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CCR Fellows & Young Investigators Newsletter

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Special Issue: The Value of Animal Models in Cancer Research

Foreword from the Editor

Insulin, virally-induced cancer, circadian rhythm, RNA interference, cell division, apoptosis, the chromosomal theory of heredity – these are just a handful of key biological discoveries that were uncovered by studies in animals. From dogs to chickens, fruit flies to nematode worms, animal models have provided the basis for several key biological discoveries.

Historically, studies in animals have yielded countless insights that often have clear analogs in humans, leading to advances in human health. These insights are not only a thing of the past; ongoing research continues to reap the benefits of research in animal models. In this special issue, researchers from the National Cancer Institute's Center for Cancer Research emphasize the critical work they do while both (1) contributing to our understanding of human health and (2) emphasizing the fact that these same experiments could not be performed without the vessel of an animal.

Experimental approaches can be described as one of six types: perturbation, visualization, substitution, characterization, reconstitution, and simulation[1]. Each has its strengths and its flaws, and the combination of these approaches will create the strongest understanding of what's happening. Human cell lines, organoids, and AI allow us to experiment with some approaches, but none alone nor all combined can emulate the complexity that exists *in vivo.*

There are a couple of words we as careful scientists tend to avoid: "always," and "never." While we cannot promise that each molecular mechanism that is discovered within an animal will *always* operate exactly the same way in humans, we hope to show you that the use of animal models in cancer research is truly *invaluable.*

Daphne Knudsen-Palmer, Ph.D.

Editor-in-Chief

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[1] PMCID: PMC7302876

Comparative Canine Genomics Offers New insights into Human Bone Cancer

Anjali Garg, Ph.D.

Molecular Imaging Branch

Osteosarcoma (OS) is the most common primary bone tumor affecting both humans and pet dogs, posing significant clinical challenges. Despite decades of research, progress in improving treatment outcomes has been limited. While OS is rare in humans, with fewer than 1,000 cases annually, it affects more than 50,000 dogs each year. The clinical and molecular similarities between human and canine OS make dogs a valuable resource for studying the human disease.

Increasingly, computational tools are available to map orthologous genes between species in support of comparative genomics research. Large sections of genes that are grouped together in dogs are often dispersed and/or rearranged in humans. For example, the proto-oncogene *MYC* is located on chromosome 13 in dogs and chromosome 8 in humans. Because human OS samples are limited, comprehensive studies are challenging. A comparative approach using pet dogs with OS can enable the discovery and validation of both predictive biomarkers and novel therapies in clinical trials, which can then inform human research and clinical practice.

Building on these findings, the CCR's Comparative Oncology Program (COP) has created a unique repository of OS tumor samples and data from over 400 dogs with naturally occurring OS. We at the LeBlanc lab have leveraged this resource to develop a genomic dataset from this one-of-a-kind, outcome-linked biobank. Analysis of the canine tumor genomes discovered new insights associated with amplification of a specific segment on canine chromosome 13, encompassing approximately 80 genes. Interestingly, many of these genes are also found dispersed across human chromosomes 4 and 8. Notably, we observed that *MYC* amplification serves as a poor prognostic indicator and is linked to alterations in genes involved in DNA damage repair, metabolism, and the cell cycle in pet dogs. *MYC* amplification is also under investigation as a prognostic factor in human OS, further strengthening the dog as a patient model for humans.

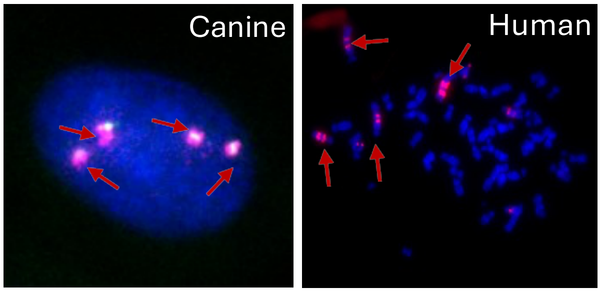


Figure. *MYC* gene locus amplification in canine (MC-KOS) and human (MG63.3) OS cell lines.

The COP has gone on to create a "bench-to-clinic" strategy to validate various gene variations from our canine OS biobank, with an initial focus on *MYC* amplification. Using both Fluorescence *In Situ* Hybridization and Droplet Digital PCR techniques, we are developing diagnostic methods to detect genomic abnormalities not only within the tumor itself but also in adjacent tissue, areas that might be missed during initial biopsy examination. Our goal is to deploy these techniques in patient-derived materials such as diagnostic tissue biopsies collected during clinical care, to provide improved patient stratification and facilitate matching to targeted therapies.

These findings pave the way for further exploration of new druggable genes in human OS, with the potential to improve prognostic assessments and guide the development of new therapies.

Using Cas9 to Decode Immune Therapies in Head and Neck Cancer

Seth Niemann, B.S.

Surgical Oncology Program

Head and neck cancer remain a significant global health burden. Despite advances in surgery, chemotherapy, and radiotherapy, many patients' diseases become recurrent or metastatic. This has driven research in alternative treatments such as immunotherapies.

The immune therapy with the most clinical success has been immune checkpoint blockade inhibitors (ICBI). ICBIs target inhibitory pathways that cancer cells exploit to evade immune destruction, enabling T cells to recognize and eliminate malignant cells. Compared to conventional chemotherapy, ICBIs can extend survival while reducing adverse side effects like fatigue or nausea. However, only a small subset of patients responds to the treatment, and the factors driving sensitivity remain unclear. Identifying genetic and molecular predictors will be key to refining patient selection and developing targeted combination therapies. No reliable model exists to study how oncogenic drivers influence immune responses, hindering the development of more precise immunotherapies.

To address this issue, the Nguyen Lab has generated two murine oral squamous cell carcinoma (mCas9-OSCC) lines that have been engineered to stably express Cas9. Preliminary injections of the cells into immunocompetent mice have shown that the cells grow reliably and that they metastasize to the lungs. There is currently an absence of metastatic murine oral squamous cell carcinomas with gene editing capabilities, so this opens an avenue for pre-clinical investigation of metastatic head and neck cancer.

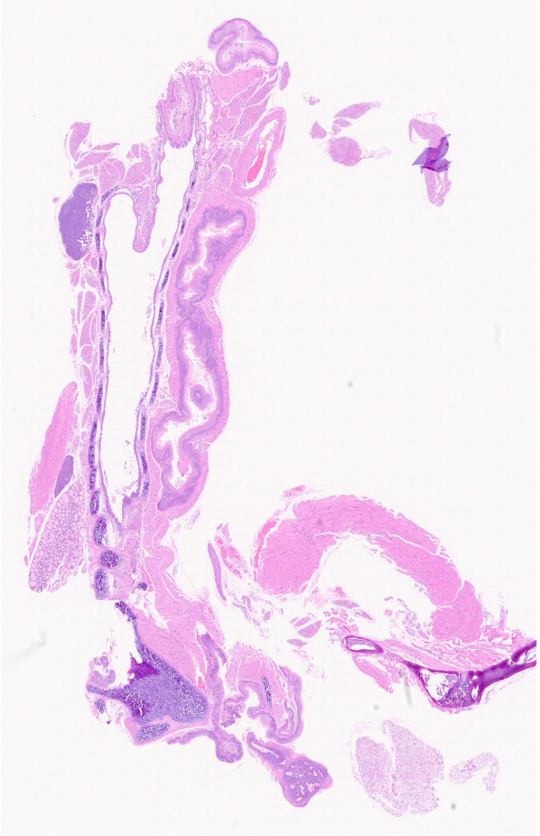


Figure. Murine oral squamous cell carcinoma from mCas9-OSCC injection showing viability to grow in an immune competent mouse model.

These new tools and immunocompetent mouse models enable researchers to investigate immune evasion mechanisms that parallel human disease and accelerate the discovery of oncogenic targets. To assess these mechanisms and identify opportunities for synthetic lethality, iterative deletions of candidate genes could be made by Cas9, followed by injection of the altered mCas9-OSCC cell lines into the flank or tongue of immunocompetent mice. Then, the immunotherapy response could be quantified.

To derive the two cell lines, genetically engineered C57BL/6 mice expressing Cas9 were exposed to 4NQO, a tobacco-mimetic carcinogen, to induce oral tumors. Tumors were isolated after the disease developed, enzymatically dissociated, and cultured. Following expansion, epithelial tumor cells were enriched by EpCAM selection. These cells reliably formed tumors when transplanted into immunocompetent mice, and tumor identity was confirmed by histological staining. The cell lines were further characterized using whole-genome sequencing, methylation profiling, and proliferation and migration assays. Additional characterization assays like RNA bulk sequencing, metastasis profiling, and flow experiments will be conducted in the next fiscal year to prepare for publication.

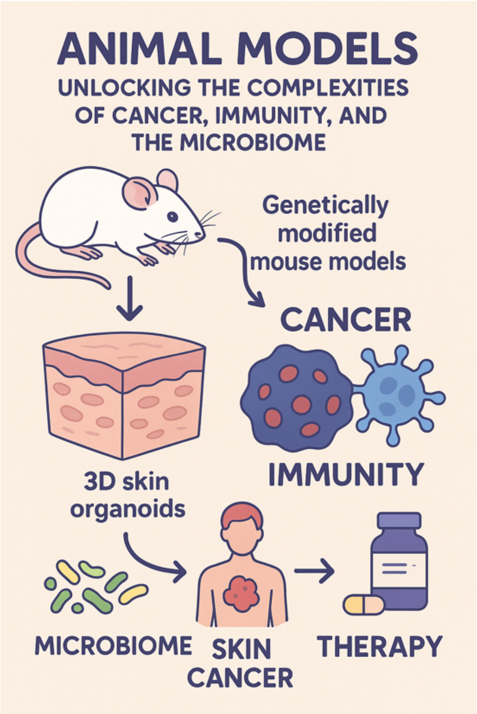
These mCas9-OSCC cell lines empower precise gene editing to reveal how specific genetic changes shape immune responses and therapy outcomes *in vivo*. By inducing targeted mutations and testing immunotherapy in immunocompetent mice, these models have the potential to illuminate pathways that drive resistance or sensitivity, critical knowledge for guiding new drug development and preclinical studies. Such insights unlock more personalized strategies, driving progress for patients whose head and neck cancers resist current ICBI therapies.

Animal Models: Unlocking the Complexities of Cancer, Immunity, and the Microbiome

Amit Singh, Ph.D.

Cancer Innovation Laboratory

Cancer is far more than uncontrolled cell growth. It is a dynamic ecosystem where tumor cells, immune cells, and microbial communities continuously interact. To understand this complexity, researchers need experimental systems that mimic the physiology of an intact organism. This is why animal models remain indispensable in biomedical research, especially for uncovering mechanisms that cannot be replicated in standard cell culture.



In the Inflammation and Tumorigenesis Section at the National Cancer Institute, our work centers on IKKα, a key signaling protein involved in skin development, inflammation, and cancer. Using advanced genetic mouse models, including conditional knockouts, kinase-inactive knockins, and transgenic overexpression lines, we investigate how IKKα shapes normal tissue homeostasis and contributes to disease. These models provide powerful insight into physiological interactions that lie beyond the reach of conventional in vitro systems.

Between traditional cell culture and whole-animal studies is an important intermediate tool: mouse 3D skin organoids. These miniature tissues mimic many aspects of human skin, allowing us to study tumor initiation, inflammatory pathways, and epithelial–microbial interactions with precision. While organoids offer scalability and experimental control, they cannot reproduce the full immune, vascular, and microbial complexity found in living organisms. This is where animal models remain unparalleled.

Our research uses this integrated approach to probe how the immune system and microbiome influence squamous cell carcinoma (SCC), one of the most common epithelial cancers. We found that SCC is consistently associated with reduced IKKα expression, not only in the skin but also in cancers of the esophagus, lung, and head and neck, highlighting its broad relevance to human malignancies.

To examine how microbial signals contribute to tumorigenesis, we studied IkkaΔKC/+; Tlr4–/– mice, which showed a striking increase in SCC development. Tumors from these mice lost the remaining wild-type Ikka allele, supporting a two-hit mechanism of tumor initiation. Microbial profiling revealed elevated bacterial load, particularly Gram-positive Firmicutes. When 3D skin organoids were exposed to tumor-associated microbiota, they developed increased DNA damage, higher IL-1β expression, and altered lipid metabolism. These effects were dramatically reduced in Il4R–/– organoids, and notably, IkkaΔKC/+; Il4R–/– mice were completely resistant to SCC. Antibiotic treatment further suppressed tumor formation, demonstrating that the microbiota plays a functional and necessary role.

Beyond the skin, the gut microbiome adds another layer of complexity. Using germ-free and antibiotic-treated mice, we have shown that microbial communities can regulate antitumor immunity, influencing T cell infiltration and overall immune tone within tumors. This work opens the door to therapeutic strategies that pair immunotherapy with targeted microbiome modulation.

Animal models are equally essential for preclinical therapy testing. Before new cancer treatments reach patients, they must be evaluated for efficacy, toxicity, and effects on immunity in a whole-organism context. Mouse models provide a rigorous and reliable platform for this critical step.

By integrating genetic mouse models, organoid systems, and microbiome research, we bridge the gap between molecular mechanisms and clinical translation. This combined approach reflects years of collaborative work and underscores why animal models remain central to advancing human health. With each study, we move closer to developing therapies that improve survival and quality of life for patients facing cancer.

Announcements

Editorial Resource for Fellows

The **NIH Fellows Editorial Board (FEB)** is an all-volunteer board composed of NIH fellows that edits various scientific documents such as manuscripts, book chapters, and grant proposals for grammar, form, and clarity. We review essential elements pertinent to the document, such as figures and figure legends, but do not consider scientific merit. Authors generally receive written feedback in 10 business days. This free service is open to all NIH and FDA fellows (postbac, predoctoral, postdoctoral, research, and clinical).

For more information, check out the FEB website or by e-mail at ncieditors@mail.nih.gov.

Join us for the 26th CCR-FYI Colloquium!

The CCR Fellows and Young Investigators (FYI) Association is excited to announce that registration is now open for the 26th CCR-FYI Colloquium: “The NIH Advantage: Enabling High-Risk, High-Reward Research for Long-Term Impact.” **The Colloquium will be held May 14th – 15th at the NCI Shady Grove Campus in Rockville, MD.**

All NCI fellows (including post-baccalaureate fellows, postdoctoral fellows, graduate students, clinical research fellows, research fellows, and volunteers) are encouraged to participate. Registration and abstract submission can be completed at https://events.cancer.gov/cct/fyi-colloquium.

The deadline for oral presentation abstracts is **February 23rd, 2026**. The deadline for poster-only abstract submissions is **April 1st, 2026.** Registration without an abstract will close on **May 1st, 2026.**

The CCR-FYI Colloquium is an exceptional opportunity for NCI fellows at all levels from all branches of the CCR to showcase their work, learn about some of the extraordinary ongoing cancer research from both intramural and extramural speakers, participate in various career development workshops, and interact with their peers. We welcome ALL research topics encompassing clinical, pre-clinical, and basic research and encourage all CCR fellows to attend and present their work in this safe environment.

For any questions, please contact the 2026 Colloquium co-chairs Ashlie Santaliz Casiano (santalizcasiaam@nih.gov) or Christine Brugger-Muli (christine.muli@nih.gov).

Interesting in writing for the Colloquium issue of the CCR-FYI Newsletter? Be on the lookout for a call for writers and editors in the month leading up to the Colloquium.