

## Oral Abstract

OR28

### The role of protein kinase C $\delta$ in osteoclasts

Khor EC<sup>1</sup>, Davey T<sup>1</sup>, Li B<sup>2</sup>, Nakayama KI<sup>3</sup>, Nakayama K<sup>3</sup>, Zheng MH<sup>1</sup> and Xu J<sup>1</sup>

<sup>1</sup>Molecular Orthopaedic Laboratory, Centre for Orthopaedic Research, School of Surgery, the University of Western Australia, Nedlands, Western Australia, 6009; Australia, <sup>2</sup>Institute of Molecular and Cell Biology, Proteos, Singapore; <sup>3</sup>Department of Molecular and Cellular Biology, Medical Institute of Bioregulation, Kyushu University, Higashi-ku, Fukuoka, Japan

Osteoclasts are responsible for bone resorption and play a pivotal role in the pathogenesis of osteolytic bone diseases. They are formed from the fusion of macrophage precursor cells stimulated with the receptor activator of NF- $\kappa$ B ligand (RANKL). The signalling pathways that regulate osteoclast formation are not fully understood. We have previously shown that protein kinase C (PKC) activity regulates RANKL signalling pathways and osteoclastogenesis. To further investigate specific the role of PKC isoforms in osteoclast biology, we have compared the gene expression profile of PKC  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\epsilon$ ,  $\delta$ ,  $\eta$ ,  $\theta$ ,  $\zeta$  and  $\iota$  in RAW cell-derived osteoclasts and found that PKC $\delta$  is highly expressed compared to all PKC isoforms in osteoclasts. Further studies using isoform-specific agonists and antagonists of PKC activity support a role for PKC $\delta$  in osteoclasts. Inhibition of PKC $\delta$  by Rottlerin inhibited osteoclastogenesis and bone resorption, whereas activation of PKC $\delta$  by Bryostatin 1, enhanced osteoclastogenesis and osteoclast size. RT-PCR showed that the expression of osteoclast fusion gene DC-STAMP is up-regulated in Bryostatin 1 treated cells. Using luciferase reporter gene assays, we showed that the expression of a constitutively active PKC $\delta$  mutant promotes NFATc1 and NF- $\kappa$ B activity, which are essential for osteoclastogenesis. Interestingly,  $\mu$ CT and histology analysis demonstrates that PKC $\delta$  deficient (PKC $\delta$ -/-) mice exhibit a profound osteopetrotic (increased bone mass) phenotype, consistent with a defect in osteoclast activity. These findings suggest PKC $\delta$  mediates osteoclast function by regulating NFATc1 and NF- $\kappa$ B signalling, and the expression of osteoclastic fusion gene DC-STAMP.