or an interaction between the two. A biomarker may or may not correlate perfectly with clinical efficacy/toxicity, but could be used for internal decision-making within a pharmaceutical company."[16] Both of these definitions encompass a wide range of methods and techniques that span the length of the drug discovery and development process. Fortunately, it is possible to categorize biomarkers based on their purpose and the type of information that they provide. These categories include target engagement biomarkers, mechanism biomarkers, outcome biomarkers, toxicity biomarkers, pharmacogenomics biomarkers, and diagnostic biomarkers.

As the name implies, target engagement biomarkers provide insight into whether or not a candidate compound is interacting with the macromolecular target of interest. This type of biomarker can be effectively used to validate or invalidate the relationship between a disease and a specific biomolecular target, or explain why a compound fails to produce the expected result with a previously validated target. Consider, for example, a biomarker that definitively demonstrates that a candidate compound is interacting with a biomolecule that is hypothesized to be linked to the progression of a specific disease. If an *in vivo* response is also observed, then the biomarker has validated the link between the disease and the biomolecular target of interest. On the other hand, if the same candidate compound's interaction with the targeted biomolecule fails to provide a physiological response, this suggests that the targeted biomolecule is not a suitable target for the treatment of the disease or condition of interest. Imaging techniques designed to determine the location of radiolabeled compounds, such as PET and SPECT have been particularly useful in demonstrating that a candidate compound is interacting with GPCRs in the brain.[17] Additional details on imaging techniques and their practical application will be provided later in this chapter.

Mechanism biomarkers represent a second class of biomarkers. This class of biomarkers provides information on the physiological impact of a candidate compound. They measures changes in specific events theorized to be associated with the targeted disease or condition that occurs as a result of target engagement. Exemplary physiological events that could be measured include changes in enzymatic activity, gene expression, protein expression, behavioral changes in the subject, or even plasma concentration of specific chemicals. Blood glucose levels, for example, are an established biomarker for candidate compound efficacy in the treatment of diabetes,[18] while sleep induction is an easily detected indication of the efficacy of a candidate compound designed to treat insomnia.[19] It is important to keep in mind that mechanism biomarkers are not necessarily tied to efficacy, especially if the link between the targeted mechanism and the disease/condition of interest has not been established.

Outcome biomarkers, on the other hand, are biomarkers with a defined link to the disease or condition of interest that can be used as an indication