meeting approaching, patient-centered outcomes are critical to inform the development of treatments relevant to patients. Therefore, the goals of NAAF are 1) to develop a curriculum and implement a training to educate our patient community about patient-centered outcomes research and prepare them to participate in patient-driven processes to inform research; and 2) to initiate a PRO Consortium to develop a single, consensus-defined PRO instrument that will support the evaluation of treatment benefit in medical product clinical trials for patients with AA, with the intention to support claims in product labeling.

PCORI: ENGAGING PATIENTS IN CLINICAL TRIALS & OUTCOMES RESEARCH
Kara Odom Walker
Patient-Centered Outcomes Research Institute

The Patient-Centered Outcomes Research Institute (PCORI) was authorized by Congress in 2010 to fund research designed to give patients, caregivers and clinicians the information they need to make better-informed decisions about health and health care. In this panel discussion, learn how PCORI is pursuing that ambitious challenge, and what they hope to learn from the research supported through our research funding programs. Alopecia Areata Research Summit audience members will hear an overview of PCORI’s Research Agenda and refining the agenda in response to input from patients and other stakeholders across the country.

Learning Objectives: 1) To achieve an understanding of how PCORI views Patient-Centered Outcomes Research – and how this is related to funding for clinical trials; 2) To understand PCORI’s major funding mechanisms – broad announcements, targeted announcements, and pragmatic clinical studies.
### REGISTERED ATTENDEES

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<th>Name</th>
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<td>Marta Bertolini, PhD</td>
<td>SPEAKER</td>
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<td>University of Münster, Germany</td>
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<td>Leslie A. Castelo-Soccio, MD, PhD</td>
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