Table 1 Ethical orientations by religious denomination

	Percentage of respondents						
Ethical	Catholic	Orthodox	Protestant	Muslim	Nonreligious	Other	Total orientation
Strong duty	18%	12%	20%	14%	27%	22%	20% of care
Moderate duty	37%	38%	35%	27%	42%	36%	37% of care
Moderate sanctity	29%	31%	25%	27%	20%	26%	26% of life
Strong sanctity	16%	19%	20%	32%	12%	15%	18% of life

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George Gaskell, Sally Stares & Alain Pottage

London School of Economics and Political Science, London, UK.
e-mail: g.gaskell@lse.ac.uk

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The many faces of Bruton's tyrosine kinase

To the Editor:

I recently read the News story in the March issue regarding Bruton's tyrosine kinase (BTK) immunokinase[1], and it reminded me of work that I presented at Cold Spring Harbor way back in 2003 (ref. 2). On the basis of studies previously published on the receptor activator of nuclear factor κB (NF-κB) ligand RANKL receptor[3], which ultimately led to the development of Prolia (denusomab) for osteoporosis, we sought to identify an intermediate in the RANKL pathway that could be targeted by a kinase inhibitor. To identify RANKL-induced signal transduction intermediates in this process, we differentiated RAW264 cells into osteoclast-like cells upon treatment with RANKL.

Initial events in cytoskeletal rearrangement appeared to be dependent upon activation of phosphatidylinositol 3 (PI3) kinase. Further biochemical evaluation and cell-based immunofluorescence studies suggested the involvement of Btk as a key intermediate in the cytoskeletal reorganization of these mouse cells. *Btk*$^{-/-}$ mouse proximal tibias were evaluated for bone mineral density by peripheral quantitative computed tomography and showed evidence of osteopetrosis compared with wild-type mice. However, in parallel studies with Btk^{xid} × BALB/C mice, which contained a point mutation in the pleckstrin homology (PH) domain of Btk, the Btk^{xid} mice showed evidence of osteopenia, a presumably 'reverse' phenotype. Upon insertion of a wild-type Btk transgene into a Btk^{xid} × BALB/C background, bone mass increased with copy number. Btk^{xid} osteoclasts had multiple sealing zones with what appeared to be a double layer of podosomes indicating a 'hyperactive' osteoclast.

These studies established the role of BTK as a critical enzyme in bone resorption and metabolism. But the phenotypic differences between the two distinct mutations in the same gene also gave us some degree of pause when reflecting on the use of 'knockout' mice for drug discovery applications.

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C Patrick McAtee

Global Product Manager–Biotechnology, SACHEM, Inc., Austin, Texas, USA.
e-mail: pmcatee@sacheminc.com

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