



## Workshop Abstract

### W6

#### What makes the osteoclast tick?

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The current explosion in knowledge of osteoclast biology mostly relates to their differentiation and we continue to have a relatively poor understanding of how mature osteoclasts are regulated. Twenty years ago the factors known or suspected to act directly on mature osteoclasts were limited to calcitonin (and other stimulators of cAMP), M-CSF,  $\alpha\nu\beta 3$  ligands and an unknown factor expressed by osteoblasts/stromal cell (now identified as RANKL). This list now includes  $Ca^{++}$ ,  $H^+$ , ROS, IL-1,  $TNF\alpha$ , glucocorticoids, cannabinoids, TSH, and others. Although no convincing evidence exists that gonadal steroids act directly on osteoclasts, FSH does so to activate resorption.

Traditional osteoclast isolation methods invariably resulted in contamination with osteoblasts/ stromal cells, lymphocytes etc, so direct effects on osteoclast function could not be determined in the absence of indirect effects. Although we are now able to generate relatively pure osteoclast cultures by treating haemopoietic precursors with RANKL and M-CSF, considerable overlap exists between the various processes so that it is often not possible to separate effects on differentiation from those on mature osteoclast resorption and survival. However, by generating osteoclasts en mass in plastic flasks then dissociating and transferring the cells to dentine/bone substrate, it is now possible to investigate direct effects of various factors on osteoclast resorption and survival.

In this model, we have used CFU-GM-derived human osteoclasts and find that they survive for many days in media containing FBS in the absence of RANKL, M-CSF or IL-1. However, the presence of RANKL is absolutely required for resorption. Lower concentrations of M-CSF (25 ng/mL or lower) act synergistically with RANKL to enhance osteoclast activation and resorption, associated with increased activation of AP-1 and  $NF\kappa B$ . This suggests the existence of cross-talk between RANK and fms signaling pathways, possibly mediated by Map kinases or src-TRAF6 interaction. The pathways mediating this interaction and other recent findings will be discussed in the workshop.