**The National Cancer Institute’s Integrative Cancer Biology Program**

**2014 Summer Cancer Research Fellowships/Internships**

**Research Project Descriptions**

The following list describes the research projects the fellows will pursue during their nine week research program. The applicants should use this list to select their 1st and 2nd choices of projects. Each project will be carried out at the location noted for the individual NCI – Integrative Cancer Biology Program Center.

**Broad Institute/Dana-Farber Cancer Institute**

**Boston, MA**

**Location of training site: Broad Institute/Dana-Farber Cancer Institute**

**Boston, MA**

**Website:** <http://www.broadinstitute.org/science/programs/cancer/icbp/broad-institute-icbp>

**Principal Investigator: Todd R. Golub, M.D.**

**Mentor: Jesse Boehm, Ph.D.**

*Duration of Program:  June 2 through August 1, 2014*

**Title:** Predicting Cancer Vulnerabilities Based on Genomic Features of Tumors

**Project Description:** The overarching goal of the Broad Institute CCSB is to predict the **vulnerabilities of tumors based upon their genomic features**. To accomplish this goal we are systematically cataloging cancer dependencies utilizing genome-wide RNA interference screens on hundreds of cancer cell lines that have been undergone comprehensive genomic characterization. Despite this exciting experimental progress, major challenges in **computational modeling** (e.g., can we develop statistical and analytical methods to link tumor features with dependencies?) as well as **experimental confirmation** (e.g., are experiments done in cell lines predictive of the vulnerabilities of established tumors in vivo?) must be overcome if we are to understand how to use **genomic biomarkers to predict how to effectively kill real tumors** in humans.

We are looking for a highly **motivated, dedicated and talented individual** for the 2014 Summer Internship Program to help further this work on either computational or experimental fronts (or both), depending on the interests of the applicant. The project may include work in the cancer laboratory performing **overexpression and RNAi experiments in cancer cell lines** as well as confirmatory studies in mouse models, and/or **developing computational methods** on these genome-scale tumor vulnerability data sets.

**Requirements:** The ideal applicant will have a **strong passion and drive** to learn new concepts and work with others. Prior experience in a molecular biology laboratory and having basic programming skills are ideal but not a requirement.

**Project Type:** In their application, the student should state which type of project **(computational or experimental)** they are interested in and describe their rationale.

**Columbia University**

**New York, NY**

**Location of training site: Columbia University**

**New York NY**

**Websites:** <http://systemsbiology.columbia.edu>

<http://magnet.c2b2.columbia.edu/>

**Principal Investigator:  Andrea Califano, Ph.D.**

**Mentor: Gloria Su, Ph.D.**

*Duration of Program:  June 2 through August 1, 2014*

**Project Description**: Our lab is committed to translational research of **pancreatic cancer** and **head and neck cancer** using both **mouse modeling** and human **cancer genetics**. Currently we focus on experimental investigations of **Kras**, **p16**, **activin** signaling, and **PI3K** signaling pathways in vitro and in vivo.

**Primary Field of Study**: Pancreatic cancer or head and neck cancer.

**Requirements**: Molecular biology and prior bench experiences preferred but not required.

**Keywords**: Pancreatic cancer, head and neck cancer, Ras Signaling, p16 signaling, activin signaling, and PI3K signaling.

**Project Type**: Biological wet lab project.

**GeneSys Research Institute / Tufts University School of Medicine**

**Boston, MA**

**Location of training site: GeneSys Research Institute / Tufts University School of Medicine**

**Boston, MA**

**Website:** [http: //www.cancer-systems-biology.org](http://www.cancer-systems-biology.org/)

**Principal Investigator: Lynn Hlatky, Ph.D.**

**Mentors: Kathleen Wilkie, Ph.D.**

**Christine Briggs, Ph.D.**

**Lili Ma, M.D.**

*Duration of Program:  June 2 through August 1, 2014*

**Title:** Exploring Cancer Cell Response to Systemic Host Effects

**Project description:** Cancers are classically thought to arise from single cells that have randomly acquired a number of genetic mutations which drive their carcinogenic transformation. Recently there has been considerable focus on how cancers are modulated by, and in turn modulate, their local microenvironment. But, cancer is also very much a systems-level disease, where interactions of tumor cells with host differentiated and progenitor cells can profoundly modulate the most fundamental aspects of cancer-growth, metastatic spread and response to treatment. To fully understand the molecular and genetic regulations driving tumor cell growth and cancer progression, and thereby effectively target cancer, one needs to take into account how interactions between host cells and cancer cells modulate the genetic signaling networks of the cancer cell.

This project investigates, both experimentally and quantitatively, various means of communication (including exosome exchange) between cancer cells and local and more distant host tissues. In particular, we will investigate both how the molecular fingerprint of the cancer cell is altered and how the “cancer stem cell” compartment of the cancer cell population is modulated by such interactions. We focus on two human tumor types that our lab has extensive expertise in, brain tumors (i.e., glioblastoma, the most common and aggressive type of brain tumor, with a median survival of about 14 months), and prostate cancer (i.e. adenocarcinoma, a disease that kills 30,000 men per year in the US). Through this investigation, the student, working with the mentoring team (a clinician/molecular biologist, a mathematical modeler, and a bioinformatics expert), will gain exposure to a panel of multiscale approaches to analyze cancer cell interactions: including molecular characterization using Illumina gene array and methylation platforms, RT PCR, immunohistochemical analysis of cells and tissues, *in vitro* cell culture and *in vivo* tumor studies. In turn, these investigations will provide insight for quantitative model construction, along with parameter values for formulating and refining our ongoing mathematical modeling efforts. Thus, in addition to wet-lab investigations, the student will have the opportunity to learn and participate in both computational bioinformatics and the construction of mathematical models of tumor-host interactions, while investigating the very critical and timely topic of host impact on cancer cell signaling networks.

**Requirements:** General familiarity with a biological laboratory setting and mathematical/computational experience is desirable.

**Keywords:** brain tumors, glioblastoma, prostate cancer, adenocarcinoma, cancer stem cells, cell culture, *in vitro* and *in vivo* tumor models, gene arrays, bioinformatics, methylation status, gene enrichment analysis, data mining, mathematical and quantitative analysis, differential equation models.

**Project Type:** Equal mix of wet-lab studies and computational/mathematical analyses.

**Georgetown University**

**Washington, D.C.**

**Location of training site: Georgetown University**

**Washington, D.C.**

**Websites:** <http://lombardi.georgetown.edu/breastcancer/ccsb/>

<http://clarkelabs.georgetown.edu/web/res_robert.php>

**Principal Investigator: Robert Clarke, Ph.D.**

**Mentor: Ayesha N. Shajahan-Haq, Ph.D.**

*Duration of Program:  June 2 through August 1, 2014*

**Title:** Function of HSP90 in Anti-estrogen Resistance

**Project description:** Seventy percent of human breast cancers are initially dependent upon estrogen-related signals for proliferation and survival, and are thus sensitive to a wide range of hormonal antagonists or anti-estrogens. However, many such tumors develop resistance to these agents, and ultimately develop resistance to common chemotherapy agents as well. HSP90 is increased in drug resistant cells. We now plan to extend these studies by determining pathways that are regulated by HSP90. Students will learn to conduct PCR arrays under control and anti-HSP90 drug treatment conditions in sensitive and resistant cells to determine the regulation of pathways by this protein in development of anti-estrogen resistance.

**Primary Field of Study:** Molecular and cellular biology.

**Requirements:** Some familiarity with cell culture and a basic understanding of biochemistry and/or molecular biology.

**Keywords:** Breast cancer, anti-estrogens and molecular biology.

**Project Type:** Experimental biology.

**Massachusetts Institute of Technology (MIT)**  
**Cambridge, MA**

**Location of training site: Massachusetts Institute of Technology (MIT)**

**Cambridge, MA**

**Website:** http://web.mit.edu/icbp/

**Principal Investigator:  Douglas Lauffenburger, Ph.D.**

**Mentor: Shannon Hughes, Ph.D.**

*Duration of Program:  June 2 through August 1, 2014*

**Title:** Morphodynamic Characterization of Metastatic Cells

**Project Description:** Mena, an actin regulatory protein, is upregulated in breast cancer and is alternatively spliced to produce protein isoforms with distinct functions during tumor progression.  Changes in Mena isoform levels are linked to an increased risk for distant **metastasis in breast cancer patients**. Our preliminary results suggest that direct interactions between Mena and Integrin receptors at least partially mediate the increased rate of metastasis in Mena-expressing cells. Using a **microfluidic device** with immobilized extracellular matrix components, we will employ **computational modelling and machine learning techniques** to morphodynamically profile Mena-expressing cells haptotaxing in response to tumor-relevant cues.

**Requirements:** The ideal Fellow will be self-motivated and have a passion for learning. Some experience in mammalian cell culture would be helpful for wet lab work, but is not required. All data analysis will be performed in Matlab, so working knowledge of the environment is a plus. Computational techniques will be taught during the summer, so extensive prior knowledge is not required.

**Project Type:** Mixture of computational and wet lab work.

**Memorial Sloan-Kettering Cancer Center**

**New York City, NY**

**Location of training site: Memorial Sloan-Kettering Cancer Center**

**New York City, NY**

**Website:** <http://cbio.mskcc.org/research/index.html>

**Principal Investigators:  Chris Sander, Ph.D.**

**Johanna Joyce, Ph.D.**

**Mentor:**  **Robert Bowman**

*Duration of Program:  June 2 through August 1, 2014*

**Title:** Transcriptional Analysis of Tumor Associated Macrophage Education in the Glioblastoma Microenvironment

**Project Description:** Glioblastoma multiforme (GBM) is the most common and deadliest of brain cancers accounting for up to 15% of cases. Mean survival is only 15 months following diagnosis. Thus, new avenues of therapy must be developed to combat this deadly disease. Recent studies have turned to understanding the roles that the tumor microenvironment plays in tumor progression. We have shown that targeting tumor-associated macrophages (TAMs) is a viable therapeutic option in a murine model of proneural GBM.

Understanding the complete education process of TAMs is a necessary component in tailoring new therapeutic strategies to the tumor microenvironment. While our initial studies focused on proneural GBM, it is likely that TAM education may differ across other subtypes of GBM. This project will integrate cell culture and immune-histochemical techniques along with computational methodology to understand the subtype specific transcriptional networks driving TAM education. Students will use computational methods to integrate gene expression data from multiple sources to interrogate the GBM subtype specific TAM education programs, as well as identify paracrine-signaling pathways involved in TAM education.

**Requirements:** General experience in a laboratory setting is necessary. Programming experience in R is preferable.

**Keywords:** Glioblastoma, tumor associated macrophages, cell culture, bio-informatics, transcriptional networks.

**Project Type:** Predominantly wet-lab studies along with computational analyses.

**Methodist Hospital Research Institute**

**Houston, TX**

**Location of training site: Methodist Hospital Research Institute**

**Houston, TX**

**Website:** <http://www.methodisthealth.com/cmcd>

**Principal Investigator: Stephen Wong, Ph.D.**

**Mentor: Fuhai Li, Ph.D.**

*Duration of Program:  June 2 through August 1, 2014*

**Title:** Development and Evaluation of TmenExplorer

**Project Description**: Tumor microenvironment refers the cellular environment in which the tumor exists, including components such as surrounding blood vessels, immune cells, [fibroblasts](http://en.wikipedia.org/wiki/Fibroblast), macrophage, signaling and drug molecules, and the [extracellular matrix](http://en.wikipedia.org/wiki/Extracellular_matrix). For many decades, researchers have focused on the cancer cell itself; more recently we have begun to consider more molecularly about how the rest of our body influences the cancer cell, notably, the study of the microenvironment: the normal cells as well as molecules and other cellular components that surround tumor cells. Adding to the complexity is that a tumor itself is heterogeneous, including the existing of cancer stem cells or tumor initiating cells, which many believe to be the origin of the tumor and a major component for metastatic cancer. The tumor and its microenvironment affect the fate of one another. For example, tumors can, to some extent, control the microenvironment by releasing extracellular signals, such as in [tumor angiogenesis](http://en.wikipedia.org/wiki/Angiogenesis#Tumor_angiogenesis) while the microenvironment can affect the growth of cancerous cells, such as in [immuno-editing](http://en.wikipedia.org/wiki/Cancer_immunology), and tumor-stromal interactions.

Due to the multi-dimensional factors involved in the communication of a tumor and its microenvironment, it would be extremely costly and time consuming to perform combinatorial wet lab experiments to investigate tumor microenvironment in its entirety. A more pragmatic strategy is to first simulate and view the cancer development and progress in dry lab computer models under various experimental conditions and assumptions so that the prediction will help to select the biological experiments to be conducted. Nevertheless, such a tool does not exist today. To fill the gap, our ICBP center at Houston Methodist is developing the TmenExplorer (Tumor Microenvironment Explorer) to represent, visualize, and simulate the interaction of a tumor and its microenvironment in a four-dimensional space, three of dimensions of space, and one of time. Collaborating with our wet lab co-investigators in the center at Baylor College of Medicine and Houston Methodist, the input data to TmenExplorer includes the genomic data and high resolution 3D microscopy imaging data from preclinical model of breast cancer with identifiable cancer stem cells triggered by Wnt and other signaling pathways. The prediction results will be validated by animal model.

The summer student will join a team of computational biologists and cancer biologists in developing TmenExplorer, notably the graphical user interface and computer simulation of cancer development. The student will learn the biology of tumor microenvironment and cancer stem cells as well as experience the new integrative biology approach towards cancer research. He or she is expected to know C/C++ programming and has background in bioinformatics, computer science, engineering, or related discipline.

For more information, please contact: Dr. Fuhai Li, [FLi@houstonmethodist.org](mailto:FLi@houstonmethodist.org), Department of Systems Medicine and Bioengineering, Houston Methodist Research Institute, Weill Cornell Medical College, Houston, TX 77303.

**Primary field of study:**  Computational biology, bioinformatics, cancer stem cell biology.

**Requirements:** Background in bioinformatics, computer science, engineering or related discipline.

**Keywords:** Computational biology, bioinformatics, systems biology, cancer stem cells, tumor microenvironment, computational modeling.

**Project Type:** Computational modeling of cancer development.

**Oregon Health & Science University**

**Portland, OR**

**Location of training site: Oregon Health & Science University**

**Portland, OR**

**Website:** <http://sysbio.banatao.berkeley.edu/>

**Principal Investigator: Joe Gray, Ph.D.**

**Mentor**: **Jim Korkola, Ph.D.**

*Duration of Program:  June 1 through August 2, 2014*

**Title**: Defining the Role Cellular Plasticity Plays in Targeted Drug Resistance in Breast Cancer

**Project Description**: A major obstacle to the use of targeted therapeutics in breast cancer patients is the frequent occurrence of **drug resistance**, followed by relapse. This is largely due to the large amount of variety that exists both between tumors, and within a single tumor. Recent genomic studies have highlighted the extensive **genetic heterogeneity** within a tumor, however even amongst genetically identical clonal variants there is still a variable response to drug treatment. A compounding variable in tumor heterogeneity is **cellular plasticity**, where cancer cells can differentiate dynamically between different subtypes, allowing a sub population to survive drug treatment and repopulate the tumor.

Our lab employs cell-spot micro arrays, functional immunofluorescent assays, automated high throughput imaging platforms, and sequencing to interrogate what factors can affect and arrest breast cancer cells differentiating into drug tolerant states. Specifically we are focusing on the role **tumor microenvironment factors** (ECM proteins, growth factors, cytokines, etc.) play in driving cells into drug tolerant states.

In addition to involvement in our work studying drug resistance, a summer student project would involve using our labs microenvironment **microarray technology** to focus on other roles cellular plasticity plays in the progression of cancer. Breast cancer metastasis is believed to involve two major differentiation events; **epithelial to mesenchymal transitions** (EMT), and the **reverse mesenchymal to epithelial transition** (MET). In these events cancer cells break away from the primary tumor by taking on a more mobile phenotype, and then revert back to a more proliferative state upon tissue colonization. The student project would seek to identify which specific tissue factors in common sites of **metastasis** are responsible for initiating MET. The successful completion of this project would be a first step towards a potential treatment to inhibit metastasis in breast cancer patients.

**Requirements**: General experience in cell culture, immunohistochemistry, and biological laboratory techniques preferred. Experience in statistics, computational biology, optics, and engineering strongly encouraged.

**Project Type**: Mix of wet lab, image analysis, and bioengineering.

**Stanford University School of Medicine**

**Palo Alto, CA**

**Location of training site: Stanford University School of Medicine**

**Palo Alto, CA**

**Website:** <http://ccsb.stanford.edu>

**Principal Investigator: Sylvia Plevritis, Ph.D.**

**Mentors:  Andrew Gentles, Ph.D.**

**Jinfeng Shen, Ph.D.**

*Duration of Program:  approximately June 23 through August 16, 2014*

**Title:** Characterization of the Leukemia Stem Cell Regulatory Program in Human AML

**Project Description:** **Acute myeloid leukemia** (AML) is a malignant disease characterized by an increased number of myeloid precursor cells that fail to differentiate in the bone marrow. Growing evidence indicates that AML is organized as a hierarchy of functionally distinct subpopulations initiated and maintained by self-renewing **cancer or leukemia stem cells** (LSC). Because of this, AML stem cells are a critical target for the development of novel therapies. Previously, we investigated the association between clinical outcomes and LSC **gene expression** in four independent cohorts of more than 1000 AML patients [1]. We found that increased expression of an LSC signature correlated with worse **clinical outcomes**.

The goals of this project are to investigate the function of specific genes in regulating AML LSC and to determine the molecular mechanisms by which they executes these functions using computational and/or experimental methods.

The project will have computational and experimental components, with the balance depending on the background of the fellow:

1. Computational methods: The student will learn to analyze the microarray data, supervised by Andrew Gentles. This will include applying standard methods as well as more complex algorithms such as **network reconstruction** and **machine learning**. Experience required: knowledge of statistics; programming in a language such as Matlab or R, or similar.

2. Molecular Biology methods: The student will learn basic laboratory techniques, supervised by Jinfeng Shen. Lab reagents and experimental methods:

a. Cell lines: KG1, HL60, THP-1, K562, Kasumi, Molm-13

b. Experimental methods: AML **cell line culture**, Proliferation WST-1 assay,

trypan blue cell counting, **transient shRNA transfection**, Western blotting.

**Reference:**

1. Gentles AJ, Plevritis SK, Majeti R, & Alizadeh AA (2010). Association of a leukemic stem cell gene expression signature with clinical outcomes in acute myeloid leukemia. *Jama* 304(24):2706-2715.

**Primary Field of Study:**  Computational and experimental biology.

**Requirements:** Knowledge of statistics; programming in a language such as Matlab or R, or similar.

**Project Type:** Computational and experimental, with the balance depending on the background of the fellow.

**University of Texas Health Science Center at San Antonio,**

**San Antonio, TX / Indiana University, Bloomington, IN**

**Location of training site: Indiana University**

**Bloomington, IN**

**Websites:** <http://icbp.uthscsa.edu>

<http://www.cancer.iu.edu/research/members/member_bio.php?id=11>

**Principal Investigator: Tim Huang, Ph.D.**

**Mentor: Kenneth P. Nephew, Ph.D.**

*Duration of Program:  June 2 through August 1, 2014*

**Project Description:** **Ovarian cancer** causes more deaths than any other female reproductive tract cancer. The majority of women diagnosed with advanced-stage epithelial ovarian cancer (EOC) experience tumor recurrence associated with the development of chemo-resistance, and platinum-resistant EOC is uniformly fatal. A new paradigm to explain tumor relapse is the hypothesis of “**cancer stem cells**” recently reported in a number of solid tumors, including in EOC. While current chemotherapy may succeed initially at decreasing the size and number of tumors, they leave behind an increased proportion of the most malignant cells, which include the tumor progenitors or “cancer stem cells”.

**Ovarian cancer stem cells (CSCs**) have now been isolated from established EOC cell lines, ascites, and primary tumors. Ovarian CSC are hypothesized to be largely (or entirely) responsible for chemo-resistant tumor relapse, due to the fact that they possess many of the phenotypes associated with drug resistance (e.g., enhanced DNA repair, diminished apoptotic responses, etc.). Moreover CSC are believed to harbor a significantly altered **epigenome**, and it has been hypothesized that DNA hypo-methylating agents could “reset” these cells toward differentiation. Pre-clinical studies form our and from other groups have established the rationale for combining **DNA methylation inhibitors** with existing chemotherapeutic agents to overcome acquired drug resistance in EOC.

For the 2014 ICBP Summer Cancer Research Project, the Fellow will use perform both wet lab and computation experiments. The Fellow will isolate ovarian CSC from EOC cell lines and patient tumors and examine the **epigenomic landscape** of these cells using **next generation sequence approaches**. Specifically, the Fellow will treat the ALDH+ ovarian CSC with a new DNA hypomethylating agent SGI-110 to resensitize the ovarian CSC to chemotherapy. To establish global changes in DNA methylation and transcription induced by the epigenetic drug, the Fellow will perform rigorous experimental and bioinformatics analyses using both **Methylcapture-sequencing (methylome)** and **RNA-sequencing (whole transcriptome**) next generation sequencing and **integrate the data** using **bioinformatics** approaches. All techniques are well established in the lab, and the fellow will work closely with team members to successfully complete the summer research project.

**Project Type:** Experimental and computational biology.

**Vanderbilt University Medical Center**

**Nashville, TN**

**Location of training site: Vanderbilt University Medical Center**

**Nashville, TN**

**Website:** <http://vicbc.vanderbilt.edu/ccsb/>

**Principal Investigator: Vito Quaranta, M.D.**

**Mentors: Katherine Jameson, Ph.D.**

**Darren Tyson, Ph.D.**

*Duration of Program: June 2 through August 1, 2014*

**Title:** Quantifying Cancer Cell Response Dynamics and Heterogeneity to Targeted Therapeutics: Implications for Primary Response and Long-term Outcomes.

**Project Description:** Cancer is primarily a disease of unrestrained cellular **proliferation**. It is now understood that even cells with the same genetic background can respond differently to the same stimulus yet little is known about how individual cells make decisions to progress through the **cell cycle**. Recent technological advances have now made it possible to obtain information about cell cycle progression at the **single cell** level and these rich data sets are providing a wealth of new information about how benign and cancerous cells make these decisions. We use **fluorescent** **time-lapse microscopic imaging** of human cancer cell lines to investigate population **dynamics** and **cell-to-cell variability** of cell cycle progression in response to drug treatment. Cells with fluorescent tags will be imaged and cell age and cell cycle states are extracted to generate distributions of response. Signaling states of cells are also evaluated using immunofluorescent methods. The data is then incorporated into **mathematical models** to help understand the underlying biology of heterogeneous responses, which impact both primary response and long-term outcomes.

**Primary field of study:** The student may be involved in any or all aspects of this project, depending on background and interest, including: cell culture, live cell fluorescent microscopic imaging, image processing, statistical data analysis, and mathematical modeling.

**Requirements:** Useful experience would include: cell culture; fluorescence microscopy, image processing using Matlab or ImageJ, familiarity with the statistical analysis program R, and an understanding of the mammalian cell cycle.

**Project Type:** Experimental and computational biology.