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Review Article

# Autocrine motility factor and its receptor expression in musculoskeletal tumors

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ABSTRACT

Management of aggressive malignant musculoskeletal tumors is clinically challenging and awaits the identification of regulator(s) that can be therapeutically used to improve patient outcome. Autocrine motility factor (AMF), a secreted cytokine, is known to alter the bone microenvironment by linking to its receptor AMFR (AMF Receptor), leading to tumor progression. It was noted that both the ligand and its receptor belong to the moonlighting family of proteins, as they contribute to intracellular metabolic function such as glycolysis and gluconeogenesis by expressing glucose-6-phosphate isomerase AMF/GPI and higher protein degradation by expressing AMFR/gp78 functioning as ubiquitin ligase activity. Thus, AMF/GPI and AMFR/gp78 contribute to higher metabolic turnover of protein and glucose. Recently, a large-scale cohort study including 23 different histological types of musculoskeletal tumors revealed that patients with osteosarcoma, multiple myeloma, rhabdomyosarcoma, and angiosarcoma tend to express higher levels of AMF, whereas multiple myeloma patients expressed high levels of AMFR. Consistently, the cellular data showed that a variety of musculoskeletal tumors express AMF and components of bone microenvironment express AMFR. Thus, a novel outlook suggests a cellular link and cross-talk between musculoskeletal tumors and the skeletal milieu are regulated by AMF-AMFR signaling. This review will highlight the pharmacological need for AMF and AMFR inhibitors as unmet medical needs for patients with malignant musculoskeletal tumors.

## 1. Discovery of AMF and AMFR

Malignant musculoskeletal tumors originate in bone or soft tissues such as muscle, cartilage, connective tissues and metastatic foci from primary lesion to the skeleton(s) [1,2]. In some cases, they show wider invasion to the surrounding soft tissues, or metastatic spreading to other parts of the body. Malignant musculoskeletal tumors include osteosarcoma, Ewing's sarcoma, undifferentiated pleomorphic sarcoma, chondrosarcoma, chordoma, giant cell tumor, multiple myeloma, bone metastasis of prostate cancer, breast cancer or other origins, synovial sarcoma, liposarcoma, rhabdomyosarcoma, leiomyosarcoma, fibrosarcoma, angiosarcoma, hemangiopericytoma, malignant peripheral nerve sheath tumor, alveolar soft part sarcoma, clear cell sarcoma and epithelioid sarcoma, to name but a few [3–6]. To understand the aggressive behavior of malignant musculoskeletal tumors, several factors associated with invasion and metastasis have been identified.

In 1986, a cell motility-stimulating factor was isolated from the cell culture medium of human melanoma cells. The molecule has been termed 'Autocrine Motility Factor (AMF)' [7]. Then in 1991, AMF was found to stimulate cell motility *via* a receptor-mediated signaling pathway by binding of a receptor, cell surface glycoprotein of 78 kDa (gp78) [8]. The ability to locomote is fundamental to the acquisition of invasive and metastatic properties of tumor cells, so it was expected to be one of the crucial therapeutic targets for patients with malignant tumors. Following AMF and AMFR isolation from culture medium of human fibrosarcoma cells [9], AMF was cloned [10], and was found to be a moon-lighting protein previously characterized as glucose-6-phosphate isomerase (GPI), neuroleukin (NLK) and maturation factor (MF) [9]. In addition to the fact that AMF is a potent stimulant of tumor migration, AMF has been found to induce cell proliferation [11],

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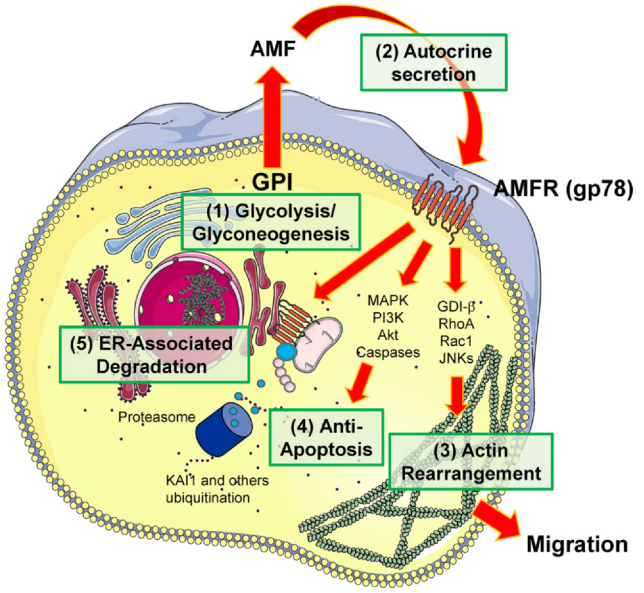


**Fig. 1.** Visualization of AMF/GPI and AMFR/gp78 function. (1) Intracellularly, AMF works as glucose-6-phosphate isomerase (GPI), contributing to glycolysis and gluconeogenesis. (2) Extracellularly, secreted AMF *via* non classical secretion pathway interact with external domain of AMFR in an autocrine manner. (3) The interaction leads to activates small Rho-like GTPase, Rac1, RhoA, JNK1 and JNK2, inducing actin fiber rearrangement, which contribute to enhance tumor migration. (4) AMF signals also activate MAPK, PI3K, and Akt, which inactivates caspases, leading to suppression of apoptosis. (5) AMFR induces protein degradation by expressing ER membrane-anchored E3 ubiquitin ligase activity, which plays a key role in ER-associated degradation (ERAD). The ERAD substrates include the metastasis suppressor KAI1. The figure was produced using Servier Medical Art with permission.

angiogenesis [12], and resistance to chemotherapy-induced apoptosis [13]. Intracellular AMF/GPI is an essential cytosolic enzyme of the sugar metabolism both in glycolysis and gluconeogenesis pathways, catalyzing the interconversion of glucose 6-phosphate and fructose 6-phosphate [14,15]. Little is known regarding the regulatory mechanism of AMF protein expression, since the genomic promoter of AMF is still lacking, except that a minisatellite in intron 9 of human PGI genes stimulated transcription from GPI promoter [16]. Certainly, hypoxia induces AMF expression via HIF-1α [17]; however, there have been few reports on the proteins or conditions that downregulate AMF expression. It would be a significant achievement to suppress AMF to inhibit the aggressive behavior of malignant musculoskeletal tumors [Fig. 1].

Previously, a purification and cloning study of AMFR revealed that intriguingly, the nucleotide and predicted amino acid sequence of the AMFR/gp78 showed significant homology with the human suppressor/oncogene p53 protein [18]. Since then, the molecular function of AMFR has been further investigated in oncology. Structurally, AMFR is one of the seven-transmembrane proteins (amino acid: 82–102, 122–142, 145–165, 186–206, 215–235, 276–296, 429–449), composed by several domains; RING-type Zinc finger (amino acid: 341–379), a CUE domain (amino acid: 456–498), and a VCP/p97-interacting motif (amino acid: 622–640), whereby the extracellular domain recognizes AMF. Following the above AMF-AMFR interaction, it activates a pertussis toxin sensitive G protein, upregulating GDI-β, which triggers small Rho-like GTPase, Rac1 and RhoA activation. It is the upregulated signaling of JNK1 and JNK2, resulting in actin fiber rearrangement, that modulates tumor cell motility, invasion, and metastasis [19,20]. AMF-AMFR interaction results in a positive feedback loop in an autocrine manner, dynamically transforming tumor cells into an aggressive phenotype [21]. Another signaling to PI3K activates Akt/PKB, leading to inactivation of BAD and caspase-9. This results in the acquisition of the apoptosis-resistant phenotype [19] [Fig. 1].

As for the intracellular domain of AMFR, over the past three decades, ubiquitin ligase activity leading to proteasome degradation has been reported to be associated with neurodegeneration disorders, and cancer progression. In detail, AMFR is localized on the cell surface, and binds with AMF. Beside the ligand-receptor interaction, intracellular AMFR/gp78, is localized at the mitochondria-associated endoplasmic reticulum (ER) domain, where it induces mitochondrial fragmentation [22]. The ER membrane-anchored E3 ubiquitin ligase plays a key role in ER-associated degradation (ERAD). The ERAD substrates processed by gp78 include ApoB lipoprotein, HMG CoA reductase, CD3-delta, T-cell receptor, and intriguingly, the metastasis suppressor KAI1 [23]. Consistently, the expression of AMFR/gp78 has been reported to be significantly correlated with more advanced tumor stage and decreased survival rates in a variety of tumors [24–32]. Similarly in sarcoma, an *in vivo* experiment clearly showed that AMFR expression was associated with shorter survival time by degradation of KAI1 [23] [Fig. 1].

## 2. Molecular profile of AMF expression in malignant musculoskeletal tumors

Malignant musculoskeletal tumors originate in bone or soft tissues such as muscle, cartilage, connective tissues and metastatic *foci* from a primary lesion to the skeleton(s) [1,2]. In some cases, they show a wider invasion to the surrounding soft tissues, and/or metastatic dissemination to other organs of the body. The umbrella of malignant musculoskeletal tumor includes osteosarcoma, Ewing's sarcoma, chordoma, giant cell tumor, multiple myeloma, bone metastasis of prostate cancer, breast cancer or other origins, synovial sarcoma, undifferentiated pleomorphic sarcoma, chondrosarcoma, liposarcoma, rhabdomyosarcoma, leiomyosarcoma, fibrosarcoma, angiosarcoma, malignant peripheral nerve sheath tumor, alveolar soft part sarcoma, clear cell sarcoma, epithelioid sarcoma, to name but a few [3–6]. Recently, it was shown in a large-scale cohort study of 1348 patients including 23 histological types of musculoskeletal tumors unveiled that the patients with osteosarcoma, multiple myeloma, rhabdomyosarcoma, and angiosarcoma tend to express higher levels of AMF [33]. Similarly, cellular expression study indicated that a higher level of AMF was observed in osteosarcoma (Saos-2 and HS-Os-1), Ewing's sarcoma (Hs-863), synovial sarcoma (HS-SY-II), liposarcoma (SW-872), rhabdomyosarcoma (KYM-1 and RMS-YM), fibrosarcoma (HT-1080), myeloma (PCM-6), leiomyosarcoma (Hs-5), liposarcoma (KMLS-1), giant cell tumor (Hs-706), chondrosarcoma (SW-1353), and epithelioid sarcoma (HS-ES-1 and HS-ES-2R) [Fig. 2-A]. The upregulated AMF secretion induces the metastasis of sarcomas, while silencing leads to mesenchymal-to-epithelial transition, and inhibition of metastasis of sarcoma [34]. AMF/GPI is suggested to be a possible predictor of metastasis in bone and soft tissue tumors [35], whereby affecting tumor stage and survival, suggesting AMF suppression to be considered as therapeutic target for malignant musculoskeletal tumors.

## 3. Prevalent expression of AMFR in bone microenvironment

In the bone microenvironment, a number of AMFR-expressing cells were identified including mature osteoclasts, osteocytes, macrophages, bone marrow mesenchymal stem cells, microvascular endothelial cells, osteoclast precursors, osteoblasts, $CD4^+$ T cells, bone marrow stromal cells, $CD8^+$ T cells, and neutrophils [Fig. 2-B]. Thus, it is suggested that a pathological insight on the cellular association among musculoskeletal tumors and the skeletal milieu are mediated, in part, by AMF-AMFR interaction [Fig. 3]. Of note, mature osteoclast are highly AMFR expressing cells, so that they are influenced by the tumor-secreted AMF in a paracrine manner, thus being sensitive responders. Consistently, recombinant AMF increased the formation of osteoclast-like multinucleated cells strongly in bone marrow cell culture [36]. In addition, osteoclasts-expressing AMFR were reported to be involved in osteoclastogenesis [37]. Also, secreted AMF interacted with osteoblasts,

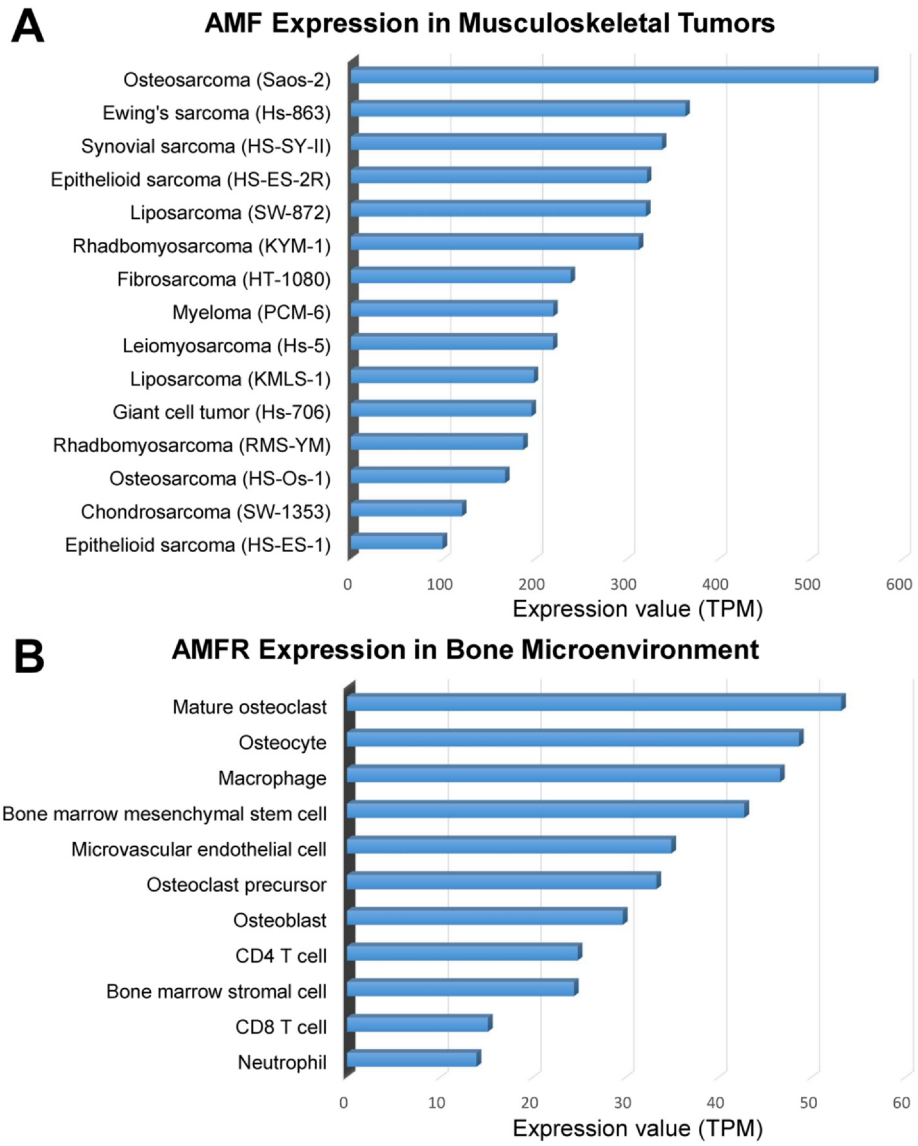


**Fig. 2.** (A) Expression of AMF in a variety of musculoskeletal tumors. (B) Expression of AMFR in the cellular compartment of bone microenvironment. The expression levels of each tumor were based on the CAGE transcriptome data. In the table, the unit of the value indicates transcripts per kilobase million (TPM). The unit defines the counts per length of transcript kilobase per million reads mapped. The values have been normalized in the datasets, allowing the molecular expression levels to be compared. The data suggest a novel cellular link and cross talking between musculoskeletal tumors and bone microenvironment via AMF-AMFR interaction.

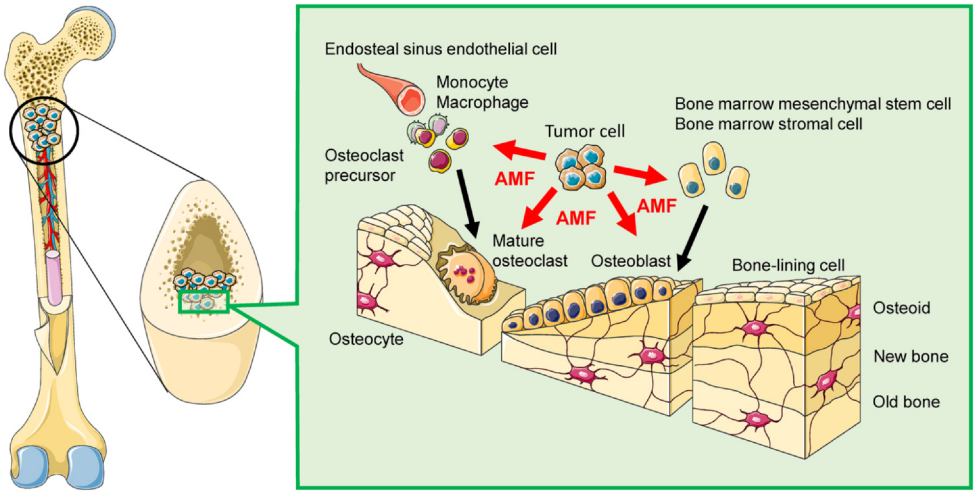


**Fig. 3.** Illustration of cellular interactions in bone tumor microenvironment. Bone microenvironment is composed by osteoblast, osteocyte, osteoclast precursor, mature osteoclast, bone marrow stromal cell, bone marrow mesenchymal stem cells, endothelial cells of endosteal sinus and immunological cells including neutrophil, lymphocyte, and macrophage. Tumor cells interact with these cellular components of bone microenvironment. The figure was produced using Servier Medical Art with permission.

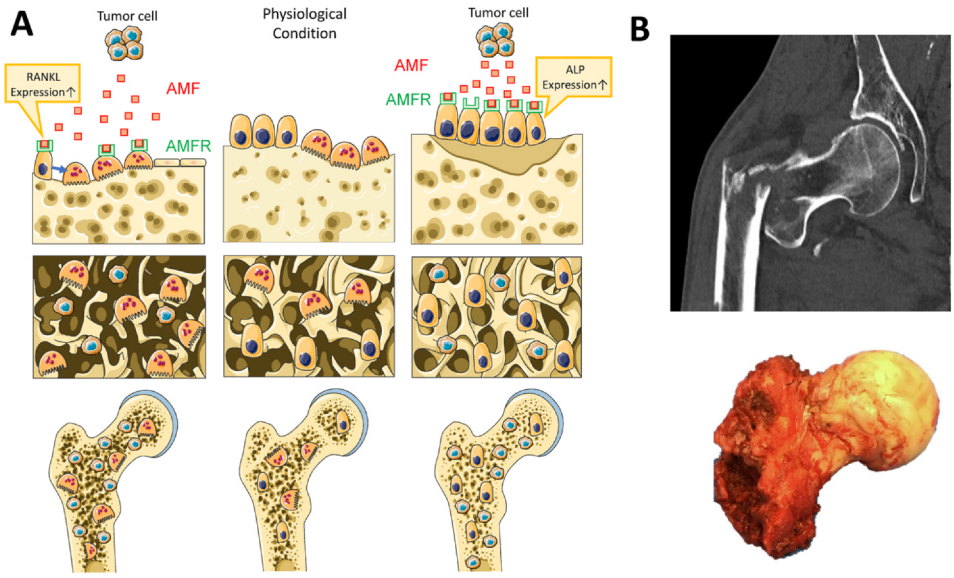


**Fig. 4.** (A) The alteration of bone microenvironment interfered by tumor cells. (Left) The influence of AMF secretion on osteoclasts. The secreted AMF interacted with the AMFR on osteoclast, leading to increase the expression of RANKL, an osteoclast differentiation regulator, which result in osteolysis. (Center) Depicting the physiological bone metabolism, whereby bone production and absorption is balanced. (Right) The influence of AMF secretion on osteoblasts. The secreted AMF interacted with the AMFR on osteoblast, leading to increase the alkaline phosphatase (ALP) activity, which result in osteosclerosis. The figure was produced using Servier Medical Art with permission. (B) Clinical consequence of aberrant bone remodeling interfered by tumor cells. The CT hip images demonstrate the pathological fracture of femoral neck lesion whereby tumor has grown. A gross specimen shows a surgically extracted femoral head as an example of osteolytic remodeling with cortical erosion and loss of cancellous bone. Clinical images were approved to present in this article by the Institutional Review Board of Karmanos Cancer Institute.

which subsequently induces RANKL, an osteoclast differentiation regulator, leads to osteoclastogenesis [36,38]. These events result in the induction of a dynamic influence of osteolysis in the vicinity of musculoskeletal tumors [Fig. 4-A: Left]. As for osteoblasts, secreting AMF possibly induces alkaline phosphatase activity and mineralization [39]. When CHO-1H6 cell line, which is a transfectant constitutively secreting AMF was inoculated in the thigh muscles of nude mouse, the femur close to the implanted lesion formed new bone at the periosteal surface [36]. These evidences indicated that AMF is an enhancer of osteoblast differentiation [Fig. 4-A: Right]. Secreted AMF affects monocyte/macrophage induced phagocytic capacity and adherence morphology [40]. Further, myeloma-secreted AMF evokes immunoglobulin secretion in T cells [41] and systemic administration of AMF induces T cell-dependent skeletal degradation [42]. Consistently, AMF triggers T cell activation and pathogenic immunoglobulin accumulation, resulting in destruction of the bone and joint [43]. These events lead to the alteration of the immunological microenvironment of musculoskeletal tumors. With regards to bone marrow mesenchymal stem cell, bone marrow stromal cells, and dendritic cells, a recent bioinformatic technology to visualize the bone tumor microenvironment detected novel AMF-AMFR interactions [33]. As a final consequence of the above aberrant bone remodeling, severe pain and pathological fracture may occur in a clinical setting [Fig. 4-B].

## 4. Development of AMF and AMFR inhibitors

Suppressing AMF expression appears to be an appropriate treatment to control tumor cell invasion and metastasis. However, so far, the pharmacological development of AMF and AMFR inhibitors has been insufficient. Since AMF works as PGI, which plays an important role in glucose metabolism for both tumors and normal cells [15,44,45], it implies that a complete blockage of AMF/PGI expression or function throughout the body may result in unpredictable side effects. This conclusion can be drawn by the fact that AMF/GPI deficiency syndrome causes an autosomal recessive genetic disorder with the typical manifestation of nonspherocytic hemolytic anemia with neurological impairment [44]. This is one of the reasons why clinical trials to suppress AMF have not been performed. Thus, to date, no clinically available agents inhibiting AMF have been reported, although some articles have reported that silencing AMF by RNA interference [46,47] or hammerhead ribozyme [34], and erythrose-4-phosphate (E4P) [9] could inhibit metastasis and the invasion of malignant tumors. Although, inhibition of AMF expression throughout the body may have a risk, the clinical significance of AMF suppression compelling us to identify procedures that regulate AMF expression locally. Hyperthermia is well known as a clinically available modality for cancer therapy. Regional hyperthermia combined with neo-adjuvant chemotherapy for soft-tissue sarcomas showed better local progression-free survival than chemotherapy alone in a randomized study [48]. The regional hyperthermia of sarcomas can control AMF secretion from tumor cells without affecting the glucose metabolism throughout the body [49] and the events contribute to prevent tumor invasion and metastasis.

The cytokine activity of AMF is inhibited *in vitro* by carbohydrate phosphate compounds as they compete for AMF binding with the carbohydrate moiety of the extracellular binding-domain of AMFR, a glycosylated seven transmembrane helix protein [50]. In order to inhibit the AMFR function, anti-AMFR monoclonal antibody, clone 3F3A, detects the extracellular domain of AMFR and is utilized for neutralization [51,52] Another anti-AMFR monoclonal antibody, clone 9A-4H, suppressed the AMF-driven growth of malignant tumors [53]. These antibodies may suppress AMF/AMFR- related tumor progression. A large scale cohort study of musculoskeletal tumor patients has been previously conducted, and the result showed that multiple myeloma highly expressed AMFR [54], indicating that these inhibitors may suppress multiple myeloma progression. It should be emphasized that Bortezomib is currently considered to be a first line therapeutic treatment for multiple myeloma, and one of the proteasome degradation inhibitor to a variety of ubiquitinated proteins through the ERAD, in which AMFR is a key player in its early step [55]. Thus, we hypothesize that a specific inhibition of AMF-AMFR interaction may induce ER stress and apoptosis in multiple myeloma, and the data may be interpreted as proof of principle providing the mode of therapeutic action of Bortezomib.

In conclusion, the above novel outlook suggests delivering a novel cellular link between musculoskeletal tumors and the skeletal *milieu* mediated through AMF-AMFR interaction. It is expected that these finding will be of value for considering a pharmacological development of AMF and AMFR inhibitors to patients suffering from malignant musculoskeletal tumors.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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