Mohammad Athar, Ph.D., UAB Professor of Dermatology since May 1, 2007, has recently published an article entitled “CP-31398 restores mutant p53 tumor suppressor function and inhibits UVB-induced skin carcinogenesis in mice” in the Journal of Clinical Investigation (December 3, 2007 issue). Dr. Athar, along with Columbia University colleagues Xiuwei Tang, Yucui Zhu, Lydia Han, Arianna Kim, Levy Kopelowich, and David Bickers, examined the role of an investigational agent known as CP-31398 in the prevention of skin cancer in mice exposed to UVB radiation.

Mutations in the p53 tumor suppressor gene can be found in over 50% of human malignancies and over 90% of cutaneous squamous cell carcinomas. CP-31398 is a styrlyquinazoline compound that has been shown to restore the tumor suppressor functions in the mutant forms of p53 in tumor cells. Dr. Athar and his colleagues demonstrated that UVB-exposed mice treated with a topical application of CP-31398 developed fewer tumors than control mice. Tumors that did develop grew significantly more slowly than in controls. In addition, CP-31398 was associated with tumor regression in mice already harboring UVB-induced cancers. The reductions in skin tumors were found function. Finally, CP-31398 was found to increase normal p53 function in a human skin cancer cell line expressing the damaged form of the p53 gene. These results have dramatic implications for the treatment and prevention of skin cancer in humans. For example, Dr. Athar envisions formulations of sunscreen incorporating CP-31398.

In addition to his position as Professor of Dermatology, Dr. Athar is a co-Director, along with Dr. David Chaplin, of the UAB Skin Diseases Research Center. Dr. Athar has an R01 from the National Institute of Environmental Health Sciences and recently received a contract from NCI to study the effects of chemopreventive agents that are known to block specific molecular targets involved in the pathogenesis of non-melanoma skin cancers.
Spotlight on Clinical Research
Amy Theos, M.D. and Kevin Boyd, M.D.

Amy Theos, M.D., Assistant Professor of Dermatology and Director of Pediatric Dermatology at UAB, is principal investigator for two projects designed to better understand the genetic disorder neurofibromatosis type 1 (NF1). A NF1 hallmark is the development of cutaneous neurofibromas and café-au-lait macules (CALMs). Assisted by Kevin Boyd, M.D., Dermatology Research Fellow, the research seeks to objectively measure these skin lesions using novel technological devices.

Dr. Theos received a pilot and feasibility study entitled “Progression of Dermal Neurofibromas in Neurofibromatosis Type 1” from the UAB Skin Diseases Research Center in August 2007. The protocol aims to: 1) systematically follow the number and size of skin tumors in adults with NF1 over a two year period; 2) develop objective tools to measure tumor number and size; and 3) determine if genetic differences exist that might explain varying growth rates among tumors.

In cooperation with the Department of Engineering, Drs. Theos and Boyd use a laser 3-D scanner to measure the surface volume of neurofibromas. Tumor growth rate will be followed for two years. Select fibromas will then be removed and genetic analysis performed to correlate rates of tumor growth with types of mutation. A germ-line mutation in the NF1 gene underlies NF1, but skin tumors develop only after a second NF1 gene mutation occurs in the tumor cells (Schwann cells). Cells from an individual patient can have the same “first-hit” (germline) mutation, but different “second-hit” (Schwann cell) mutations.

Data generated from this study will help in designing clinical trials to treat neurofibromas by allowing effects of future study drugs on tumor growth to be monitored and by uncovering environmental and genetic factors that influence tumor progression.

Dr. Theos’ second project examines café-au-lait macules in NF1 patients. This study aims to: 1) use full-body digital photography to document the number and distribution of CALMs; 2) validate the reliability, consistency, and effectiveness of reflectance spectroscopy to measure pigmentation; and 3) determine if significant differences in CALMs exist in an individual patient. Reflectance spectroscopy methods, including tristimulus reflectance colorimetry and reflectance spectrophotometry, have been used for over 50 years to objectively measure skin color. Each method measures the intensity of reflected, visible light of varying wavelengths to determine color.

Café-au-lait macules derive their color from melanocytes. Melanocytes in CALMs of NF1 patients have increased numbers of macromelanosomes relative to surrounding normal skin. No published studies have quantified and compared degrees of CALM pigmentation in NF1 patients. Recently, Dr. Ludwine Messiaen, co-investigator and Director of Laboratory Medical Genomics at UAB, and her colleagues identified a second-hit mutation from cultured melanocytes. Should large pigmentation differences be found in this study, the ability to perform genetic analysis should foster future genotype-phenotype correlation studies.

Dr. Theos can be reached at 205-824-4823 or at Amy.Theos@chsys.org. Dr. Boyd can be reached at 205-996-6589 or kpboyd@uab.edu.
Joel N. Glasgow, Ph.D., Assistant Professor of Medicine (Divisions of Cardiology and Human Gene Therapy), along with postdoctoral fellow Dr. Reinhard Waehler, have received an SDRC Year 4 pilot and feasibility award for their project entitled “A Novel Melanoma Vaccination Therapy”.

Although melanoma is treatable in early stages, once metastasized it becomes the most fatal of all skin cancers. A therapy that mounts a systemic anti-tumor response is desirable for metastatic melanoma. Immune system stimulation by use of gene therapy may foster such a response. Immunostimulatory gene therapy is attractive in that activation of relatively few immune cells can achieve a systemic anti-tumor response and the stimulated immune cells reach all areas of the body, including those harboring clinically invisible metastases.

Drs. Glasgow and Waehler seek to activate specialized cancer killing immune cells (cytotoxic T-lymphocytes or CTLs) to attack and eradicate melanoma cells. First, an antigen expressed by melanoma cells is identified and techniques are used to allow the antigen to be taken up by dendritic cells (DCs), which present it to CTLs and thereby activate them. The specifically primed CTLs then seek out and destroy melanoma cells that express the tumor antigen.

Mouse models will be employed to test several novel techniques for initiating this immune response against a known melanoma tumor antigen called tyrosinase related protein 2 (TRP2). Dr. Waehler and his colleagues will infect the skin of mice with an adenovirus that encodes the TRP2 protein fused to a known immune enhancing protein called CD40L. Neighboring DCs will preferentially take up the specially engineered virus and thereby express the TRP2-CD40L antigen. Each of these complicated processes will be optimized and the T cell immune response of the animals will be evaluated.

Once optimized, the procedures will be ultimately tested by determining if mice so immunized will be resistant to development of tumors when melanoma tumor cells are injected intravenously. These experiments will allow Drs. Glasgow and Waehler to test the hypotheses that the antigen-ligand fusion approach can be: a) simplified to facilitate broad and cost-efficient clinical application; b) enhanced to achieve therapeutic immune stimulation with a low vector dose; and c) applied to melanoma. If successful, these approaches may have the exciting potential to be rapidly translated into the clinical setting.
CLINICAL TRIALS

Are your patients interested in free treatment through a clinical study?
Do you have any patients with the following?

- Atopic Dermatitis
- Cutaneous Candidiasis
- Cutaneous Lupus
- Cutaneous T-cell Lymphoma
- Epidermolysis Bullosa
- Ocular cicatricial pemphigoid
- Onychomycosis
- Psoriasis

We also have two long-term follow-up studies including:

- OBSERVE-5 (for patients starting Enbrel)
- ATLAS (for patients already on Amevive)

Contact the UAB Dermatology research office at (205) 502-9960 / 9962 for more information or to make a referral.

Postdoctoral Fellowship
Investigative Dermatology

The Department of Dermatology at the University of Alabama at Birmingham is seeking a candidate for a T32 training grant in investigative dermatology and cutaneous biology. The incumbent should have an M.D., Ph.D., M.D./Ph.D., or the equivalent and must be an American citizen or permanent resident.

The program will provide interdisciplinary training to talented individuals who are interested in becoming independent researchers in the area of skin carcinogenesis, cell cycle regulation, signaling pathways regulating proliferation (particularly sonic hedgehog signaling) and development of suitable murine models.

In addition to mentor based research projects, trainees will participate in didactic activities that will strengthen the intellectual foundation required for innovative dermatological projects and will receive rigorous instruction in the principles necessary for ethical research.

Further information can be obtained from Jennifer Frank at (205) 975-6415. Interested candidates should forward their CV to Craig Elmets, M.D., Professor and Chairman, Department of Dermatology, via mail at EFH 414, 1530 3rd Avenue South, Birmingham, AL 35294-0009, or through email at celmets@uab.edu.
UAB Skin Diseases Research Center
Pilot and Feasibility Study Awards for 2008/2009

Preliminary applications are now being accepted for Skin Diseases Research Center Pilot and Feasibility Studies in the amount of $25,000. Funding exists for up to four studies for one year. The purpose of the Pilot and Feasibility Studies program is to provide seed money for new investigators (junior faculty) or experienced investigators new to cutaneous biology/investigative dermatology to pursue original hypotheses. It is anticipated that applicants with successful projects will expand upon them and pursue extramural funding.

The application process requires two steps. The preliminary step consists of a two-page proposal outlining the project. A budget is not required at the preliminary stage. Preliminary applications are due on Feb. 15, 2008 and will be reviewed by the committee before March 7, 2008. A select group of applicants will then be invited to participate in the second round of the proposal process by submitting a 10-page proposal in NIH format. The ten-page proposal should contain a detailed budget, budget justification, and an abstract. These proposals are due on April 4, 2008. Applications will be judged on scientific merit, originality, relevance to dermatology and likelihood of eventual extramural funding. Successful applicants will be notified by May 2, 2008.

Investigators with scientific questions should contact Craig Elmets, M.D. at 934-5188 or celmets@uab.edu. Applications should be delivered to Jennifer Frank at EFH 414 zip 0009 or, preferably, e-mailed to jfranf@uab.edu. Please call 975-6415 for questions about the application process.