ALOPECIA AREATA
Treatment Development Program

National Alopecia Areata Foundation

2008 Research Summit Summary

The Alopecia Areata Research Summit held in Bethesda, Maryland, in July 2008 had one purpose: it was "to accelerate knowledge of and movement to therapies for alopecia areata." More simply put, the summit was called to develop priorities for the NAAF research program.

The Challenge: We want to discover the best possible treatments for alopecia areata as quickly as possible and at the most reasonable cost.

The summit brought together 44 professionals from within the alopecia areata research community as well as experts in the fields of genetics, immunology, patient registries, autoimmunity, and animal models. Additionally, people involved in repositioning drugs for disease treatment were present. A presentation by a health-related nonprofit group outlined a new research program strategy to accelerate the advancement of drug treatments, and this presentation set the tone for the meeting and raised excitement regarding new possibilities for NAAF.

Summit participants discussed multiple approaches to the discovery of new drugs to treat alopecia areata. There are also multiple biologic pathways that may be possible targets for therapy. So one of the challenges we face is how to methodically determine the best possible agents to test on our animal model, the C3H/HeJ mouse. Focused experiments with this animal model will provide a benchmark for the evaluation of promising new drug treatments.

The next phase of research to find treatments for alopecia areata might take any (or many or all) of the following possible directions:

- Test FDA-approved drugs in humans or on the C3H/HeJ animal model.
- Use the animal model to test new reagents for "proof as principle."
- Use genetic linkage to validate specific targets.
- Undertake discovery research with a small molecule screen.
- Target unique mechanistic pathways with natural antagonists.
- Complete genetic analysis to generate new hypotheses for treatment.

Investigators from other fields discussed over eight drugs that were previously unknown, or had not been previously considered for use, in the field of alopecia areata.

There were in-depth discussions of each subject area at the summit, and based on these discussions, the Research Summit Planning Committee developed the following priorities for the NAAF research program. At its

January 2009 planning meeting, the NAAF Board will review these priorities and determine how best to raise the money needed to execute them.

Priority One: The Research Summit Planning Committee overwhelmingly agreed that use of the National Alopecia Areata Registry (NAAR) will provide the greatest advancement of a broad research program, as well as development of treatments for all types of alopecia areata. The patient database and repository of serum and DNA have already enabled a major NIH-funded whole genome scan to discover genetic determinants of alopecia areata. The data in the registry is the foundation on which much future research will depend.

Background: Patient registries with tissue, DNA, and data from patients are an invaluable basis for modern studies of disease pathogenesis, and the pathway to discovery of new treatments. At NAAF's urging, the National Institutes of Health (NIH) has invested $6 million over 10 years to create the National Alopecia Areata Registry (NAAR), and this registry has elevated the threshold of spectacular discoveries in the genetics of alopecia areata and all its variants. Once NIH funding of NAAR is complete, funding support will be required by NAAF to maintain NAAR as a repository and distribution center of materials for investigators.

A further note: The American Academy of Dermatology (AAD) is exploring the possibility of establishing a skin diseases registry of which the alopecia areata registry might be a part. A possible partnership is being explored with AAD at this time.

NAAF has also funded over ten years of pilot studies in alopecia areata genetic studies. The NIH has recently funded two large RO1 grants to advance this area of genetic research by Angela Christiano, Ph.D.

Priority Two: Pursue Immunological Studies to determine if MHC Class I genes (the genes in a specific subgroup of the Major Histocompatibility Complex) can be down-regulated as possible treatment for alopecia areata. How can we block the immune cells from attacking the hair follicle?

Background: Alopecia Areata is an immunological disease under genetic control, which disrupts the normal biology of the hair follicle. NAAF has funded several pilot grants in basic hair biology. The NIH and pharmaceutical companies are now providing impressive funding in this area. Research regarding the immunologic mechanisms of alopecia areata requires more funding and especially new research approaches. The summit attendees believe that we have not thoroughly explored the immunological aspects of alopecia areata that could lead to an acceptable treatment.

How do we do this?

- Convene a summit of leading worldwide immunologists to develop directions for immunological research in alopecia areata and to interest immunologists in studying alopecia areata.
- Create a new Request for Proposals (RFP) based on recommendations from such an immunological summit.
- Explore the immune status of the hair follicle in long-standing disease, focusing on melanocytes and other cell populations in the hair follicle.
- Use immunopharmacologists to find drugs that are already in Phase I studies that might be useful for testing in alopecia areata.
- Actively pursue the approved FDA use of topical immunotherapy, which has been used haphazardly for the past thirty years.

Priority Three: Use the C3H/HeJ Animal Model to screen FDA-approved drugs.

Where do we stand with the use of the mouse model of alopecia areata to screen FDA-approved drugs?

The C3H/HeJ mouse provides an important model for comparative testing of "ready to prescribe" FDA-approved drugs. It provides a quantitative comparison of the effectiveness of multiple drug combinations that may improve immunologically mediated diseases. It also provides an opportunity to test drugs identified in hypothesis-driven research as new exciting candidates for treatment (e.g. drugs that maintain immune privilege in vitro). Use of this model can compress the drug testing process, producing results more quickly and allowing more broad comparisons without the many difficulties in human drug testing (difficulties such as the need for IRB approval, patient recruitment and selection, patient heterogeneity, uncertainty of dosing, variability in evaluation at different sites).

This project can only proceed after a pilot project currently underway validates the model for drug testing and provides a manual that directs investigators. We also need to negotiate a reasonable price for testing with laboratories that do clinical studies on mice. If these pre-requisites are met, we plan to test existing single and combined FDA-approved drugs and possible repurposed drugs on the current C3H/HeJ mouse model as soon as possible. We will revisit and revise the current list of drugs for testing and add the ones discussed by various experts at the summit.

Note: In the most recent version of our contract with The Jackson Laboratory West related to use of C3H/HeJ mouse model for such tests, extensive supplemental research studies are included. These studies should only be done once a list of the most active drugs is identified. This should NOT be done in the initial screening.

Priority Four: Explore other avenues for new therapies.

Try to find drugs in the market or in clinical research that may be viable therapies.

Explore the possibility of repurposing drugs and tap into current knowledge. (This could mean partnering with a pharmaceutical or repurposing drug company to get the drug farther down the pipeline.)