Graft-versus-host disease (GVHD) is a major contributor to early and late morbidity and mortality after allogeneic stem cell transplantation. Despite results from a randomized controlled trial demonstrating an increased risk of chronic GVHD with use of growth factor-mobilized peripheral blood stem cells (PBSC) compared with bone marrow, PBSCs are the most widely used graft source in allogeneic transplantation for hematologic neoplasms in the U.S. This lecture will review established, recent, and novel strategies for GVHD prevention in unrelated donor PBSC transplantation and will highlight ongoing clinical research at Fred Hutchinson Cancer Research Center. Clinical trials aimed at defining standard-of-care GVHD prophylaxis after myeloablative and nonmyeloablative conditioning will be presented. In addition, novel pharmacologic agents and graft manipulation strategies under investigation will be discussed.