

Visiting Scholar Opportunity



Advanced Preclinical Research

Cancer Challenge

Despite the promises of “molecularly targeted therapies,” only about seven percent of cancer drugs entering clinical trials actually receive regulatory approval for therapeutic applications. 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, compounded further by an inestimable human toll exacted in the process. Furthermore, successful treatments have proven to be temporary; recurrent cancers, resistant to the initial therapy, inevitably emerge that are frequently more aggressive than the primary tumor. Detailed analyses of oncology drug attrition rates indicate that, as novel therapeutics advance through the clinical evaluation process toward regulatory approval, the majority “drop out of the race” due to the lack of clinical efficacy, strongly suggesting a shortage of reliable predictive approaches to earlier efficacy evaluation at the preclinical step.

The need to address these key challenges is a recognized NCI priority and is one of the mission foci of the Frederick National Laboratory for Cancer Research. Improving predictive preclinical animal models to faithfully mimic the multiple aspects of cancer is an unmet need that must be fulfilled to provide meaningful support to more efficacious cancer drug development.

Currently, methodologies exist to engineer mice, genetically and/or biologically, to better model many features of human cancers.¹ By their design, these models are genetically diverse and complex, and require both significant expertise and sophisticated experimental approaches to determine strategies that best mimic a given clinical course of disease in humans.

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 predicting efficacy to inform clinical development. Additionally, the introduction of orthotopic transplant models,^{2,3} including both syngeneic (mouse–mouse) and human primary tumor cell (human–mouse) xenografts, may hold promise for improved efficacy determination.

Multiple challenges remain, however, before these models can be used routinely to broadly support effective translational research. Many models, for example, have long latencies to

tumor development; others may involve difficult surgeries or other sophisticated induction methods, or may require complicated breeding strategies to build large cohorts; still others may demand complex and technologically intense methods for detecting and monitoring the disease, such as in vivo imaging or molecular diagnostics.

Visiting Scholar Opportunities

The NCI Center for Advanced Preclinical Research (CAPR) was established to address the above challenges and accelerate recruitment of GEMM resources for streamlining the development of more efficacious



and better-tolerated therapeutics and improving overall clinical care. These efforts include facilitating the selection of promising novel compounds and the most rational combinations of these compounds for clinical trials.

The Visiting Scholars Program invites mid-career investigators to submit an Expression of Interest (<http://frederick.cancer.gov/VisitingScholarProgram.aspx>) describing how the candidate will contribute to one of the following priority areas currently being addressed by CAPR investigators:

- The CAPR Program has achieved considerable progress in adopting, designing, and implementing state-of-the-art murine models for preclinical experimentation for candidate cancer therapeutics.⁴ Challenges, however, remain to either (i) retool the available models for more robust, relevant, and affordable use; or (ii) expand the existing CAPR cancer GEMM portfolio to include additional models required for optimized drug development.
We are seeking candidates to contribute to the design and development of novel preclinical GEMMs, including non-germline and orthotopic allograft-based GEMMs for such cancers as high-grade astrocytoma, pancreatic ductal adenocarcinoma, multiple metastatic melanoma, and serous type of ovarian cancer.
- CAPR scientists successfully employed GEMMs to explore the molecular signatures found to correlate with cancer initiation or progression. These efforts are aimed at discovering biological markers that indicate the presence of disease and the prognosis for its expected clinical course; reveal cancer response to therapeutic intervention; or signal the onset of resistance, tumor recurrence, and/or metastatic spread.⁵

We are seeking candidates with experience in cutting-edge, molecular approaches to the discovery and validation of clinically promising

molecular biomarkers (including, but not limited to, tissue and circulation metabolites, transcription signatures, genome aberrations, microbiome composition) that are indicative of disease progression and clinical prognosis, as well as suggestive of the most efficacious therapeutic strategies.

- To advance our understanding of the mechanistic foundation of cancer initiation, progression, and drug response, CAPR initiated several projects aimed at applying modern bioinformatics and computational systems biology approaches to interrogate complex signaling networks that are perturbed in cancer and dynamically evolve with disease progression and drug treatment. Such interrogations are accomplished via an integrated analysis of clinical, histopathologic, imaging, and molecular “omics” outcomes.⁶

We are seeking candidates who will make a substantial contribution to expanding and strengthening CAPR's expertise in applying state-of-the-art bioinformatics tools to the analysis of complex data sets, particularly those generated in the course of drug evaluation studies in preclinical GEMMs.

- CAPR is applying advanced technologies to explore the liaisons between inflammatory processes and tumorigenesis in several murine models of cancer that are prone to invoke a potent inflammatory immune system response or are known to exhibit altered cancer progression outcomes under inflammatory conditions (examples include pancreatic and ovarian carcinoma and metastatic cutaneous melanoma models that are in varying stages of development or adoption at CAPR).

We are seeking candidates with prior or current industry experience who are knowledgeable in diverse areas of cancer-related inflammation or tumor immunology.

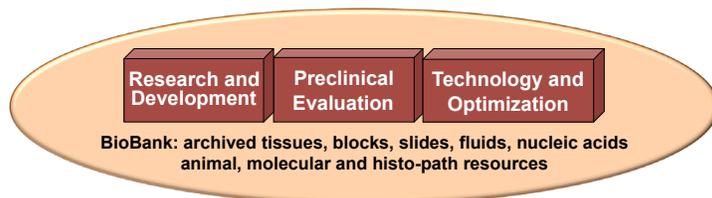
About CAPR

CAPR's three integrated scientific teams (see diagram) consist of 21 full-time staff: 6 Ph.D. scientists; a D.V.M. pathologist; a histotechnologist; 10 technicians; a mouse colony manager; and an administrative assistant. CAPR is supported by administrative/project management resources and animal research groups.

Research staff actively interact with several core capabilities of the Frederick National Laboratory and NCI, including the Small Animal Imaging Program; the Transgenic Core Facility; 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; and NCI's Core Genotyping Facility, Cancer Therapy Evaluation Program, Developmental Therapeutics Program, 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. CAPR is currently partnering with a number of nonprofit organizations, established academic laboratories, and drug development companies.

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

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To learn more about these programs, visit:

The Center for Advanced Preclinical Research:

<http://ccr.cancer.gov/research/Capr.aspx>

The Visiting Scholars Program:

<http://frederick.cancer.gov/Careers/VisitingScholar/Default.aspx>

References

1. <http://www.ncbi.nlm.nih.gov/pubmed/22974396>
2. <http://www.ncbi.nlm.nih.gov/pubmed/18547137>
3. <http://www.ncbi.nlm.nih.gov/pubmed/21907921>
4. See, for example, <http://www.ncbi.nlm.nih.gov/pubmed/22617326>.
5. See recent CAPR paper, <http://www.ncbi.nlm.nih.gov/pubmed/22969147>.
6. <http://www.ncbi.nlm.nih.gov/pubmed/22969147>



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Frederick National Laboratory is a Federally Funded Research and Development Center operated by SAIC-Frederick, Inc., for the National Cancer Institute