

## **X-ray crystal structure of MENT: the role of a cysteine proteinase inhibitor in higher order chromatin condensation**

**S. McGowan<sup>1</sup>, A. M. Buckle<sup>1</sup>, J. A. Irving<sup>1</sup>, P. Ong<sup>1</sup>, T. A. Bashtannyk-Puhlovich<sup>1</sup>, W. Kan<sup>1</sup>, Y. A. Bulynko<sup>2</sup>, E. Y. Popova<sup>2</sup>, A. I.A. Smith<sup>1</sup>, S. P. Bottomley<sup>1</sup>, J. Rossjohn<sup>1</sup>, S. A. Grigoryev<sup>2</sup>, R. N. Pike<sup>1</sup>, J. C. Whisstock<sup>1</sup>**

<sup>1</sup>*Dpt Biochemistry and Molecular Biology, Monash University, Clayton, VIC, Australia*

<sup>2</sup>*Dept Biochemistry and Molecular Biology, Penn State University College of Medicine, Milton S. Hershey Medical Center, Hershey, PA, United States*

A balance between proteolytic activity and protease inhibition is required to maintain the appropriate function of biological systems in which proteases play a role. The Myeloid and Erythroid Nuclear Termination protein, MENT, is a non-histone heterochromatin associated protein that is also a functional cysteine protease inhibitor. We have investigated the structure and dual function of this unique protein, namely chromatin condensation and protease inhibition, to discover if there was a link between these two distinct functions. Our data suggest that MENT contains at least two distinct DNA binding sites, consistent with its simultaneous binding to the two closely juxtaposed linker DNA segments on a nucleosome. Remarkably, our studies suggest that the reactive centre loop, a region of the MENT molecule essential for chromatin bridging in vivo and in vitro, is able to mediate formation of a loop-sheet oligomer. The loop-sheet oligomer was found to retain inhibitory activity against the papain-like cysteine protease, cathepsin V. Interestingly, we discovered that the interaction between MENT and cathepsin V is altered in an environment rich in DNA. We found it accelerated inhibition of cathepsin V up to 60-fold. The presence of nuclear proteases that are capable of interacting with chromatin-associated proteins has broad implications for the regulation and control of higher order chromatin structures.