The Neurokinin 1 (NK_1) Receptor, Depression, and PET Imaging: The Aprepitant Story

There are certainly many cases in which PET and SPECT imaging are used as biomarkers to demonstrate that a candidate compound is engaging its intended target (e.g., receptor occupancy) so that a correlation between target binding and functional efficacy can be drawn. It is important to understand, however, the meaning of PET and SPECT imaging study that successfully demonstrates target engagement when *in vivo* efficacy is not observed. In this case, not only is the utility of the candidate compound called into question, the overall utility of the therapeutic target must also be reconsidered. Such is the case with Emend® (Aprepitant, Figure 10.9(a)), a selective neurokinin 1 (NK_1) receptor antagonist.[67] This drug is currently marketed as an antiemetic

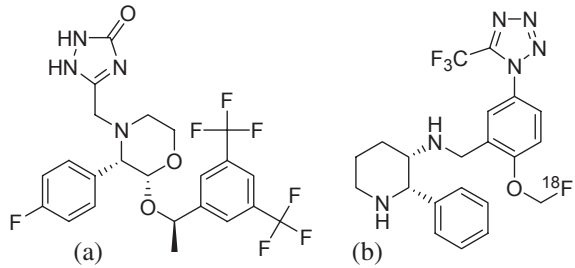

FIGURE 10.9 (a) Emend® (Aprepitant) (b) L-829,165-^{18}F.

useful for the prevention of chemotherapy-induced and postoperative nausea and vomiting.[68] It was also clinically assessed for its ability to treat major depressive disorder.

Prior to the Emend® (Aprepitant) major depressive disorder clinical trials, a substantial body of literature provided preclinical evidence suggesting a link between NK_1 receptor activation by substance P and depression and anxiety. Physiological, neuroanatomical, and behavioral studies[69] detailing the impact of activation of the NK_1 by substance P lead the scientific community to hypothesize that excessive release of substance P in areas of the brain that control emotionality could produce a cascade of psychophysiological responses that would culminate in the symptomology associated with depression and anxiety. Emend® (Aprepitant), which at the time was known as MK-869, had been identified by Merck as a highly efficacious ($EC_{50} = 90$ pM) and selective NK_1 antagonist. Pharmacokinetic studies (including blood–brain barrier penetration) indicated that sufficient exposure to the drug could be achieved in humans, and its safety profile was clean in preclinical models. Based