Mechanisms of Humoral Hypercalcemia of Malignancy in Leukemia/Lymphoma

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1. Introduction

Hypercalcemia is one of the most common paraneoplastic syndromes. The incidence of hypercalcemia is 50-90% in adult T-cell leukemia/lymphoma (ATLL), 27-35% in lung cancer, 25-30% in breast cancer, 7-30% in multiple myeloma, and less than 10% in other types of cancer patients (Mundy & Martin, 1982; Roodman, 1997). Patients with severe hypercalcemia (>12 mg/dL; >6.0 mM) usually develop neuromuscular, gastrointestinal and renal symptoms including lethargy, depression, anorexia, nausea, vomiting, polyuria and polydipsia. Patients with serum calcium concentrations >15 mg/dL (7.6 mM) can develop renal failure or cardiovascular abnormalities with arrhythmias and coma (Mundy & Martin, 1982). Depending on the sources of the stimulating factors, hypercalcemia in cancer can be divided into 3 types: (1) humoral hypercalcemia of malignancy (HHM) in which humoral factors secreted by tumor cells directly or indirectly affect cells in the target organs including bone, kidney and intestine that regulate calcium homeostasis; (2) local osteolytic hypercalcemia in which factors secreted by either primary or metastatic tumor cells locally in the bone microenvironment stimulate osteoclastic bone resorption; and (3) primary hyperparathyroidism that coexists with the malignancy (Stewart, 2005). This review will focus on HHM, although some types of cancers may induce both HHM and local osteolytic hypercalcemia, since several factors can function both systemically and locally.

2. Overview of humoral hypercalcemia of malignancy

Humoral hypercalcemia of malignancy (HHM) is characterized by (1) circulating humoral factors derived from cancer cells; (2) uncoupling of bone formation and bone resorption; (3) increased renal calcium reabsorption even though there is hypercalciuria caused by increased Ca^{2+} in the glomerular filtrate. In contrast to HHM in primary hyperparathyroidism, bone formation and resorption are both increased resulting in fibrous osteodystrophy in patients with longstanding disease.

HHM is a common complication of certain lymphoma/leukemias; squamous cell carcinomas (e.g., of the lung or other organs); renal and breast carcinomas, and occasionally other tumors (Stewart, 2002). Factors secreted by the cancer cells (see Table 1 below) stimulate osteoclastic bone resorption (directly or indirectly through osteoblasts) by increasing the activity and/or survival of osteoclast precursors or mature osteoclasts. Most
cancer-derived hypercalcemic factors stimulate osteoclastic bone resorption indirectly by inducing osteoclast-stimulating factors from osteoblasts or bone stromal cells. Under normal physiological conditions, increased serum calcium concentration can be compensated for by decreasing the intestinal calcium absorption, increasing renal calcium excretion, decreasing PTH secretion from the parathyroid glands, and decreasing bone resorption. However, secretion of the cancer-related factor, parathyroid hormone-related protein (PTHrP), also increases renal calcium reabsorption in the kidney through the activation of parathyroid hormone receptor 1 (PTH1R), which facilitates the development of HHM.

| Factors     | Origin                      | Target cells/molecule | Function in bone               |
|-------------|-----------------------------|-----------------------|--------------------------------|
| PTHrP       | Cancer cells                | Osteoblast            | Catabolic and anabolic         |
| RANKL       | Osteoblast, cancer cells    | Osteoclast            | Catabolic                      |
| OPG         | Osteoblast                  | RANKL                 | Inhibit RANKL                  |
| MIP-1α      | Cancer cells                | Osteoblast            | Catabolic                      |
| Calcitriol  | Kidney, cancer cells, tumor-associated macrophages | Intestines, kidney, osteoclast, osteoblast, parathyroid chief cells | Increases calcium in blood |
| TNF-α, IL-1, IL-6, IL-17 | T-cells | Osteoclast | Catabolic                      |
| OPG, IL-3, IL-4, IL-10, IL-13, IFN-β, IFN-γ, GM-CSF, and sFRPs | T-cells | Osteoclast | Inhibit osteoclast formation and/or function |
| Calcium (Ca^{2+}) | Bone Kidney Intestinal tract | Calcium-sensing receptor (CaR) on bone and cancer cells and parathyroid chief cells | Anabolic (bone cells) Catabolic (cancer cells) Decreases PTH secretion |

Table 1. Factors associated with HHM that cause bone formation (anabolic action) or resorption (catabolic action) in bone.

3. Factors involved in the pathogenesis of HHM

3.1 Parathyroid hormone-related protein (PTHrP)

PTHrP was first cloned by Suva et al. (Suva et al., 1987) and purified by Broadus et al. (Broadus et al., 1988). PTHrP is widely expressed in normal tissues and functions as an endocrine, autocrine, paracrine and intracrine hormone. PTHrP is a polyhormone that results from alternative mRNA splicing and post-translational proteolytic processing. During development, PTHrP is essential for the growth and regulation of endochondral bone (Karaplis et al., 1994; Wysolmerski et al., 1998), epithelial-mesenchymal interactions in mammary gland (Wysolmerski et al., 1998), and has important functions in many other tissues. PTHrP knockout mice die soon after birth due to asphyxia caused by developmental abnormalities of bones in the thorax (Karaplis et al., 1994). PTHrP has been shown to be the principal factor in most cases of cancer-induced HHM. The expression of PTHrP is up-
regulated by NF-κB, TGF-β, and/or Ras-MAPK signaling (Nadella et al., 2007; Richard et al., 2005). In adult T-cell leukemia/lymphoma, the promoter of PTHrP can be activated by the binding of HTLV-1 oncoprotein, Tax (Ejima et al., 1993; Watanabe et al., 1990). The functions of PTHrP depend on the activation of different signal transduction pathways, including cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) and protein lipase C/protein kinase C (PLC/PKC) cascades. In addition, PTHrP fragments have different functions that depend on the tissue-specific expression of distinct receptors. Activation of the cAMP-PKA pathway is required for PTHrP to induce bone resorption through the PTH1R, which recognizes both PTH and PTHrP (Greenfield et al., 1995).

Besides the catabolic effect of PTHrP on bone, intermittent administration or pulsatile secretion of the N-terminal fragment of PTH (1-34) and PTHrP (1-36) by a neuroendocrine tumor, such as islet cell carcinoma, can induce bone anabolic effects (Takeuchi et al., 2002). When osteoblastic cells were transiently exposed to the C-terminus of PTHrP (107-139), anabolic effects were induced by the upregulation of vascular endothelial growth factor receptor 2 (VEGFR2) through PKC/ERK activation (de Gortazar et al., 2006).

3.2 Receptor activator of nuclear kappa-B ligand (RANKL) and osteoprotegerin (OPG)

RANKL belongs to the tumor necrosis factor (TNF) family and represents one of the most common mediators for inducing osteoclastic bone resorption. Mature osteoblasts produce two forms of RANKL, a membrane-bound and secreted form. Both are important for osteoclast stimulation (Leibbrandt & Penninger, 2008). The expression of RANKL in osteoblasts and stromal cells is activated by the RUNX2 transcriptional factor under the regulation of PTHrP, 1,25-dihydroxyvitamin D₃, and prostaglandins (Lipton et al., 2009). RANKL binds and activates its receptor, RANK, which is expressed on the surface of osteoclasts. The binding of RANKL to RANK activates at least three major signaling pathways, NFAT, p38 and JNK, resulting in up-regulation of genes that are required for induction of osteoclast fusion, differentiation, activation and survival (Leibbrandt & Penninger, 2008). The secreted form of RANKL is important for the recruitment of osteoclast precursors and osteoclastogenesis. RANKL is an essential activator for normal bone remodeling. RANKL knockout mice have severe osteopetrosis (Lomaga et al., 1999).

OPG, or osteoclastogenesis inhibitory factor (OCIF), is a secreted member of the tumor necrosis receptor superfamily that is expressed by osteoblasts and functions as a RANKL ‘decoy receptor’ (Simonet et al., 1997). OPG binds to RANKL and blocks its interaction with RANK on osteoclast precursors (Lacey et al., 1998); therefore, it is a potent inhibitor of osteoclast formation and bone resorption. OPG knockout mice have early-onset osteopenia (Bucay et al., 1998; Mizuno et al., 1998), whereas OPG overexpressing mice develop osteopetrosis that results from the failure to form osteoclasts (Simonet et al., 1997). PTH and PTHrP suppress OPG expression by downregulating the promoter of OPG through activation of the cAMP/PKA pathway (Yang et al., 2002). PTHrP, on the other hand, stimulates RANKL expression to induce bone resorption. The ratio between RANKL and OPG levels in osteoblasts is a key factor in the regulation of osteoclast activity (Horwood et al., 1998).

In ATLL, the expression of RANKL in tumor cells correlated with hypercalcemia in patients. RANKL on the surface of leukemia cells induced osteoclastogenesis through direct contact with precursor cells (Nosaka et al., 2002). The direct activation of osteoclasts by tumor cells may play a key role in the decoupling of bone formation and bone resorption in HMM.
Therefore, RANKL from either osteoblasts or tumor cells is an important mediator of bone resorption in many forms of HHM.

### 3.3 Cytokines

The increased secretion of inflammatory cytokines from cancer cells, such as tumor necrosis factor-α (TNF-α), IL-1, IL-6, M-CSF, CCL2 and CXCL12, is one of the key mechanisms by which NF-κB is constitutively activated in tumor cells (Lu & Stark, 2004). The proinflammatory cytokine, TNF-α, is a critical factor in the pathogenesis of many inflammatory and non-inflammatory diseases which are characterized by increased osteoclastic bone resorption including rheumatoid arthritis (Chu et al., 1991), osteoporosis (Horowitz, 1993), osteomyelitis (Meghji et al., 1998) and aseptic loosening (an osteolysis syndrome caused by macrophages in joint replacements) (Merkel et al., 1999). TNF-α mediates lipopolysaccharide-stimulated osteoclastogenesis through the p55 receptor expressed on bone marrow macrophages and activation of NF-κB (Abu-Amer et al., 1997; Abu-Amer et al., 1998). Whether osteoclastogenesis induced by TNF-α depends on RANKL or not remains controversial. Some studies have shown that without exogenous RANKL, TNF-α is sufficient to induce osteoclast differentiation (Kudo et al., 2002), and the increase of osteoclastogenesis was inhibited by OPG (Hounoki et al., 2008). However, Boyle et al. have shown that administration of TNF-α to RANK-deficient mice failed to induce osteoclastogenesis and restore hypocalcemia, suggesting that TNF-α cannot substitute for RANKL (Li et al., 2000). Teitelbaum et al. have reported that TNF-α alone was not able to induce osteoclastogenesis in murine osteoclast precursors; rather, RANKL was required for TNF-α to stimulate osteoclast precursors to form osteoclasts (Lam et al., 2000). Regardless, TNF-α has shown its potential to be a therapeutic target for bone resorption. Increased TNF-α levels have been found in patients with advanced chronic lymphocytic leukemia (CLL) and acute nonlymphocytic leukemia with HHM (Ferrajoli et al., 2002).

Increased plasma IL-6 has been found in cancer patients with HHM, including patients with multiple myeloma, squamous cell carcinoma of the liver, acute nonlymphocytic leukemia, and adult T-cell leukemia/lymphoma (Asanuma et al., 2002; Kounami et al., 2004; Roodman, 1997). IL-6 increases osteoclast recruitment by binding to its receptor on osteoblasts and inducing the signal of transducer and activator of transcription (STAT)-1/3 and mitogen-activated protein kinase (MAPK) signaling pathways (Sims et al., 2004). It also enhances the effects of PTH and PTHrP and mediates the effects of inflammatory cytokines, such as IL-1 and TNF-α, on osteoclast formation (Roodman, 2001). IL-6 does not directly increase RANKL expression; therefore, its osteoclastogenic effect is RANKL-independent (Hofbauer et al., 2000). However, there is no correlation between serum IL-6 and HHM in cancer patients, suggesting that IL-6 functions additively or synergistically with other factors and may be a redundant factor for development of HHM (Vanderschueren et al., 1994).

Granulocyte macrophage-colony stimulating factor (GM-CSF) also plays a role in osteoclastogenesis and it has two distinct effects on osteoclast activity depending upon the presence of RANKL. GM-CSF increases the proliferation of osteoclast progenitors when RANKL is absent. On the other hand, it induces osteoclast progenitors to differentiate into dendritic cells when RANKL is present (Gillespie, 2007).

Macrophage colony-stimulating factor (M-CSF) is essential for osteoclast differentiation and proliferation of osteoclast progenitor cells (Tanaka et al., 1993). Increased serum M-CSF
concentration has been reported in acute nonlymphocytic leukemia patients with HHM (Kounami et al., 2004). Interferon (IFN)-γ disrupts JAK/STAT signaling in osteoblasts to induce the expression of OPG and Wnt, causing decreased cathepsin K and tartrate-resistant acid phosphatase (TRAP) in mature osteoclasts (Gallo et al., 2008; Gillespie, 2007). Transgenic mice with the HTLV-1 viral oncoprotein, Tax, and knockout of IFN-γ developed more severe osteolytic bone lesions and increased osteoclast activity. Administration of IFN-γ to mice transplanted with Tax-positive tumors inhibited tumor growth and decreased hypercalcemia, suggesting a protective role for IFN-γ in HHM development (Xu and Hurchla et al., 2009).

Cytokines have been shown to play a more important role in the pathogenesis of HHM in patients with lymphoma and leukemia compared to patients with carcinoma. However, further investigation is needed to clarify the additive and synergistic roles of cytokines in causing hypercalcemia because multiple cytokines are often produced by the tumor cells.

### 3.4 Macrophage inflammatory protein-1 alpha (MIP-1α)

MIP-1α is a pro-inflammatory chemokine expressed by many different cell types including macrophages, dendritic cells and lymphocytes. It normally functions as a chemoattractant for T-cells, macrophages, and other proinflammatory cells at the site of inflammation. It also regulates the transendothelial migration of NK cells, monocytes and dendritic cells (Maurer & von, 2004). Therefore, it plays an important role in autoimmune and inflammatory diseases, such as multiple sclerosis, rheumatoid arthritis, asthma, and organ transplant rejection (Maurer & von, 2004). MIP-1α binds to several chemokine (c-c motif) G-protein-coupled receptors including CCR1, CCR5 and CCR9, which are expressed in lymphocytes and monocytes/macrophages. It activates several signaling pathways, including PI3K, PLC, PKC, MAP kinase and JAK/STAT pathways (Tsubaki et al., 2007). MIP-1α can potently inhibit the binding of HIV to CCR5 on macrophages (Baba et al., 1999; Maurer & von, 2004).

Both CCR1 and CCR5 are expressed in bone marrow stromal cells. MIP-1α is chemotactic for osteoclasts and osteoclast precursors (Fuller et al., 1995). MIP-1α was first identified as a putative osteoclastogenic factor in a human myeloma cDNA expression library derived from marrow samples of myeloma patients (Zlotnik & Yoshie, 2000). Subsequently, CCR1 and CCR5 expression was demonstrated in human and murine multiple myeloma cell lines (Menu et al., 2006). Furthermore, MIP-1α enhances osteoclast formation induced by IL-6, PTHrP and RANKL in multiple myeloma (Han et al., 2001) and increases adhesion of myeloma cells to bone marrow cells through its binding to both CCR1 and CCR5 receptors (Oba et al., 2005). In vivo, mice bearing Chinese hamster ovary cells that overexpress MIP-1α develop more severe osteolytic lesions after intramuscular inoculation (Oyajobi et al., 2003). The mechanisms by which MIP-1α induces osteoclastic bone resorption are controversial. One study demonstrated that a RANKL-dependent pathway was responsible for activation of osteoclasts (Tsubaki et al., 2007). MIP-1α enhances RANKL expression in mouse bone marrow stromal cells and osteoblasts through the MAPK and PI3K/Akt signaling pathways. On the other hand, RANK-Fc did not block the activation of osteoclasts by MIP-1α, indicating that MIP-1α used a RANKL-independent pathway to increase bone resorption (Han et al., 2001). Therefore, it has been suggested that MIP-1α is a RANKL-independent osteoclastogenic factor that acts directly on osteoclast precursors (Choi et al., 2000). In any case, it is apparent that MIP-1α is a significant osteoclast activator. The role of MIP-1α in...
HHM is highlighted by the fact that HTLV-1 infected T-cells express and secrete MIP-1α (Shu et al., 2007; Shu et al., 2010), and the increased serum levels of MIP-1α correlated well with the development of HHM in HTLV-1-infected patients (Okada et al., 2004).

3.5 1α,25-Dihydroxyvitamin D (Calcitriol)
Vitamin D is an essential hormone for calcium homeostasis. Its active form, 1α,25-dihydroxyvitamin D₃ or calcitriol, is synthesized by hydroxylation of vitamin D in the kidney. The renal 25-hydroxyvitamin D 1α hydroxylase is the rate limiting enzyme for production of calcitriol. Calcitriol increases calcium absorption from the intestinal tract, increases osteoclastic bone resorption, and decreases PTH gene expression in the parathyroid glands (Guise et al., 2005). Calcitriol is an uncommon primary cause of HHM in patients with leukemia or lymphoma even though serum calcitriol concentrations may be increased in up to 50% of patients (Seymour & Gagel, 1993). Some lymphomas or tumor-associated macrophages express 25-hydroxyvitamin D 1α hydroxylase, which is responsible for the increased production of calcitriol (Hewison et al., 2003).

3.6 Cell membrane calcium-sensing receptor (CaR)
CaR is expressed on multiple cell types including the chief cells of the parathyroid gland where it regulates PTH expression and secretion. Under normal conditions, CaR, a G protein-coupled receptor, senses extracellular calcium concentrations and activates downstream signaling pathways, such as the PLC/inositol trisphosphate (IP3) and ERK1/2 pathways, in a tissue-specific manner (Saidak et al., 2009). In bone, CaR is expressed in osteoblasts, osteoclasts, stromal cells, monocytes-macrophages, and chondrocytes. CaR promotes osteoblast proliferation, differentiation and mineralization (Sharan et al., 2008). It also mediates osteoclast differentiation and apoptosis. Therefore, CaR in bone cells promotes the bone formation phase of bone remodeling (Yamaguchi, 2008). CaR is also expressed in some cancer cells, such as breast and prostate cancers (Liao et al., 2006). However, in these cells, increased extracellular calcium leads to increased PTHrP expression (Chattopadhyay, 2006). Increased PTHrP induces osteoclastic bone resorption and renal calcium reabsorption, resulting in HHM. The positive feedback loop formed by PTHrP, calcium and CaR is a unique phenomena in HHM. In addition to the specific activation of PTHrP expression, gain-of-function mutations in CaR have been demonstrated in breast cancer. Lorch et al. have found single nucleotide polymorphisms in CaR in human lung squamous cell carcinoma (Lorch et al., 2011). Functional evaluation of a nonconservative amino acid substitution (R990G) in CaR induced HHM in patients with lung squamous cell carcinoma. Dysregulation of PTHrP expression and HHM caused by CaR signaling has been demonstrated in breast and prostate cancer (Saidak et al., 2009). However, the role of CaR in HHM induced by lymphoma/leukemia remains to be determined.

3.7 Role of T cells in calcium homeostasis
The skeletal and immune systems share many regulatory molecules and systems. An interdisciplinary research area called “Osteoimmunology” has been developed recently to understand the interplay between these two systems. Cytokines, receptors, signaling molecules and transcriptional factors, and their signaling pathways are comprehensively reviewed by Takayanagi (Takayanagi, 2007). T-cells have both pro- and antiresorptive effects on osteoclasts. The proresorptive effect is present in osteoclast-stimulating T-cells,
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which secrete a soluble form of RANKL. TNF-α is also expressed by activated T-cells to act in concert with RANKL. IL-1, IL-6 and IL-17 secreted from T-cells increase RANKL expression in osteoblasts. This mechanism is important for rheumatoid arthritis where TH17 cells have been shown to be an immunomodulator of osteoclastic bone resorption (Sato et al., 2006). In addition, T-cells produce IL-7 which increase bone resorption in a RANKL-independent mechanism (Weitzmann & Pacifici, 2005). T-cells also play a major role in postmenopausal osteoporosis induced by decreased estrogen levels and decreased transforming growth factor (TGF)-β expression in bone cells (Gillespie, 2007).

In contrast, T-cells can also exert an antiresorptive effect directly by secreting OPG, IL-3, IL-4, IL-10, IL-13, IFN-β, IFN-γ, GM-CSF, and secreted frizzled-related proteins (sFRPs) to inhibit osteoclastogenesis (Quinn & Gillespie, 2005). In addition, T-cells can inhibit osteoclast formation and activity indirectly by expressing GM-CSF (induced by the upregulation of IL-18 in bone microenvironment), IFN-γ (by IL-12) and OPG (by leptin) (Horwood et al., 2001). It will be important to understand the effects of T-cells on osteoblast and stromal cell function, as well as signaling in the immune response to further understand the interactions between the immune system and bone biology.

4. HHM in leukemia/lymphoma in humans and animals

4.1 Adult T-cell leukemia lymphoma (ATLL)

50-90% of ATLL patients develop HHM and osteolytic lesions in the long bones and calvaria (Olivo et al., 2008). Bone resorption may act as a ‘vicious cycle’ for ATLL growth in bone, since factors released by resorbing bone increased the growth of ATLL and HTLV-1-infected T-cells in vitro (Shu et al., 2010). The mechanisms by which HTLV-1 induces HHM are not completely known. We and others have demonstrated that ATLL primary cell lines (T-cell lines derived from leukemic ATLL patients) and in vitro HTLV-1 transformed T-cell lines express and secrete PTHrP, particularly transcripts from the P3 promoter (Nadella et al., 2007; Richard et al., 2005; Shu et al., 2010) (Figure 1). The expression of PTHrP was upregulated by both oncoviral protein Tax-dependent and -independent pathways. Tax cooperates with Ets to activate the P3 promoter of PTHrP, while constitutive activation of NF-xB in ATLL cells contributes to expression of the PTHrP P2 promoter (Nadella et al., 2007; Richard et al., 2005). Despite the essential role of PTHrP in HHM in carcinomas (such as lung, breast and prostate cancers), the correlation between the plasma PTHrP and HHM in ATLL patients has been controversial. It has been concluded that PTHrP is not the sole factor that induces HHM in ATLL, but it likely plays an important cooperative or synergistic role with other humoral factors (Figure 1).

In ATLL, there were increased plasma MIP-1α concentrations in mice with human ATLL cells and HHM (Shu et al., 2007). In a human clinical study, plasma MIP-1α concentrations had a strong correlation with HHM in ATLL patients (Okada et al., 2004). MIP-1α expression in ATLL cells is induced by Tax and increased plasma calcium concentrations may further up-regulate MIP-1α expression through the calmodulin-dependent protein kinase cascade (CaM-KK) cascade (Matsumoto et al., 2008; Sharma & May, 1999). Treatment with a neutralizing MIP-1α antibody decreased osteoclast formation induced by ATLL cells in vitro (Okada et al., 2004).

The increase in RANKL expression observed in the ATL leukemic cells has been shown to correlate with the occurrence of HHM in ATLL patients (Nosaka et al., 2002). Although the levels of RANKL expression were not high in HTLV-1-infected cell lines in vitro (Shu et al., 2007),
leukemic cells isolated from ATLL patients did have up-regulation of RANKL expression (Nosaka et al., 2002). In addition, HTLV-1 infected leukocytes in vitro were able to convert 25-dihydroxyvitamin D₃ to its active form, 1α,25-dihydroxyvitamin D₃ or calcitriol (Fetchick et al., 1986). High levels of calcitriol have been found in ATLL patients with hypercalcemia (Johnston & Hammond, 1992; Seymour & Gagel, 1993).

Fig. 1. HHM in ATLL is caused by increased osteoclastic bone resorption. Cancer cells secrete bone regulatory factors, including PTHrP, MIP-1α, calcitriol, and RANKL to increase osteoclast activity. The resorbing bone secretes bone-derived growth factors that increase ATLL cell growth. In osteoblasts, the RANKL/OPG expression ratio increases when cells are co-cultured with T-cell leukemia lines. Antibodies against HTLV-1 Gp46 can inhibit OPG and contributes to the pathogenesis of hypercalcemia.

In addition to the direct effects of factors secreted from ATLL cells on osteoclasts, we recently found decreased OPG expression and secretion in osteoblasts that were co-cultured with leukemic T-cell lines (Shu et al., 2010). This suggests that the regulation of gene expression in osteoblasts by leukemic T-cells plays an indirect role in HHM in ATLL.

Finally, an endogenous antibody recognizing the HTLV-1 viral envelope protein Gp46-197 can occur in ATLL patients, which correlated with disease progression. The amino acid sequence of Gp46-197 is homologous with the C-terminus of OPG. Rabbits immunized with the Gp46-197 peptide developed hypercalcemia and died. Sprague-Dawley rats injected with Gp46-197 peptide developed decreased bone mineral density and hypercalcemia. Administration of recombinant human OPG restored femoral bone growth. These data suggest that HTLV-1 Gp46 contributes to the pathogenesis of hypercalcemia due to cross-reactive antibodies in the patients that antagonize the action of OPG (Sagara et al., 2009).

Other factors proposed to be humoral factors for HHM in ATLL include TNF-β (lymphotoxin) (Ishibashi et al., 1992), IL-6 (Chiba et al., 2009), and IL-1 (Wano et al., 1987).
4.2 Other leukemias/lymphomas that develop HHM (Table 2)

4.2.1 De novo acute nonlymphocytic leukemia (ANLL)

Hypercalcemia in de novo ANLL patients can be caused by either local osteolytic hypercalcemia or HHM. Elevated circulating concentrations of several humoral factors, including PTHrP, TNF-α, IL-6, and M-CSF, in de novo ANLL patients with HHM have been reported supporting a role for HHM in ANLL (Kounami et al., 2004). Generalized osteoporosis with normal renal function was observed in these patients, indicating that the increased calcium was mainly from bone.

| Cancer Type                          | Incidence of HHM | Humoral factor(s)          |
|--------------------------------------|------------------|----------------------------|
| ATLL                                 | 50-90%           | PTHrP, MIP-1α, RANKL, IL-1, TNF-β, IL-6 |
| Diffuse large B cell lymphoma        | Rare             | PTHrP, IL-6, 1,25-dihydroxyvitamin D |
| Acute nonlymphocytic leukemia        | Rare             | PTHrP, IL-6, TNF-α, M-CSF    |
| Primary cutaneous B-cell lymphoma    | Rare             | 1,25-dihydroxyvitamin D     |
| Canine T-cell lymphoma               | 40% in mediastinal lymphoma; 10-20% in multicentric lymphoma | PTHrP, 1,25-dihydroxyvitamin D |
| Feline lymphoma                      | Has been reported| PTHrP                      |
| Feline leukemia virus associated leukemia/lymphoma | Has been reported | Unknown                    |
| Avain malignant lymphoma             | Has been reported| Unknown                    |

Table 2. Incidence and humoral factors of HHM in leukemia/lymphoma in humans and animals. Other undefined factors or cytokines may also be involved.

4.2.2 Diffuse large B-cell lymphoma

Increased PTHrP, IL-6, and 1,25-dihydroxyvitamin D concentrations have been reported in the serum from patients with diffuse large B cell lymphoma that developed hypercalcemia (Amezyane et al., 2008; Chang et al., 2008). Diffuse osteolytic lesions and nephrocalcinosis also occurred in these patients.

4.2.3 Primary cutaneous B-cell lymphoma

Hypercalcemia has been reported in patients with primary cutaneous B-cell lymphoma (Habra et al., 2007; Narimatsu et al., 2003). Increased serum 1,25-dihydroxyvitamin D and undetectable PTH and PTHrP levels were found in one patient. The pathogenesis of hypercalcemia in these patients has not been determined.

4.2.4 HHM in animals with leukemia/lymphoma

HHM occurs in 10-40% of dogs with T-cell lymphoma (Fournel-Fleury et al., 2002). Increased circulating PTHrP and 1,25-dihydroxyvitamin D were found in dogs with lymphoma and HHM, but the serum concentrations did not always correlate with...
hypercalcemia. Therefore, it was speculated that additional cytokines are involved in the pathogenesis of HHM in dogs with lymphoma (Mellanby et al., 2006; Rosol et al., 1992). In a xenograft mouse model of canine lymphoma, there was increased expression of TNF-α in the tumor \textit{in vivo} (Nadella et al., 2008). Bone histomorphometry indicated that increased osteoclastic bone resorption was the major cause of HHM in these mice. Increased circulating PTHrP has also been reported in cats with lymphoma and HHM (Bolliger et al., 2002). Cats may also develop HHM due to unknown humoral factors induced by feline leukemia virus infection (Engelman et al., 1985). Hypercalcemia has also been reported in an Amazon parrot with lymphoma (de Wit et al., 2003).

5. Therapy of HHM in leukemia/lymphoma

For urgent care, saline hydration is the first step to correct hypercalcemia by diluting the serum calcium concentration and increasing the clearance of calcium by the kidneys. Treatment of the underlying leukemia/lymphoma, including chemotherapy and radiation therapy, is necessary. Several drugs have been used for long-term management of hypercalcemia associated with HHM.

5.1 Bisphosphonates

Bisphosphonates are structural analogs of pyrophosphoric acid and have been widely used to treat cancer patients with hypercalcemia, heritable skeletal disorders in children, and postmenopausal and glucocorticoid-induced osteoporosis patients with significant bone loss (Fleisch, 1997). Intravenous aminobisphosphonates are a standard of care for the treatment of HHM. The newest generation of bisphosphonates, nitrogen-containing aminobisphosphonates, inhibits farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) synthetases in the mevalonic acid metabolic pathway resulting in decreased prenylation of low-molecular-weight G proteins including Ras. Functional Ras signaling is necessary for osteoclast activity and survival (Fleisch, 1998). It also has been suggested that bisphosphonates exert a cytotoxic effect on HTLV-1-infected T-cells. However, high doses of bisphosphonates were needed for cytotoxic effects \textit{in vitro} and \textit{in vivo} (Gao et al, 2005; Ishikawa et al., 2007; Shu et al., 2007; Hirbe et al., 2009). The clinical relevance of a direct effect of bisphosphonates on ATLL cells needs to be further evaluated. Bisphosphonates have a high affinity for bone mineral and bind to hydroxyapatite crystals \textit{in vivo}. Therefore, bisphosphonates are rapidly depleted from the circulation and extracellular fluid and become highly concentrated in bone. Bisphosphonate therapy may have complications including hypocalcemia, osteonecrosis of the jaw, low bone turnover with pathologic fractures, and increased incidence of atrial fibrillation (Drake et al., 2008). In addition to the effects on osteoclasts, a new bisphosphonate, YM527/ONO-5920, decreased MIP-1α expression and secretion through inhibition of the transient increase of phosphorylated ERK1/2 and Akt in mouse myeloma cells after lipopolysaccharide (LPS) stimulation (Drake & Rajkumar, 2009). Since MIP-1α has been shown to play an important role in cancer cell growth and osteolysis in multiple myeloma, bisphosphonates may be useful for inhibiting the growth of myeloma cells and to prevent osteolysis by decreasing MIP-1α expression. This may also apply to ATLL. Commonly used bisphosphonates include pamidronate and zoledronic acid.

5.2 Calcitonin

Calcitonin is a 32-amino acid peptide secreted by thyroid C-cells. It inhibits calcium absorption in the intestine and reabsorption of calcium and phosphate in renal tubules. It is
a potent (but transient) inhibitor of osteoclastic bone resorption. The mechanisms of action have been shown to involve several signaling pathways including cAMP/PKA, PKC, and pyk2/src activity. It has also been shown that calcitonin up-regulates renal 1α-hydroxylase, an important enzyme for the synthesis of calcitriol, through the binding of C/EBPβ and brahma-related gene 1 (BRG1), an ATPase in the SWItch/Sucrose NonFermentable (SWI/SNF) chromatin remodeling complex, on the 1α-hydroxylase promoter (Zhong et al., 2009). Because of its potent inhibitory effect on bone resorption, calcitonin has clinical applications in the treatment of Paget’s disease, osteoporosis, and hypercalcemia. However, due to its short duration of action, calcitonin may not be suitable for treatment of chronic hypercalcemia. Salmon calcitonin is used clinically due to its greater potency compared to human calcitonin (Zaidi et al., 2002).

5.3 Corticosteroids
Corticosteroids have been used for the treatment of hypercalcemia induced by multiple myeloma and certain types of lymphoma. Corticosteroids act by decreasing calcium absorption in gastrointestinal tract, decreasing bone resorption, and increasing renal calcium excretion (Unal et al., 2008; Yarbro et al., 2003). Corticosteroids generally are not effective in patients with HHM induced by solid tumors.

5.4 Bortezomib (PS-341)
Bortezomib is a selective proteasome inhibitor that decreases the ubiquination of IkB, the inhibitor for NF-κB, thereby stabilizing IkB and inhibiting NF-κB. NF-κB is necessary for osteoclast function and constitutively activated NF-κB plays an important role in ATLL cells. Bortezomib has been shown to inhibit tumor growth in models of ATLL (Mitra-Kaushik et al., 2004b; Nasr et al., 2005; Satou et al., 2004; Shu et al., 2007; Tan & Waldmann, 2002). Shu et al. reported that bortezomib not only decreased tumor burden in mice bearing ATLL cells, but also decreased the severity of HHM (Shu et al., 2007). Although the decrease in serum calcium concentrations was mainly due to the decreased tumor burden, several studies have shown that bortezomib inhibited osteoclastogenesis by decreasing p38, AP-1 and NF-κB activity in osteoclasts (von Metzler et al., 2007) and increased bone formation by decreasing the expression of Dkk-1, a potent osteoblast inhibitor (Drake & Rajkumar, 2009; Heider et al., 2009; Pennisi et al., 2009; Qiang et al., 2009; Terpos et al., 2006). Bortezomib is now a standard of care for treatment of multiple myeloma patients. Several clinical trials involving bortezomib are ongoing for the treatment of prostate cancer, nonsmall cell lung cancer, acute myelogenous leukemia, and other cancers.

5.5 Humanized anti-parathyroid hormone-related protein antibody and small molecule antagonists of the PTH/PTHrP receptor (PTH1R)
Although bisphophonates have been widely used for treatment of HHM to inhibit osteoclastic bone resorption, they do not function on the kidney to decrease renal calcium reabsorption. To eliminate the actions of PTHrP in bone and kidney, an anti-PTHrP antibody has been developed and tested (Sato et al., 2003). Anti-PTHrP antibody prevented hypercalcemia and skeletal metastasis, but not visceral metastasis, induced by PTHrP-producing cancer cells in mice (Guise & Mundy, 1996; Sato et al., 2003). Although it has been difficult to identify small molecule antagonists for type B G-protein-coupled receptors, including the PTH1R, two compounds have been recently developed that antagonize PTH1R. SW106 was discovered by Bristol-Myers-Squibb Company by screening compounds...
that inhibited targets downstream of the PTHR1 (Carter et al., 2007). The benzoxazepinone non-peptide inhibits the cAMP response induced by a PTH1R agonist. The pharmacological behavior of SW106 is not yet completely understood. A similar compound, 1,3,4-benzotriazepine was identified and serves as a base molecule to develop non-peptide PTH1R antagonist derivatives (McDonald et al., 2007). Using a radioligand binding assay that measures cAMP production, N-1 anilino-substituted compounds were identified that have up to a 1000-fold more potency at inhibiting PTH1R compared to the original compound. Efforts are ongoing to determine the effects of these compounds on bone metastasis, hypercalcemia and hyperparathyroidism.

5.6 RANKL inhibitors
Ever since RANKL and OPG were discovered to be major regulators of osteoclastic bone resorption, RANK-Fc, Fc-OPG, antibodies targeting RANKL or inhibitors imitating OPG function have been developed for the treatment of osteolytic bone diseases (Schwarz & Ritchlin, 2007). RANK-Fc was generated by combining the carboxyl-terminus of RANK with the Fc portion of human IgG1. It has been shown to decrease tumor burden in two multiple myeloma mouse models, inhibit prostate cancer bone metastasis, and decrease the incidence of lung metastasis and bone lysis in a osteosarcoma mouse model (Lamoureux et al., 2008; Sordillo & Pearse, 2003; Zhang et al., 2003). Fc-OPG was generated by combining the Fc portion of the immunoglobulin heavy chain to the amino-terminus of OPG. The inhibitory effect of Fc-OPG on bone resorption is similar to pamidronate (Bekker et al., 2001; Body et al., 2003). However, Fc-OPG and RANK-Fc have been replaced by denosumab (Amgen), which is a fully human monoclonal antibody developed using the xenomouse technology that specifically inhibits primate RANKL (Green, 1999). Denosumab does not bind to murine RANKL, human TRAIL, or other TNF family proteins and has a longer half-life than Fc-OPG (Kostenuik et al., 2009). Denosumab has been tested in patients with varying diseases/conditions, including osteoporosis, treatment-induced bone loss, bone metastases, multiple myeloma and rheumatoid arthritis, and is now a standard of care for patients with solid tumor bone metastases (Schwarz & Ritchlin, 2007). Denosumab can significantly delay or prevent skeleton-related events (SREs), including hypercalcemia, in patients with bone metastasis (Castellano et al., 2011). Due to its longer half life, higher specificity and lower toxicity, the therapeutic potential of denosumab is superior to that of Fc-OPG and RANK-Fc (Schwarz & Ritchlin, 2007).

6. Development of in vivo models of HHM in leukemia/lymphoma

6.1 Mouse models of HHM and ATLL
Animal models of ATLL are divided into infectious models, which are useful to study viral infection, viral transmission and the immune response, and pathogenesis models, which are useful for preclinical therapy studies. Pathogenesis models, including tumor xenografts and transgenic mice that develop tumors, are useful to study the development and treatment of HHM in ATLL. Unfortunately, there are few animal models of ATLL that develop HHM. The following animal models are currently available for studying HHM in ATLL.

6.1.1 Human RV-ATL xenograft mouse model of ATLL
The RV-ATL model was first developed by the laboratory of Dr. Irvin Chen by injecting RV-ATL cells, derived from an ATLL patient, into severe combined immunodeficient (SCID)
mice (Feuer et al., 1993). Richard et al. characterized the tumorigenesis and HHM of this cell line in SCID/beige mice (Richard et al., 2001). SCID/beige mice developed severe hypercalcemia one month after intraperitoneal injection of RV-ATL cells. The mice had bone loss due to increased osteoclastic bone resorption. Shu et al. introduced the luciferase gene into the RV-ATL cells by lentiviral infection and developed a bioluminescent model of HHM in ATLL for preclinical studies (Shu et al., 2007). It was found that both zoledronic acid, a nitrogen-containing bisphosphonate, and PS-341, a selective proteasome inhibitor, decreased tumor burden and HHM in mice. No complication of using the combination of PS-341 and zoledronic acid was observed in this preclinical study (Shu et al., 2007).

6.1.2 Uchiyama human xenograft mouse model of ATLL
The laboratory of Dr. Takashi Uchiyama developed a mouse xenograft model by injecting cells from the lymph node of a lymphoma-type ATLL patient intraperitoneally into SCID mice (Imada et al., 1996). The mice developed tumors and hypercalcemia within three weeks. There was a marked increase in serum C-terminal PTHrP concentrations with decreased bone formation rates reported in the mice (Takaori-Kondo et al., 1998). However, no significant increase in bone resorption measured by bone histomorphometry was observed in the mice, which is in contrast to ATLL patients with HHM.

6.1.3 Human MET-1 xenograft mouse model of ATLL
Recently, a NOD/SCID mouse model using human ATLL MET-1 cells has been developed (Phillips et al., 2000). The mice developed leukemia and HHM after intraperitoneal injection. Marked infiltration of tumor cells in multiple organs including spleen, lungs, liver, lymph nodes was observed. Increased plasma PTHrP concentrations in the mice and expression of PTHrP and RANKL in MET-1 cells were reported (Parrula et al., 2009). It is not known whether the HHM in this model was caused by an increase in bone resorption or other mechanisms.

6.1.4 HTLV-1 LTR-Tax transgenic model
Transgenic mice have been used to study the pathogenesis and role of the HTLV-1 viral oncoprotein, Tax. Several Tax transgenic mice have been developed using different promoters. A transgenic mouse model overexpressing Tax under the regulation of the HTLV-1 long terminal repeat (LTR) was generated (Ruddle et al., 1993). These mice developed neurofibromas and adrenal medullary tumors, but did not develop leukemia or lymphoma. Unexpectedly, a significant increase in bone remodeling with a net increase in bone volume was observed. This was surprising because the authors also demonstrated that osteoclasts were increased in number, size and degree of multinucleation, which would have been expected to lead to a net decrease in bone volume. It was not reported whether HHM developed in the mice.

6.1.5 Human granzyme B-Tax transgenic mice
The laboratory of Dr. Lee Ratner developed a tissue-specific Tax overexpressing mouse model (Grossman et al., 1995). Tax expression in the mice was under the regulation of the human granzyme B promoter, which limited Tax expression primarily to activated CD4+ and CD8+ T-cells and NK cells. The mice developed mild hypercalcemia and multifocal osteolytic bone lesions, especially in the tail, with increased osteoclastic bone resorption (Gao et al., 2005).
mice have increased serum IL-6 concentrations, which is a potent osteoclast activator. When the mice were crossed to mice that overexpressed OPG, they were protected from the development of osteolytic lesions and soft tissue tumors, indicating that increased bone resorption in Tax transgenic mice was induced, at least in part, through a RANKL-dependent pathway. The mouse model also has been used for preclinical studies and zoledronic acid not only prevented the osteolytic bone lesions but also decreased tumor burden. After crossing the mice with IFN-γ knockout mice, the resulting Tax^+IFN-γ^-/- mice had accelerated tumor formation, dissemination, and death, when compared with Tax^+IFN-γ^+/− or Tax^+IFN-γ^+/+ mice (Mitra-Kaushik et al., 2004a). The mice also develop increased osteolytic bone lesions, increased osteoclast formation and more severe hypercalcemia compared to Tax^+IFN-γ^+/+ mice (Xu et al., 2009). These data indicate that IFN-γ may contribute to the host defense systems that prevent HTLV-1-induced malignancy, bone metastasis and HHM.

6.2 Mouse model of canine lymphoma and HHM
A bioluminescent NOD/SCID mouse model of canine T-cell lymphoma and HHM has been developed (Nadella et al., 2008). The mice developed multicentric lymphoma in the mesenteric lymph nodes after intraperitoneal injection of tumor cells. Moderate to marked splenomegaly and enlarged thymuses were observed. There was increased osteoclastic bone resorption in trabecular bone in mice with lymphoma. HHM developed 6-8 weeks after injection of tumor cells. The increase in plasma PTHrP concentrations likely played a central role in HHM in the mice. The cause of canine T-cell lymphoma is unknown and retroviruses have not been identified as a cause of lymphoma in dogs (in contrast to humans and cats).

7. Conclusion
HHM is a life-threatening complication in certain patients with lymphoma or leukemia. As outlined in this review, progress has been made in elucidating the mechanisms by which humoral factors from neoplastic lymphocytes induce HHM, including increased osteoclastic bone resorption and renal calcium reabsorption. However, further efforts are needed to fully understand the pathogenesis of HHM, including the endocrine or paracrine role of interactions between tumor-associated and host-produced cytokines. PTHrP plays a major endocrine and paracrine role in HHM, but the effects of other factors secreted from tumor cells or host cells cannot be neglected. For example, the expression of RANKL in ATLL cells suggests that ATLL cells may function directly as inducers of osteoclastic bone resorption. Additional effective treatments are needed for this paraneoplastic syndrome. Small molecules or humanized antibodies targeting essential factors or their receptors may be an attractive future therapeutic strategy for treatment of HHM.

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9. References
Abu-Amer, Y.; Ross, F. P.; Edwards, J. & Teitelbaum, S. L. (1997). Lipopolysaccharide-stimulated osteoclastogenesis is mediated by tumor necrosis factor via its P55 receptor. J.Clin.Invest, 100, No.6, pp. 1557-1565, 0021-9738
Abu-Amer, Y.; Ross, F. P.; McHugh, K. P.; Livolsi, A.; Peyron, J. F. & Teitelbaum, S. L. (1998). Tumor necrosis factor-alpha activation of nuclear transcription factor-kappaB in marrow macrophages is mediated by c-Src tyrosine phosphorylation of IkappaBalpha. J.Biol.Chem., 273, No.45, pp. 29417-29423, 0021-9258

Amezyane, T.; Lecoules, S.; Bordier, L.; Blade, J. S.; Desrame, J.; Bechade, D.; Coutant, G. & Algayres, J. P. (2008). [Humoral hypercalcemia revealing a malignant non hodgkin lymphoma]. Ann.Endocrinol.(Paris), 69, No.1, pp. 58-62, 0003-4266

Asanuma, N.; Hagiwara, K.; Matsumoto, I.; Matsuda, M.; Nakamura, F.; Kouhara, H.; Miyamoto, M.; Miyashita, Y.; Noguchi, S. & Morimoto, Y. (2002). PTHrP-producing tumor: squamous cell carcinoma of the liver accompanied by humoral hypercalcemia of malignancy, increased IL-6 and leukocytosis. Intern.Med., 41, No.5, pp. 371-376, 0918-2918

Baba, M.; Nishimura, O.; Kanzaki, N.; Okamoto, M.; Sawada, H.; Iizawa, Y.; Shiraiishi, M.; Aramaki, Y.; Okonogi, K.; Ogawa, Y.; Meguro, K. & Fujino, M. (1999). A small-molecule, nonpeptide CCR5 antagonist with highly potent and selective anti-HIV-1 activity. Proc.Natl.Acad.Sci.U.S.A, 96, No.10, pp. 5698-5703, 0027-8424

Bekker, P. J.; Holloway, D.; Nakanishi, A.; Arrighi, M.; Leese, P. T. & Dunstan, C. R. (2001). The effect of a single dose of osteoprotegerin in postmenopausal women. J.Bone Miner.Res., 16, No.2, pp. 348-360, 0884-0431

Body, J. J.; Greipp, P.; Coleman, R. E.; Facon, T.; Geurs, F.; Fermand, J. P.; Harousseau, J. L.; Lipton, A.; Mariette, X.; Williams, C. D.; Nakanishi, A.; Holloway, D.; Martin, S. W.; Dunstan, C. R. & Bekker, P. J. (2003). A phase I study of AMGN-0007, a recombinant osteoprotegerin construct, in patients with multiple myeloma or breast carcinoma related bone metastases. Cancer, 97, No.3 Suppl, pp. 887-892, 0008-543X

Bolliger, A. P.; Graham, P. A.; Richard, V.; Rosol, T. J.; Nachreiner, R. F. & Refsal, K. R. (2002). Detection of parathyroid hormone-related protein in cats with humoral hypercalcemia of malignancy. Vet.Clin.Pathol., 31, No.1, pp. 3-8, 0275-6382

Broadus, A. E.; Mangin, M.; Ikeda, K.; Insogna, K. L.; Weir, E. C.; Burtis, W. J. & Stewart, A. F. (1988). Humoral hypercalcemia of cancer. Identification of a novel parathyroid hormone-like peptide. N.Engl.J.Med., 319, No.9, pp. 556-563, 0028-4793

Bucay, N.; Sarosi, I.; Dunstan, C. R.; Morony, S.; Tarpley, J.; Capparelli, C.; Scully, S.; Tan, H. L.; Xu, W.; Lacey, D. L.; Boyle, W. J. & Simonet, W. S. (1998). Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. Genes Dev., 12, No.9, pp. 1260-1268, 0890-9369

Carter, P. H.; Liu, R. Q.; Foster, W. R.; Tamasi, J. A.; Tebben, A. J.; Favata, M.; Staal, A.; Cvijic, M. E.; French, M. H.; Dell, V.; Apanovitch, D.; Lei, M.; Zhao, Q.; Cunningham, M.; Deciccio, C. P.; Trzaskos, J. M. & Feyen, J. H. (2007). Discovery of a small molecule antagonist of the parathyroid hormone receptor by using an N-terminal parathyroid hormone peptide probe. Proc.Natl.Acad.Sci.U.S.A, 104, No.16, pp. 6846-6851, 0027-8424

Castellano, D.; Sepulveda, J. M.; Garcia-Escobar, I.; Rodriguez-Antolin, A.; Sundlov, A. & Cortes-Funes, H. (2011). The role of RANK-ligand inhibition in cancer: the story of denosumab. Oncologist., 16, No.2, pp. 136-145, 1083-7159
Chang, P. Y.; Lee, S. H.; Chao, T. K. & Chao, T. Y. (2008). Acute renal failure due to hypercalcemia-related nephrocalcinosis in a patient of non-Hodgkin's lymphoma featuring swelling of bilateral kidneys. Ann. Hematol., 87, No.6, pp. 489-490, 0939-5555

Chattopadhyay, N. (2006). Effects of calcium-sensing receptor on the secretion of parathyroid hormone-related peptide and its impact on humoral hypercalcemia of malignancy. Am. J. Physiol. Endocrinol. Metab., 290, No.5, p. E761-E770, 0193-1849

Chiba, K.; Hashino, S.; Izumiya, K.; Toyoshima, N.; Suzuki, S.; Kurosawa, M. & Asaka, M. (2009). Multiple osteolytic bone lesions with high serum levels of interleukin-6 and CCL chemokines in a patient with adult T cell leukemia. Int. J. Lab Hematol., 31, No.3, pp. 368-371, 1751-5521

Choi, S. J.; Cruz, J. C.; Craig, F.; Chung, H.; Devlin, R. D.; Roodman, G. D. & Alsina, M. (2000). Macrophage inflammatory protein 1-alpha is a potential osteoclast stimulatory factor in multiple myeloma. Blood, 96, No.2, pp. 671-675, 0006-4971

Chu, C. Q.; Field, M.; Feldmann, M. & Maini, R. N. (1991). Localization of tumor necrosis factor alpha in synovial tissues and at the cartilage-pannus junction in patients with rheumatoid arthritis. Arthritis Rheum., 34, No.9, pp. 1125-1132, 0004-3591

de Gortazar, A. R.; Alonso, V.; Alvarez-Arroyo, M. V. & Esbrit, P. (2006). Transient exposure to PTHrP (107-139) exerts anabolic effects through vascular endothelial growth factor receptor 2 in human osteoblastic cells in vitro. Calcif. Tissue Int., 79, No.5, pp. 360-369, 0171-967X

de Wit, M.; Schoemaker, N. J.; Kik, M. J. & Westerhof, I. (2003). Hypercalcemia in two Amazon parrots with malignant lymphoma. Avian Dis., 47, No.1, pp. 223-228, 0005-2086

Drake, M. T.; Clarke, B. L. & Khosla, S. (2008). Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin. Proc., 83, No.9, pp. 1032-1045, 0025-6196

Drake, M. T. & Rajkumar, S. V. (2009). Effects of bortezomib on bone disease in multiple myeloma. Am. J. Hematol., 84, No.1, pp. 1-2, 0361-8609

Ejima, E.; Rosenblatt, J. D.; Massari, M.; Quan, E.; Stephens, D.; Rosen, C. A. & Prager, D. (1993). Cell-type-specific transactivation of the parathyroid hormone-related protein gene promoter by the human T-cell leukemia virus type I (HTLV-I) tax and HTLV-II tax proteins. Blood, 81, No.4, pp. 1017-1024, 0006-4971

Engelman, R. W.; Tyler, R. D.; Good, R. A. & Day, N. K. (1985). Hypercalcemia in cats with feline-leukemia-virus-associated leukemia-lymphoma. Cancer, 56, No.4, pp. 777-781, 0008-543X

Ferrajoli, A.; Keating, M. J.; Manshouri, T.; Giles, F. J.; Dey, A.; Estrov, Z.; Koller, C. A.; Kurzrock, R.; Thomas, D. A.; Faderl, S.; Lerner, S.; O’Brien, S. & Albitar, M. (2002). The clinical significance of tumor necrosis factor-alpha plasma level in patients having chronic lymphocytic leukemia. Blood, 100, No.4, pp. 1215-1219, 0006-4971

Fetchick, D. A.; Bertolini, D. R.; Sarin, P. S.; Weintraub, S. T.; Mundy, G. R. & Dunn, J. F. (1986). Production of 1,25-dihydroxyvitamin D3 by human T cell lymphotrophic virus-I-transformed lymphocytes. J. Clin. Invest, 78, No.2, pp. 592-596, 0021-9738

Feuer, G.; Zack, J. A.; Harrington, W. J., Jr.; Valderama, R.; Rosenblatt, J. D.; Wachsman, W.; Baird, S. M. & Chen, I. S. (1993). Establishment of human T-cell leukemia virus type...
I T-cell lymphomas in severe combined immunodeficient mice. Blood, 82, No.3, pp. 722-731, 0006-4971

Fleisch, H. (1997). Mechanisms of action of the bisphosphonates. Medicina (B Aires), 57 Suppl 1, pp. 65-75, 0025-7680

Fleisch, H. (1998). Bisphosphonates: mechanisms of action. Endocr.Rev., 19, No.1, pp. 80-100, 0163-769X

Fournel-Fleury, C.; Ponce, F.; Felman, P.; Blavier, A.; Bonnefont, C.; Chabanne, L.; Marchal, T.; Cadore, J. L.; Goy-Thollot, I.; Ledieu, D.; Ghernati, I. & Magnol, J. P. (2002). Canine T-cell lymphomas: a morphological, immunological, and clinical study of 46 new cases. Vet.Pathol., 39, No.1, pp. 92-109, 0300-9858

Fuller, K.; Owens, J. M. & Chambers, T. J. (1995). Macrophage inflammatory protein-1 alpha and IL-8 stimulate the motility but suppress the resorption of isolated rat osteoclasts. J.Immunol., 154, No.11, pp. 6065-6072, 0022-1767

Gallo, J.; Raska, M.; Mrazek, F. & Petrek, M. (2008). Bone remodeling, particle disease and individual susceptibility to periprosthetic osteolysis. Physiol Res., 57, No.3, pp. 339-349, 0862-8408

Gao, L.; Deng, H.; Zhao, H.; Hirbe, A.; Harding, J.; Ratner, L. & Weilbaecher, K. (2005). HTLV-1 Tax transgenic mice develop spontaneous osteolytic bone metastases prevented by osteoclast inhibition. Blood, 106, No.13, pp. 4294-4302, 0006-4971

Gillespie, M. T. (2007). Impact of cytokines and T lymphocytes upon osteoclast differentiation and function. Arthritis Res.Ther., 9, No.2, p. 103, 1478-6354

Green, L. L. (1999). Antibody engineering via genetic engineering of the mouse: XenoMouse strains are a vehicle for the facile generation of therapeutic human monoclonal antibodies. J.Immunol.Methods, 231, No.1-2, pp. 11-23, 0022-1759

Greenfield, E. M.; Shaw, S. M.; Gornik, S. A. & Banks, M. A. (1995). Adenyl cyclase and interleukin 6 are downstream effectors of parathyroid hormone resulting in stimulation of bone resorption. J.Clin.Invest, 96, No.3, pp. 1238-1244, 0021-9738

Grossman, W. J.; Kimata, J. T.; Wong, F. H.; Zutter, M.; Ley, T. J. & Ratner, L. (1995). Development of leukemia in mice transgenic for the tax gene of human T-cell leukemia virus type I. Proc.Natl.Acad.Sci.U.S.A, 92, No.4, pp. 1057-1061, 0027-0924

Guise, T. A.; Kozlow, W. M.; Heras-Herzig, A.; Padalecki, S. S.; Yin, J. J. & Chirgwin, J. M. (2005). Molecular mechanisms of breast cancer metastases to bone. Clin.Breast Cancer, 5 Suppl, No.2, p. S46-S53, 1526-8209

Guise, T. A. & Mundy, G. R. (1996). Physiological and pathological roles of parathyroid hormone-related peptide. Curr.Opin.Nephrol.Hypertens., 5, No.4, pp. 307-315, 1062-4821

Habra, M. A.; Weaver, E. J. & Prewitt, P. V., III (2007). Primary cutaneous large B-cell lymphoma of the leg and acute hypercalcemia. J.Clin.Oncol., 25, No.36, pp. 5825-5826, 0732-183X

Han, J. H.; Choi, S. J.; Kurihara, N.; Koide, M.; Oba, Y. & Roodman, G. D. (2001). Macrophage inflammatory protein-1alpha is an osteoclastogenic factor in myeloma that is independent of receptor activator of nuclear factor kappaB ligand. Blood, 97, No.11, pp. 3349-3353, 0006-4971
Heider, U.; Kaiser, M.; Mieth, M.; Lamottke, B.; Rademacher, J.; Jakob, C.; Braendle, E.; Stover, D. & Sezer, O. (2009). Serum concentrations of DKK-1 decrease in patients with multiple myeloma responding to anti-myeloma treatment. Eur.J.Haematol., 82, No.1, pp. 31-38, 0902-4441

Hewison, M.; Kantorovich, V.; Liker, H. R.; Van Herle, A. J.; Cohan, P.; Zehnder, D. & Adams, J. S. (2003). Vitamin D-mediated hypercalcemia in lymphoma: evidence for hormone production by tumor-adjacent macrophages. J.Bone Miner.Res., 18, No.3, pp. 579-582, 0884-0431

Hirbe, A.C., Roelofs, A.J., Floyd, D.H., Deng, H., Becker, S.N., Lanigan, L.G., Apicelli, A.J., Xu, Z., Prior, J.L., Eagleton, M.C., Piwnica-Worms, D., Rogers, M.J., & Weilbaecher, K. (2009). The bisphosphonate zoledronic acid decreases tumor growth in bone in mice with defective osteoclasts. Bone, 44, No. 5, pp. 908-916, 8756-3282

Hofbauer, L. C.; Khosla, S.; Dunstan, C. R.; Lacey, D. L.; Boyle, W. J. & Riggs, B. L. (2000). The roles of osteoprotegerin and osteoprotegerin ligand in the paracrine regulation of bone resorption. J.Bone Miner.Res., 15, No.1, pp. 2-12, 0884-0431

Horowitz, M. C. (1993). Cytokines and estrogen in bone: anti-osteoporotic effects. Science, 260, No.5108, pp. 626-627, 0036-8075

Horwood, N. J.; Elliott, J.; Martin, T. J. & Gillespie, M. T. (1998). Osteotropic agents regulate the expression of osteoclast differentiation factor and osteoprotegerin in osteoblastic stromal cells. Endocrinology, 139, No.11, pp. 4743-4746, 0013-7227

Horwood, N. J.; Elliott, J.; Martin, T. J. & Gillespie, M. T. (2001). IL-12 alone and in synergy with IL-18 inhibits osteoclast formation in vitro. J.Immunol., 166, No.8, pp. 4915-4921, 0022-1767

Hounoki, H.; Sugiyama, E.; Mohamed, S. G.; Shinoda, K.; Taki, H.; Abdel-Aziz, H. O.; Maruyama, M.; Kobayashi, M. & Miyahara, T. (2008). Activation of peroxisome proliferator-activated receptor gamma inhibits TNF-alpha-mediated osteoclast differentiation in human peripheral monocytes in part via suppression of monocyte chemoattractant protein-1 expression. Bone, 42, No.4, pp. 765-774, 8756-3282

Imada, K.; Takaori-Kondo, A.; Sawada, H.; Imura, A.; Kawamata, S.; Okuma, M. & Uchiyama, T. (1996). Serial transplantation of adult T cell leukemia cells into severe combined immunodeficient mice. Jpn.J.Cancer Res., 87, No.9, pp. 887-892, 0910-5050

Ishibashi, K.; Kodama, M.; Hanada, S. & Arima, T. (1992). Tumor necrosis factor-beta and hypercalcemia. Leuk.Lymphoma, 7, No.5-6, pp. 409-417, 1042-8194

Ishikawa, C.; Matsuda, T.; Okudaira, T.; Tomita, M.; Kawakami, H.; Tanaka, Y.; Masuda, M.; Ohshiro, K.; Ohta, T. & Mori, N. (2007). Bisphosphonate incadronate inhibits growth of human T-cell leukaemia virus type I-infected T-cell lines and primary adult T-cell leukaemia cells by interfering with the mevalonate pathway. Br.J.Haematol., 136, No.3, pp. 424-432, 0007-1048

Johnston, S. R. & Hammond, P. J. (1992). Elevated serum parathyroid hormone related protein and 1,25-dihydroxycholecalciferol in hypercalcaemia associated with adult T-cell leukaemia-lymphoma. Postgrad.Med.J., 68, No.803, pp. 753-755, 0032-5473
Karaplis, A. C.; Luz, A.; Glowacki, J.; Bronson, R. T.; Tybulewicz, V. L.; Kronenberg, H. M. & Mulligan, R. C. (1994). Lethal skeletal dysplasia from targeted disruption of the parathyroid hormone-related peptide gene. Genes Dev., 8, No.3, pp. 277-289, 0890-9369

Kostenuik, P. J.; Nguyen, H. Q.; McCabe, J.; Warmington, K. S.; Kurahara, C.; Sun, N.; Chen, C.; Li, L.; Cattley, R. C.; Van, G.; Scully, S.; Elliott, R.; Grisanti, M.; Morony, S.; Tan, H. L.; Asuncion, F.; Li, X.; Ominsky, M. S.; Stolina, M.; Dwyer, D.; Dougall, W. C.; Hawkins, N.; Boyle, W. J.; Simonet, W. S. & Sullivan, J. K. (2009). Denosumab, a fully human monoclonal antibody to RANKL, inhibits bone resorption and increases BMD in knock-in mice that express chimeric (murine/human) RANKL. J.Bone Miner.Res., 24, No.2, pp. 182-195, 0884-0431

Kounami, S.; Yoshiyama, M.; Nakayama, K.; Hiramatsu, C.; Aoyagi, N. & Yoshikawa, N. (2004). Severe hypercalcemia in a child with acute nonlymphocytic leukemia: the role of parathyroid hormone-related protein and proinflammatory cytokines. Acta Haematol., 112, No.3, pp. 160-163, 0001-5792

Kudo, O.; Fujikawa, Y.; Itonaga, I.; Sabokbar, A.; Torisu, T. & Athanasou, N. A. (2002). Proinflammatory cytokine (TNFalpha/IL-1alpha) induction of human osteoclast formation. J.Pathol., 198, No.2, pp. 220-227, 0022-3417

Lacey, D. L.; Timms, E.; Tan, H. L.; Kelley, M. J.; Dunstan, C. R.; Burgess, T.; Elliott, R.; Colombo, A.; Elliott, G.; Scully, S.; Hsu, H.; Sullivan, J.; Hawkins, N.; Davy, E.; Capparelli, C.; Eli, A.; Qian, Y. X.; Kaufman, S.; Sarosi, I.; Shalhoub, V.; Senaldi, G.; Guo, J.; Delaney, J. & Boyle, W. J. (1998). Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell, 93, No.2, pp. 165-176, 0092-8674

Lam, J.; Takeshita, S.; Barker, J. E.; Kanagawa, O.; Ross, F. P. & Teitelbaum, S. L. (2000). TNF-alpha induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. J.Clin.Invest, 106, No.12, pp. 1481-1488, 0021-9738

Lamoureux, F.; Picarda, G.; Rousseau, J.; Gournen, C.; Battaglia, S.; Charrier, C.; Pitard, B.; Heymann, D. & Redini, F. (2008). Therapeutic efficacy of soluble receptor activator of nuclear factor-kappa B-Fc delivered by nonviral gene transfer in a mouse model of osteolytic osteosarcoma. Mol.Cancer Ther., 7, No.10, pp. 3389-3398, 1535-7163

Leibbrandt, A. & Penninger, J. M. (2008). RANK/RANKL: regulators of immune responses and bone physiology. Ann.N.Y.Acad.Sci., 1143, pp. 123-150, 0077-8923

Li, J.; Sarosi, I.; Yan, X. Q.; Morony, S.; Capparelli, C.; Tan, H. L.; McCabe, S.; Elliott, R.; Scully, S.; Van, G.; Kaufman, S.; Juan, S. C.; Sun, Y.; Tarpley, J.; Martin, L.; Christensen, K.; McCabe, J.; Kostenuik, P.; Hsu, H.; Fletcher, F.; Dunstan, C. R.; Lacey, D. L. & Boyle, W. J. (2000). RANK is the intrinsic hematopoietic cell surface receptor that controls osteoclastogenesis and regulation of bone mass and calcium metabolism. Proc.Natl.Acad.Sci.U.S.A, 97, No.4, pp. 1566-1571, 0027-8424

Liao, J.; Schneider, A., Datta N.S., & McCauley, L.K. (2006). Extracellular calcium as a candidate mediator of prostate cancer skeletal metastasis. Cancer Res., 66, No. 18, pp. 9065-9073, 0008-5472
Lipton, A.; Uzzo, R.; Amato, R. J.; Ellis, G. K.; Hakimian, B.; Roodman, G. D. & Smith, M. R. (2009). The science and practice of bone health in oncology: managing bone loss and metastasis in patients with solid tumors. J.Natl.Compr.Canc.Netw., 7 Suppl 7, pp. S1-29, 1540-1405

Lomaga, M. A.; Yeh, W. C.; Sarosi, I.; Duncan, G. S.; Furlonger, C.; Ho, A.; Morony, S.; Capparella, C.; Van, G.; Kaufman, S.; van der Heiden, A.; Itie, A.; Wakeham, A.; Khoo, W.; Sasaki, T.; Cao, Z.; Penninger, J. M.; Paige, C. J.; Lacey, D. L.; Dunstan, C. R.; Boyle, W. J.; Goeddel, D. V. & Mak, T. W. (1999). TRAF6 deficiency results in osteopetrosis and defective interleukin-1, CD40, and LPS signaling. Genes Dev., 13, No.8, pp. 1015-1024, 0890-9369

Lorch, G.; Viatchenko-Karpinski, S.; Ho, H. T.; Dirksen, W. P.; Toribio, R. E.; Foley, J.; Györke, S. & Rosol, T. J. (2011). The calcium-sensing receptor is necessary for the rapid development of hypercalcemia in human lung squamous cell carcinoma. Neoplasia, 13, No.5, pp. 428-438, 1522-8802

Lu, T. & Stark, G. R. (2004). Cytokine overexpression and constitutive NFkappaB in cancer. Cell Cycle, 3, No.9, pp. 1114-1117, 1538-4101

Matsumoto, K.; Murao, K.; Imachi, H.; Nishiuchi, T.; Cao, W.; Yu, X.; Li, J.; Ahmed, R. A.; Iwana, H.; Kobayashi, R.; Tokumitsu, H. & Ishida, T. (2008). The role of calcium/calmodulin-dependent protein kinase cascade on MIP-1alpha gene expression of ATL cells. Exp.Hematol., 36, No.4, pp. 390-400, 0301-472X

Maurer, M. & von, S. E. (2004). Macrophage inflammatory protein-1. Int.J.Biochem.Cell Biol., 36, No.10, pp. 1882-1886, 1357-2725

McDonald, I. M.; Austin, C.; Buck, I. M.; Dunstone, D. J.; Gaffen, J.; Griffin, E.; Harper, E. A.; Hull, R. A.; Kalindjian, S. B.; Linney, I. D.; Low, C. M.; Patel, D.; Pether, M. J.; Raynor, M.; Roberts, S. P.; Shaxted, M. E.; Spencer, J.; Steel, K. I.; Sykes, D. A.; Wright, P. T. & Xun, W. (2007). Discovery and characterization of novel, potent, non-peptide parathyroid hormone-1 receptor antagonists. J.Med.Chem., 50, No.20, pp. 4789-4792, 0022-2623

Meghji, S.; Crean, S. J.; Hill, P. A.; Sheikh, M.; Nair, S. P.; Heron, K.; Henderson, B.; Mawer, E. B. & Harris, M. (1998). Surface-associated protein from Staphylococcus aureus stimulates osteoclastogenesis: possible role in S. aureus-induced bone pathology. Br.J.Rheumatol., 37, No.10, pp. 1095-1011, 0263-7103

Mellanby, R. J.; Craig, R.; Evans, H. & Herritage, M. E. (2006). Plasma concentrations of parathyroid hormone-related protein in dogs with potential disorders of calcium metabolism. Vet.Rec., 159, No.25, pp. 833-838, 0042-4900

Menu, E.; De, L. E.; De, R. H.; Coulton, L.; Imanishi, T.; Miyashita, K.; Van, V. E.; Van, R., I; Van, C. B.; Horuk, R.; Croucher, P. & Vanderkerken, K. (2006). Role of CCR1 and CCR5 in homing and growth of multiple myeloma and in the development of osteolytic lesions: a study in the 5TMM model. Clin.Exp.Metastasis, 23, No.5-6, pp. 291-300, 0262-0898

Merkel, K. D.; Erdmann, J. M.; McHugh, K. P.; Abu-Amer, Y.; Ross, F. P. & Teitelbaum, S. L. (1999). Tumor necrosis factor-alpha mediates orthopedic implant osteolysis. Am.J.Pathol., 154, No.1, pp. 203-210, 0002-9440

www.intechopen.com
Mitra-Kaushik, S.; Harding, J.; Hess, J.; Schreiber, R. & Ratner, L. (2004a). Enhanced tumorigenesis in HTLV-1 tax-transgenic mice deficient in interferon-gamma. Blood, 104, No.10, pp. 3305-3311, 0006-4971

Mitra-Kaushik, S.; Harding, J. C.; Hess, J. L. & Ratner, L. (2004b). Effects of the proteasome inhibitor PS-341 on tumor growth in HTLV-1 Tax transgenic mice and Tax tumor transplants. Blood, 104, No.3, pp. 802-809, 0006-4971

Mizuno, A.; Amizuka, N.; Irie, K.; Murakami, A.; Fujise, N.; Kanno, T.; Sato, Y.; Nakagawa, N.; Yasuda, H.; Mochizuki, S.; Gomibuchi, T.; Yano, K.; Shima, N.; Washida, N.; Tsuda, E.; Morinaga, T.; Higashio, K. & Ozawa, H. (1998). Severe osteoporosis in mice lacking osteoclastogenesis inhibitory factor/osteoprotegerin. Biochem.Biophys.Res.Commun., 247, No.3, pp. 610-615, 0006-291X

Mundy, G. R. & Martin, T. J. (1982). The hypercalcemia of malignancy: pathogenesis and management. Metabolism, 31, No.12, pp. 1247-1277, 0026-0495

Nadella, M. V.; Dirksen, W. P.; Nadella, K. S.; Shu, S.; Cheng, A. S.; Morgenstern, J. A.; Richard, V.; Fernandez, S. A.; Huang, T. H.; Guttridge, D. & Rosol, T. J. (2007). Transcriptional regulation of parathyroid hormone-related protein promoter P2 by NF-kappaB in adult T-cell leukemia/lymphoma. Leukemia, 21, No.8, pp. 1752-1762, 0887-6924

Nadella, M. V.; Kisseberth, W. C.; Nadella, K. S.; Thudi, N. K.; Thamm, D. H.; McNiel, E. A.; Yilmaz, A.; Boris-Lawrie, K. & Rosol, T. J. (2008). NOD/SCID mouse model of canine T-cell lymphoma with humoral hypercalcaemia of malignancy: cytokine gene expression profiling and in vivo bioluminescent imaging. Vet.Comp Oncol., 6, No.1, pp. 39-54, 1476-5810

Narimatsu, H.; Morishita, Y.; Shimada, K.; Ozeki, K.; Kohno, A.; Kato, Y. & Nagasaka, T. (2003). Primary cutaneous diffuse large B cell lymphoma: a clinically aggressive case. Intern.Med., 42, No.4, pp. 354-357, 0918-2918

Nasr, R.; El-Sabban, M. E.; Karam, J. A.; Dbaibo, G.; Kfoury, Y.; Arnulf, B.; Lepelletier, Y.; Bex, F.; de, T. H.; Hermine, O. & Bazarbachi, A. (2005). Efficacy and mechanism of action of the proteasome inhibitor PS-341 in T-cell lymphomas and HTLV-I associated adult T-cell leukemia/lymphoma. Oncogene, 24, No.3, pp. 419-430, 0950-9232

Nosaka, K.; Miyamoto, T.; Sakai, T.; Mitsuya, H.; Suda, T. & Matsuoka, M. (2002). Mechanism of hypercalcemia in adult T-cell leukemia: overexpression of receptor activator of nuclear factor kappaB ligand on adult T-cell leukemia cells. Blood, 99, No.2, pp. 634-640, 0006-4971

Oba, Y.; Lee, J. W.; Ehrlich, L. A.; Chung, H. Y.; Jelinek, D. F.; Callander, N. S.; Horuk, R.; Choi, S. J. & Roodman, G. D. (2005). MIP-1alpha utilizes both CCR1 and CCR5 to induce osteoclast formation and increase adhesion of myeloma cells to marrow stromal cells. Exp.Hematol., 33, No.3, pp. 272-278, 0301-472X

Okada, Y.; Tsukada, J.; Nakano, K.; Tonai, S.; Mine, S. & Tanaka, Y. (2004). Macrophage inflammatory protein-1alpha induces hypercalcemia in adult T-cell leukemia. J.Bone Miner.Res., 19, No.7, pp. 1105-1111, 0884-0431
Olivo, R. A.; Martins, F. F.; Soares, S. & Moraes-Souza, H. (2008). Adult T-cell leukemia/lymphoma: report of two cases. Rev.Soc.Bras.Med.Trop., 41, No.3, pp. 288-292, 0037-8682

Oyajobi, B. O.; Franchin, G.; Williams, P. J.; Pulkrabek, D.; Gupta, A.; Munoz, S.; Grubbs, B.; Zhao, M.; Chen, D.; Sherry, B. & Mundy, G. R. (2003). Dual effects of macrophage inflammatory protein-1alpha on osteolysis and tumor burden in the murine 5TGM1 model of myeloma bone disease. Blood, 102, No.1, pp. 311-319, 0006-4971

Parrula, C.; Zimmerman, B.; Nadella, P.; Shu, S.; Rosol, T.; Fernandez, S.; Lairmore, M. & Niewiesk, S. (2009). Expression of tumor invasion factors determines systemic engraftment and induction of humoral hypercalcemia in a mouse model of adult T-cell leukemia. Vet.Pathol., 46, No.5, pp. 1003-1014, 0300-9858

Pennisi, A.; Li, X.; Ling, W.; Khan, S.; Zangari, M. & Yaccoby, S. (2009). The proteasome inhibitor, bortezomib suppresses primary myeloma and stimulates bone formation in myelomatous and nonmyelomatous bones in vivo. Am.J.Hematol., 84, No.1, pp. 6-14, 0361-8969

Phillips, K. E.; Herring, B.; Wilson, L. A.; Rickford, M. S.; Zhang, M.; Goldman, C. K.; Tso, J. Y. & Waldmann, T. A. (2000). IL-2Ralpha-Directed monoclonal antibodies provide effective therapy in a murine model of adult T-cell leukemia by a mechanism other than blockade of IL-2/IL-2Ralpha interaction. Cancer Res., 60, No.24, pp. 6977-6984, 0008-5472

Qiang, Y. W.; Hu, B.; Chen, Y.; Zhong, Y.; Shi, B.; Barlogie, B. & Shaughnessy, J. D., Jr. (2009). Bortezomib induces osteoblast differentiation via Wnt-independent activation of beta-catenin/TCF signaling. Blood, 113, No.18, pp. 4319-4330, 0006-4971

Quinn, J. M. & Gillespie, M. T. (2005). Modulation of osteoclast formation. Biochem.Biophys.Res.Commun., 328, No.3, pp. 739-745, 0006-291X

Richard, V.; Lairmore, M. D.; Green, P. L.; Feuer, G.; Erbe, R. S.; Albrecht, B.; D'Souza, C.; Keller, E. T.; Dai, J. & Rosol, T. J. (2001). Humoral hypercalcemia of malignancy: severe combined immunodeficient/beige mouse model of adult T-cell lymphoma independent of human T-cell lymphotropic virus type-1 tax expression. Am.J.Pathol., 158, No.6, pp. 2219-2228, 0002-9580

Richard, V.; Nadella, M. V.; Green, P. L.; Lairmore, M. D.; Feuer, G.; Foley, J. G. & Rosol, T. J. (2005). Transcriptional regulation of parathyroid hormone-related protein promoter P3 by ETS-1 in adult T-cell leukemia/lymphoma. Leukemia, 19, No.7, pp. 1175-1183, 0887-6924

Roodman, G. D. (1997). Mechanisms of bone lesions in multiple myeloma and lymphoma. Cancer, 80, No.8 Suppl, pp. 1557-1563, 0008-543X

Roodman, G. D. (2001). Biology of osteoclast activation in cancer. J.Clin.Oncol., 19, No.15, pp. 3562-3571, 0732-183X

Rosol, T. J.; Nagode, L. A.; Couto, C. G.; Hammer, A. S.; Chew, D. J.; Peterson, J. L.; Ayl, R. D.; Steinmeyer, C. L. & Capen, C. C. (1992). Parathyroid hormone (PTH)-related protein, PTH, and 1,25-dihydroxyvitamin D in dogs with cancer-associated hypercalcemia. Endocrinology, 131, No.3, pp. 1157-1164, 0013-7227

Ruddle, N. H.; Li, C. B.; Horne, W. C.; Santiago, P.; Troiano, N.; Jay, G.; Horowitz, M. & Baron, R. (1993). Mouse transgenic for HTLV-I LTR-tax exhibit tax expression in
Mechanisms of Humoral Hypercalcemia of Malignancy in Leukemia/Lymphoma

bone, skeletal alterations, and high bone turnover. Virology, 197, No.1, pp. 196-204, 0042-6822

Sagara, Y.; Inoue, Y.; Sagara, Y. & Kashiwagi, S. (2009). Involvement of molecular mimicry between human T-cell leukemia virus type 1 gp46 and osteoprotegerin in induction of hypercalcemia. Cancer Sci., 100, No.3, pp. 490-496, 1347-9032

Saidak, Z.; Mentaverri, R. & Brown, E. M. (2009). The role of the calcium-sensing receptor in the development and progression of cancer. Endocr.Rev., 30, No.2, pp. 178-195, 0163-769X

Sato, K.; Onuma, E.; Yocum, R. C. & Ogata, E. (2003). Treatment of malignancy-associated hypercalcemia and cachexia with humanized anti-parathyroid hormone-related protein antibody. Semin.Oncol., 30, No.5 Suppl 16, pp. 167-173, 0093-7754

Sato, K.; Suematsu, A.; Okamoto, K.; Yamaguchi, A.; Morishita, Y.; Kadono, Y.; Tanaka, S.; Kodama, T.; Akira, S.; Iwakura, Y.; Cua, D. J. & Takayanagi, H. (2006). Th17 functions as an osteoclastogenic helper T cell subset that links T cell activation and bone destruction. J.Exp.Med., 203, No.12, pp. 2673-2682, 0022-1007

Satou, Y.; Nosaka, K.; Koya, Y.; Yasunaga, J. I.; Toyokuni, S. & Matsuoka, M. (2004). Proteasome inhibitor, bortezomib, potently inhibits the growth of adult T-cell leukemia cells both in vivo and in vitro. Leukemia, 18, No.8, pp. 1357-1363, 0887-6924

Schwarz, E. M. & Ritchlin, C. T. (2007). Clinical development of anti-RANKL therapy. Arthritis Res.Ther., 9 Suppl 1, p. S7, 1478-6354

Seymour, J. F. & Gagel, R. F. (1993). Calcitriol: the major humoral mediator of hypercalcemia in Hodgkin's disease and non-Hodgkin's lymphomas. Blood, 82, No.5, pp. 1383-1394, 0006-4971

Sharan, K.; Siddiqui, J. A.; Swarnkar, G. & Chattopadhyay, N. (2008). Role of calcium-sensing receptor in bone biology. Indian J.Med.Res., 127, No.3, pp. 274-286, 0971-5916

Sharma, V. & May, C. C. (1999). Human T-cell lymphotrophic virus type-I tax gene induces secretion of human macrophage inflammatory protein-1alpha. Biochem.Biophys.Res.Commun., 262, No.2, pp. 429-432, 0006-291X

Shu, S. T.; Martin, C. K.; Thudi, N. K.; Dirksen, W. P. & Rosol, T. J. (2010). Osteolytic bone resorption in adult T-cell leukemia/lymphoma. Leuk.Lymphoma, 51, No.4, pp. 702-714, 1042-8194

Shu, S. T.; Nadella, M. V.; Dirksen, W. P.; Fernandez, S. A.; Thudi, N. K.; Werbeck, J. L.; Lairmore, M. D. & Rosol, T. J. (2007). A novel bioluminescent mouse model and effective therapy for adult T-cell leukemia/lymphoma. Cancer Res., 67, No.24, pp. 11859-11866, 0008-5472

Simonet, W. S.; Lacey, D. L.; Dunstan, C. R.; Kelley, M.; Chang, M. S.; Luthy, R.; Nguyen, H. Q.; Wooden, S.; Bennett, L.; Boone, T.; Shimamoto, G.; DeRose, M.; Elliott, R.; Colombero, A.; Tan, H. L.; Trail, G.; Sullivan, J.; Davy, E.; Bucay, N.; Renshaw-Gegg, L.; Hughes, T. M.; Hill, D.; Pattison, W.; Campbell, P.; Sander, S.; Van, G.; Tarpley, J.; Derby, P.; Lee, R. & Boyle, W. J. (1997). Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell, 89, No.2, pp. 309-319, 0092-8674
Sims, N. A.; Jenkins, B. J.; Quinn, J. M.; Nakamura, A.; Glatt, M.; Gillespie, M. T.; Ernst, M. & Martin, T. J. (2004). Glycoprotein 130 regulates bone turnover and bone size by distinct downstream signaling pathways. J.Clin.Invest, 113, No.3, pp. 379-389, 0021-9738

Sordillo, E. M. & Pearse, R. N. (2003). RANK-Fc: a therapeutic antagonist for RANK-L in myeloma. Cancer, 97, No.3 Suppl, pp. 802-812, 0008-543X

Stewart, A. F. (2002). Hyperparathyroidism, humoral hypercalcemia of malignancy, and the anabolic actions of parathyroid hormone and parathyroid hormone-related protein on the skeleton. J.Bone Miner.Res., 17, No.5, pp. 758-762, 0884-0431

Stewart, A. F. (2005). Clinical practice. Hypercalcemia associated with cancer. N.Engl.J.Med., 352, No.4, pp. 373-379, 0028-4793

Suva, L. J.; Winslow, G. A.; Wettenhall, R. E.; Hammonds, R. G.; Moseley, J. M.; Diefenbach-Jagger, H.; Rodda, C. P.; Kemp, B. E.; Rodriguez, H.; Chen, E. Y. & . (1987). A parathyroid hormone-related protein implicated in malignant hypercalcemia: cloning and expression. Science, 237, No.4817, pp. 893-896, 0036-8075

Takaori-Kondo, A.; Imada, K.; Yamamoto, I.; Kunitomi, A.; Numata, Y.; Sawada, H. & Uchiyama, T. (1998). Parathyroid hormone-related protein-induced hypercalcemia in SCID mice engrafted with adult T-cell leukemia cells. Blood, 91, No.12, pp. 4747-4751, 0006-4971

Takayanagi, H. (2007). Osteoimmunology: shared mechanisms and crosstalk between the immune and bone systems. Nat.Rev.Immunol., 7, No.4, pp. 292-304, 1474-1733

Takeuchi, Y.; Fukumoto, S.; Nakayama, K.; Tamura, Y.; Yanagisawa, A. & Fujita, T. (2002). Parathyroid hormone-related protein induced coupled increases in bone formation and resorption markers for 7 years in a patient with malignant islet cell tumors. J.Bone Miner.Res., 17, No.5, pp. 753-757, 0884-0431

Tan, C. & Waldmann, T. A. (2002). Proteasome inhibitor PS-341, a potential therapeutic agent for adult T-cell leukemia. Cancer Res., 62, No.4, pp. 1083-1086, 0008-5472

Tanaka, S.; Takahashi, N.; Udagawa, N.; Tamura, T.; Akatsu, T.; Stanley, E. R.; Kurokawa, T. & Suda, T. (1993). Macrophage colony-stimulating factor is indispensable for both proliferation and differentiation of osteoclast progenitors. J.Clin.Invest, 91, No.1, pp. 257-263, 0021-9738

Terpos, E.; Heath, D. J.; Rahemtulla, A.; Zervas, K.; Chantry, A.; Anagnostopoulos, A.; Pouli, A.; Katodritou, E.; Verrou, E.; Vervessou, E. C.; Dimopoulos, M. A. & Croucher, P. I. (2006). Bortezomib reduces serum dickkopf-1 and receptor activator of nuclear factor-kappaB ligand concentrations and normalises indices of bone remodelling in patients with relapsed multiple myeloma. Br.J.Haematol., 135, No.5, pp. 688-692, 0007-1048

Tsubaki, M.; Kato, C.; Manno, M.; Ogaki, M.; Satou, T.; Itoh, T.; Kusunoki, T.; Tanimori, Y.; Fujiwara, K.; Matsuoka, H. & Nishida, S. (2007). Macrophage inflammatory protein-1alpha (MIP-1alpha) enhances a receptor activator of nuclear factor kappaB ligand (RANKL) expression in mouse bone marrow stromal cells and osteoblasts through MAPK and PI3K/Akt pathways. Mol.Cell Biochem., 304, No.1-2, pp. 53-60, 0300-8177
Unal, S.; Durmaz, E.; Erkocoglu, M.; Bayrakci, B.; Bircan, O.; Alikasifoglu, A. & Cetin, M. (2008). The rapid correction of hypercalcemia at presentation of acute lymphoblastic leukemia using high-dose methylprednisolone. Turk.J.Pediatr., 50, No.2, pp. 171-175, 0041-4301

Vanderschueren, B.; Dumon, J. C.; Oleffe, V.; Heymans, C.; Gerain, J. & Body, J. J. (1994). Circulating concentrations of interleukin-6 in cancer patients and their pathogenic role in tumor-induced hypercalcemia. Cancer Immunol.Immunother., 39, No.5, pp. 286-290, 0340-7004

von Metzler, I.; Krebbel, H.; Hecht, M.; Manz, R. A.; Fleissner, C.; Miett, M.; Kaiser, M.; Jakob, C.; Sterz, J.; Kleeberg, L.; Heider, U. & Sezer, O. (2007). Bortezomib inhibits human osteoclastogenesis. Leukemia, 21, No.9, pp. 2025-2034, 0887-6924

Wano, Y.; Hattori, T.; Matsuoka, M.; Takatsuki, K.; Chua, A. O.; Gubler, U. & Greene, W. C. (1997). Interleukin 1 gene expression in adult T cell leukemia. J.Clin.Invest, 80, No.3, pp. 911-916, 0021-9738

Watanabe, T.; Yamaguchi, K.; Takatsuki, K.; Osame, M. & Yoshida, M. (1990). Constitutive expression of parathyroid hormone-related protein gene in human T cell leukemia virus type 1 (HTLV-1) carriers and adult T cell leukemia patients that can be trans-activated by HTLV-1 tax gene. J.Exp.Med., 172, No.3, pp. 759-765, 0022-1007

Weitzmann, M. N. & Pacifici, R. (2005). The role of T lymphocytes in bone metabolism. Immunol.Rev., 208, pp. 154-168, 0105-2896

Wysolmerski, J. J.; Philbrick, W. M.; Dunbar, M. E.; Lanske, B.; Kronenberg, H. & Broadus, A. E. (1998). Rescue of the parathyroid hormone-related protein knockout mouse demonstrates that parathyroid hormone-related protein is essential for mammary gland development. Development, 125, No.7, pp. 1285-1294, 0950-1991

Xu, Z.; Hurchla, M. A.; Deng, H.; Uluckan, O.; Bu, F.; Berdy, A.; Eagleton, M. C.; Heller, E. A.; Floyd, D. H.; Dirksen, W. P.; Shu, S.; Tanaka, Y.; Fernandez, S. A.; Rosol, T. J. & Weilbaecher, K. N. (2009). Interferon-gamma targets cancer cells and osteoclasts to prevent tumor-associated bone loss and bone metastases. J.Biol.Chem., 284, No.7, pp. 4658-4666, 0006-291X

Yamaguchi, T. (2008). The calcium-sensing receptor in bone. J.Bone Miner.Metab, 26, No.4, pp. 301-311, 0914-8779

Yang, X.; Halladay, D.; Onyia, J. E.; Martin, T. J. & Chandrasekhar, S. (2002). Protein Kinase C is a mediator of the synthesis and secretion of osteoprotegerin in osteoblast-like cells. Biochem.Biophys.Res.Commun., 290, No.1, pp. 42-46, 0006-291X

Yarbro, C. E.; Frogge, M. H. & Goodman, M. (2003). Cancer Symptom Management, p. 455, 0763721425

Zaidi, M.; Inzerillo, A. M.; Moonga, B. S.; Bevis, P. J. & Huang, C. L. (2002). Forty years of calcitonin--where are we now? A tribute to the work of Iain Macintyre, FRS. Bone, 30, No.5, pp. 655-663, 8756-3282

Zhang, J.; Dai, J.; Yao, Z.; Lu, Y.; Dougall, W. & Keller, E. T. (2003). Soluble receptor activator of nuclear factor kappaB Fc diminishes prostate cancer progression in bone. Cancer Res., 63, No.22, pp. 7883-7890, 0008-5472
Zhong, Y.; Armbrecht, H. J. & Christakos, S. (2009). Calcitonin, a regulator of the 25-hydroxyvitamin D3 1alpha-hydroxylase gene. J.Biol.Chem., 284, No.17, pp. 11059-11069, 0021-9258

Zlotnik, A. & Yoshie, O. (2000). Chemokines: a new classification system and their role in immunity. Immunity., 12, No.2, pp. 121-127, 1074-7613
The purpose of this book is to provide a comprehensive review of the scientific advances in T-cell malignancies and to highlight the most relevant findings that will help the reader understand both basic mechanisms of the disease and future directions that are likely to lead to novel therapies. In order to assure a thorough approach to these problems, contributors include basic scientists, translational researchers and clinicians who are experts in this field. Thus, the target audience for this book includes both basic scientists who will use this book as a review of the advances in our fundamental knowledge of the molecular mechanisms of T-cell malignancies, as well as clinicians who will use this book as a tool to understand rationales for the development of novel treatments for these diseases.

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