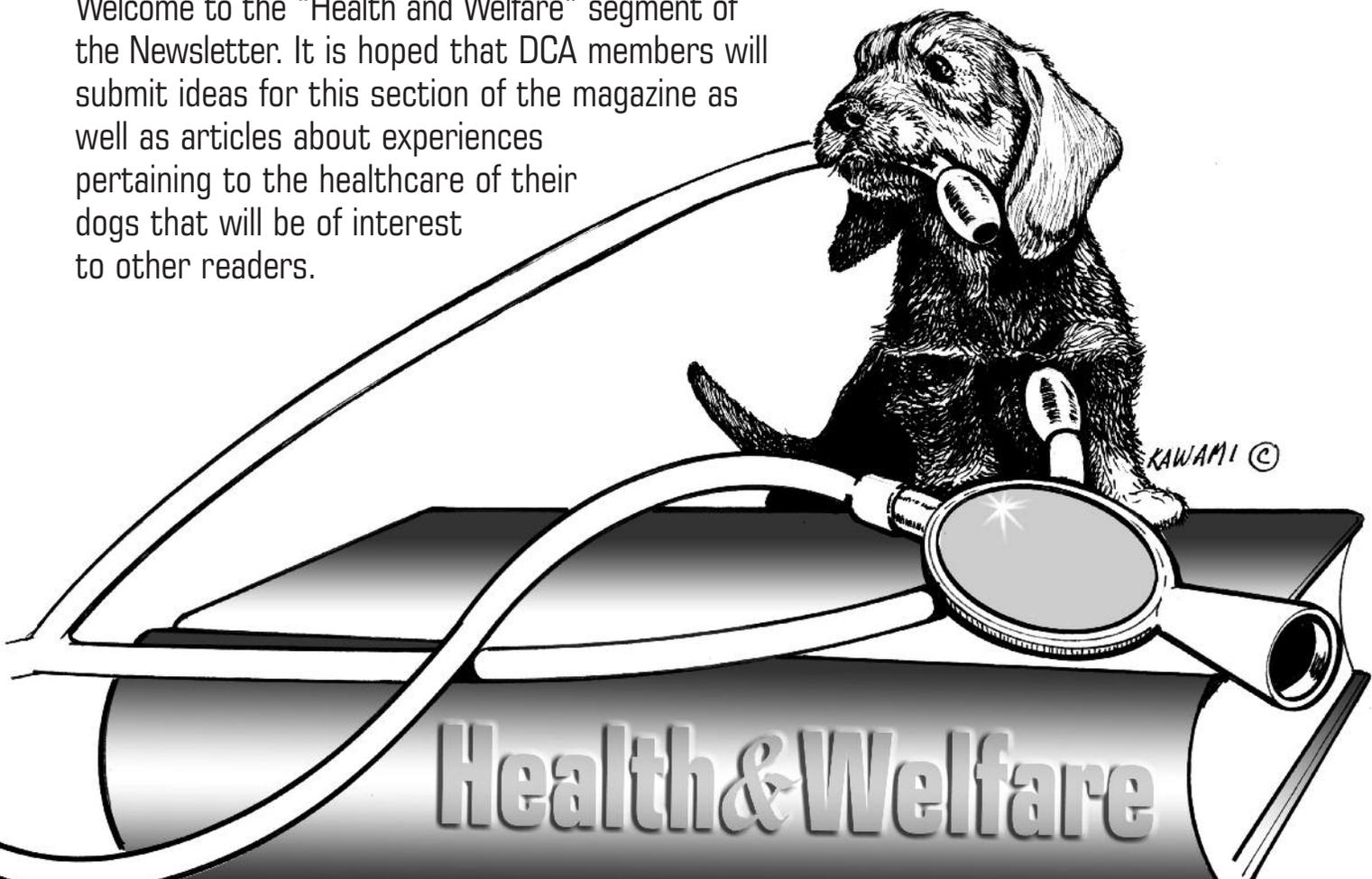


Welcome to the "Health and Welfare" segment of the Newsletter. It is hoped that DCA members will submit ideas for this section of the magazine as well as articles about experiences pertaining to the healthcare of their dogs that will be of interest to other readers.



Please send ideas, suggestions and articles to: Charlotte Borghardt, DCA Health & Welfare Committee, P.O. Box 1126, Sierra Vista, AZ 85636-1126, teckelhofaz@yahoo.com

# Cancer Stem Cells

*A New Way to Look at an Old Disease*

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## Cancer and Public Health

Undoubtedly, cancer is among the conditions that will have the most significant impact on the health and well being of people and their pets during the 21st century. The entity that is cancer has been recognized since the times of the ancient Greeks, but it was only the latter part of the 20th century that we began to understand why cancer happens. As the art and science of medicine and veterinary medicine reduced morbidity and mortality from other causes and

the expected lifespan increased, cancer became more prevalent in the human and canine populations. Today, cancer is the leading cause of death in people under the age of 85, and it is the most common cause of disease-related death in dogs. It is estimated that 30% of people and dogs will get cancer in their lifetime and in dogs, more than half of those affected will die from their disease.

Despite these grim statistics, we cannot ignore advances that we have achieved in diagnosis and treatment of cancer. With proper standard of care, cancer patients can reasonably expect to add at least 10% of a

lifetime after their diagnosis and many patients survive cancer and lead normal productive and healthy lives. Because cures are difficult to define, the treatment goal today is to make cancer a manageable chronic disease.

Improved application of existing therapies (surgery, chemotherapy and radiation) as well as new therapies coming on line can achieve this for a large number of patients. However, sometimes the price is too high – either because the side effects are unacceptable or because the treatment is cost prohibitive. Both of these are greater obstacles in veterinary medicine, where quality of life is paramount and where health care reimbursements from insurance are not the norm. It is this segment of the population, then, that most preoccupies us and fuels our desire to continue probing the inner workings of cancer so that we can realistically design better strategies to prevent, diagnose and treat this condition.

## Cancer as a Disease of Stem Cells

With that background, we can appreciate the importance of thinking outside the box. What if we ask questions about why we fail so often, as opposed to trying incrementally build small gains? It is



this type of thinking that has led to a revised theory about the origins of cancer that may revolutionize how we approach this disease.

For over 40 years, we have known that cancers arise from the single cell (clonal expansion) and that a series of mutations are necessary for the cell of origin to acquire the malignant phenotype. However, the dominant theory assumed that all cells possessed an equal capacity for self-renewal. It also assumed that proliferation was a stochastic (“random”) process driven entirely by environmental selection of favorable mutations. However, self-renewal and differentiation potential are the key elements that define what a stem cell is. So a competing theory now exists whose main tenet is that cancer is a consequence of malignant transformation of cells that retain properties of stem cells, but harbor defined mutations that endow them with malignant properties. It is not entirely a different concept, but simply a different way of looking at the same data, and it is intellectually satisfying because it explains much about cancer that was difficult to reconcile with the old models.

## What is a Cancer Stem Cell?

The first and most important thing to note is that normal stem cells, such as those harvested for regenerative therapies are not the same as cancer stem cells. The American Association for Cancer Research (AACR) convened a workshop in February 2006 to achieve a consensus definition of a cancer stem cell. Based on that workshop, the consensus definition was “a cell within a tumor that possess the capacity to self-renew and to cause heterogeneous lineages of cancer cells that comprise the tumor.” For this reason, it is important to define cancer stem cells based on their ability to recapitulate a continuously growing tumor. In essence, this means a tumor that can be serially passaged in vivo (in a laboratory mouse) by one (or very few) cell (s), and thus the term in its strictest definition is synonymous with “tumor-initiating cell” or “tumorigenic cell”. The term “cancer stem cell” is somewhat unfortunate as it can easily be interpreted to mean that such cells derive from stem cells of the corresponding tissue. In fact, the cancer stem cells may indeed arise from normal stem cells by mutations that make them cancerous, but this may not be the case in all tumors. That is, it is possible that more differentiated cells can acquire the capacity for self-renewal and become immortalized through multiple mutations, so it is this differentiated cell and

not the tissue stem cell, that eventually evolves to become a full-blown cancer stem cell.

It is important to note that proliferation is not the same as self-renewal. A self-renewing cell division results in one or both daughter cells (progeny) that have essentially the same ability to replicate and generate differentiated cell lineages as the progenitor cell. Stem cells can undergo symmetrical self-renewing capacity, or asymmetrical self-renewing division, resulting in one stem cell and one more differentiated cell that can continue along a defined lineage or lineages. It also is possible that some stem cells may divide symmetrically to form two progenitor cells leading to stem cell depletion. Promoting this latter form of division would be a way to deplete the cancer stem cell population by differentiation and may hence constitute an alternative strategy to inducing cell death to treat cancer.

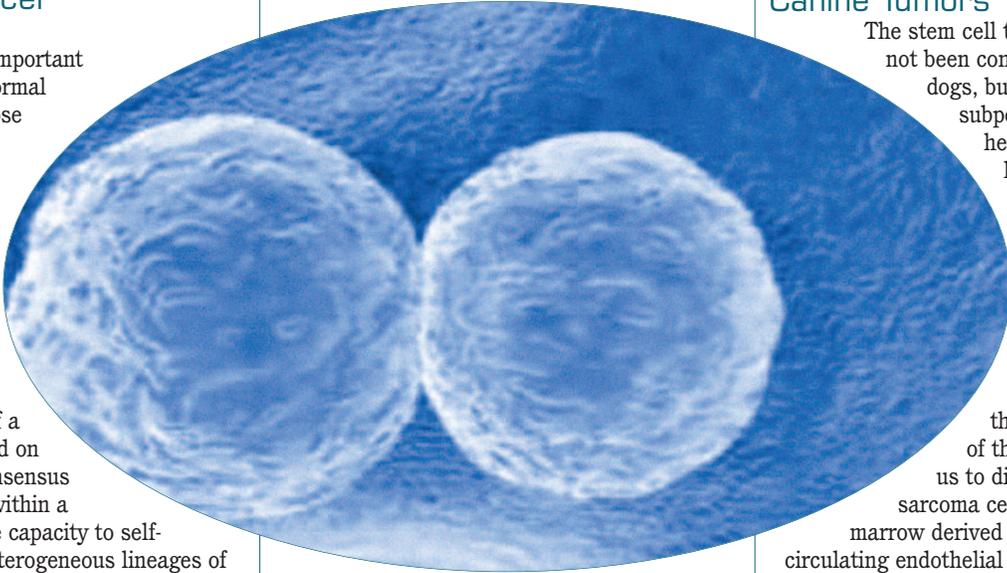
## Do Cancer Stem Cells Really Exist?

The existence of cancer stem cells is now documented; they are characterized by peculiar phenotypes, by defined sets of genetic

reproductive age and attain long lines without cancer, and perhaps most importantly, for the observed nature of tumor relapse and metastasis. Cancer stem cells divide infrequently and are thus resistant to most of the types of treatments we use for cancer (which rely on killing rapidly dividing cells). Even though they divide rarely, cancer stem cells have the potential to regenerate the full complement of progeny that originally comprised the tumor. Thus, failure to eliminate cancer stem cells with – or after cessation of – chemotherapy sets the stage for tumor re-growth and relapse, which would not occur if the surviving cells lacked capacity for self-renewal. The acquisition of additional mutations, possibly due to the therapy itself, allows the remaining cancer stem cells to generate new progeny with enhanced survivability in novel environments, favoring aggressive, metastatic phenotypes. This suggests that, in order to achieve sustained remissions, we will need to devise treatment regimens that target the cancer stem cell compartment.

## Cancer Stem cells and Canine Tumors

The stem cell theory of cancer has not been conclusively proven in dogs, but we have seen subpopulations of cells in hemangiosarcoma and lymphoma that have phenotypes consistent with stem cell origin. For hemangio-sarcoma, we extended these observations to define a phenotype that firmly established the bone marrow origin of this tumor, and allowed us to distinguish hemangio-sarcoma cells from other bone-marrow derived cells and from normal circulating endothelial cells. This led to the development of a useful diagnostic test for hemangiosarcoma. More recently, we have shown that the tumors harbor specific subpopulations that retain the “primitive” (stem cell –like) characteristics and may harbor unique gene expression signatures. In fact, the relative frequency of these cells may explain the observed differences in the clinical behavior of these tumors. Our current work focuses on defining these cancer stem cell populations and their usefulness to predict responses to standard of care, as well as to identify new treatments to effectively target these cells. The premise that appropriate activation of the immune system might be able to eliminate both the cancer stem cells and their progeny is among the concepts that we plan to explore in an ongoing clinical trial for osteosarcoma that is supported jointly by the NCI and the AKC CHF. ❄️



mutations, and by their ability to form tumors that can be serially passaged in laboratory animals. In the case of lymphoma or leukemia, over 1 in 250,000 tumor cells has the properties that define a cancer stem cell. Similar results have been obtained for a variety of solid tumors, although much work remains to be done to define the “cancer stem cell” of many types of cancer.

## Clinical Implications of Cancer Stem Cells

The cancer stem cell model can explain various paradoxical findings regarding tumors and their natural history. It accounts for the relatively small numbers of genes that are disproportionately associated with a multitude of cancers, for the ability of multicellular organisms (like people and dogs) to reach