

# Nanotechnologies: New Opportunities for Old Drugs. The Case of Aminobisphosphonates

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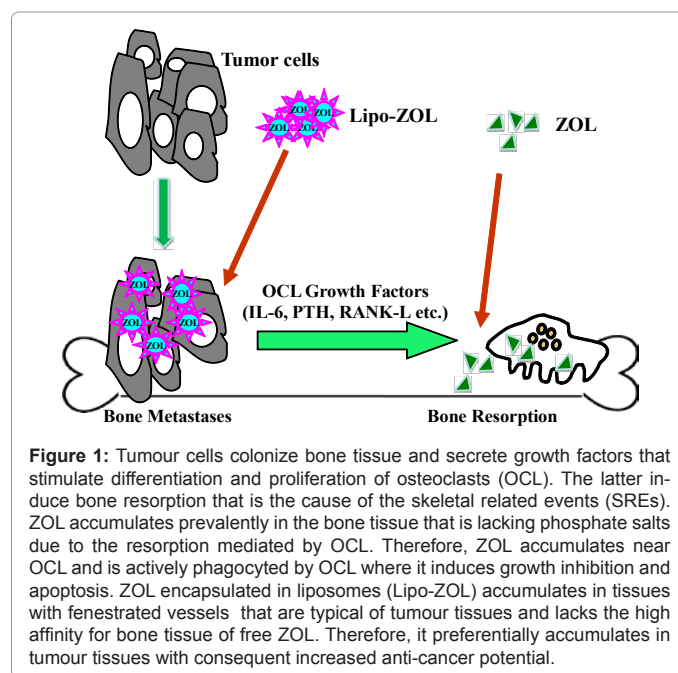
## Introduction

The main challenge of cancer therapy is certainly to develop therapy with higher specificity for target tissues or cells. Indeed, in the case of the classical chemotherapy agents (i.e. doxorubicin, cisplatin, etc.), systemic administration results in cytotoxic effects not only into tumor cells, but also in healthy tissues. Moreover, once into the target site, anticancer drugs cannot distinguish between healthy and cancer cells. In addition to classic cytotoxic agents, the so-called target-based agents offer today new weapons to fight cancer. These new generations of drugs are raised against specific molecular structures that are specifically involved in cell transformation and development. However, also in this case the signal transduction pathways regulated by these molecules can be responsible for the maintenance of the homeostasis also of normal cells and consequently also target-based agents can have undesirable effects on normal tissues [1]. Moreover, the therapeutic efficacy of these new drugs is limited by their pharmacokinetics, with consequent low drug levels at the tumor site. This can be due to the rapid enzymatic inactivation (i.e. in the case of peptides/proteins or nucleic acids) into the biological fluids or to a disadvantageous drug distribution [2]. This is the case of nitrogen-containing bisphosphonates (NBP) that are potent inhibitor of critical enzymes, such as farnesyl pyrophosphate synthase, thus affecting the synthesis of both farnesylpyrophosphate and geranylgeranylpyrophosphate, resulting in inhibition of isoprenylation processes including both farnesylation and geranylgeranylation [3-6]. The latter effects cause the suppression of physiological processes such as prenylation of small GTPases, including Ras proteins, that regulate the proliferation, invasion and pro-angiogenic activity of human tumour cells. Indeed, the prenylation process is essential for correct localization to the inner surface of the cell membrane, a requirement for the activation of Ras family proteins and their function in signal transduction and cell transformation. Several preclinical evidence has suggested that NBP has pleiotropic anti-cancer effects inducing apoptosis and cell growth arrest and inhibiting invasion and metastatic processes and potentiating the anti-cancer immune response through  $\gamma/\delta$  lymphocyte proliferation [3-6].

However, following i.v. administration, bisphosphonates are rapidly cleared and accumulate into the bone and their blood levels rapidly drop down. For these reasons, bisphosphonates are only used, at the moment, as anti-resorptive agent for the treatment of skeletal-related diseases. Indeed, although their promising antitumor activity on cancer cell lines, the in vivo efficacy of bisphosphonates are negligible in extraskelatal tumors, mainly due to inefficient drug concentrations at the target sites [7]. In fact, NBPs, due to their high bone affinity, accumulate where bone tissue is lacking close to osteoclasts that are mediators of bone resorption. Tumour cells metastasized to the bone can stimulate differentiation and proliferation of far osteoclasts through the secretion of several osteoclast growth factors. Therefore, ZOL is actively phagocytied by osteoclasts together with bone tissue and can act inhibiting osteoclast proliferation and differentiation and inducing apoptosis (Figure 1). Therefore, the direct anti-proliferative effect of NBPs on tumour cells colonized in the bone is limited by its

prevalent distribution in osteoclasts. This could be the reason of the high activity of ZOL in preventing SREs but almost no evidence of bone metastases regression.

In this context, nanotechnologies offer a great opportunity to develop new products against cancer. Nanotechnologies have been largely investigated in the case of classic chemotherapy agents such as doxorubicin, with its two derived products, Myocet<sup>®</sup> and Doxil<sup>®</sup>/Caelyx<sup>®</sup>, based on liposomes and presently on the market. The main advantage of this product is the reduction of the side effects, especially cardiotoxicity, compared with doxorubicin administered in the free formulation [8]. Therefore, in principle, each anti-cancer drug employed by systemic administration could take advantage by the development of a nanotechnological formulation in order to reduce



**Figure 1:** Tumour cells colonize bone tissue and secrete growth factors that stimulate differentiation and proliferation of osteoclasts (OCL). The latter induce bone resorption that is the cause of the skeletal related events (SREs). ZOL accumulates prevalently in the bone tissue that is lacking phosphate salts due to the resorption mediated by OCL. Therefore, ZOL accumulates near OCL and is actively phagocytied by OCL where it induces growth inhibition and apoptosis. ZOL encapsulated in liposomes (Lipo-ZOL) accumulates in tissues with fenestrated vessels that are typical of tumour tissues and lacks the high affinity for bone tissue of free ZOL. Therefore, it preferentially accumulates in tumour tissues with consequent increased anti-cancer potential.

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site effects and/increase the drug concentration at the tumor site. In the case of conventional cytotoxic drugs such as doxorubicin no advantage in the anti-cancer activity has been demonstrated due to the non specific mechanism of action of the drug.

However, we believe that the design of new nanotech-based formulations could be very advantageous in the case of target-based agent such as NBPs. The type of nanotechnological device to be used to encapsulate the anti-cancer agent depends upon the tissue to be targeted. For example, NBPs such as pamidronate and alendronate, have been successfully encapsulated into liposomes to target the reticulo-endothelial system in order to induce a macrophage-depleting effect. This was achieved by exploiting the pharmacokinetic properties of “conventional” liposomes that are rapidly cleared from the bloodstream by Kupffer cells and macrophages [7]. Recently, our group reported that the use of long circulating liposomes can change zoledronic acid (ZOL), the most potent NBP, in a powerful anticancer drug. In fact, we have demonstrated that pegylated liposomes encapsulating ZOL induces a significant tumour growth inhibition and survival increase in nude mice subcutaneously xenografted with either human prostate cancer or multiple myeloma cells [9]. In the same experimental conditions, the same concentrations of free ZOL has no effect on both tumor growth and mice survival. Similar results were achieved by using a newly developed auto-assembled calcium phosphate nanoparticles containing ZOL [10]. Higher selectivity of the nanocarriers toward cancer cells can be achieved by using targeting moieties, i.e. folate, on the nanocarrier surface [11].

Therefore, as observed with NBPs, we believe that new therapies for cancer can also come not only by new chemical entities, but also by new formulations for “old” drugs. This is especially true when considering the possibilities coming from nanotechnologies. This should be one of the main strategy on which the pharmaceutical companies should invest. Of course, financial support should also come from public institutions to invest in the defence of the public health.

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