Clot formation is essential for hemostasis, yet inappropriate clot formation (thrombosis) is the leading cause of morbidity and mortality in the Western World. Clots are stabilized by a meshwork of fibrin that traps cells and protects the clot from mechanical rupture and chemical dissolution. Fibrin formation is regulated by contributions from plasma and cellular activities, however the mechanisms involved in these interactions are not well understood. We have used in vitro and ex vivo models of blood coagulation to understand how cells and plasma proteins contribute to thrombin generation and fibrin formation, structure and stability. I will present data on mechanisms by which plasma proteins and vascular cells regulate this process, and discuss how these mechanisms contribute to vascular bed-specific thrombus formation.