CANINE HEREDITARY CANCER CONSORTIUM

Forecasting Risk: Toward Genetically-Informed Clinical Trials in the Dog

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INTRODUCTION

Roughly half of all dogs will succumb to cancer. In many cases, these malignancies are thought to arise spontaneously, resulting from the stochastic processes that accompany aging. Disproportionate breed predilections, however, argue for a hereditary (germline) influence of certain cancer histologies in the dog. This observation suggests a research opportunity—to apply the latest methods of genetic mapping to identify regions in the dog genome that are significantly associated with greater cancer risk. If successful, these studies will lead to improvements in the way canine cancers are diagnosed and treated. Genetics also holds promiese for forecasting risk, identifying those dogs that are at greatest risk, with an eye toward early intervention and possibly even prevention.

BACKGROUND

Dogs and humans share nearly all of 23,000 genes, which comprise the mammalian genome. Generally there is a known one-to-one correspondence between human and canine genes, and this eases the transfer and translation of genetic knowledge between the two species. Over the past 20 years, canine genetics has benefited enormously from discoveries made first through human genetics. Genes found to cause or contribute to a disease state in human were quickly interrogated in the dog (candidate gene testing) to test for a similar contribution to a canine disease counterpart. The power of genetics within breed populations, where causal mutations are shared among affected dogs through common ancestry, is substantially greater than in human populations, where patients can have entirely distinct mutations contributing to the same disease. The power of canine genetics, matched now by the same genomic tools available to human geneticists, mean that gene discoveries can be made first in the dog, and then explored for similar influences in human patients.

TRANSLATION OF DISCOVERIES IN CANINE CANCER

The advantages of breed genetics hold promise for accelerating cancer research and driving forward advances in five distinct areas. Firstly, canine genetics can **implicate novel biochemical pathways** in cancer. Genetics is an unbiased approach; the geneticist is led by the disease to the root causes in the DNA. Thus there is the potential to identify new genes and the pathways within which those genes function. Secondly, genetics can be used to screen a large number of individuals to **identify dogs at greatest risk**, even prior to the onset of disease. Once identified, at-risk individuals can receive checkups earlier and more frequently to search for early signs of disease. Early intervention tends to improve clinical outcomes—early stage cancers respond more favorably to treatment. Thirdly, causal genes **reveal biomarkers of disease detectable in the blood**. By studying at-risk individuals through the period of risk (5-7 yrs for osteosarcoma, for instance), researchers can assay biochemical indicators to search for correlates of disease progression and outcome. Fourthly, the genetic knowledge gleaned from mapping cancer genes in the dog **suggest specific points of therapeutic interventions** that might be more efficacious and less toxic than currently applied treatments. A more comprehensive understanding of a patient's cancer allows clinicians to tailor treatments in a more precise manner. This 'personalized' ap-

proach will define the next decade of cancer treatment, both in human medicine and veterinary medicine. Ultimately, the personalized approach will transition from treatment to prevention. These innovative steps to change the landscape of cancer treatment can happen more readily in veterinary medicine, where the interaction between the clinician, the owner, and the research are less constrained bureaucratically. Finally, DNA tests will enable breeders to selectively reduce the frequency of contributing mutations, thereby improving the health of dogs in future generations.

Canine Hereditary Cancer Consortium

The Canine Hereditary Cancer Consortium (CHCC) is an unrivaled alliance of researchers, veterinarians, physicians, breeders, and owners who are working together to unravel the genetic factors that contribute to canine cancer. Academic researchers and clinicians from more than 20 institutions were awarded a two-year, multi-million dollar grant from the National Institutes of Health as part of the 'Grand Opportunity' research program. Research starts in the veterinary setting as owners voluntarily elect to submit biological samples (blood and tumor tissue) for analysis in the laboratory. The research is meant to end in the clinical setting as well, both veterinary and human, with refined diagnostics, improved biomarkers for personalizing treatments, and innovative therapeutics that initially improve treatment outcomes, and that ultimately may aid in prevention. The CHCC's first clinical trial, a feasibility study for precision medicine for canine cancer patients, is now underway. Subsequent clinical trials are now being planned. These upcoming trials will test for improved efficacy of treatment relative to the current standard-of-care. To our knowledge, these will be the first clinical trials that emphasize breed-specific predisposition for certain tumor types (e.g., osteosarcoma). Clinical benefits to canine patients are expected to help prioritize clinical trials in human medicine. This is especially important that many of the cancers that dogs suffer are either rare in human (e.g., hemangiosarcoma), or tend to be childhood cancers (i.e., pediatric osteosarcoma).

About The Author

Dr. Mark Neff is a classically trained geneticist. He earned his Ph.D. from the University of Virginia where he studied the cellular mechanisms that guard against cancer. He has more than 15 years of experience in canine genetics, beginning as a Human Genome Distinguished Postdoctoral Scholar at UC Berkeley in 1993. He worked with Dr. Jasper Rine on the first Dog Genome Project. Dr. Neff is now Director of the Program for Canine Health and Performance. This unique program is aligned across two different non-profit research agencies, the Van Andel Research Institute (VARI) in Grand Rapids (MI) and the Translational Genomics Research Institute (TGen) in Phoenix (AZ). In addition to directing the program, Dr. Neff also heads The Laboratory of Neurogenetics and Canine Behavior, and holds the position of Associate Professor at both VARI and TGen.

This research is made possible by the voluntary submission of blood samples from canine cancer patients. There is no cost to participate; blood draws can be reimbursed, and the costs of shipping can be billed to the recipient with FedEx. To enroll your dog in the study, please contact:

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