On October 5, 1981, Fortune magazine published a cover article entitled the “Next Industrial Revolution: Designing Drugs by Computer at Merck”. I began my career at Merck a few years later, at a time when Computer-Aided Drug Design (CADD) was one of the hottest new tools in the drug discovery arsenal. As with all new tools, the reality hasn’t always lived up to the hype. But in some cases, CADD has played a pivotal role in helping to bring new medicines to market. In the late 1980’s, a new public health crisis, the AIDS epidemic, led to the first broad-based example of this with the design of HIV protease inhibitors. Due to the early and ongoing availability of structural information for this target, CADD was heavily employed in the design and optimization of the initial (and more recent) HIV protease inhibitors. These drugs played a significant role in transforming AIDS from a death sentence to a manageable disease. Another more recent CADD success story is the design of NS3/4A protease inhibitors for the treatment of Hepatitis C. The combination of grazoprevir (NS3/4A inhibitor) and elbasvir (NS5A inhibitor) in the recently approved Zepatier™ holds out the promise of not just treating, but curing, Hepatitis C in a large number of affected patients. While CADD is no longer the new kid on the block, it has proven its worth and has become an essential part of many drug discovery programs.