Review Article

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Nanotechnology revolutionizing osteosarcoma treatment: Advances in targeted kinase inhibitors

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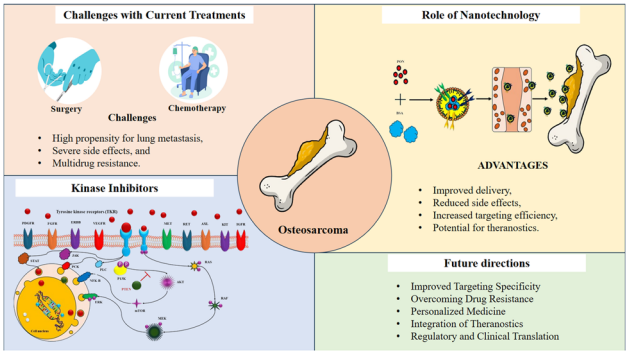
Abstract: Osteosarcoma (OS) is the most frequent primary malignant bone tumor in adolescents and young adults. Despite the advances in therapy, OS remains an ominous problem because of its high metastatic potential, resistance to standard therapy, and great physical, psychological, and financial burden on patients. Available treatment options like surgery and high-dose chemotherapy are limited by high chemotoxicity, multimed resistance, and adverse effects on the quality of life of patients. Extrapolated from the wide array of *in vitro* and *in vivo* studies, the application of kinase inhibitors targeting oncogenic signaling pathways, such as insulin-like growth factor 1 receptor, PDGFR, and the PI3K/AKT/mTOR pathway, appears quite promising. However, OS patients are plagued with challenges like poor bioavailability, off-target effects, and resistance mechanisms, which prevent clinical application. This review explores how nanotechnology is beginning to meet these challenges. Liposomes, polymeric nanoparticles, and metallic nanoparticles are among the nanoparticles that provide new solutions for the delivery and bioavailability of kinase inhibitors, reducing systemic toxicity and enhancing therapeutic accuracy. Active or passive targeting is enabled by these nanocarriers, which enable the drugs to specifically act on tumor tissues while minimizing the adverse effects on healthy cells. Additionally, diagnostic and therapeutic functionalities are combined into nanotechnology theranostic platforms through nanotechnology that pave the way for personalized medicine approaches. Nanoparticle-based kinase inhibitors have shown efficacy in the preclinical setting to overcome drug resistance, improve tumor targeting, and for sustained release of the drug. These advances have dramatic effects on improving therapeutic outcomes at much less toxicity than currently available treatments. This shows the need for further exploration to bridge these exciting findings to clinical practice. Future studies should seek to optimize nanoparticle design to evade resistance mechanisms, enhance target specificity, and reduce time-dependent toxicity. Further, the incorporation of nanotechnology into a personalized medicine strategy has the possibility of changing how OS is treated and bringing the promise of better patient outcomes and quality of life.



Graphical abstract

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1 Introduction

Osteosarcoma (OS) (a type of bone cancer that starts in the osteoblasts, which are the cells responsible for bone production; it usually appears in long bones like the arms and legs, though it can develop in any bone) is the most common primary malignant bone tumor and is seen in teenagers as well as young adults. The most affected age group is between the age of 10–20, as this is the group that undergoes rapid skeletal growth. Therefore, OS entails about 3% of pediatric malignancies and 20% of all primary bone cancers, establishing it as a leading oncological challenge [1,2]. An average of 900 new OS cases are reported annually and it primarily impacts children between the age of 10 and adolescents of up to 30 years. OS has bimodal age distribution with the first mode in the age group 15–19 (8 cases/million/year) and the second one – in the age group 75–79 (6 cases/million/year) [3,4]. The first peak of OS in the adolescent group is attributed to the rate of linear bone growth that is very high at this age [5]. Tumors are localized in long bones because of the rate of ossification, which is usually faster in the extremities, knees, and shoulders. Syndromes of inherited cancer predispositions also can affect the high appearance of this kind of tumor in young patients [3]. Second, less frequent recurrence is observed in senile patients, often in connection with Paget's disease or radiation therapy. This might change the behavior of the OS and its sensitivity to treatment in older patients due to these pre-existing diseases and disorders [6,7].

OS is more commonly found in patients presenting with localized pain and/or swelling around the knee or shoulder that may get worse as night approaches or during activity [8]. Other symptoms include the inability to move joints properly and, in advanced cases, pathological fractures [9]. Furthermore, this incidence depends on the region, with developed countries experiencing a higher rate than developing countries. This is partly because of variances in the availability of and the ability to diagnose diseases in affected regions [10]. Males and females are both affected by these populations, but there is a general trend that shows females are less affected than males, with a ratio of roughly 1:1.3. These changes have been linked to hormonal changes and peoples' genetic code [11]. Another factor associated with OS incidences is the race and ethnicity of a person. According to the hierarchy, Caucasians have the highest rate of OS as compared to African Americans and Asians [12]. This variation may be due to genetic and/or environmental differences or, more likely, social-economic differences. Thus, some of the previous investigations revealed that the epidemiological differences mentioned could be associated with genetic factors, differences in growth rates, and/or nutrition [13], as illustrated in Figure 1. Diagnosis of soft tissue tumors is established by a combination of imaging studies such as X-ray, magnetic resonance imaging (MRI), computed tomography (CT) scans, biopsy, and histopathological analysis, which confirms malignancy and subtype of tumor [14,15]. Current treatment strategies in OS are a multimodal approach that includes surgery, chemotherapy, and, in certain cases, radiotherapy [1,16]. In most situations, limb-salvage surgery has replaced amputation and improved the patients' quality of life [17].

1.1 Impact on patients and healthcare system

Consequently, the experience of the disease causes not only physical but also non-physical consequences that affect the lives of OS patients. Essentially, the disease has a profound impact on patients' quality of life because cancer is usually advanced, and the therapeutic protocols are very rigorous. OS demands high-concentration chemotherapy together with many operations, which makes it have severe complications and life-threatening for the patients [18].

Adjuvant chemotherapy for OS involves the use of several drugs, which include methotrexate, doxorubicin, and cisplatin. These drugs help to shrink the size of the tumor and arrest its ability to spread throughout the body but are known to have severe complications [19]. Nephrotoxicity, cardiotoxicity, and myelosuppression are among the most frequent and significant side effects that affect the patient's health condition and require additional management. The intensity of these protocols often brings on long-term chronic health effects that include vulnerability to secondary malignancies [20].

Since OS is highly sensitive to chemotherapy, the surgical treatment can either be limb salvage or amputation based on the location, size, and response of the tumor to chemotherapy [21]. Surgical intervention is based on limb-salvage operations that attempt to remove the tumor while preserving the limb and its function; however, such interventions have certain drawbacks, including local infection, poor wound healing, and functional limitation [22]. These surgeries can alter the patient's mobility and truly involve tremendous efforts from both the patient and the family concerning rehabilitation. Even with modern techniques in surgery, the optimization of the extent of tumor resection and maintaining function is still not easy.

This exerts a strong influence on the patients as well as their families in the realms of emotions and psychological stability. The identification of OS, therefore, raises anxiety and stress not only about the disease but also from the treatment modalities that may span a longevity of time. Counseling and psychosocial interventions are also important to assist the patients and families in managing the psychosocial aspects arising from the disease [23]. As far as the aspect of health care is concerned, the financial implication of OS is not insignificant. The various forms of treatment, including chemotherapy, surgery, and follow up all put a lot of pressure on healthcare facilities. Furthermore, the components of costs include direct medical expenses and costs associated with productivity loss, transportation to specialized clinics, and other supportive requirements incurred by patients and their families. The chronicity of the treatment of OSs and their management tends to complicate treatment costs further, making it even more important to design efficient and economic strategies for the management of the condition [24].

1.2 Challenges in current treatment approaches

Even though there have been improvements in handling OS, the disease still poses a difficult task in various aspects. Of these, the highest degrees of invasiveness have been found to present with a higher tendency to metastasize, especially to the lungs [25]. The spread of disease to other parts of the body increases the complexity of the disease and considerably reduces the patients' survival probability. Thus, OS patients who present with metastasis at diagnosis have considerably worse prognosis, with five-year survival being 20–30% or lower [26].

There are several limitations that seem to be associated with the current treatment options for OS. One of them is the problem of multi-drug resistance, mainly displaying itself in chemotherapy. Chemoresistance of OS cells can occur due to increased drug pumps, changes in the target site, and increased DNA repair mechanism. All such mechanisms of resistance should be overcome to optimize treatment effectiveness and patients' status [27]. Another major concern is the side effects and complications of chemotherapy, as high concentrations of drugs are needed for OS treatment. Such high doses of these drugs are also likely to have severe side effects, such as organ toxicity and a weakened immune system [28]. Alleviating these toxicities is a major concern since they also endanger the lives of the patients and shorten their tolerance to treatment.

Another challenge in OS management is surgical-related issues regarding surgery complications. Surgical resection to the point of negative margins, together with limb functional preservation, is still challenging. The local recurrence rate is

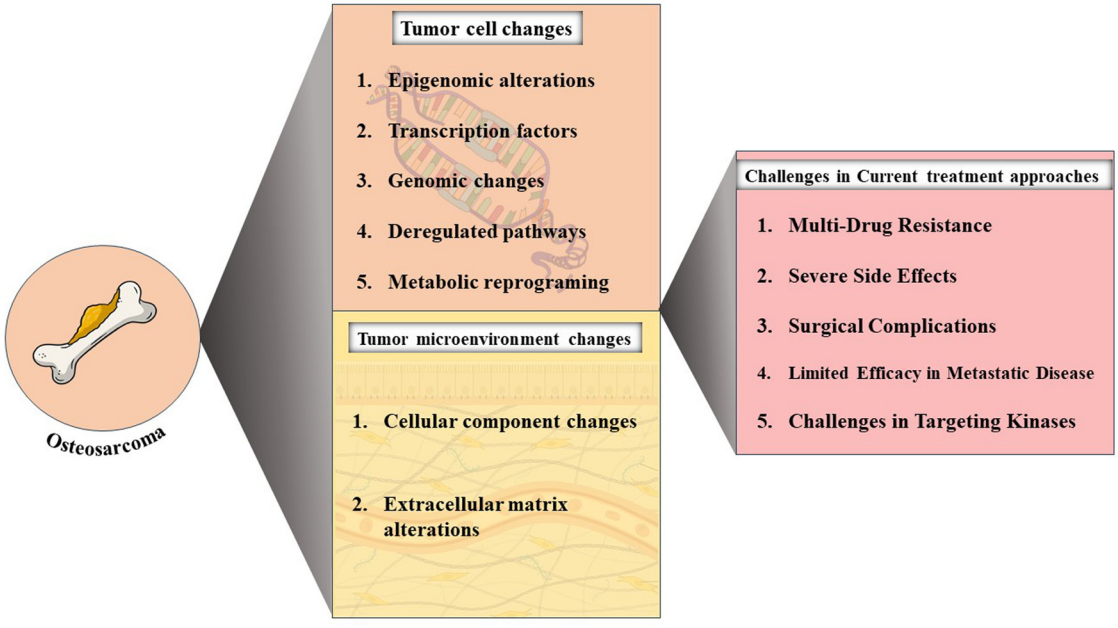

Figure 1: Key alterations in bone tumors and treatment. Epigenomic alterations, transcription factors, genomic changes, deregulated pathways, and metabolic reprogramming occur in the tumor cell as changes. Changes in the tumor microenvironment comprise cellular component changes and extracellular matrix alterations. Major problems in existing treatment approaches include multi-drug resistance, serious side effects, surgical complications, limited efficacy in metastatic disease, and difficulty in targeting kinases.

high; thus, complications that are related to limb-salvage procedures interfere with the standard of living and durability of the patients [29]. Also, when the disease has progressed to the metastatic stage, especially if it has reached the lungs, treatment becomes more challenging. Modern treatments exhibit a lower level of efficacy for metastatic lesions, which creates the need for applying new treatment strategies.

1.3 Significance of kinase inhibitors

Kinase inhibitors can be identified as one of the most essential groups of agents in cancer therapeutics based on their potential for selective targeting of oncogenic signaling pathways [30]. Kinases are signal-transducing enzymes that phosphorylate and dephosphorylate substrates within cells, controlling cell division, growth, metabolism, and death. Abnormality in kinase function is well documented in diverse cancers, including OS; thus, these enzymes might be potential drug targets [3,31].

The discovery of kinase inhibitors has been a breakthrough in cancer treatment since it has cut across conventional treatments and targeted newer therapies [32]. Unlike conventional chemotherapy that targets both cancerous and normal cells, kinase inhibitors have the benefit of attacking infamously errant kinases that are responsible for cancerous developments. This has the positive effect of bringing down the side effects that are associated with normal chemotherapy and, at the same time, enhances the effectiveness of treatment. For instance, imatinib targeting the BCR–ABL fusion protein in CML and erlotinib targeting epidermal growth factor receptor (EGFR) in NSCLC have proved to produce efficient clinic outcomes [33], and have opened the way for similar drugs in other malignancies, including OS.

Specifically, kinases are involved in the development and progression of OS through modulation of different signaling cascades that are pro-tumor and pro-survival. Among the kinases, the PTEN/PI3K pathway is suggested as one of the primary promoters of tumorigenic processes in OS and can be a target for treatment [34]. Insulin-like growth factor 1 receptor (IGF-1R) and PDGFR are well-known RTKs that are involved in the OS cells' growth and survival. IGF-1R is overexpressed in OS tissues, providing a poor prognosis for patients, as it stimulates cell survival and metastasis [35]. Inhibition of IGF-1R, including antibodies such as figitumumab, has demonstrated potential in preclinical models [36]. PDGFR signaling is also active in OS, contributing positively to tumor growth and the formation of new blood vessels. The use of inhibitors against PDGFR with drugs such as imatinib has shown effectiveness in pre-clinical studies; RTKs are implicated in OS treatment [37,38].

Src kinases are a group of non-receptor tyrosine kinases that are often overexpressed in OS and facilitate tumor development by enhancing cell migration, invasion, and apoptosis. Downregulation of SRC with dasatinib reduced OS cell migration and invasion; therefore, SFKs could be a possible therapeutic target [39,40]. PI3K/AKT/mTOR signaling pathway is another key molecule prominently involved in controlling the growth and survival of OS cells [41]. It has been reported that this pathway was activated in OS; therefore, it is a viable biomarker for treatment. Preclinical evidence for the activity of PI3K, AKT, and mammalian target of rapamycin (mTOR) inhibitors in OS also exists and is the basis for studies on these agents.

1.3.1 Challenges in targeting kinases

As much as kinase inhibitors might be useful in the treatment of OS through the mechanisms mentioned above, the following are some of the challenges that interfere with their functions. Among the primary challenges, one can identify the emergence of resistance to kinase inhibitors. Resistance can occur through secondary mutations in the kinase domain, cross-phosphorylation, activation of other signaling pathways, and feedback activation of other pathways. For instance, there is a failure in IGF-1R inhibitors due to the activation of the downstream pathways by insulin receptors or other growth factor receptors, thereby reducing their effectiveness [42].

Kinase inhibitors also offer disadvantages, such as the fact that they are specific, making it hard to target multiple pathways. Most kinases have close homology in their structure, which is a challenge in the design of inhibitors for specific kinases without affecting the rest [43]. This lack of specificity upon binding can result in off-target effects, which often contribute to enhanced toxicity. For instance, even though targeting protein kinases, in this case, SRC kinases could slow tumor progression, the process also harms normal cells that require SRC signals to perform their typical functions, as seen in the case of cancer therapy [44].

The tumor microenvironment is significant when it comes to the use of kinase inhibitors. The heterogeneity of solid tumors, which can be an environment that includes such conditions as hypoxia, the influence of components of the extracellular matrix, and the presence of immune cells, may affect the availability and efficacy of kinase inhibitors [45,46]. It has been postulated that some cancers develop a

protective tumor microenvironment that can protect the cancer cells from the effects of these inhibitors; therefore, combination therapies are used to bypass these barriers [47].

Another limitation occurs when OS has affected other parts of the body and metastasizes to the brain since the brain is surrounded by the blood–brain barrier. The blood–brain barrier prevents most expected kinase inhibitors from entering the brain tissues, limiting their effectiveness against metastasized tumors of the brain [48].

On a genetic and molecular level, OS is notably heterogeneous, and this aspect poses further challenges to comprehension. Recent studies have shown that OS tumors harbor a variety of genetic heterogeneity, with different subclones within the tumor having different mutations and activation of signaling pathways [49]. These oncogenic drivers may exhibit intertumor heterogeneity, which can result in varying sensitivity to kinase inhibitors within the same tumor type, thereby hampering the attainment of optimal and maintenance of durable therapeutic responses [50].

1.4 Nanotechnology in cancer therapy

Nanotechnology has offered an alternative way of treating cancer since it can build materials and structures at the nanoscale level that can interact with biological systems [51]. These interactions have been bestowed with several gross advantages over conventional cancer therapies. Thus, one of the most striking features is the enhanced efficiency of delivering drugs to the intended site within the body. The nanoparticles being agents intended for delivery of anticancer agents, they might enhance the solubility, stability, and/or bioavailability of the drugs. This would allow for higher concentrations of the drug to be delivered at sites containing the tumor to reduce the probability of toxicity, which is a major attribute of orthodox chemotherapy [52]. For example, using nanoparticles, drugs can be designed to be released at given conditions; changes in the tumor microenvironment, such as pH or certain enzymes, ensure proper delivery of the drug at the site of action [53].

An additional advantage of employing nanotechnology in cancer treatment is that therapy can be localized. These nanocarriers can deliver medications to tumor tissues without toxicity to the other healthy cells by subsequently functionalizing nanoparticles' surface with ligands that can only bind to receptors that are overexpressed in cancer cells [54]. This targeting ability also enhances the specificity of the treatment and reduces the considerable damage to other healthy cells, which is always a problem with many conventional therapy forms [54]. Furthermore, due to the multifunctionality of nanotechnology, both diagnostic and therapeutic processes can be united in one construct, which is called theranostics [55]. This helps in monitoring the administration of drugs and the therapeutic intervention in real-time and this makes it useful in the implementation of the philosophy of personalized medicine.

Among all the primary malignant bone tumors, OS is the most frequently diagnosed type of cancer that responds positively to the use of nanotechnology in its treatment. The advantages of the approach involve the potential for overcoming drug resistance, which is a hurdle to the treatment of OS. Incorporation of more than one drug or therapeutic agent can be done in nanoparticles that help in overcoming individual resistance mechanisms of the targeted cancer cells [56]. For instance, nanocarriers that can transport both chemotherapy and RNA interference molecules target and block several pathways associated with drug resistance, thus increasing cancer cell vulnerability [57].

Moreover, the advantages of nanoparticles to modify the physical and chemical characteristics can also be applied to enhance the targeting efficiency of OS cells. Targeted nanoparticles have the potential to localize bone tissue, thus increasing the concentration of anticancer drugs in the place of the tumor [58]. Also, the nanoparticles can be designed to have the capability to cross the dense matrix that composes the bone tissue extracellular matrix and deliver the therapeutic agents close to the tumor cells [58]. Imaging and diagnostics are also enhanced by nanotechnology, and this forms a central area in the management of OS [59]. Conjugation of nanoparticles with imaging agents results in better tumor targeting and assessment of treatment efficacy in MRI, CT, or positron emission tomography scans [60]. This improved imaging ability is helpful in detecting metastases in its nascent stage, which is vital if an OS patient's survival is to be improved.

2 Nanotechnology-driven approaches

Cancer therapy has benefited from nanotechnology through the discovery of very effective drug delivery systems. Thus, in the case of OS, the use of nanoparticle-based delivery systems has a vast opportunity to improve the effectiveness and selectivity of therapies, especially with respect to targeted kinase inhibitors. Liposomes are round spheroids composed of phospholipids with two layers that can

encapsulate aqueous and lipid-soluble drugs. Due to their biocompatibility and drug-protective characteristics, they are very effective in chemotherapy. Thus, in OS, formulation of drugs in liposomes increases the pharmacokinetics and minimizes the side effects of systemic toxicity [28]. Further, the targeted liposomes that bear ligands matching markers expressed on OS cells help in improved drug uptake at the tumor site, thus improving the therapeutic effects of the treatment [61]. Current research has shown that some of the liposomal formulations act as carriers to deliver kinase inhibitors to the OS cells effectively with minimized toxic side effects [62].

Polymeric nanoparticles prepared from biodegradable polymers like poly (lactic-co-glycolic acid) are more effective and biocompatible because they control the release of the drug and protect the drug from early degradation [63]. These nanocarriers can be designed to be sensitive to certain conditions found within the tumor, including pH and enzyme activity, allowing for controlled and selective release of the drug [63]. In the case of OS, PLGA nanoparticles have been implicated in the delivery of kinase inhibitors such as sorafenib and dasatinib to boost their bioavailability and targeting efficiency [63,64]. Moreover, adjuvant polymers can be fabricated to cover many drugs to enhance the therapeutic ratio as well as to overcome the resistance mechanisms frequently seen in OS cells [65]. The application of polymeric nanoparticles gets rid of the barrier of drug resistance and enhances the therapeutic efficacy of kinase inhibitors in OS [66].

Metallic nanoparticles, for example, gold and silver nanoparticles, have distinctive optical and electronic features, which ensure their use in the sphere of cancer therapy. After synthesized with biomolecules, these nanoparticles may offer targeted drug delivery [67]. Thus, osteosarcoma therapy uses gold nanoparticles to deliver kinase inhibitors. For example, gold nanoparticles, in combination with the EGFR kinase inhibitor erlotinib, have better cellular uptake and retention in malignant cells: they function as antitumor agents [68]. Moreover, these nanoparticles can be used for simultaneous diagnosis and treatment, which helps control changes. In this way, the usage of metallic nanoparticles in the case of OS is very promising because it can provide a higher delivery efficiency of kinase inhibitors either *via* physical means or *via* simultaneous treatment and diagnosing.

2.1 Mechanisms of targeted delivery

The nanoparticle-based drug delivery system utilizes several complex processes in order to deliver the therapeutic agents that are kinase inhibitors to OS cells. Such

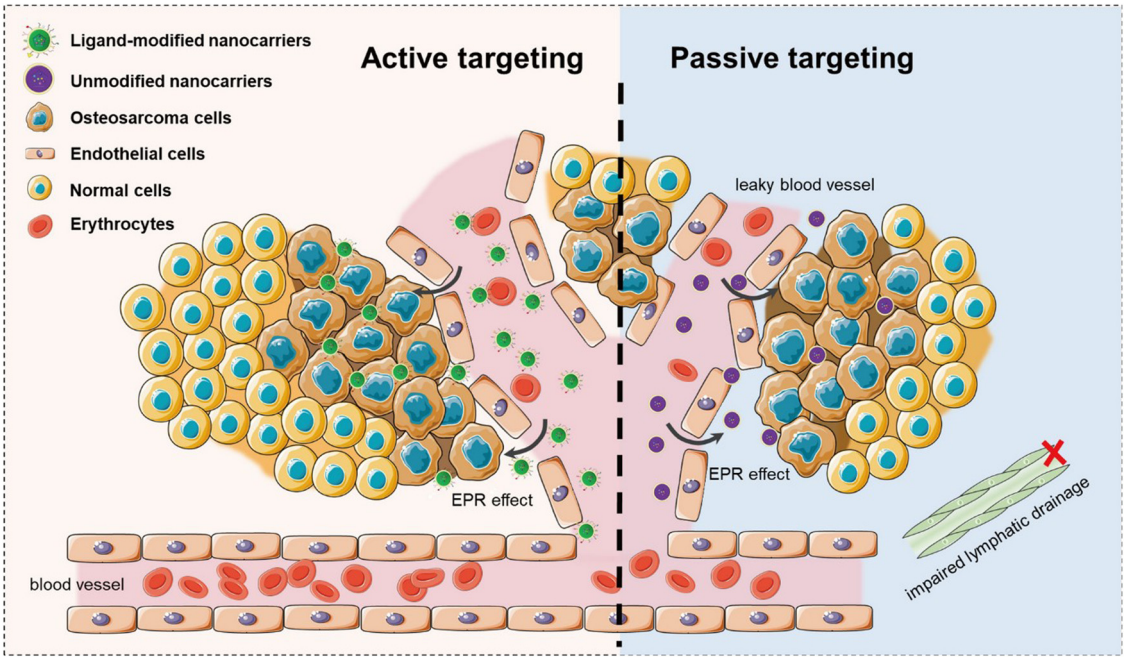

Figure 2: Illustration of active targeting and passive targeting of nano-delivery system in anti-tumor therapy. EPR effects are passive targeting. Circulation of nanocarriers in the bloodstream, extravasation, and accumulation into tumor tissue is through leaky tumor vasculature. Ligand-containing nanocarriers can bind to high-affinity receptors expressed on the tumor cell and mediate local delivery of drugs or internalization through receptor-mediated endocytosis. Adapted from Ref. [73].

mechanisms are aimed at achieving the highest therapeutic effect in drug activity while keeping the amount of the drug that enters the system toxic or causes side effects to the minimum.

Passive targeting primarily relies on the enhanced permeability and retention (EPR) effect. This is due to the peculiar characteristics of the tumor tissues, which are characterized by poor blood circulation and slow lymphatic drainage [69]. These characteristics are used by nanoparticles for their preferential uptake in tumor tissues rather than the normal tissues. This passive targeting enables the intracellular concentration and retention of higher levels of kinase inhibitors within the OS, leading to improved therapeutic efficacy with minimal impact on normal cells [70], as illustrated in Figure 2.

Active targeting is the process of altering the surface of nanoparticles through the attachment of ligands that have a tendency to bind to certain receptors that are found abundantly in malignant cells [71]. These ligands involve antibodies, peptides, and other small molecules that have specific affinities for certain cell surface markers. For example, antibodies-conjugated nanoparticles have been developed to selectively enhance uptake and targeting by conjugating anti-CD44 antibodies that have specific binding to OS stem cells and have demonstrated better therapeutic outcomes in OS animal models [72]. This targeted approach means that the therapeutic agents enter the cancer cells and hence improve treatment specificity since the agents are least likely to affect other cells, as illustrated in Figure 2.

There are other nanoparticles that are developed to respond to the stimuli that are within the tumor microenvironment where the nanoparticles are applied. These stimuli may encompass a change in pH, temperature differences, and enzyme activity [74]. Tissues of OS contain characteristics of acid nature owing to the high proliferation rate of cancerous cells as well as enhanced metabolism. pH-sensitive nanoparticles can take advantage of this feature to deliver kinase inhibitors only at the areas with low pH in the tumor mass. This means that the targeted release mechanism optimizes drug effectiveness while at the same time reducing the exposure of the system to the drug with its relative side effects [75,76].

Furthermore, modern progress in nanotechnology has enabled the synthesis of nanoparticles with passive targeting, active targeting, and responsiveness to stimuli. These nanoparticles can be designed to have more than one function at a time, including drug delivery to OS cells, delivery of kinase inhibitors, and imaging for evaluating response to therapy. For instance, transcendent nanoparticles functionalized with RGD peptides for active targeting, besides the incorporation of pH-sensitive drug release properties, can be realized in OS model systems; the latter can be regarded as a multifaceted approach to targeted drug delivery [77].

2.2 Functionalization and targeting strategies

Nanoparticles need to be functionalized since this property influences their targeting ability and efficiency in the treatment of OS. By conjugating different molecules to the surface of nanoparticles like PEG, peptides, antibodies, or even small molecules, different properties of the nanoparticles can be enhanced for use in the field. For example, PEGylation refers to the process of attaching a PEG layer onto the surface of nanoparticles to avoid recognition and elimination by the body's immune system and, hence, enhance circulation time [78]. This further improves the accumulation of the nanoparticles at the tumor site using the EPR effect; that is, nanoparticles are selectively retained at the tumor site because of the vessel's permeability [77].

Besides PEGylation, it is possible to incorporate specific targeting ligands on the surface of nanoparticles, which will increase their affinity to the receptors and enhance their concentration over OS cells. Thus, folate receptors, for instance, are often seen to be overexpressed in several cancers such as OS. These receptors on the OS cells can be targeted using nanoparticles that have been modified with folic acid; this enlarges the uptake of nanoparticles by cancer cells while at the same time decreasing the effects on other normal cells [77]. Thus, RGD peptides that target integrins ($\alpha v\beta 3$ and $\alpha v\beta 5$) upregulated in OS can be employed to increase specificity and accumulation of nanoparticles by tumor cells [79].

The functionalization of nanoparticles with specific ligands has several advantages. Higher targeting efficiency means that nanoparticles are accumulated in OS cells rather than healthy ones, which means that the concentration of the therapeutic agent is higher in the tumor area and lower in the rest of the body. Selective to the cancer cells, it reduces the off-target effects on the neighboring normal cells and also increases the therapeutics of the delivered drugs. Lower side effects are reported since the damaging effects of chemotherapy on other body cells are reduced, enhancing the safety of the treatment regimen. Additionally, functionalized nanoparticles can be developed to release multiple therapeutic molecules, which can enhance the options for combining treatments to address multiple facets of tumor development.

3 Recent advances in nanotechnology-driven kinase inhibitors for OS

3.1 Overview of recent preclinical and clinical studies

The use of kinase inhibitors in OS over the past few years has revealed a new promise for the enhancement of treatment based on the concept of nanotechnology. Previous studies at the animal model level have been vital in establishing the possibilities of these nanotechnology-based therapies. For example, recent studies have shown that nanoparticles can work as carriers and improve the bioavailability and targeting of kinase inhibitors to increase the efficacy of drugs [65].

In recent preclinical studies, researchers have investigated liposomal, polymeric, and metallic nanoparticles for selective targeting of kinase inhibitors like dasatinib and sorafenib to OS cells. These studies have indicated that conjugating kinase inhibitors into liposomal nanoparticles increases the stability of the drug and also ensures a slow release of the drug, which is vital when aiming at maintaining the therapeutic concentration of the drug through long durations [80–82]. Also, polymeric nanoparticles like those prepared from PLGA have been used to release multi-kinase inhibitors like regorafenib. These nanoparticles have caused inhibition of tumorigenicity and metastatic potential in OS models [83].

In clinical trials, steps are taken to convert promising preclinical data into therapeutic modalities useful for patients. The nanoparticle-based kinase inhibitors have been tried and tested in the first phase clinical trial in OS patients. For example, phase I is concerned with the use of nanoparticle albumin-bound (nab) paclitaxel combined with dasatinib in patients with advance OS. The outcomes of the study revealed that the administered combination was safe and signified the promise of anticancer properties, hence creating a basis for subsequent clinical investigations [84].

Another clinical study related to the application of mesoporous silica nanoparticles was the drug delivery of the kinase inhibitor sorafenib in OSs. The detailed analysis of the test results demonstrated that, owing to the nanoparticles, drug delivery to the tumor occurred with high efficiency, which led to regression of the tumor size and increase in the survival rates compared with traditional treatment [75].

3.1.1 Key findings and implications

Key findings from recent preclinical and clinical research demonstrate how kinase inhibitors powered by nanotechnology may be able to improve OS treatment outcomes. A major observation is the improved nanoparticle tumor targeting to deliver relatively high-dose kinase inhibitors directly onto a tumor and significantly decrease systemic toxicity. This targeted mode of treatment is more effective in exerting therapeutic effects with minimal side-effect profiles, which are generally associated with traditional chemotherapy [62].

A further implication of these studies is the sensitivity-reversal capabilities in drug-resistant cells. One unique strategy associated with vehicle design for nanoparticle-based delivery systems would be to prevent extraction caused by efflux mechanisms, known as resistance agents in OS cells. They can improve the efficacy of kinase inhibitors in resistant tumor populations by shielding the drug payload from premature degradation and aiding its uptake by cancer cells [85].

In addition, this use of nanoparticles facilitates combination therapy strategies by allowing the co-delivery of multiple kinase inhibitors or therapeutic agents to target more than one pathway at once. Preclinical studies have demonstrated the use of a multi-target approach with synergistic effects and reductions in tumor size, which surpass the efficacies observed from single-agent therapies resulting from combined kinase inhibitors plus chemotherapeutic action [86].

One of the most exciting possible solutions is a type, such as “smart” nanoparticles, that could react on their characteristics in the tumor microenvironment. For instance, pH-responsive nanoparticles, for releasing their drug payload only in the acidic tumor environment, have improved the therapeutic benefit with minimal systemic toxicity [77]. These kinds of advances in nanoparticle technology are likely to be an essential piece of the puzzle related to what is ahead for OS therapies (Table 1).

3.2 Novel nanocarrier designs

Over the past few years, improvements in nanoparticle design have substantially improved the delivery of kinase inhibitors in OS therapy. The increasing use of nanoparticles is accompanied by several notable improvements, including the use of multifunctional nanoparticles capable of acting as carriers, diagnostic agents, and release control of drugs, as illustrated in Figure 3. These multifunctional nanoparticles usually consist of gold, silica, and polymers that can be manipulated in order to react to stimuli such as pH, temperature, and magnetic field in the tumor environment [87,88]. Another advancement here is the production of nanoparticles with surface coatings to improve their binding and internalization by OS cells. For instance, the surface of the nanoparticles can be functionalized with

OS-specific ligands, including peptides or antibodies that have high affinity and specificity to the receptors on the surface of the OS cell. It does enhance the drug delivery at the tumor site besides minimizing side effects on other tissues and organs as well as the toxicity impact of the drug [79].

Besides coating ligands, surface modification with hydrophilic polymers like PEG can enhance the pharmacokinetics of nanoparticles by prolonging particles in circulation and decreasing recognition from the immune system. Such a feature enables nanoparticles to avoid the immunosuppressive action and, therefore, be retained in the tumor tissues with the help of the EPR effect [89]. Other new developments in nanoparticles have also targeted the stability of the kinase inhibitors and their controlled delivery. Most kinase inhibitors have low solubility and stability in biological surroundings and are often lipophilic molecules [90]. Complexing them in nanoparticles can shield them from degradation and solve the problem of their poor solubility. For example, polymeric nanoparticles using biodegradable polymers like PLGA can encapsulate hydrophobic kinase inhibitors, which enshroud

Table 1: Summary of studies that feature nanotechnology-based delivery for OS treatment

S. no	Title	Summary	Ref.
1	Recent advances in nanotechnology-based diagnosis and treatments of human OS	This review discusses the application of nanotechnology in enhancing the diagnosis and treatment of OS, focusing on various nanomaterials and their mechanisms of action	[56]
2	Advances of Smart nano-drug delivery systems in os treatment	This study reviews the latest developments in smart nanocarriers designed for OS treatment, emphasizing their responsiveness to internal and external stimuli	[130]
3	Nano-based drug delivery systems: potential developments in the therapy of metastatic OS	This narrative review highlights recent advancements in nanotechnology for the treatment of metastatic OS, discussing the potential of various nanocarriers	[131]
4	Doxorubicin and edelfosine combo-loaded lipid–polymer hybrid nanoparticles for synergistic anticancer effect against drug-resistant OS	This study presents a novel folate receptor-targeted lipid–polymer hybrid nanoparticle system co-loaded with doxorubicin and edelfosine, demonstrating enhanced anticancer effects against drug-resistant OS. The nanoparticles showed improved cellular uptake, synergistic cytotoxicity *in vitro*, and significant tumor growth suppression *in vivo*, suggesting their potential for effective combination chemotherapy in OS treatment	[132]
5	Research progress of nanomaterials in chemotherapy of OS	This review summarizes the current research on nanomaterials used in chemotherapy for OS, highlighting their advantages in drug delivery	[85]
6	Graphene-based nanomaterials and their potential in advanced drug delivery and cancer therapy	This study explores the potential of graphene-based nanomaterials for drug delivery and cancer therapy, including applications in OS treatment	[133]
7	*In vivo* pharmacological evaluation and efficacy study of methotrexate-encapsulated polymer-coated layered double hydroxide nanoparticles for possible application in the treatment of OS	This study investigates methotrexate (MTX)-encapsulated polymer-coated LDH nanoparticles for OS treatment. The nanoparticles demonstrated improved safety and pharmacokinetics compared to free MTX. *In vivo* studies showed significant tumor growth suppression and prolonged survival in OS-bearing mice, suggesting that this formulation could enhance the therapeutic efficacy of MTX in OS	[121]
8	Doxorubicin-loaded lipid nanoparticles coated with calcium phosphate as a potential tool in human and canine OS therapy	This study examines the use of doxorubicin-loaded lipid nanoparticles in OS therapy, focusing on their enhanced therapeutic efficacy	[134,135]
9	Nanotechnology-boosted biomaterials for osteoarthritis treatment: current status and future perspectives	This review discusses various nanotechnology approaches for OS treatment, including targeted delivery systems and their clinical implications	[136]
10	Multifunctional nanoparticles for the treatment and diagnosis of OS	This research explores the design and application of multifunctional nanoparticles for targeted therapy in OS, emphasizing their potential in improving treatment outcomes	[59]

them from enzymatic degradation and have a gradual release profile over a period of time [91].

The other factor that has been enhanced in the newly designed nanoparticles is the controlled release of kinase inhibitors. Nanoparticles can be designed to release the drug at certain stimuli in the tumor microenvironment. For instance, pH-sensitive nanoparticles will only release their contents at a certain pH environment; in this case, the tumor vicinity is acidic, and the drug is released exactly where it is needed. This targeted release mechanism also strengthens the recovery impact of the drug and, at the same time, reduces the probabilities of side effects attributed to systemic drug distribution [90,92].

In addition, nanoparticles can be programmed for sustained drug delivery, ensuring the steady release of drugs in the body, thereby increasing the concentration of the drug in the target site and decreasing the frequency of drug administration. It is especially desirable for kinase inhibitors; thus, the sustained-release capability will keep the kinase activity inhibited constantly as required for efficient cancer therapy. The state-of-the-art in the area of material science involves synthesizing polymers capable of responding to specific stimuli owing to the enhancements of physicochemical properties under chemical signals; this creates highly controlled drug delivery systems in terms of the rate at which the drug is released from the polymer matrix [93].

4 Mechanisms of action

4.1 Cellular uptake and intracellular trafficking

Nanoparticles can be endocytosed to malignant cells *via* clathrin-coated pits *via* caveolae or by macropinocytosis and phagocytosis [94]. The selection of the pathway can be influenced by the physicochemical characteristics of nanoparticles; for example, size, shape, and surface charge. Nanoparticle uptake through cell membranes is generally characterized by clathrin-mediated endocytosis, which is the most common endocytosis. This process includes the development of clathrin-coated pits on the cell's outer membrane, which impinges to infold to make vesicles with the nanoparticles [95]. Caveolae-mediated endocytosis can also be ranked among the most important routes – these are flask-shaped invaginations present in the plasma membrane and contain cholesterol and sphingolipids. This path is commonly used by smaller particles and by those particles that have been coated to recognize caveolin-1, a protein vital for caveolae formation [96].

Endocytosis is a process of taking in materials and objects into a cell, and macropinocytosis is a type of non-selective endocytosis in which large volumes of extracellular fluid and its contents, including nanoparticles, are

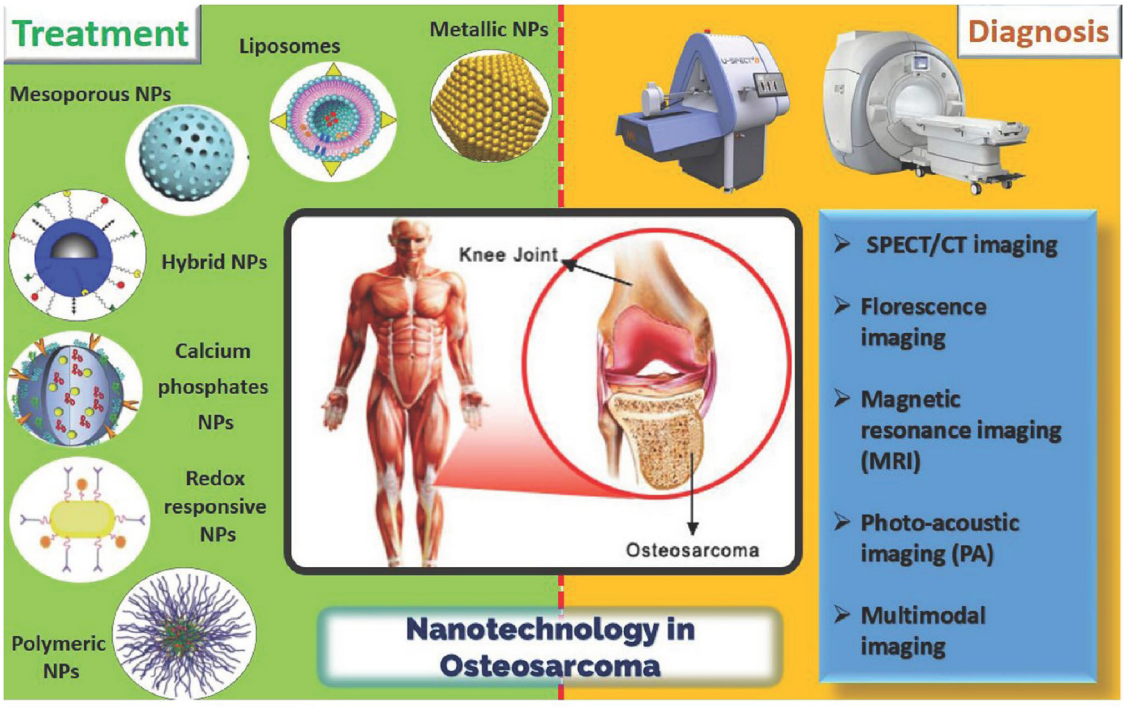

Figure 3: Recent advances in nanotechnology-based diagnosis and treatments of human OS showcase the innovative approaches integrating nanotechnology for early detection and targeted therapy. Adapted from Ref. [56].

recognized to be engulfed [97]. This pathway is most effective for large nanoparticles or for those that form aggregates. Receptor-mediated endocytosis is used by normal cells and is potent in responding to large nanoparticles or particles coated with antibodies [98]. Knowledge of these pathways is vital in the process of engineering the nanoparticles with better efficiency in aspects of endocytosis by the OS cells to improve the effectiveness of the therapies.

4.1.1 Distribution and localization within cells

Intracellularly, they traverse the various compartments that are endosomes early endosomes, late endosomes, and lysosomes. The transportation of these nanoparticles inside these vesicles is essential for their release into the cytoplasm and with cellular targets. The first of these vesicles are called early endosomes, which are formed shortly after endocytosis and function as sorting endosomes that can either recycle the nanoparticles back to the plasma membrane or sort and send them to late endosomes and lysosomes for degradation [99]. Due to the acidic nature of the endosomes and lysosomes, therapeutic agents can be released from pH-sensitive nanoparticles that assist their transport in the cytoplasm [100].

Therefore, the cellular localization of nanoparticles in the cell compartment can determine the overall efficiency of the treatment. For example, nanoparticles with endosomal escape can be excluded from being targeted, internalized, and degraded within lysosomes, thus allowing the intact therapeutic agents to gain access to the cytoplasm. Some of these are there are pH-sensitive materials that swell or lyse under the acidic endosomal environment, thus forming pores in the endosomal membrane or the use of certain peptides that disrupt the endosomal membrane through the proton sponge effect [100].

In the cytoplasm, the nanoparticles can bind to the target molecules like the kinases participating in the signaling pathways of OS cells [101]. Delivery to certain compartments within the cell, like the nucleus or the mitochondria, is possible given that the surface of the vectors is modified in such a way that they are recognizable by the cell's transport systems. For instance, when nanoparticles are conjugated with nuclear localization signals, they can move across the nuclear membrane, thus targeting the nucleus and having a direct effect on gene regulation and cell division [102].

In addition, several methods involving imaging have also helped in the investigation of intracellular transport and destinations of the nanoparticles, including the use of fluorescence microscopy and electron microscopy. These techniques allow the determination of the mechanisms of nanoparticle translocation in cells and help to design more effective nanoparticles for therapy [103].

4.2 Targeted kinase inhibition

4.2.1 Specific kinases targeted by nanoparticle-based inhibitors in OS

Kinases are involved in signal transduction pathways that control the survival, proliferation, and migration of cancer cells. In OS, certain kinases are either overexpressed or hyperactivated, which makes them ideal for the application of an effective treatment. Overall, the use of nanoparticles as carriers to deliver kinase inhibitors shows great potential to increase the bioavailability and target selectivity of these molecules.

Among all the targets, IGF-1R has been most explored in OS [104]. IGF-1R signaling plays a function in cell proliferation, survival, and metastasis. It has also been observed that nanoparticle-based delivery systems for IGF-1R inhibitors, like NVP-AEW541, can dramatically decrease the tumor and metastatic growth in various cancer models through enhanced solubility and targeting capability [36]. Likewise, mTOR signaling is another common pathway involved in growth and metabolism. Biodegradable nanoparticles containing mTOR inhibitors such as rapamycin also yield increased effectiveness and lesser toxicity with regard to OS [105].

EGFR is another significant factor in OS tissue properties, which relates it to high activity and unfavorable outcomes. Similarly, gefitinib or other EGFR inhibitors have been efficient when loaded to nanoparticles and used for OS treatment due to efficient cellular uptake, reduced proliferation, and increased apoptosis [80]. Specifically, mitotic cyclin-dependent kinases (CDKs), such as CDK4 and CDK6, play pivotal roles in the cell cycle. Ideally, nanoparticle-mediated models of CDK4/6 inhibitors such as palbociclib have been effective in the cell cycle arrest and apoptosis of OS cells [80,106,107].

Moreover, vascular endothelial growth factor receptor (VEGFR) is also involved in blocking angiogenesis, which is essential for tumor growth and metastasis phenomena. VEGFR inhibitors like axitinib have been delivered by nanoparticles and have been found to be effective in inhibiting tumor growth and metastasis in OS due to the restricted formation of blood vessels in the tumor [108].

4.2.2 Downstream effects on OS cell signaling and survival

The suppression of these specific kinases results in significant alterations of OS cell signaling and viability, interfering with important molecular pathways. Through the modulation of IGF-1R, nanoparticle-based inhibitors inhibit

PI3K/Akt/mTOR signaling, which is a critical pathway needed for cell proliferation, survival, and metabolism. It leads to reduced cell growth and division, enhanced cell death, and reduced ability of the cancer to spread [105]. For example, several studies have demonstrated that downregulation of IGF-1R lowers cyclin D1 level and elevates pro-apoptotic proteins Bax [27,109].

mTOR antagonism impacts both the mTORC1 and mTORC2 categories, which subsequently decreases protein synthesis, cell growth arrest, and initiation of autophagy. All these effects jointly inhibit the proliferation and survival of OS cells [41]. It was revealed that rapamycin-loaded nanoparticles lead to G1-phase cell cycle arrest and autophagy-mediated OS cell deaths [110,111]. EGFR inhibitors encapsulated in nanoparticles interact with the MAPK/RAS/RAF and PI3K/Akt signaling network, decrease cell growth, invasion, and metastasis, and dampen angiogenesis, as illustrated in Figure 4. This leads to the downregulation of tumor development, as well as improved responsiveness to the chemical treatment known as chemotherapy. Numerous works have demonstrated that EGFR inhibition is associated with the suppression of downstream targets, including ERK and Akt, as it induces apoptosis [112,113].

Cell cycles are inhibited by CDK intervention, especially at the G1 phase, and cells are unable to enter the S phase. This inhibition not only checks further cell division but also triggers apoptosis in OS cells. *In vitro* study revealed that palbociclib-loaded nanoparticles had higher cellular uptake, cell arrest, and apoptotic effects compared to free palbociclib [114]. Further, targeting VEGFR hampers the formation of new blood vessels, thus depriving the tumor of nutrients and oxygen. Nanoparticles with VEGFR inhibitors, such as axitinib, have proved to have a strong antitumor activity, hence, bringing down MVD in OS tumors, resulting in tumor remission [115,116].

4.3 Overcoming drug resistance

4.3.1 Strategies to counteract resistance mechanisms

OS can be referred to as a highly malignant bone tumor. Additional challenges emerge with the treatment of this cancer since the disease often exhibits resistance to chemotherapeutic drugs. Some of these mechanisms in OS include the enhanced ability to pump drugs out of the cancer cells, changes in target proteins or enzymes, and enhanced ability in the DNA repair process.

One of the mechanisms of resistance is through the increased synthesis of ATP-binding cassette transporters

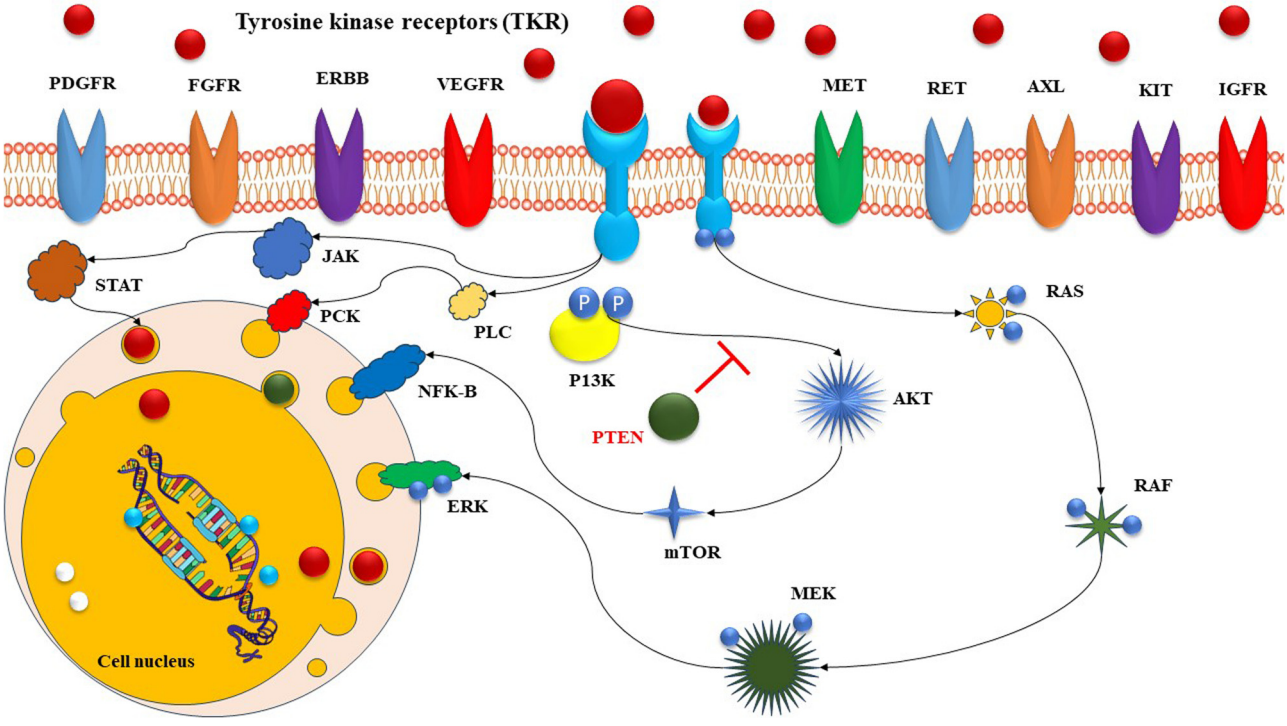

Figure 4: Key downstream oncogenic pathways activated by ligand-binding and dimerization of transmembrane tyrosine-kinase receptors (TKRs) in primary bone tumors, highlighting their potential as therapeutic targets: JAK/STAT, PLC/PKC, PI3K/Akt/mTOR, and RAS/RAF/MEK/ERK (MAPK).

that include P-glycoprotein (P-gp) in OS cells. These transporters continuously transport chemotherapeutic drugs out of the cells and lower their concentration within the cells, making the drugs less effective. These efflux pumps can be avoided using nanoparticles where the drugs can be encapsulated within the nanoparticles and released directly within the OS cell. Such an approach aids in keeping a higher concentration of the drug inside the cellular structure, eliminating the efflux mechanism. For instance, the literature compiles information on a study establishing the ability of doxorubicin-loaded liposomes to overcome P-gp-associated drug resistance in OS cells [117].

Drugs work by binding to targets that may be proteins, enzymes, or receptors, and changes in these targets, for instance, through a mutation, may make a drug ineffective in an OS cell. Advanced nanoparticles are developed and used for delivering the kinase inhibitors that can bind to multiple locations on the kinase to avoid the problem of resistance. The concept of using kinase inhibitors and drugs designed for mutated proteins together in systems of multiple functional nanoparticles can help to cope with the problem of target alterations. For instance, the development of nanoparticle formulations of dasatinib, which is an inhibitor of Src kinase alone, has been described as having the ability to treat mutated kinases in OS [75,81].

OS cells can develop higher levels of DNA repair mechanisms to allow the cells to survive the effects of chemotherapy. PARP inhibitors are proteins that have been shown to inhibit DNA repair enzymes; nanoparticles can be utilized to transport them directly to the OS cells, increasing their sensitivity to DNA damage agents. PARP inhibitors, when used in combination with other conventional therapies, such as chemotherapy, have been proven to work better in different preclinical models for OS [118].

5 Challenges and future perspectives

5.1 Biocompatibility and toxicity

Nanotechnology in OS treatment raises important biocompatibility and toxicity issues. Thus, the safety of nanoparticle-based therapies requires stringent preclinical and clinical testing for toxicity. Biocompatibility studies evaluate whether nanoparticles can exert cytotoxic effects or trigger an immune response and inadvertently interact with nontarget tissues [119].

Recent studies have shown that nanoparticles can serve as efficient vehicles for delivering therapeutic agents to OS cells, but their small dimensions and unique characteristics may produce toxicological profiles that cannot be anticipated. For example, gold and silver metallic nanoparticles showed different therapeutic efficacies but also potential cytotoxicity in which a safe dosage range is required to balance therapy with safety [67]. Additionally, the surface chemistry of nanoparticles, through coatings or functionalization, plays a critical role in biocompatibility. Thus, extensive *ex vivo* and *in vitro* assays are needed to search for the right combination of NP physicochemical properties that minimize undesired toxic effects but maximize the therapeutic benefits.

Furthermore, it is very important to investigate the long-term effects of therapies driven by nanotechnologies. It has been shown that the nanoparticles can accumulate in organs, including the kidney, liver, and spleen, with a risk of chronic toxicity or organ damage [120,121]. Such long-term studies that probe into the biodistribution, metabolism, and excretion of nanoparticles are required to assess their sustained impact.

It is important to monitor patients who undergo nanoparticle-based treatments continuously for delayed adverse effects and ongoing safety. This involves designing effective biomarkers and imaging methods for tracing the movement of nanoparticles in the body [122] (Figure 5). It also tells us that while regulatory agencies continue to demand rigorous, long-term safety data when considering approvals of new nanoparticle therapies for clinical use, the message is clear: this area will need continued research and watching overtime.

5.2 Scalability and manufacturing

Production of nanoparticle-based therapies is a complex and costly operation to expand. The control of size, shape, and surface properties, along with ensuring reliable drug loading amount, is essential for controlling nanoparticle efficacy and reproducibility. However, translating these laboratory-scale formulations to large-scale manufacturing can be challenging and cost-prohibitive.

To maintain consistency and quality across batches, the manufacturing processes need to be standardized. This includes making high-quality nanoparticle synthesis, validation, and identification. Complex tools and procedures need to be used in making liposomes or polymeric nanoparticles as they provide stable system properties [123,124]. Furthermore, the scalability of nanoparticle techniques like 3D printing and microfluidics requires extensive improvements to satisfy the need for mass production.

The regulatory environment is changing for nanotechnologies in medicine, and new protocols are being implemented to cope with nanoparticles. First, comprehensive data are often required to be provided by regulatory agencies such as FDA and EMA before a nanoparticle formulation is approved for clinical use in terms of safety, efficacy, and quality [125–127]. It provides a comprehensive review of the manufacturing process, nanoparticle characterization and preclinical as well as clinical studies. Furthermore, navigating the regulatory pathway includes dealing with several important issues. Nanoparticles should be properly characterized based on their physical–chemical parameters, such as the particle size, shape morphology, zeta potential surface charge, and drug entrapment capacity. It is crucial that standardized approaches for characterization are developed to enable cross-study comparisons and regulatory acceptance [125].

Nanoparticle-based therapies require extensive preclinical investigations that establish their safety and efficacy. This includes toxicology studies, pharmacokinetics, and biodistribution assessments. These observations need subsequent confirmation among human subjects through clinical trials to provide evidence for therapeutical benefits and acceptable safety profiles [128].

Moreover, there must be robust quality control systems in place to ensure batch-to-batch consistency. This will require the establishment of standardized nanoparticle synthesis, purification, and storage protocols. To be authorized for human use, regulatory submissions need to provide all information about the manufacturing process and quality control [129].

Post-approval, ongoing monitoring, and surveillance to early identify any long-term or rare adverse effects is paramount. This will involve maintaining registries and implementing pharmacovigilance programs for monitoring the safety and performance of nanoparticle-based therapies in real-world settings.

5.3 Market availability and characterization challenges

OS is characterized by challenges when dealing with market availability and therapeutic options. Although targeted therapies, including kinase inhibitors, promise to be highly effective, numerous patients face substantial barriers to obtaining these drugs. In this context, regulatory agencies have a key role to play because they are the providers of authorization (and sometimes monitoring) of new medicines. However, these processes can be lengthy and complex, in some cases resulting in delays to make effective treatments available in the market [137]. Moreover, stringent regulations can constrain the accessibility of cutting-edge medications in some areas, for example, developing nations where healthcare infrastructure may not be ready for the fast reception of these medications [138].

However, there exist inconsistencies in the characterization of available OS treatments in addition to regulatory hurdles. However, many existing therapies are hindered in their clinical effectiveness due to issues such as poor bioavailability and off-target effects [137]. Emerging nanotechnology-based delivery systems have shown potential to overcome these challenges through the improvement of drug targeting and reduction in systemic toxicity [139]. Nevertheless, the use of such leading-edge technologies in common treatment protocols remains in its nascent stages, and more research and development are needed. Additionally, resistance mechanisms toward kinase inhibitors are beginning to emerge in front of an already complex treatment scenario [140]. In the evaluation of a new therapy, these factors must be considered by regulatory agencies not only because they can affect

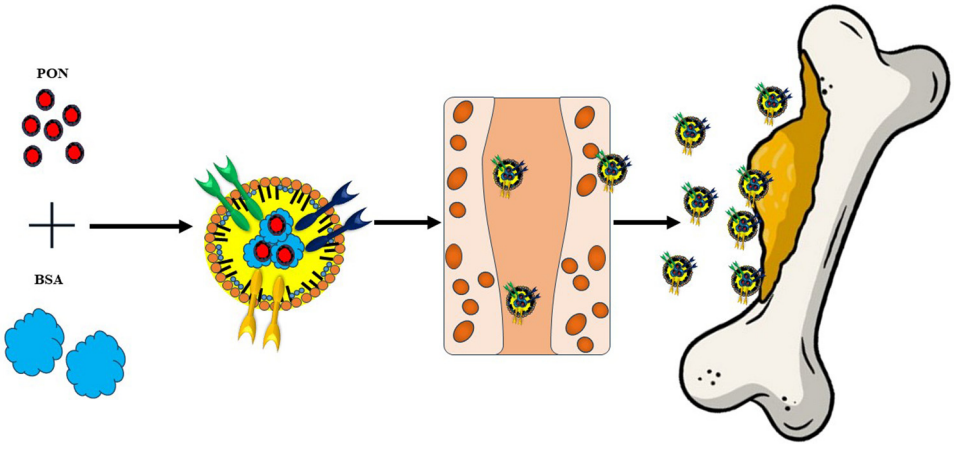

Figure 5: Biomimetic nanoparticles loaded with tyrosine kinase inhibitors for OS treatment.

efficacy, but also because they can affect the safety profiles of treatments. A complete understanding of these resistance mechanisms is essential to developing the best methods of therapy and for improved patient outcomes.

5.4 Future directions

As such, the design of nanocarriers for OS treatment has advanced over time to improve both efficacy and safety through targeted delivery. Future advancements in nanocarrier architecture would be directed toward improving stability, drug loading capacity, and OS- targeted specificity. By developing hybrid nanoparticles, these nanocarriers consisting of both liposomes and other materials can fulfill not only these properties but also other requirements of a drug delivery system [141–143].

In addition, the presence of responsive agents within nanocarriers, such as pH-sensitive or enzyme-responsive materials, allows for triggered drug release in response to custom modifications of the tumor microenvironment. The targeted release offers a favorable way to diminish systemic toxicity and increase therapeutic efficiency. Furthermore, surface modification methods have advanced to the extent that a variety of targeting ligands or antibodies specific for OS cell markers can be coupled on liposomal particles, thus allowing better accuracy in drug delivery [65,72].

5.4.1 Emerging technologies and their implications

New technologies are poised to transform OS nanomedicine. One example is CRISPR/Cas9-based gene editing, which can be employed in combination with nanoparticle delivery systems to target OS–specific mutations. It does provide the possibility of highly targeted genetic-level therapeutic interventions to address the underlying root causes driving both cancer progression and resistance [144].

Additional useful technology will be in the development of AI and ML algorithms to assist nanoparticle design and predict how these nanoparticles continue to interact with biological systems. The assessment of these large datasets by AI-driven methods can uncover the best properties of nanoparticles and predict their *in vivo* fate, leading to faster development of efficient nanocarriers [145].

Moreover, the emergence of 3D printing technology permits the production of personalized nanoparticles and scaffolds specifically designed for individual patient requirements. Such a level of personalization in nanomedicine has the potential to enhance treatment compatibility and efficiency, thus supporting the spirit of personalized medicine.

5.4.2 Prospects for personalized medicine approaches in OS treatment

The concept of personalized medicine, which provides the ability to individualize treatment based on patient-specific genotypic/phenotypic information, has been increasingly recognized as a tool in OS therapy. The science of nanotechnology in personalized drug delivery has been critical to this strategy as it allows the development of both patient-specific nanocarriers and therapeutic regimens. In personalized nanomedicine, biomarkers help pinpoint molecular targets that are highly specific and can be matched to the patient's individual tumor profile before designing a suitable nanocarrier [146].

The progress in genomics and proteomics offers a comprehensive view of the genetic signatures as well as protein expression profiles of OS tumors. This information will facilitate the choice and design of selective kinase inhibitors to deliver those in targeted NPs loaded for cancer cells. For example, nanocarriers laden with kinase inhibitors could be delivered as tumor-specific kinase mutations and, thus, could help in improved treatment outcomes plus lesser side effects of the drug administered [147,148].

In addition, nanotechnology-based imaging and diagnostic tools that can be used to monitor the response of cancers to treatment in real time could also play a role in extending personalized medicine approaches. The specific use of nanoparticles, loaded with imaging agents, can provide further detail on drug distribution, tumor response, and resistance mechanisms to enable altering the treatment regimen at an earlier phase [64,73,149].

6 Conclusion

This review highlights how nanotechnologies driving kinase inhibition hold promise to usher in the new paradigm of OS treatment. Advanced nanoparticle-based systems of liposomal, polymeric, and metallic nanoparticles, along with nanotechnological methods, have been used to achieve precise and efficacious drug delivery by integrating kinase inhibitors with nanotechnology. These systems overcome challenges such as off-target effects, poor bioavailability, and drug resistance, providing major advances in therapeutic precision and patient outcomes. The review presents and fortifies previous studies that have shown that nanoparticle-mediated techniques improve drug stability, targeting efficiency, and release kinetics. In addition, this review presents the novelty in focusing on the dual role of nanoparticles

in therapeutic and diagnostic applications, which now paves the way for theranostic and personalized medicine strategies. In addition, this review points out the possible synergies between nanotechnology and immuno-gene therapy to provide multifunctional cancer treatment modalities. It also directs toward the impact of therapeutic efficacy and bioavailability of the nanoformulated immuno therapeutic moiety. However, these advances hold some challenges, such as the clinical translation of these promising technologies needs to address the issues of biocompatibility and toxicity, scalability, and regulatory hurdles. Overcoming these barriers requires long-term safety assessment and monitoring. Perspectives for the future based on this review stress the necessity for ongoing investigation of how to design nanocarriers better, utilizing different types of materials, and improving the efficiency of nanoparticle targeting. In addition, multifunctional and responsive nanocarriers that respond to tumor microenvironments contribute to improved therapeutic outcomes. Importantly, personalized medicine approaches utilizing patient-specific tumor profiles are anticipated to provide the best opportunity to capitalize on these technologies.

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