Anti-Osteoclast Therapy in Bone Disease

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The balance of bone resorption and formation maintains skeleton homeostasis. Osteoclasts are cells essential for bone resorption. Increased osteoclast generation, activity, or survival is directly associated with osteoporosis and other bone diseases with increased bone resorption. Our understanding of osteoclast biology has advanced rapidly in the last decade with the identification of key factors that regulate osteoclast formation, activation, and survival following their knockout in mice or mutations in humans. This led to the development or identification of specific inhibitors of some of these key factors as possible drugs for the prevention of osteoclast-mediated bone loss. In the past 30 year, bisphosphonates are the major therapeutic agents prescribed for the prevention of bone loss in a variety of pathologic conditions, but the side-effects have limited their usages in some patients. Based on the growing knowledge of the pathways regulating osteoclast function, pharmaceutical companies have spent enormous efforts to identify compounds that could be developed into new anti-osteoclast drugs. Among them, two classes of compounds have obtained great attention. One is the compounds that target the RANKL/RANK/OPG system and its downstream molecules NF-kB, c-Fos, and NFAT through regulation of osteoclast formation. Another is c-Src and Src family kinase inhibitors that affect osteoclast activity and survival. In addition to these attempts to develop specific anti-catabolic agents, many investigators have been attempting to determine the active ingredients in a variety of naturally occurring compounds in herbal remedies or foods that appear to have osteo-protective effects. In this presentation, I will first review briefly 1) the recent progress in osteoclast study including the development of osteoclast lineage from hematopoietic stem cells and essential pathways for osteoclastogenesis and activity; and 2) effects of specific inhibitors of bone resorption that have been developed to date. Then, I will describe the effects of RANK pathway inhibitors in the treatment of various forms of bone disorders in pre-clinic animal models and introduce bone targeted src kinase inhibitors, developed by ARIAD Pharmaceuticals, USA, that have been targeted to bone to limit potential unwanted side-effects. The *in vitro* and *in vivo* effects of a bone-targeted src inhibitor AP23451 will be described.