Radiolabeled agents are being developed for TRT (Targeted Radionuclide Therapy). Included in the 50 to 200 nm scale of this project are liposomes, short segments of DNA or RNA, nanoparticles and proteins. Because of possibly multiple lesion sites, these radiopharmaceuticals (RPs) are usually given by IV injection. Targeting, which requires a number of hours to days to accomplish, is effected by various means. The simplest method is to have the agent pass out of the blood and into the tumor space using the fenestrations in tumor capillaries. Liposomes are one such example whose membranes are dissolved in the lesion so as to release vesicle contents. Among the most specific localization processes is protein binding to a molecular marker on - or near - the tumor cell. Among such markers are Carcinoembryonic Antigen (CEA) and human epidermal growth factor receptor 2 (HER2). CEA is associated with colon, lung and some breast cancers, while HER2 is a breast cancer marker in approximately 25% of patients. These antigens are found in normal colon lumen and heart muscle respectively. A protein used in finding a molecular target may be something as simple as a mouse-derived antibody or an engineered protein construct. One constraint is that proteins from alien species eventually generate their own human antibodies when repeatedly used in a given patient. This effect can be moderated by DNA manipulation of the alien antibody to change its structure to a more human-like amino-acid sequence. Use of a blood-injection for the RP may result in sequestration by a normal tissue such as the liver or kidneys. In the renal case, small proteins (<25 kDa) would be very rapidly taken out of circulation so as to prevent significant tumor targeting. Various strategies have been developed to minimize sequestration; e.g., blocking or use of polyethylene glycol covering molecules (“stealth”) to prolong protein circulation. Because of the large numbers of possible RPs, it is necessary that preselection be done on any putative clinical RP. A figure of merit (FOM) may be used to choose one of a series of agents dedicated to the same tumor type; e.g., cognate antibodies to CEA. Both imaging and therapeutic FOMs have been developed. These indicators are used to differentiate RPs using animal data. This preferential ordering process is needed since the number of agents is large while volunteers for research studies are only a small fraction (2 to 5%) of the total patient population. One is still left with the question of the relationship between animal and clinical biodistribution data.

Learning Objectives:

1. Know the types of agents presently being studied for TRT.
2. Understand the reasons for tumor targeting by engineered pharmaceuticals (RPs).
3. Realize the importance of the RP blood curve for the targeting process.
4. Use of Figures of Merit to select an optimal imaging or therapy agent.