Cornish J, Bava U, Callon KE, Bai J, Naot D, Reid IR. Bone-bound bisphosphonate inhibits growth of adjacent non-bone cells. Bone. 2011;49:710–716.

This in-vitro study examines if cells other than osteoclasts are affected by bone-bound bisphosphonates. Conventional thought is that bisphosphonates are taken up by bone surfaces and then incorporated into bone-resorbing osteoclasts resulting in the inhibition of farnesyl pyrophosphate (FPP) synthase. Inhibition of FPP activity obstructs the attachment of the osteoclast cytoskeleton to the inner leaflet of the cell membrane (prenylation) at the site of the roughened boarder. This lack of cytoskeleton attachment prohibits cathepsin K release and therefore the bone is not resorbed by the osteoclast.

The investigators seeded Caco-2 (human colorectal adenocarcinoma epithelial cells) and Chinese hamster ovary (CHO) cells with bone slice cultures. The epithelial cells (Caco-2) are of interest to dentistry in that this may help explain a portion of the mechanism associated with bisphosphonate related osteonecrosis of the jaw (BRONJ). Bisphosphonates examined were zoledronate, pamidronate, clodronate, ibandronate, and alendronate in100 μM concentrations. Cell proliferation (cell number and thymidine incorporation) was measured at 4–72 h. Cell adhesion on the bone slices pretreated with bisphosphonates was normal at 4 h, but cell numbers progressively decreased beyond 48 h and with even greater reduction in thymidine incorporation beyond 24 h. Growth inhibition correlated to the clinical potency of the bisphosphonate tested. There was no sign of increased apoptosis in Caco-2 or CHO cells cultured on bisphosphonate-coated bone, but levels of unprenylated Rap1A were increased, indicating inhibition of FPP synthase and therefore decreased cytoskeleton attachment. It was concluded that biphosphonates bound to a bone surface might act on adjacent non-bone cells resulting in inhibition of their growth. This could explain effects of bisphosphonates on cells other than osteoclasts and contribute to bisphosphonate efficacy in reducing rates of cancer recurrence. Additionally, it could explain the reduced osteoblast activity observed following long-term use of these medications and the pathogenesis of BRONJ.

James L Rutkowski
Editor-in-Chief, *Journal of Oral Implantology*