while the third conclusion would only be an indictment of the single candidate compound examined in the assay.

In order to pin down the link between DPP-IV, GLP-1, glucose, and diabetes progression, additional translational assays were necessary. The scientists at Merck, the company that developed Januvia® (Sitagliptin), chose to develop assays using GLP-1 plasma concentration and plasma DPP-IV activity as biomarkers.[48] Essentially, C57BL/6N male mice were treated with a candidate compound using conditions known to induce GLP-1 release (e.g., orally delivered glucose or dextrose), plasma samples were obtained, and the samples were analyzed for the presence of active GLP-1 and DPP-IV activity. If lower DPP-IV activity was detected in the plasma samples of the treated animals as compared to the control, this would indicate that the candidate compound had reached its intended target. Similarly, increased concentrations of GLP-1 in treated animal plasma versus control animals would be an indication that DPP-IV inhibition was, in fact, having an impact on GLP-1 concentration. Treatment of mice with Januvia® (Sitagliptin) produced a dose-dependent increase in active GLP-1 plasma concentrations, decreased DPP-IV activity, and improved glucose tolerance. Studying these biomarkers in human clinical trials provided an early indication of the clinical utility of Januvia® (Sitagliptin). Dose-dependent increases in active GLP-1 concentration, decreased DPP-IV activity, and improved glucose tolerance were observed in phase I clinical trials. These observations highlighted the importance of biomarkers in the identification of novel DPP-IV inhibitors for the treatment of diabetes and were supportive of further clinical study of Januvia® (Sitagliptin) for this purpose.[52] The FDA approved this drug for marketing in 2006.

Physiological Measurements as Biomarkers: Orexin Antagonists

As discussed earlier in this chapter, there are a number of physiological responses that can be used as biomarker to assist in the identification of novel therapeutic agents. Monitoring changes in blood pressure and heart rate are well-known and somewhat obvious biomarkers that are widely employed, but there are others that are less apparent. Consider, for example, the development of novel treatments for insomnia. If all types of sleep were equal, then identifying a compound capable of inducing sleep would be as simple as dosing animals with a candidate compound and monitoring for loss of consciousness and overall sleep duration. Of course, this simplistic view is not sufficient, as sleep is a complex phenomenon. Sleep is not simply the suppression of CNS activity. It consists of several stages, such as REM (rapid eye movement) sleep, non-REM sleep, slow wave sleep, and delta sleep. In addition, changes in the amount of time spent in each sleep