

## Translating Biophysics to Molecular Medicine

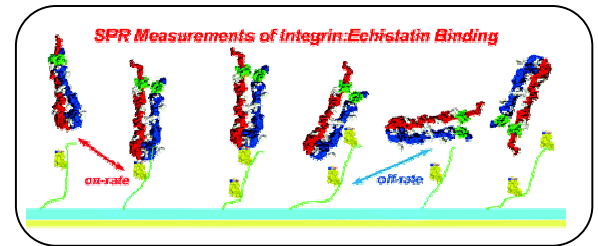
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This talk will examine the hypothesis that understanding the biophysical bases of molecular recognition can lead to safer, more effective drugs to prevent and treat cardiovascular disease.

Cardiovascular disease remains the leading cause of death in our society; every year, about 1 million people in the US have heart attacks and almost half of them do not recover. At the core of the problem is a *thrombus*, formed by activated platelets that adhere rapidly and tightly to an injured artery and that are reinforced by a dense network of clotted fibrin. Integrin receptors, especially the platelet integrin  $\alpha\text{IIb}\beta\text{3}$ , are the “*molecular glue*” that binds this cellular knot.

Drugs designed to block these interactions, *integrin antagonists*, have proven quite effective when used in with *coronary angioplasty*, a mechanical procedure that often enables a cardiologist to disrupt an occlusive thrombus and restore normal blood flow to a patient’s heart. Three of these drugs, eptifibatide, tirofiban, and roxifiban, are small molecules that mimic RGD integrin-targeting sites on adhesive proteins like fibrinogen and fibronectin. While these drugs bind tightly to their target, the platelet integrin  $\alpha\text{IIb}\beta\text{3}$ , they also change the receptor’s shape in unexpected ways that limit their clinical efficacy.

My colleagues and I use the tools of biophysics and protein chemistry to uncover the mechanisms responsible for this integrin antagonist/agonist dichotomy. This talk will review our studies of the conformational states of the  $\alpha\text{IIb}\beta\text{3}$  integrin and its interactions with pharmacologic integrin antagonists. I will also discuss our studies of  $\alpha\text{IIb}\beta\text{3}$ ’s interactions with *echistatin*, a 5 kDa disintegrin protein found in pit viper venom – but one that we clone, express, mutate and purify with the tools of protein engineering.

As director of our *Macromolecular Interactions Core Laboratory*, I will also discuss the array of biotechnologies that our facility makes available to our colleagues regionally, nationally, and internationally.

### References

1. Rocco, M., Rosano, C., Weisel, J. W., Horita, D. A., and Hantgan, R. R. (2008) Integrin conformational regulation: uncoupling extension/tail separation from changes in the head region by a multiresolution approach, *Structure*. 16, 954-964.
2. Hantgan, R. R., Stahle, M. C., and Horita, D. A. (2008) Entropy drives integrin  $\alpha\text{IIb}\beta\text{3}$ :echistatin binding--evidence from surface plasmon resonance spectroscopy, *Biochemistry*. 47, 2884-2892.
3. Hantgan, R. R., Stahle, M. C., Connor, J. H., connor, R. F., and Mousa, S. A. (2007)  $\alpha\text{IIb}\beta\text{3}$  priming and clustering by orally active and intravenous integrin antagonists, *J Thromb. Haemost.* 5, 542-550.