Personalized and Molecularly-derived medicine for cancer in dogs

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PERSONALIZED MEDICINE IN CANCER

WHY IS THIS A REVOLUTION IN HUMAN ONCOLOGY?
HOW THIS IS A NATURAL EXTENSION OF CARE IN VETERINARY ONCOLOGY?

Although highly similar in many ways, as articulated in the one health approach to medicine, there is a fundamental difference in the practice of veterinary medicine and human medicine, that coincidentally will allow a much easier adoption of personalized and precision medicine in the veterinary field, compared to the human field.

**What is the matter?** A simplification of this difference, recognizes that human medicine starts with the simple question for the patient of “what is the matter?”. This simple question then leads to an **algorithmic approach to medicine**, which will progressively move from validating and verification diagnostics, to standardized and expected steps leading to the delivery of a standard of care. This algorithmic approach is highly evidence-based, and therefore necessarily inflexible. Accordingly, a transition that defines therapeutic intervention on the basis of an individual (like personalized cancer medicine), does not neatly fit into a disease wide algorithm. Furthermore, this perceived large transition in medical practice, is often complicated by emotional reaction to terminology (i.e. the term personalized medicine), that seems to incorrectly suggest the algorithmic approach to be impersonal, hence the suggestion to consider” precision—medicine” as an alternative.

Distinct of this algorithmic approach to human medicine, is what I have described as a communicative approach to medicine, embraced fully by most veterinary clinicians. This communicative approach to medicine begins the distinct question of **what matters?** For many reasons, the question “what matters?” Requires thoughtful communication, and in my practice requires the answer to the following questions of my clients;

1. Is the goal of intervention (whether diagnostic or therapeutic) in your interest?
2. Are the risks of this intervention acceptable?
3. Are the costs of this intervention feasible?

If the response to these questions is affirmative, the option/intervention in question should be recommended and should be pursued within this communicative approach to medicine. If the outcome to any of these questions is negative, the clinician should be expected to present an alternative option.

Although time-consuming, not as consistently evidence-based, this communicative approach is by definition flexible, highly considerate of the patient/patient family needs and interests, and naturally accepting of a highly individualized or personalized delivery of care. For this reason our communicative approach to medicine, in the veterinary field, is more naturally amenable to the concept of personalized medicine and its implications. It is for these reasons that I believe personalized medicine receives much less opposition in the veterinary field. This provides a natural opportunity for veterinary medicine to take more rapid advantage of the promise of personalized medicine.

In this presentation, I will discuss the promise of personalized, i.e., molecularly derived personalized medicine in veterinary oncology, its current commercial availability for dogs with cancer, and the ongoing work to clarify how this innovative transition in the practice of medicine can help all of our patients.

**Foundations of Precision Medicine: The genetic basis of cancer**

Cancer is a genetic disease that arises as a consequence of the stepwise accumulation of disruptive mutations in genes that regulate cell life and death. Clonal expansion of cell populations bearing cancer gene mutations
fuels the formation of malignant tumors. This genetic model of cancer emerged in the latter 20th century as a product of advances in genetics, evolution, and cancer medicine. Through this mutational process, cancers acquire specific key properties including self-sufficient growth signaling, resistance to growth inhibitory signaling, invasion and metastasis, unlimited replication potential, angiogenic signaling, immune modulation, DNA instability, metabolic dysregulation, and immune evasion. The genetic model and its downstream phenotypes have since been validated in many cancer types and provide a framework for our growing genomic understanding of cancer.

**Precision Medicine (PMed) for human and canine oncology**

PMed is ushering in a new era in cancer therapy in which clinical and translational value are applied to advances in the genomic analysis of cancer. The discoveries and tools described above have provided new opportunities to tailor cancer therapy to the individual molecular characteristics of a specific cancer in a specific patient to guide diagnosis, prognosis, and treatment selection. In many cases, these genetic alterations can be matched to specific therapeutic agents as a means to uniquely improve outcomes for patients. Tumor samples and matched germline samples (from peripheral blood or cheek swabs) are collected, preserved, and then analyzed for genetic alterations in a core set of cancer genes which are ultimately matched to an individualized therapeutic recommendation.

**How Precision Medicine differs from the current practice of oncology**

The use of patient-specific information as a means to deliver precision medicine is not new to the treatment of cancer patients (see above for differences in human and veterinary medicine). In general, through the history of human medicine, treatments have been administered in a patient-specific and personalized manner. Even in the modern era, it is the use of molecular data to guide the therapy of specific individuals with cancer that is not entirely novel. The use of specific immunohistochemical or cytogenetic markers to guide diagnosis and prognosis has been a critical and routine practice in pathology laboratories for many decades. Further, in some cancers, tumor markers have been used to guide treatment selection as well. For example, in human breast cancer, it has been long-standing practice to define the expression of hormone receptors as a means to deliver specific therapeutics that alter downstream signaling pathways. More recently in veterinary medicine, our understanding of the clinical and biological importance of c-kit mutations, in canine mast cell tumors, has directed distinct therapeutic plans for patients with and without such mutations.

**Human cancer Precision Medicine**


Cancer medicine is ultimately aimed at the recommendation of the most effective treatment for an individual patient based on supporting scientific evidence. The use of a PMed approach to cancer diagnosis and therapy may deliver a variety of outcomes related to this goal:

1. Improved outcomes for patients with a specific cancer.
2. Improved outcomes for patients with cancers that are not effectively managed with conventional treatment approaches.
3. Data that would support the grouping of patients in clinical trials that is agnostic to histology (i.e. “basket study designs”).
4. Data that provides an accelerated alternative to conventional clinical trials of a specific therapy in a specific cancer (so-called. “accelerated reverse directional drug development”).
Although genomic data is expected to dramatically impact the above outcomes, genomic data have been slow to enter the clinic. One of the first pilot studies incorporating molecular profiling to guide therapy in advanced cancers was published by our collaborators in 2010:


This study faced considerable challenges, but found that 27% of 68 patients treated according to molecular profiling recommendations experienced a longer progression-free survival than during the most recent treatment on which they had progressed. Although perhaps intuitively beneficial to incorporate precise target identification into patient treatment, this approach still faces significant hurdles and it remains to be proven through prospective trials that treatment based on PMed outperforms physician’s choice of treatment. Now, multiple clinical trials incorporating genomics-guided therapy selection are underway to test this very hypothesis with some early results published recently. One such trial - the Stand Up To Cancer and Melanoma Research Alliance Dream Team Clinical Trial is assessing molecularly-guided therapy in non-V600 BRAF metastatic melanoma. This is now an ongoing randomized treatment study. The non-treatment pilot study is described here:


Returning clinically relevant and actionable information based on genomic analysis within a window that enables effective treatment selection is a substantial challenge. Notable hurdles include those associated with, tumor biopsy, sample preservation and transport, nucleic acid extraction and quality control, genomic sequencing infrastructure and platform, data analysis and integration, generation of digestible genomic reports for physicians, veterinarians and scientists alike, and conduct of tumor board review to provide a treatment recommendation. Additional hurdles to the implementation of Precision Medicine in the clinic include:

1. **Matching biological targets to drugs:** A hierarchy of molecular events. Many gene expression (RNA) signatures have been hypothesized to predict treatment response, however few such alterations have been validated in clinical studies. As such, the simple expression of a cancer gene or its associated protein is not necessarily sufficient to be considered a highly valuable target in the biology or therapy of that cancer. Conversely, we believe that mutations in DNA that comprise the fundamental reducible phenomena behind oncogene activation or tumor suppressor inactivation are often the gold standard for predictive capacity.

2. **Discrimination of driver versus passenger mutations.** Even though cancer is a fundamentally genetic disease driven by mutations in cancer genes, not all mutations contribute to cancer fitness (i.e. not all mutations are cancer “drivers”). Many mutations are “passenger” mutations. They occur as collateral damage of normal replicative processes and/or mutational processes in cancer cells, but do not directly contribute to the growth phenotype. It is not always straightforward to identify the functional impact of a specific mutation, particularly if that mutation has not been previously extensively characterized. Therefore driver/passenger discrimination remains a key challenge for individualized genomic analysis.

3. **Context may influence the role of a driver.** In keeping with the above observation, driver mutations may have variable clinical relevance depending on the presence or absence of other mutations. For example, activating mutations in the *BRAF* oncogene are common in both melanoma and colorectal cancer. In melanoma, these mutations confer sensitivity to selective *BRAF* inhibitors. However, colorectal cancer has proven to be resistant to such drugs due to the presence of concomitant activation of genes upstream of *BRAF*. Mutation status of single genes has not always proven to be predictive across cancer types in diverse mutational backgrounds.

4. **Drug matching rules, evidence, report generation, and molecular tumor boards.** The above considerations all factor into the daunting task of cataloguing rules for matching drugs to specific
aberrations based on various levels of evidence from preclinical and clinical literature. Evidence levels range from direct evidence of a positive predictive biomarker in prospective randomized clinical trials to laboratory experiments assessing molecular alterations and drug sensitivity in cell lines or animal models. An actively curated, literature-linked drug rule database must be created, maintained, and intersected with genomic reports. Ultimately, these reports must be automated, precise, and comprehensive enough to enable an expert team of clinicians and scientists to interpret, discuss, and reach consensus on a treatment recommendation. The molecular tumor board thereby necessitates a high degree of art, interpretation, and expertise.

An ever-growing array of tests designed to inform diagnostic and treatment decisions in the human clinic is available from more than 100 academic and 50 commercial laboratories. These tests range in scope from single genes to gene panels, exomes, and even whole genomes. In everyday clinical practice, cost is still prohibitive and the expertise and infrastructure that are required to bring them to bear on patient care are also largely lacking. Finally, more comprehensive data showing improvements in genomics-correlated clinical outcomes is needed to support the use of these tests and of off-label drug use.

The path to PMed for canine cancer patients
Although much work remains to be done to chart the genomic landscapes of canine cancers, the precision medicine approach is nonetheless poised to make a dramatic impact on the care of canine cancer patients. Indeed, we have published on the clinical feasibility of this approach in dogs:

Khanna and Colleagues., *Prospective molecular profiling of canine cancers provides a clinically relevant comparative model for evaluating personalized medicine (PMed) trials.* PLoSOne. 2014 Mar 17;9(3)e90028.

Precision medicine now represents a cutting edge opportunity in veterinary cancer care. In fact, not only would this approach make great headway in the care of canine cancer patients, but given the unique aspects of naturally occurring cancer in pet dogs and the forwar-thinking perspectives of the veterinary profession on the whole may be able to provide key data validating this model and refining its implementation for human medicine.

Changing outcome for canine Hemangiosarcoma using PMed.
As a means to change the biology of an important canine cancer problem, we have initiated a research agenda that will deliver personalized medicine for the canine cancer hemangiosarcoma through clinical trials that are planned to be launched in July 2017.

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