Metabolomics in dogs as a translational model of human disease: A pilot on lymphoma

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Summary. This project will combine world-leading expertise in biobanking at the Cornell College of Veterinary Medicine and omics-analysis at Weill Cornell Medicine. We will use metabolomics as an integrative biomarker readout for canine and human lymphoma. Metabolomics technology has produced novel insights for most major diseases, including new markers of disease progression and drug target identification. This pilot project will focus on B-cell lymphoma, due to the high prevalence of this disease in dogs, its known parallels to human disease, and the established expertise at both campuses. We propose to generate and analyze blood metabolomics data from canine biospecimens and compare the derived metabolic signatures to existing human data. The preliminary data generated here are expected to lead to an R01/U01 format NIH grant application. Importantly, the paradigm of parallel animal/human metabolic pathways that we want to establish here could be extended to other cancers or to neurodegenerative diseases, such as Alzheimer's, in the future.

Castelhano, Cornell Veterinary Biobank. Dogs serve as an ideal translational model, as they share the environment with their human counterparts, have a shorter lifespan (making it easier to obtain biospecimens and data throughout their life), and share the spontaneous occurrence of many diseases that are seen in human populations. The dog biospecimens for the proposed project will be collected and processed by the Cornell Veterinary Biobank (CVB), a core resource at the Cornell College of Veterinary Medicine. Dr. Castelhano is the Director of the CVB, and has 14 years of experience in biobanking, particularly in the standardized collection, processing, storage, quality testing, analysis, and distribution of biospecimens and associated data. Dr. Castelhano represents the US position in biobanking as an International Organization for Standardization (ISO) expert and delegate, for technical committee (ISO/TC) 276 – Biotechnology, and has assisted in the development of the first ISO standard for biobanks (ISO 20387: General Requirements for Biobanking). In April 2019, she led the CVB through third party conformity assessment to become the first biobank in the world to receive accreditation to this standard. Dr. Castelhano has experience in translating clinical findings into research innovations using genomic tools for several spontaneous models of human disease, such as the dog, the cat, and the horse.

Krumsiek, Metabolomics, Weill Cornell Medicine. Metabolomics provides an integrated, functional readout reaching beyond the information covered by genetic technologies. Importantly, metabolites are widely transported through the blood system, making metabolomics technology an ideal readout for liquid biopsy samples. Dr. Krumsiek has over 10 years of experience in developing computational methods for metabolomics data. He has worked on various clinical outcomes, including diabetes, asthma, Alzheimer's disease, and cancer. A special focus lies on methods for inferring biochemical pathways from large-scale omics data, as well as biomarker discovery through machine learning methods. In cancer research, he recently described a compensatory upregulation of the choline pathway upon administration of the HDACi 'panobinostat' in diffuse

large B-cell lymphoma (DLBCL). Targeting this escape mechanism led to a synergistic reduction of tumor growth in cell lines and was further validated in a mouse xenograft model.

Synergies between Research Groups. This project will optimally leverage the respective areas of expertise of PIs Krumsiek and Castelhano. PI Castelhano as a biobanking expert will provide easy access to high-quality, clinically annotated canine biospecimens. PI Krumsiek will then coordinate metabolomic measurements on these specimens and derive metabolic cancer signatures that can be directly compared to already-available human data. With both PIs' research programs generally funded and ongoing, the seed fund will provide the necessary kickstart to explore this new avenue of translational research, potentially benefiting canine and human patients alike in the future. We expect to make significant progress in a short amount of time, leading to an NIH grant proposal.

Proposed project. We propose to compare human and canine metabolomic cancer signatures of diffuse large B-cell lymphoma (DLBCL). DLBCL is the most common subtype of lymphoma in both humans and dogs. The disease has a similar clinical presentation, diagnostic features, and therapeutic approach in both species. Notably, DLBCL has a higher incidence rate in the dog (20-100 per 100,000 individuals, depending on dog breed, compared to 20 per 100,000 in humans). The similarities in disease presentation coupled with a shorter lifespan and faster disease progression in dogs enable timely assessments and comparisons between the human and canine cancer patients. We will here establish the common pathways of DLBCL-related blood metabolome changes between dogs and humans. Specifically, this will include both metabolic signatures of disease vs. normal as well as metabolic signatures of disease progression. These resulting signatures will then be compared across species. Human metabolomics data for 49 DLBCL patients and 24 healthy controls is already available in the Krumsiek lab, while dog metabolomics data will be generated for this project from 50 affected individuals and 50 matching controls by submitting plasma samples to Metabolon, Inc. Preliminary analysis of the human metabolomics data has shown a variety of highly significant changes between healthy and diseased individuals. After preprocessing and quality control of the raw canine metabolomics data, we will perform differential statistical analysis and pathway analysis between the two data sets to identify signatures of disease. Unraveling which pathways are similarly affected between human and canine patients, and which ones differ, will allow us to better establish the dog as an ideal translational model for accelerated metabolic biomarker discovery.