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Targeted delivery to bone and mineral deposits using bisphosphonate ligands☆,☆☆

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ABSTRACT

The high concentration of mineral present in bone and pathological calcifications is unique compared with all other tissues and thus provides opportunity for targeted delivery of pharmaceutical drugs, including radiosensitizers and imaging probes. Targeted delivery enables accumulation of a high local dose of a therapeutic or imaging contrast agent to diseased bone or pathological calcifications. Bisphosphonates (BPs) are the most widely utilized bone-targeting ligand due to exhibiting high binding affinity to hydroxyapatite mineral. BPs can be conjugated to an agent that would otherwise have little or no affinity for the sites of interest. This article summarizes the current state of knowledge and practice for the use of BPs as ligands for targeted delivery to bone and mineral deposits. The clinical history of BPs is briefly summarized to emphasize the success of these molecules as therapeutics for metabolic bone diseases. Mechanisms of binding and the relative binding affinity of various BPs to bone mineral are introduced, including common methods for measuring binding affinity *in vitro* and *in vivo*. Current research is highlighted for the use of BP ligands for targeted delivery of BP conjugates in various applications, including (1) therapeutic drug delivery for metabolic bone diseases, bone cancer, other bone diseases, and engineered drug delivery platforms; (2) imaging probes for scintigraphy, fluorescence, positron emission tomography, magnetic resonance imaging, and computed tomography; and (3) radiotherapy. Last, and perhaps most importantly, key structure–function relationships are considered for the design of drugs with BP ligands, including the tether length between the BP and drug, the size of the drug, the number of BP ligands per drug, cleavable tethers between the BP and drug, and conjugation schemes.

Contents

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1. Introduction

Bone pathologies and pathological calcifications in soft tissues can be diagnosed and treated by targeted delivery of imaging probes and pharmaceuticals to these mineral sites. Metabolic bone diseases are characterized by an increase in bone resorption resulting in an imbalance between bone formation and resorption [1]. These diseases include osteoporosis, Paget's disease, bone cancers or metastases, and osteomalacia. The imbalance between bone formation and resorption results in undesired effects such as bone loss, enlarged or weak bones, and fractures [1]. Pathological calcifications are deposits of mineral in soft tissues, such as arterial calcifications in atherosclerosis [2–4], microcalcifications in breast tissue [5], and kidney stones [6]. These abnormal mineral deposits can cause pain, tissue malfunction, and possibly even death if not detected and treated.

The high concentration of mineral present in bone and pathological calcifications is distinct compared with all other tissues and thus provides opportunity for targeted delivery of drugs, including radiosensitizers and imaging probes. Targeted delivery enables the specific accumulation of a high local concentration of a therapeutic or imaging contrast agent to diseased bone or pathological calcifications. One approach to target agents with little or no affinity for bone or mineral deposits is to conjugate the agent to a mineral-binding molecule. Bisphosphonates (BPs) are the most widely utilized bone-binding ligand due to exhibiting high binding affinity to hydroxyapatite mineral. The high binding affinity of BPs for hydroxyapatite is a well-established property of BPs that was discovered in the 1960s and has led to the widespread use of BPs as drugs to treat metabolic bone disorders [7].

The overall goal of this review is to summarize the current state of knowledge and practice for the use of BPs as ligands for targeted delivery to bone and mineral deposits (Fig. 1). The clinical history of BPs is first summarized to highlight the success of these molecules as drugs for metabolic bone diseases, due to the high binding affinity between BPs and bone mineral. Mechanisms of binding and the relative binding affinity of various BPs to bone mineral are introduced, including common methods for measuring binding affinity *in vitro* and *in vivo*. Current research is highlighted for the use of BP ligands for targeted delivery in various applications, including therapeutic drug delivery, imaging probes, and radiotherapy (Fig. 1). Last, and perhaps most importantly, key structure–function relationships are considered for the design of drugs with BP ligands, including the tether length between the BP and drug, the size of the drug, the number of BP ligands per drug, cleavable tethers between the BP and drug, and conjugation schemes.

2. History of bisphosphonates

BPs are a class of molecules used clinically to treat metabolic bone diseases by inhibiting the process of bone resorption. The first evidence for the biological function of BPs was reported by Fleisch and colleagues in 1968 [8]. Inorganic pyrophosphate (Fig. 2) was discovered to inhibit the formation and dissolution of calcium phosphonate crystals [9], suggesting that pyrophosphate regulates bone resorption and formation.

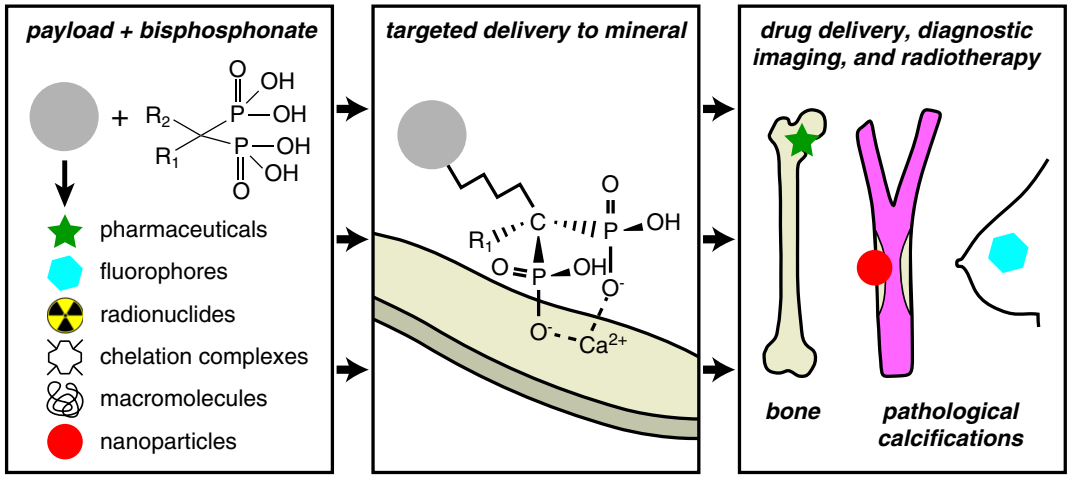

Fig. 1. Schematic diagram showing the use of bisphosphonates, either alone or conjugated to various pharmaceuticals, fluorophores, radionuclides, chelation complexes, macromolecules, and nanoparticles, for targeting mineral in bone and pathological calcifications for drug delivery, diagnostic imaging, and radiotherapy.