

Research Update by Dr Rob Layfield, University of Nottingham

Mutations affecting the *SQSTM1* gene are commonly found in Patient's with Paget's disease of bone, although precisely how they contribute to osteoclast dysfunction and ultimately disease progression is far from clear. We have made significant progress in understanding the mechanistic relationship between SQSTM1 protein (dys)function and Paget's disease [1-14]. Notably, all of the separate disease-associated mutations identified to date cluster in or around the ubiquitin-associated (UBA) domain of SQSTM1, the region of the protein that mediates its ubiquitin-binding properties. These include truncating mutations that delete most of or all of the UBA domain and missense mutations located within the UBA. We have previously shown that some mutations have detrimental effects on the ubiquitin-binding properties of SQSTM1 *in vitro* [5,6], leading to our proposal that the disease mechanism in these cases is likely to involve the inability of SQSTM1 to establish regulated protein-protein interactions with an ubiquitinated osteoclast protein(s) [7,8]. With funding from the NARPD we have now confirmed that all of the UBA domain mutations we have tested, and indeed a novel non-UBA domain mutation of SQSTM1, have similar detrimental effects on the ubiquitin-binding function of SQSTM1 [12-14]. Ongoing research (with continued NARPD support) will establish precisely how this loss of binding function leads to activation of osteoclasts, and whether the disease mechanism involves dysregulation of NF- κ B signalling pathways [8,11] and/or protein turnover [10].

* denotes publications which NARPD support has contributed to

- [1] Hocking LJ, Lucas GJA, Daroszewska A, Cundy T, Nicholson GC, Donath J, Walsh JP, Finlayson C, Cavey JR, Ciani B, Sheppard PW, Searle MS, Layfield R, Ralston SH. *J Bone Miner Res* 2004, 19:1122-7
- [2] Ciani B, Layfield R, Cavey JR, Sheppard PW, Searle MS. *J Biol Chem* 2003, 278:37409-12
- [3] Layfield R, Ciani B, Ralston SH, Hocking LJ, Sheppard PW, Searle MS, Cavey JR. *Biochem Soc Trans* 2004, 32:728-30
- [4] Layfield R, Hocking LJ. *Calcif Tissue Int* 2004, 75:347-57
- [5] Cavey JR, Ralston SH, Hocking LJ, Sheppard PW, Ciani B, Searle MS, Layfield R. *J Bone Miner Res* 2005, 20:619-24
- [6] Cavey JR, Ralston SH, Sheppard PW, Ciani B, Gallagher TR, Long JE, Searle MS, Layfield R. *Calcif Tissue Int* 2006, 78:271-7
- [7] Layfield R, Cavey JR, Najat D, Long J, Sheppard PW, Ralston SH, Searle MS. *Biochem Soc Trans* 2006, 34:735-7
- *[8] Layfield R. *Expert Rev Mol Med* 2007, 9:1-13
- [9] Long J, Gallagher TR, Cavey JR, Sheppard PW, Ralston SH, Layfield R, Searle MS. *J Biol Chem* 2008, 283:5427-40
- *[10] Layfield R, Searle MS. *Biochem Soc Trans* 2008, 36:469-71
- [11] Layfield R, Shaw B. *BMC Biochem* 2007, 22:8 Suppl 1:S5.
- *[12] Najat D, Garner T, Hagen T, Shaw B, Sheppard PW, Falchetti A, Marini F, Brandi ML, Long JE, Cavey JR, Searle MS, Layfield R. *J Bone Miner Res* 2008, under revision
- *[13] Rea SL, Walsh JP, Ward L, Magno AL, Ward BK, Layfield R, Kent GN, Xu J, Ratajczak T. *J Bone Miner Res* 2008, under revision
- *[14] Najat D, Bradley L, Brownless K, Martin S, Falchetti A, Marini F, Brandi ML, Shaw B, Cavey JR, Layfield R. Presented at 2007 International Symposium on Paget's disease, Oxford, UK [Abstract P11].