CHAPTER

3

Classical Targets in Drug Discovery

As the drug discovery process has evolved, a great deal of effort has been focused on developing an understanding of the macromolecular targets. In the first half of the twentieth century, structural information and a true understanding of the mechanistic aspects of drug–protein interactions were limited by the technologies of the time. As technology and the drug discovery process evolved, however, tools such as X-ray crystallography, molecular modeling, PCR, and recombinant DNA technologies provided a sharper and sharper picture of the biological targets impacted by drugs. While the true number of potentially "druggable" targets (macromolecules that can be effectively manipulated with therapeutic entities) remains a subject of debate,[1a–1c] genomic sequencing of pathogenic organisms and humans has shed some light on the subject.

The Human Genome Project, which was completed in 2003, demonstrated that the 23 chromosomes necessary to support human existence are comprised of just over three billion DNA base pairs that encode approximately 20,000–25,000 protein coding genes.[2] Microbial genomes[3] are much smaller, of course, but still represent a significant number of protein-encoding genes. While not all of these genes and their gene-products are directly, or even indirectly, involved in disease progression, pathogenesis, or the therapeutic action of drugs, the sheer number of possible macromolecular targets for drug discovery is quite large. Recent estimates suggest that there are approximately 5000 potential "druggable" macromolecular targets suitable for small molecule therapeutics and an additional 3200 targets that may be suitable for biological therapeutics (Figure 3.1).[1]

Fortunately, nature is fond of recycling its methods, structures, and techniques, creating sets of distinct classes of macromolecules that can be studied together. In fact, an analysis of the full spectrum of marketed drugs demonstrates quite clearly that the vast majority of drugs target only four classes of macromolecules: enzymes, G-protein-coupled receptor (GPCR), ion channels, and transporters. While there are additional

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