ELSEVIER

Seminars in
NUCLEAR
MEDICINE

Perspectives in Molecular Imaging Through Translational Research, Human Medicine, and Veterinary Medicine

Clifford R. Berry, DVM, DACVR,* and Predeep Garg, PhD†

The concept of molecular imaging has taken off over the past 15 years to the point of the renaming of the Society of Nuclear Medicine (Society of Nuclear Medicine and Molecular Imaging) and Journals (*European Journal of Nuclear Medicine and Molecular Imaging*) and offering of medical fellowships specific to this area of study. Molecular imaging has always been at the core of functional imaging related to nuclear medicine. Even before the phrase molecular imaging came into vogue, radionuclides and radiopharmaceuticals were developed that targeted select physiological processes, proteins, receptor analogs, antibody-antigen interactions, metabolites and specific metabolic pathways. In addition, with the advent of genomic imaging, targeted genomic therapy, and theranostics, a number of novel radiopharmaceuticals for the detection and therapy of specific tumor types based on unique biological and cellular properties of the tumor itself have been realized. However, molecular imaging and therapeutics as well as the concept of theranostics are yet to be fully realized. The purpose of this review article is to present an overview of the translational approaches to targeted molecular imaging with application to some naturally occurring animal models of human disease.

Semin Nucl Med 44:66-75

The advancement of nuclear medicine in veterinary medicine has paralleled most of the usage in humans, except in the area of myocardial imaging, as myocardial infarction secondary to primary atherosclerosis is a rare event in veterinary patients, particularly dogs and cats. However, planar scintigraphy (bone, renal, and thyroid scans) has remained a clinical tool used in a variety of orthopedic, renal, and thyroid disorders in veterinary patients.[1] As PET has become a primary diagnostic technique and an accepted method for the evaluation of the human oncology patient, it seems that planar imaging has become a secondary player.[2,3] Due to the costs involved in equipment, personnel, and infrastructure, PET, PET/CT, cyclotrons, and other PET techniques have not become a widespread primary imaging modality in veterinary medicine.[4]

However, translational medicine and the concept of "one health" amalgamation has provided a forum for continued research in the area of spontaneous disease in veterinary patients as it relates to human disease. Although these terms have a variety of meanings depending on context, the current environment provides for the exploration of spontaneous diseases in animals.[5] Starting with some basic definitions, translational medicine would be considered the science of taking the basic bench research to the patient and back. The bigger picture of translational medicine implies an interdisciplinary approach for understanding the pathobiology of a disease process based on the current understanding of the physiology of the cells involved (host's normal and abnormal cells) and how to then target specific therapies to these processes so that health can be restored to the affected individual. In the concept of one health or one medicine, we have purposefully used the term "amalgamation" to solidify the concept of union and unification between human and veterinary medicine.[5] There are definitely differences. However, there are strong similarities in many of the spontaneous diseases and specific tumor types that occur in animals and their human counterparts.[6]

*Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL.
†Department of Radiology, School of Medicine, Wake Forest University, Winston-Salem, NC.
Address reprint requests to Clifford R. Berry, DVM, DACVR, Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, 2015 SW 16th Ave., Gainesville, FL 32610. E-mail: berryk@UFL.edu

0001-2998/14/$-see front matter
http://dx.doi.org/10.1053/j.semnuclmed.2013.10.002

Certain animal vectors (bird species in particular) have been used as early indicators of new viral strains; whereas other diseases, specifically tumors, have been shown to be models of human tumors, such as canine osteosarcoma of the appendicular skeleton.[6] The purpose of this review article is to look at radiopharmaceutical and other molecular imaging techniques that have been used for the evaluation of human and veterinary patients in a research or clinical context. Three areas that are discussed include a historical overview, current concepts of targeted imaging and therapy, and finally, an overview of spontaneously occurring animal models of human disease.

Historical Survey and Antibody Imaging

Early nuclear medicine studies focused on spontaneous canine tumors[6] and uptake of amino acids using N-13 as the radionuclide.[7] Although a small number of dogs were used in this study, a wide variety of tumor types had an affinity for active accumulation (and presumed incorporation) of the radiolabeled amino acid L-glutamate for active protein synthesis in a hypermetabolic tumor.[7]

The search for an ideal imaging agent for a specific tumor type initially led to the use of monoclonal antibodies and antibody fragments. The early techniques for antibody formation described in 1975 provided the groundwork for antibody development and labeling.[8] Tumor-associated antigens became an immediate antibody-antigen target that resulted in the development of a number of radiolabeled antibodies, Fab and $F(ab')_2$, diabodies, and single-chain variable fragments.[9] Although antibodies have the ability for selective binding and the potential for a high sensitivity and specificity for specific tumor protein (typically located at the level of the cell membrane), cell receptor, or other form of antigen, their utilization has been limited because of slow blood pool clearance, long retention in normal tissues, nonspecific binding to a number of different tumor-associated antigens found in normal tissues, and the complex process of labeling and isolation before patient injection.[9] In addition, intratumoral factors related to antibody-labeled radionuclide delivery include blood supply, tumor type, cellular microenvironment, and target antigen specificity with antigen expression levels associated with the tumor cells (cell membrane antigen turnover). Over time, other tumor proteins (peptides), small molecular ligands and synthetic graft copolymers have been developed and utilized.[9] A number of Food and Drug Administration–approved IgG antibodies and Fab and $F(ab')_2$ radiopharmaceuticals are available for current use as primary radiopharmaceuticals for tumor identification, as well as diabodies and single-chain variable fragments using ^{99m}Tc, ^{111}In, and ^{123}I as the radionuclides for single-photon emission computed tomography imaging are in preclinical trials pending approval by the Food and Drug Administration.[9] In the case of PET radiolabeled antibody imaging, ^{18}F is not an ideal radionuclide because of its short physical half-life; however, other radionuclides of importance for antibody conjugation could include ^{68}Ga, ^{124}I, ^{64}Cu, and ^{89}Zr.

In veterinary medicine, one of the first antibody-labeled techniques developed was used for the noninvasive imaging diagnosis of active heartworm infestation (*Dirofiliaria immitis*) in dogs.[10] In this study, a monoclonal antibody was successfully labeled using a diethylenetriaminepentaacetic acid chelation technique. However, this technique and the Fab or $F(ab')_2$ follow-up studies were not developed into a routine imaging application although this early research cleared the way for development of blood kits used today for plasma detection of canine heartworm antigen. In later studies, nonspecific immunoglobulin accumulation was evaluated in a viral arthritis goat model.[11] Nonspecific radiolabeled leukocyte imaging has also used for imaging the feline pancreas and detecting pancreatitis in cats.[12,13] Going one step further, other clinical applications of nonspecific inflammatory techniques for imaging in small animals have included ^{111}In-labeled transferrin for imaging protein-losing enteropathies in dogs as well as ^{111}In-chloride, which was used in the evaluation of a canine osteomyelitis model.[14,15]

A number of dog models have been used for antibody labels using planar and single-photon emission computed tomography scintigraphy as well as PET imaging. For myocardial imaging, an instant kit method for Fab ′-labeled ^{99m}Tc was developed and tested in variety of clinical and research applications.[16] Dogs with experimentally induced myocardial infarctions were imaged and showed equivalent levels of uptake compared with ^{111}In-antimyosin at the area of infarction. At the same time, ^{18}F-labeled antimyosin monoclonal antibody fragments had active accumulation and uptake was seen in areas of damaged myocardium and ischemia with specific accumulation in a subendocardial position; however, owing to the sustained blood pool radioactivity, subtraction techniques using (^{15}O) carbon monoxide were suggested by the authors.[17] A sympathetic analog PET tracer was also developed that was tested in a canine myocardial arterial occlusion model where it was shown that (^{18}F)-parafluorobenzyl guanidine uptake was delayed even after myocardial perfusion (imaged using $^{13}NH_3$) was reestablished.[18]

Fab fragment labeled with ^{18}F was used in a group of dogs with naturally occurring osteosarcoma, a model for human appendicular skeletal osteosarcoma.[19] In this study, ^{18}F-labeled Fab fragment of TP-3, a monoclonal antibody for human and canine osteosarcoma, had a biphasic blood clearance with a short half time and rapid radiopharmaceutical uptake in the primary osteogenic sarcoma site; 3 dogs with metastatic disease also had increased uptake. In a different study using ^{99m}Tc-methylene diphosphonate, the patterns of uptake in 25 dogs with spontaneously occurring osteogenic sarcoma showed that when there was a large tumor area and higher tumor radioactivity, the dogs were more likely to have early metastatic disease showing the predictive utility of bone scintigraphy.[20] In a similar recent human study, these data were affirmed when it was shown that high (^{18}F)-FDG maximum standardized uptake value numbers before and