Abstract: Simulation-based engineering science has radically transformed the way research is done across most science and engineering disciplines and emerged as a powerful approach for tackling the major societal problems of our time related to human health, environmental sustainability, and renewable energy. Fluid mechanics problems that are frequently at the center of many of these challenges are often so complex that simulation-based research is the only viable approach for tackling them. Typical examples range from optimizing the hemodynamic performance of medical devices in patient-specific anatomies, to manipulating turbulence in natural waterways to enable physics-based stream restoration, to developing strategies for reducing the cost of energy and mitigating environmental impacts when harnessing wind and water energy resources. Accurate numerical simulation of such flows poses a formidable challenge to even the most advanced computational methods available today. In this talk I will discuss the advances we have made in my group toward the development of a powerful computational framework for simulating such flows that integrates an immersed boundary approach with curvilinear grids, features accurate and robust fluid-structure interaction algorithms, and is capable of carrying out coherent-structure-resolving simulations of turbulent flows in arbitrarily complex domains with dynamically evolving boundaries. The capabilities of the method will be demonstrated by discussing applications to study: 1) left-heart hemodynamics; 2) the hydrodynamics of aquatic swimming; 3) turbulent flow and transport processes in natural waterways; and 4) hydrokinetic and wind turbine flows. Future grand challenges and opportunities for simulation-based fluid mechanics research will also be discussed.