Summary of the 2010 Alopecia Areata Clinical and Translational Research Summit

Alopecia Areata Clinical/Translational Research Summit met at Columbia University in New York City on October 22, 2010. The purpose of this summit was to discuss the need for new treatments in alopecia areata patients, to discuss new scientific and translational opportunities that point to new therapies, and to develop a strategy to bring new therapies to clinical trial, and eventually to clinical use in patients with alopecia areata.

The need for treatments for alopecia areata and quality of life issues to prove that need. Review of past clinical studies of alopecia areata to see what worked and what did not work.

As clearly stated by Maria Hordinsky, Hordinsky: "Patient groups are demanding more!!!" The Mission of the Alopecia Areata Clinical Research Task Force is to “Fast track” possible treatments that are both effective and safe. Members of the team are already investigating new promising approaches: Excimer laser (McMichael), Targretin (Duvic), Zithranol (Shapiro), new autoimmune therapies (multiple investigators).

Wilma Bergfeld reported that previous Quality of Life (QOL) investigations have shown that alopecia areata produces significant psychological distress, body image distortion, and dissatisfaction with the treatments and information available. Maria Hordinsky reported that the QOL data obtained by the National Alopecia Areata Registry is now being organized and studied, and shows that the patients perceive that alopecia areata is a
significant problem for them. She feels that the alopecia areata QOL data must be compared to results in patients with chronic diseases affecting other organ systems.

Over the past five years, significant effort has been invested in studying promising therapies including modern biologics as treatments for alopecia areata. Vera Price reviewed the outstanding Efalizumab (Raptiva) study, which measured hair regrowth, QOL, and physician and patient assessment. It was expected that this drug, which inhibits T cell function, would be effective in alopecia areata; unfortunately, it showed no effect. Bruce Strober reviewed an alopecia areata clinical trial with Alefacept (Amevive) a soluble LFA3 that inhibits T cell function. Even though the trial showed decreases in circulating T cell levels, there was no effect on hair regrowth in alopecia areata patients. Further trials with the TNF-a inhibitor Etanercept (Enbrel) were also negative. Neither anti-T cell or anti-TNF drugs produced significant responses in alopecia areata.

There was considerable discussion about why these trials were not effective in regrowing hair in alopecia areata. Some suspected that study of AU or AT patients may have been too difficult a challenge; patchy persistent disease might be more appropriate for initial trials (50-75% hair loss on the scalp). Maria Hordinsky felt that prior biopsies establishing the inflammatory phase of alopecia areata are necessary before instituting immunosuppressive drugs. Angela Christiano suggested that studies might need a hedgehog agonist to stimulate anagen follicle activation. Wilma Bergfeld added that minoxidil might need to be added as an accelerator. David Whiting felt that patients needed to be staged as acute, subacute and chronic before enrollment in studies. It is evident that there is still disagreement on the best clinical stage of disease to enroll in modern treatment protocols.

**Insights into immune targets for alopecia areata to see what drugs might be possible candidates to study**

Raphael Clynes provided a detailed discussion of the best drug targets in autoimmunity, and began the discussion of which immune pathways should be targeted in alopecia areata. Three cellular targets are evident from modern research in alopecia areata, and each can be targeted through specific protein or signaling pathways: Innate/NKG2D response (UBLP3, UBLP6, MICA), antigen presenting cells/sentinel (HLA, TAP, IFN-γ), Adaptive immunity (CTLA4, iCOS, IL-2, IL2R, IL-21). IL-15 drives the NKG2d axis and may itself be a good target. Most of the genes upregulated in alopecia areata at IFN-γ response genes, so blocking IFN-γ effects is a logical approach. CTLA4 inhibition may enhance T reg suppressor cells, inhibit TH1 cytokines, and inhibit CTL – which would block the immune response in alopecia areata. Jak inhibitors might block TH1 cytokines that drive alopecia areata. These treatments fall into 3 broad categories: Blocking natural killer innate immunity, putting the brakes on activated T cells, and jamming the inflammatory cytokine network. These approaches are being used effectively in many autoimmune diseases.

**New drug treatment opportunities based on the results of Dr. Christiano’s genetic studies**

Angela Christiano noted that the recently published alopecia areata GWAS study noted 8 strong drugable targets. Outside of HLA loci, these targets were not strongly shared with other autoimmune diseases. Type I diabetes, celiac disease and rheumatoid arthritis all share one NK locus with alopecia areata. She feels that NK-related genes provide some of the most promising targets for future treatment.

**New treatment opportunities based on drugs being developed for other autoimmune diseases**

Based on our current knowledge of the genetics and immunology of alopecia areata, there are multiple drugs currently being evaluated for other autoimmune diseases that might be very effective in alopecia areata. Elise Olsen reviewed the possible drug candidates available for topical and systemic use and discussed some of the
pitfalls facing drug development in alopecia areata. To repurpose FDA approved drugs, we would need to perform fairly large clinical trials because of the large spontaneous remission rate in alopecia areata. For drugs that are not yet FDA approved, selection of drugs in Phase III of development would be most practical. She also noted that we need better consideration of topical agents such as topical nitrogen mustard, cyclosporine, or imiquimod.

From the discussions of the day, a number of approaches would be reasonable choices for clinical trials in alopecia areata; all of these have drugs in development or already FDA approved:

a. Anti CD25: kills activated T cells
b. Anti-CTLA-4 blocks CD86-dependent activation of APC
c. Jak 1/2 inhibitor: blocks TH1 response
d. Anti-NKG2D- inhibits natural killer cells
e. Syk inhibitor
f. Anti-IL-15
g. Anti-IL-6
h. Anti-IFN
i. Anti-TAP2 (Sundberg mouse model)
j. Anti IL-1
k. Anti-IL-17
l. Anti-PDE4

Most of these are antibodies or peptides that block specific immune functions. Small molecule inhibitors of targets such as Jak and Syk may be ideal drugs for topical use because of their small size and lack of polarity.

**New treatment opportunities for devices and drugs that might work for alopecia areata patients**

Amy McMichael reviewed additional approaches that might be effective. Light therapies have been proposed for alopecia areata for years, with questionable effectiveness. New photodynamic therapy using Levulan and blue light is ineffective. However, the Excimer laser is a promising approach, effective in small pilot studies, that needs further investigation.

**Review of different drug delivery systems**

Timothy Wiedmann reviewed the issues involved in drug delivery for topical agents in alopecia areata. Existing means of delivery may be appropriate for small molecules, but larger polar molecules will need enhanced delivery systems, preferably through the hair follicle. Antibodies or peptides will be difficult to deliver unless new approaches are developed for follicular delivery. The practicality of systemic drug delivery will depend on the balance of benefit and risk.

**How to standardize all future alopecia areata clinical trials in organization, selection of patients, and regrowth measurement**

Irv Katz and Jerry Shapiro reviewed the issues involved in clinical trial design and execution in alopecia areata. It is clear that previous studies in alopecia areata have been inadequate; a recent Cochrane review concluded that there is no convincing evidence of lasting effect of any treatment in alopecia areata. It is clear that we need to have better standardized trial design with unambiguous and reliable endpoints, physician and patient evaluations of effect, and biomarkers to quantitate effectiveness.
Although open pilot studies may provide useful information on effectiveness of promising drugs, randomized clinical trial with large numbers are necessary to establish drug effectiveness. “Half-head” topical trials are a unique advantage of alopecia areata as a model for drug assessment and should be more widely used.

**Future Directions**

David Norris led a discussion of the elements of the meeting, the conclusions reached, and future directions. This included assignments of tasks to the participants.

**Conclusions from the Summit**

1. Multiple highly promising drugs are available for testing in alopecia areata, based on findings of the recent GWAS study and on drugs available from other autoimmune disease programs.
2. There are abundant excellent choices for topical and systemic therapy for alopecia areata, but we cannot afford another clinical trial from which we learn nothing.
3. The alopecia areata research community lacks a uniform clinical research protocol with validated biomarkers to study clinical and mechanistic response to treatment.
4. We need an alopecia areata biobank with tissues available for study.
5. The Cochrane review on alopecia areata treatments did not give proper consideration to “half head” studies that show effectiveness for topical diphencyprone contact sensitization therapy. Such studies will be useful in assessing future topical treatments for alopecia areata.
6. Well coordinated multi-center trials using a robust clinical trial protocol with excellent biomarkers and unambiguous endpoints are essential in establishing the safety and efficacy of new drugs for use in treating alopecia areata.

**Assignments from the Summit Meeting:**

1. Produce the Summary of the Summit to be submitted for publication, submission to drug companies, and NAAF donors. Dr. Norris.
2. Mine the National Alopecia Areata Registry data and publish quality of life data on alopecia areata. (How does alopecia areata quality of life compare to liver and heart disease patients quality of life? If disease is observable metrics have to be compared to controls) Drs. Duvic and Hordinsky.
3. Develop a uniform alopecia areata clinical protocol: (Stratify extent, duration. Have crossover component. Develop case report booklets. Design must have an unambiguous end point.) Drs Shapiro and Bergfeld.
4. Research the literature for all alopecia areata biomarkers and submit a paper for publication. Drs Katz and Hordinsky.
5. Research and submit to the task force the biomarkers from the Raptiva study: Drs. Price and Whiting.
6. Develop a plan for developing a translational platform with biomarkers (Skin, serum, whole blood, RNA, DNA) Drs. Clynes and Christiano.
7. Develop a plan for approaching the 22 pharmaceutical companies developing drugs that need to be pursued for alopecia areata. McMichael, Kalabokes et al.
8. Apply for the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Clinical Pilot and Feasibility Studies. Dr. Christiano for November 18 deadline and future submissions not determined as of yet.
10. Change the name of the registry in October 2011 to Alopecia Areata Clinical Trials Registry – Dr. Duvic and Kalabokes.