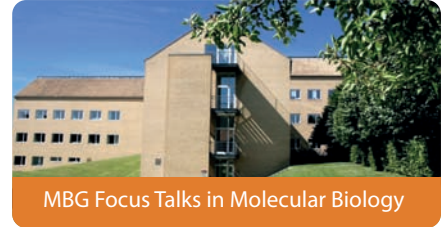


# MBG FOCUS TALK

hosted by Peter A. Andreasen



**Wednesday December 16th 2015 15.15 - 16.00**

3130-303 Science Park Conference Room

## **Professor Hans Brandstetter**

Department of Molecular Biology, University of Salzburg, Austria

### **Crystal structure of legumain reveals distinct activities with significance in neurodegeneration**

Legumain or Asparagine Endopeptidase (AEP) is usually associated with its cysteine endopeptidase activity in lysosomes where it contributes to antigen processing for class II MHC presentation. However, newly recognized functions disperse previously assumed boundaries with respect to their cellular compartmentalisation and enzymatic activities. We show that legumain can develop a carboxypeptidase activity which remains stable at neutral pH, contrasting its endopeptidase activity. Moreover, legumain features a peptide ligase activity, which dominates at near neutral pH. These non-classical legumain activities become particularly relevant in pathological settings, such as cancer or Alzheimer's disease (AD), where the proper association of legumain activities with the corresponding cellular compartments is breached. Legumain is upregulated and activated in normally aged brain and human AD brain, and plays a critical role in mediating the pathophysiology of AD. We report the crystal structure of an orally bioactive and brain permeable legumain inhibitor that blocks the cleavage of tau and APP, and alleviates the cognitive deficits in mouse models of AD.