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Seminar Title: “Structural and Functional Studies of Myostatin, a Strong Regulator of Muscle Mass, and Its Interaction with the Antagonist Follistatin”.

Abstract: Myostatin is a member of the transforming growth factor- β (TGF- β) family and is a strong negative regulator of muscle growth. We have determined the crystal structure of myostatin in complex with the antagonist follistatin 288 (Fst288). We have established that the prehelix region of myostatin very closely resembles that of TGF- β class members, and that this region is a major determinant for the ability of myostatin to signal through the non-canonical type I receptor Alk5. Furthermore, we have discovered that the N-terminal domain of Fst288 undergoes conformational rearrangements to bind myostatin and acts as a site of specificity for the antagonist. Additionally, a unique continuous electropositive surface is created when myostatin binds Fst288, which greatly increases its affinity for heparin. This in turn leads to an increased rate of endocytosis and degradation of myostatin, especially in comparison to activin A:Fst complexes. Overall, we have identified several characteristics unique to myostatin that will be paramount to the rational design of myostatin inhibitors that could be used in the treatment of muscle-wasting disorders.