Atherosclerotic cardiovascular disease, the leading cause of death world wide, is driven by inflammatory processes carried out by various types of immune cells. Hypercholesterolemia and autoimmunity are two key triggers of the atherogenic inflammatory response. Moreover, atherosclerosis is accelerated in autoimmune diseases, notably rheumatoid arthritis (RA), where it drives mortality. For decades, research in this area has relied upon mouse models, but there are major differences between the immune system of mice and humans. We propose an interdisciplinary approach in which CUMC experts in the areas of atherosclerosis; reconstitution of mice with a human immune system (hu-mice); and autoimmunity collaborate for the first time to address this problem. Using an innovative, human-relevant technique to render hu-mice hypercholesterolemic to enable atherogenesis, we will study the inflammatory and immune responses during early and advanced atherosclerosis in comparison with control mice reconstituted with a murine immune system ("mu-mice"). Data will analyzed in the context of findings with actual human atherosclerotic specimens. Next, using hypercholesterolemic mice reconstituted with hematopoietic stem cells from patients with RA, which will enable the creation of the most advanced murine model of human RA to date, we will study in-depth mechanisms and therapeutic strategies in RA-accelerated atherosclerosis. These interdisciplinary studies will be the first of their kind to study the human immune system in atherosclerosis for the purposes of in-depth mechanistic analysis and therapeutic modeling; provide preliminary data for a variety of grant applications in the near future; and establish this CUMC team as an international leader in this critical area.