Collaborations

The Herlyn laboratory has a long history of collaborations with members of Wistar and the University of Pennsylvania, with private foundations and melanoma advocates.

Collaborative grants:

- **SPORE in Cancer - NIH/NCI Specialized Program Of Research Excellence**
  Funding Period: October 2014 Through September 2019

**Summary.** The intent of the Penn/Wistar SPORE in Skin Cancer is to decrease the morbidity and mortality of skin cancers through the development of targeted therapies. This SPORE investigates three major skin cancers—melanoma, cutaneous T cell lymphoma (CTCL) and squamous cell carcinoma (SCC). The projects and cores focus on the leading cause of skin cancer deaths, melanoma. Our overarching hypothesis is that maximal long-lasting clinical impact achieved by interfering with signaling pathways and/or stimulating the host immune response requires that we take into account tumor-specific and host-specific genetic and epigenetic signatures. Each of the four projects has clear translational objectives and specific hypotheses that rest on a solid body of preliminary studies.

The specific goals for this highly interactive program project are summarized below:

Aim 1: Develop effective therapies in melanoma. In three of the four projects we propose clinical trials in patients with advanced melanoma. The overall hypothesis is that melanoma is a complex and heterogeneous disease and therefore should be treated with rationally combinatorial therapeutic approaches. Project 1 proposes a clinical trial of combination therapies for patients with BRAF mutant metastatic melanoma that concurrently targets both the BRAF and PI3K pathways. Project 2 combines an autophagy inhibitor with an inhibitor of mutant BRAF (vemurafenib), addressing the hypothesis that dual therapy will elicit a stronger tumor inhibitory response compared to targeting mutant BRAF alone. This project also will identify effective combinations of targeted therapies with autophagy inhibitors for BRAF wild type/NRAS wild type and NRAS mutant melanoma. Project 4 focuses on immunotherapy of melanoma using adoptive transfer of lymphocytes that are genetically engineered to target tumor cells. This project is built on highly encouraging data from other malignancies that engineered T-cells can achieve effective tumor regression and lasting clinical responses. We
expect all three projects to yield critical information to guide further development of new therapies.

Aim 2: Establish effective biomarkers in melanoma. Our group has a long history of defining different steps of tumor progression in melanoma using clinical, histopathologic, genetic, biological, and immunological criteria for each step. In this SPORE application, we focus on advanced, metastatic disease, hypothesizing that integrated and comprehensive biomarker analyses will not only increase our knowledge of the dynamics of disease regression and progression before, during, and after therapy, but also will directly inform and impact management itself. Biomarker development will allow for the tailored selection of therapy for patients, identify which drugs in a given class are most effective, improve assessment during therapy and enhance outcome prediction. Biomarkers also will be used to understand the genetic basis for response to therapy and potential adverse effects of therapy. Thus, we propose to use biomarkers for the following:

i. Patients’ selection for therapy and follow up. Prior to subjecting patients to therapy we will analyze their melanomas for genetic abnormalities and their plasma for circulating biomarkers with the intent of stratifying them into different disease groups that will inform therapeutic decision-making. These analyses are critical for Projects 1 and 2. We will determine whether therapy-related biomarker modulation can be detected in sera (Project 2) and tumors (Projects 1, 2 and 4).

ii. Prediction of adverse events and outcome of the therapy. We will test the hypothesis that inherited genetic variations in part determine the clinical outcome of treatment with immunomodulatory therapy as well immune related adverse events using the anti-CTLA4 drug ipilimumab. These analyses are critical for Project 3.
SPOR E in Skin Cancer
Meenhard Herlyn, PI
Lynn Schuchter, Co-PI

Projects
1. Meenhard Herlyn and Lynn Schuchter
   Dual BRAF and PI3K inhibition in melanoma
2. Ravi Amaravadi and Dave Speicher
   Targeting autophagy in melanoma
3. Kate Nathanson and Peter Kanetsky
   Predictive germline markers for immunotherapy
4. Robert Vanderheide and Carl June
   CAR-mediated therapy of melanoma

Cores
Core A Administration (M. Herlyn, Lynn Schuchter)
Core B Tissue Accrual (George Xu, Mike Feldman)
Core C Biostats (Phyllis Gimotty)

Career Development Awards (Lynn Schuchter)
Development Research Projects (Bob Vanderheide)
PROGRAM PROJECT GRANT ON ESOPHAGEAL CARCINOGENESIS

Principal Investigator: Anil Rustgi, University of Pennsylvania
Co-PI: Meenhard Herlyn
Funding Period: 2003 – present

Summary. Esophageal cancer, especially squamous cell cancer, carries with it a dismal prognosis as the preponderance of patients present at late stages, thereby defying traditional
chemoradiation therapy. Advances in molecular pathogenesis and therapy will provide a foundation for squamous cell cancers at other sites. This is a competing renewal of the NCI P01 entitled "Mechanisms of Esophageal Carcinogenesis" that has made substantial progress in elucidating the molecular mechanisms underlying squamous cell carcinogenesis with translation to new strategies in therapy.

Project 1 (Rustgi, Project Leader) will focus upon the biological roles of the EGFR oncogene and cooperation with p120-catenin and p53 tumor suppressor genes in esophageal carcinogenesis, and the role of activated stromal fibroblasts in augmenting tumor cell invasion in the microenvironment.

Project 2 (Herlyn, Project Leader) defines the relationship between fibroblasts and endothelial cells in the tumor microenvironment, and exploits this information to develop new therapeutics.

Project 3 (Diehl, Project Leader) elucidates the manner in which cyclin D1 is regulated and defines the novel role of the Fbx4 mutations in esophageal carcinogenesis, with translation into the development of therapeutic approaches.

**Outreach:**

**SOCIETY FOR MELANOMA RESEARCH**

The principal goal of the Society for Melanoma Research (SMR) is to bring together members who vary widely in their professions—from basic researchers to translational researchers to clinicians—but share an abiding devotion to improving the lives of those suffering from melanoma through research. Through yearly congresses, workshops, and its website, SMR plays the role of a catalyst to form multidisciplinary collaborations that will help the melanoma community at large secure funding, build infrastructure, and gain expertise in new technologies.

**MELANOMA RESEARCH FOUNDATION**

The Melanoma Research Foundation (MRF) is the largest independent, national organization devoted to melanoma in the United States. Committed to the support of medical research in
finding effective treatments and eventually a cure for melanoma, the MRF also educates patients and physicians about prevention, diagnosis and the treatment of melanoma. The MRF is an active advocate for the melanoma community, helping to raise awareness of this disease and the need for a cure. The MRF's website is the premier source for melanoma information seekers.

MELANOMA RESEARCH ALLIANCE

In 2007, melanoma touched the lives of Debra and Leon Black when Debra was diagnosed with the disease. The Blacks formed the Melanoma Research Alliance (MRA) under the auspices of the Milken Institute. Thanks to their generous ongoing support, all public donations to MRA go directly to melanoma research. MRA is the largest private funder of melanoma research. To date, it has awarded $30 million to 73 research programs to make transforming advances in the prevention, diagnosis, staging, and treatment of melanoma.

NATIONAL DISEASE RESEARCH INTERCHANGE

NDRI is a nonprofit, federally funded organization that was founded in 1980 by Lee Ducat, the mother of a diabetic son. Back then, obtaining adequate numbers of pancreas for diabetes research was an incredible challenge for most researchers who were forced to rely on their own, local contacts. Scientists voiced their need and with their guidance, the concept of a national human tissue and organ retrieval system became a reality. Soon, researchers studying other types of diseases and conditions recognized the success of NDRI’s national network. They began to request help in finding human biomaterials for their research projects. Today, researchers from universities, medical centers and hospitals in just about every major U.S. city rely on NDRI to deliver the specimens they need to advance their studies. Genetic studies are provided with DNA and data on valuable, well-characterized families.

MELANOMA PATIENT INFORMATION PAGE

MPIP is the oldest and largest community of people affected by melanoma, hosted through the Melanoma Research Foundation. It is designed to provide support and information to caregivers, patients, family and friends.
PANAMERICAN SOCIETY FOR PIGMENT CELL RESEARCH

The PanAmerican Society for Pigment Cell Research (PASPCR) is a scientific society devoted to those interested in various aspects of pigment cells. PASPCR is a very interactive and interdisciplinary society that meets on an annual basis.

INTERNATIONAL FEDERATION OF PIGMENT CELL SOCIETIES

The International Federation of Pigment Cell Societies (IFPCS) was founded in 1990 to foster interactions in the various disciplines of pigment cell research.