ADAMTS13 is the primary molecular regulator of the blood clotting protein Von Willebrand Factor (VWF). It helps to control VWF platelet capturing activity by cleaving high molecular weight multimers under appropriate shear conditions. However, it is unclear how ADAMTS13 activity is regulated to prevent excessive VWF degradation at sites of vessel injury, where platelet recruitment is required to stop bleeding. ADAMTS13 is not regulated by any mechanisms known to control the activity of other proteases in the cardiovascular system. It is secreted as an active protease and has a circulating half-life of 4 days, which is exceptionally long for an active protease in blood. ADAMTS13 is therefore resistant to every known circulating protease inhibitor. Whether this resistance to inhibition is a consequence of exquisite specificity for VWF or due to other features is not well understood. In this seminar, I will describe the development and implementation of high throughput screening techniques that we have used to explore the mechanisms of ADAMTS13 regulation.