Pre-Clinical Evaluation of New Radioindicators

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The opportunity to explore biochemical and physiological mechanisms in normal and diseased human subjects has been greatly advanced with the advent of PETT. Synthesizing and qualifying new compounds for use in patients is a time consuming and difficult task. The short half-life of ^{11}C, ^{15}O, ^{13}N, and ^{18}F poses challenges to the chemist. The low resolution (5–10 mm FWHM of the best in vivo imaging systems) precludes studies in the small animals ordinarily used in medical research. Screening of compounds in small animal models of disease is best approached using commercially available well characterized ^{14}C-, and ^{3}H- labeled compounds to establish biochemical pathways, disease correlations, and to validate mathematical models of metabolic systems. The selection of which compound to synthesize with short half-life β^+-emitters, can then be based upon the results of such preliminary studies. The next step that is of great importance is the development and testing of gamma-labeled tracers to establish simpler methods better suited to routine clinical practice.

The ARG methods make it possible to obtain high spatial resolution images of the biological distribution of radiolabeled compounds when the decay scheme of the nuclide includes charged particles as primary or secondary emissions. The use of dual and triple isotope images of the same specimen makes it possible to establish spatial and temporal patterns for one or more compounds in the same specimen and to correlate these with histopathologic changes. For example, ^{14}C-2DG can be compared to ^{18}F-2DG to validate the distribution of a new in-house synthesized ^{18}F-2DG; sequential studies can also be performed to establish effects of interventions made between the injection of ^{14}C-2DG and ^{18}F-2DG in animals sacrificed 30–45 minutes following the injection of ^{18}F-2DG in normal rats or animals with coronary artery lesions. Furthermore, the intactness of the long-lived labeled compound can be established using samples taken from selected regions in the ARG specimens or from larger samples from homologous regions taken from adjacent uncut portions of the tissue block.

A second common problem is the determination of the relative merits and mechanisms of localization of different gamma-labeled tracers. One such approach we are taking involves the use of high purity germanium (HPGe) detectors to count tissues removed from rodents with experimentally-induced diseased abscesses and tumors. A comparison of ^{67}Ga-citrate, ^{97}Ru-transferrin, and ^{111}In-neutrophils can be accomplished in the same animal based upon tissue counting techniques, using the high energy resolution of the HPGe detectors. The counting of blood samples taken prior to sacrifice permits a separation of contributions from the extracellular fluid (ECF), Plasma, and RBC spaces to the measured activity in the abscess region by the addition of ^{82}Br, ^{131}I Albumen,

and ^{99m}Tc-RBC to the injected mixture.

A further extension of this method can be accomplished by combining the multi-isotope study with assessment of physiological parameters characterizing the abscess (or tumor). This could be accomplished by injecting ^{18}F-2DG, 45 minutes prior to sacrifice along with the 6 previously tested tracers. ARG sections cut through the abscess, imaged onto film for several half lives of the ^{18}F-2DG would reveal the glucose metabolic gradients in the abscess. Samples taken from adjacent regions in the block can be counted to establish the fixed tissue versus ECF and circulating contributions. Further, the correlation of the radiopharmaceuticals used in clinical nuclear medicine (or proposed new compounds) can be correlated with the β^+-labeled compounds which usually are the most valid indicators of underlying mechanisms/processes involved in the disease under study. Such investigations, in animals seem appropriate and useful as part of the qualification of a new procedure for use in man.

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Invitation Lecture II

Receptor Specific Binding

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The greatest strength of Nuclear Medicine lies in its ability to detect and quantitate biologic function rather than fixed anatomical properties. In recent years the research emphasis has been toward not only those tracers that measure flow but also those tracers that measure biochemistry. The prime example of the latter has been the measurement of glucose metabolism using F-18 2-fluoro-2-deoxyglucose.

There are several classes of radiotracers that can be studied. Of these, receptor binding radiotracers are especially interesting in that changes in receptor concentration are thought to be related to certain disease states.

Because there are a limited number of receptors in the target organ, radiotracers must be prepared using no-carrier-added radionuclides and the product must be purified to obtain high effective specific activity. These requirements have added to the difficulty in producing appropriate radiotracers.

To date a number of receptor specific radiotracers have been prepared. Of these some have been validated as receptor specific radiotracers but few have been tested in humans. The most promising studies are those involving estrogen receptor binding radiotracers. These radiotracers have been used to determine qualitatively the presence or absence of receptor dependent disease. Other