Frederick National Laboratory for Cancer Research

Visiting Scholar Opportunity

Advanced Preclinical Research

Cancer Challenge

Despite the promise of "molecularly targeted therapies," only about 7 percent of cancer drugs entering clinical trials are actually approved. The majority of new cancer treatments fail due to lack of efficacy in patients, indicating that the current preclinical approaches for testing cancer drug efficacy have limited accuracy.

The failure of new cancer treatments comes at an estimated average cost of $1.7 billion per drug, with an inestimable human toll exacted in the process. Furthermore, successful treatments have proven to be temporary; aggressive cancers, resistant to the initial therapy, inevitably emerge.

Currently, methodologies exist to engineer mice, genetically and/or biologically, to better model human cancers. By definition, these models are genetically diverse and complex, and require significant expertise and experimentation to determine approaches that best mimic a given human scenario.

Early genomic, biomarker, and pilot preclinical therapeutic studies have illustrated both the value of using such genetically engineered mouse models (GEMMs) to accelerate biomarker/molecular discovery, and the potential for significantly increased accuracy in efficacy determination. Additionally, development of orthotopic transplant models, including both syngeneic (mouse–mouse) and human primary tumor cell (human–mouse) xenografts, may hold promise for improved efficacy determination.

Many challenges remain, however, before these models can be used routinely to support broadly effective translational research. For example, many models have long latencies to tumor development, involve difficult surgeries or other induction methods, or require complicated breeding strategies to build large cohorts.

Visiting Scholar Opportunity

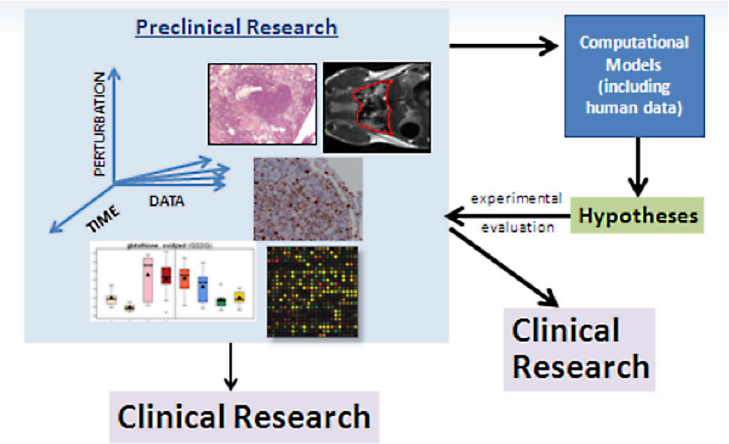
The NCI Center for Advanced Preclinical Research (CAPR) was established to address the above challenges and to facilitate the contribution of GEMMs to the improvement in overall clinical care, including the process of selecting novel compounds and biologics for clinical trials.

CAPR Center for Advanced Preclinical Research

Applicants are asked to propose how a collaborative residency at the Frederick National Laboratory might contribute to addressing this Cancer Challenge and advance progress in one of the following initiative areas:

- Design, development, and preclinical validation of novel mouse models for serous type ovarian cancer
- Therapy evaluation and biomarker discovery studies in non–small cell lung cancer models, including resistance to clinically applied chemotherapeutics
- Retooling of mouse models of high-grade astrocytoma for preclinical evaluation, as well as systems biology studies in these models to augment the mechanistic foundation of brain cancer and to identify drug targets and biomarkers;

CAPR's Approach to Systems Analysis of Disease and Treatment Response



- Adoption of embryonic stem cell and induced pluripotent stem cell technologies as robust experimental platforms for next-generation preclinical mouse models (non-germline GEMs).

CAPR's three integrated scientific teams (see diagram below) consist of 23 full-time staff: 7 Ph.D. scientists (including a project manager); a D.V.M. pathologist; a histotechnologist; 10 technicians; and an administrative assistant. All staff are supported by administrative/project management and animal research groups.

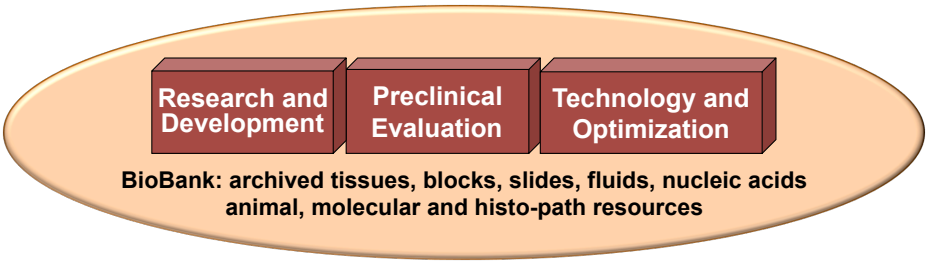
CAPR has access to the core capabilities of the Frederick National Laboratory, including the Small Animal Imaging Program; the Laboratory of Molecular Technology; the Pathology and Histotechnology Laboratory; the Advanced Biomedical Computing Center; and the Laboratory of Proteomics and Analytical Technologies.

In addition, CAPR has established interactions with the SAIC-Frederick Nanotechnology Characterization Laboratory; the NIH Chemical Genomics Center (for HTP cell-based screens); and NCI's Core Genotyping Facility, Cancer Therapy Evaluation Program, Developmental Therapeutics Program, cancer Biomedical Informatics Grid, and the Mouse Models of Human Cancers Consortium. At present, CAPR manages a portfolio of more than 20 model design, drug evaluation, biomarker discovery, and technology development projects. In addition, CAPR is currently collaborating with a number of nonprofit organizations and established academic laboratories.

Who Should Apply?

Candidates with proposals from a broad spectrum of projects aimed at advancing preclinical and translational research are welcome; in particular, we seek candidates pursuing novel avenues in preclinical characterization; in-depth histopathological, cellular, and next-generation molecular analyses of complex in vivo cancer model systems; and technology development. Interested candidates are expected to demonstrate prior experience with genetically engineered animal models and are encouraged to contact the CAPR leadership team directly for further information and a summary of available resources, as well as to discuss the rationality and feasibility of suggested proposals for CAPR strategic objectives.

MISSION: Develop strategies for predictive preclinical research in genetically and biologically engineered murine cancer models AND to facilitate routine application in clinical research for optimal outcomes in cancer patient management.



- Derivation, modification and validation of more predictive GEMMs
- Biomarkers/molecular signatures of tumorigenesis
- Breeding strategies for scale-up of mouse cohorts
- Efficacy studies on drug candidates
- Develop molecular and in vivo imaging endpoints
- Biodistribution (PK/PD)
- Biomarkers/molecular signatures of treatment response
- New methodologies for expanding and scaling up preclinical study design
- ES and iPSC technologies for non-germline cohorts and preservation
- Optimization/retooling of GEMs

For more information, please contact:

Dr. Terry Van Dyke
Phone: 301-846-1988
E-mail: vandyket@mail.nih.gov

Dr. Serguei Kozlov
Phone: 301-846-1752
E-mail: kozlovse@mail.nih.gov

203446