Chelator approaches are often applied when labeling large molecules like peptides, proteins, antibodies, and nanoparticles, where the ligand's active site can be separated from the chelator via a spacer group. Many small molecules do not accommodate such manipulations and metal-based PET ligands usually cannot be applied within CNS research as they do not cross the blood–brain barrier. Compared to ^{18}F and ^{11}C, ^{68}Ga-based ligands have an inferior β^+-branching ratio, spatial resolution, and dosimetry. Nevertheless, ^{68}Ga-based ligands are routinely applied in PET scans. The popularity of ^{68}Ga stems from the fact that it is readily accessible via a simple generator system that easily can be set-up in a standard laboratory, whereas the use of ^{11}C and ^{18}F requires access to a cyclotron—a particle accelerator requiring very extensive dedicated infrastructure and know-how.

The application of longer-lived metal nuclides like ^{64}Cu and ^{89}Zr is also chelator-based in analogy to ^{68}Ga-based ligands. The advantages and disadvantages discussed before are also valid for these nuclides. The main advantage of ^{64}Cu and ^{89}Zr is the longer half-life, but their β^+-branching ratios are substantially lower meaning that a major fraction of the decay of these nuclides does not contribute to the PET image. This results in a higher radiation burden for the patients.

In conclusion, shorter-lived isotopes are preferable with respect to dosimetry. But many important targeting processes like the accumulation of monoclonal antibodies are slow (usually up to several days) and cannot be imaged with short-lived nuclides. Therefore, the choice of nuclide is strongly dependent on the biological process that is investigated, target localization, the nature of the ligand, and the pharmacokinetics of that ligand's interaction with the target.

8.6 LABELING CHEMISTRY

Besides the obvious decaying characteristics, there is a fundamental difference between the synthesis of radioactive materials and classical organic synthesis. In the synthesis of PET ligands a very large excess ($\times 10^6$) of the precursor is reacted with a minute amount of radioactive material (like [^{11}C]MeI or [^{18}]F$^-$, see below). Consequently, radioactive reactions usually follow pseudo-first reaction order kinetics whereas standard organic or inorganic reactions often follow binary reaction kinetics. Therefore, it is often necessary to substantially alter and modify standard reaction conditions when applied to radioactive procedures. In addition, special precautions have to be considered while working with radioactive material, and there is a strong focus on automation in the development of radiochemical procedures to limit exposure and increase reproducibility.

8.6.1 ^{11}C-Labeling

One of the biggest challenges when labeling molecules with ^{11}C is the short half-life of 20.4 minutes. ^{11}C is primary accessible from cyclotrons as [^{11}C]CO_2 or [^{11}C]CH_4. All of the chemical transformations known for CO_2 can in principle be applied to [^{11}C]CO_2, as long as the critical time perspective is addressed. In Figure 8.5, a representative ^{11}C-labeling strategy starting from [^{11}C]CO_2 is shown. The sequence starts with the addition of an alkyl Grignard reagent giving [^{11}C]propionic acid. Conversion to the corresponding acid chloride and addition of the appropriate amine, followed by a reduction gives [^{11}C]PHNO which is used to image dopamine $D_{2/3}$ receptors, see Chapter 18.

[^{11}C]CH_3I is another very popular reagent that can be accessed from [^{11}C]CH_4. Although this is an effective alkylating agent it is often converted into the even more reactive [^{11}C]CH_3OTf. Both [^{11}C]CH_3I and [^{11}C]CH_3OTf can be used to perform standard alkylation of a range of different nucleophiles—typically amines and phenols. Figure 8.5 shows representative PET ligands that have been labeled via alkylation of a suitable precursor with either [^{11}C]CH_3I or [^{11}C]CH_3OTf.

It is also possible to perform more complex transformations—like cross-coupling reactions. [^{11}C]CH_3I can be trapped by a Pd-catalyst and reacted with a suitable organometallic reagent—usually based on Sn or B. Vortioxetine and Stavudine (both marketed drugs) have been ^{11}C-labeled using this approach, see Figure 8.5. The examples in Figure 8.5 are far from exhaustive and a plethora of other PET ligands, labeling procedures, and ^{11}C-synthons have been developed.