Reviewer's report

Title: Anti-tumor effect of bisphosphonate (YM529) on non-small cell lung cancer

Version: 6 Date: 25 November 2006

Reviewer: Takeshi Yuasa

Reviewer's report:

General
In their additional data of the revised Figure 4, YM529 apparently induce the expression of Ras (not only unprenylated Ras but also prenylated Ras). However, authors concluded YM529 inhibited Ras-ERK1/2 pathway. I cannot understand why the author concluded Ras-ERK1/2 pathway was inhibited by YM529 from their Western blotting result. They used Pan-Ras antibody (not unprenylated Ras antibody) in the Western blotting analysis. From their results, I understand the unprenylated Ras was increased by YM529. However, the prenylated Ras (functional form of Ras) also apparently increased in the expression. Their results are consistent with the previous report (Nogawa et al., Oncol Res 2005). Inhibition of geranylgeranylated proteins rather than farnesylated proteins may be important for the growth inhibitory effect of YM529 against NSCLC cells.

I know that recent reports have revealed that bisphosphonates prevent prenylation of the mevalonate pathway, which is essential to activate small GTP-binding proteins (G-proteins) such as Ras, as authors described in the Discussion section. Because nobody has demonstrated the inhibition of farnesylation and/or geranylgeranylation of the small G-protein in NSCLC cells, authors should demonstrate the prenylation inhibitory effect of YM529 in NSCLC cells. From their Western blotting analysis, I cannot find Ras-ERK1/2 pathway was inhibited by YM529.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Molecular target of YM529 remains unknown. I recommend authors should demonstrate the inhibitory of geranylgeranylation and/or farnesylation in NSCLC cells. It is very simple additional experiment.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

There is not Ras in the legend of Figure 4.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No