Many technological challenges facing humanity today, in areas as diverse as energy, electronics, and quantum information, are fundamentally materials problems. The space of possible materials is vast, suggesting improvements are possible, but materials discovery has historically proceeded haphazardly. In this talk, I will discuss a variety of efforts as part of the Materials Genome Initiative at NIST (mgi.nist.gov) to rationalize materials design and discovery using computational techniques. I will use ab initio density functional theory, combined with high-throughput computation, databases, machine-learning, and systematic physics-based model-building to understand and predict materials properties. Example application areas include new ferroelectrics, thermoelectrics, and topological materials. Along these lines, I will discuss ongoing efforts to build a predictive tight-binding model for the entire periodic table.