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New Therapeutic Opportunities from Old Drugs: The Role of Nanotechnology?

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Editorial

The therapeutic use of a pharmacological active molecule results by the drug activity at the action site, as well as by the drug biodistribution and bioavailability into the human body. Drug bioavailability and biodistribution are frequently the responsible for the discrepancy in the pharmacological activity encountered when moving from *in vitro* to *in vivo* experiments. Thus, new chemical entities with *in vitro* promising pharmacological activity are often discarded following *in vivo* studies. However, a deep investigation on the reasons for this discrepancy is often lacking. The drug instability in the biological fluids or, for intracellular targets, the poor uptake into the cell can be frequently the reasons of low drug bioavailability. This is the case of molecules from biotechnological origins, such as protein/peptide based agents or nucleic acids, i.e. siRNAs, antisense oligonucleotides, miRNAs or plasmids. In other cases, the limited pharmacological activity can be ascribed to a heterogeneous drug accumulation into the body. This is the case of the bisphosphonates (BPs), synthetic analogues of naturally occurring pyrophosphate, used as treatment of choice in different bone-associated diseases, such as osteoporosis, Paget's disease and bone metastases [1,2]. However, when using BPs *in vitro*, a strong inhibition of the cell growth can be found in different cancer cell lines [3]. In the case of the most modern and powerful BP, i.e. zoledronic acid (ZOL), this effect has been mainly attributed to the inhibition of farnesyl diphosphate (FPP) synthase, a key enzyme of the mevalonate pathway [4]. However, the antitumor activity of BPs *in vivo* is negligible in the case of extra-skeletal tumors. This discrepancy between the *in vitro* and *in vivo* activity has been justified with the pharmacokinetics of BPs. In particular, ZOL intravenous administration results in approximately 55% of the initially administered dose retained in the skeleton, with a following slow release back into circulation [5]. Thus, the maximum plasma concentration of ZOL is about from 10- to 100-fold less than that required *in vitro* to induce apoptosis and growth inhibition in tumour cell lines.

The development of nanotechnology-based formulations can be considered an efficient strategy to increase drug bioavailability in extra-skeletal tissues, thus revaluing the antitumor potential of BPs. Indeed, the encapsulation of a drug into a stealth lipid or polymeric nanovector can result in a prolonged circulation time into the blood with a preferential extravasation in organs/tissues characterized by capillary with fenestrated endothelium (i.e. liver, spleen, etc.) or in tumors due to an enhanced permeability of the vessels generally associated to a lack of lymphatic drainage (EPR effect). Thus, different stealth nanovectors encapsulating ZOL for tumor targeting were developed by our and other groups [6-8]. ZOL circulation time was significantly increased by using liposomes [6]. Interestingly, in different cancer cell lines, namely prostate, breast, head/neck, lung, pancreas, and multiple myeloma, we found that ZOL had an enhanced cytotoxicity, when encapsulated into stealth nanovectors, compared

with free ZOL [7,8]. In different experimental animal model of cancer, we found that ZOL had a negligible effect on the tumor growth [7-9]. On the contrary, ZOL encapsulated into liposomes showed a significant tumor weight inhibition and tumor growth delay, together with increased mice survival. Moreover, a reduced number of tumor associated macrophages as well as a significant inhibition of the neo-angiogenesis were observed [7]. Finally, the absence of acute toxicity was demonstrated by analysis on blood of ZOL-treated animals in which no significant changes in serum creatinine, urea and calcium in animals were found [7]. In alternative to liposomes, a new nanovector, namely self-assembling nanoparticles (NPs) encapsulating ZOL, was developed to facilitate the scale-up process [8]. ZOL encapsulated into self-assembling NPs elicited a superior anticancer activity compared to that observed in animals treated with ZOL-encapsulating liposomes, with complete remission of tumour xenografts in a significant number of animals [8,9]. Also in the case of animals treated with self-assembling NPs encapsulating ZOL, toxic effects affecting the mice weight or inducing deaths were not found [9,10]. Experiments carried out and in progress in our labs are demonstrating an interesting potential of this approach also in other form of tumors, such as glioblastoma, characterized by a poor prognosis. We also found that BPs can have other interesting therapeutic potential, despite cancer treatment. In particular, glial cells, such as microglia and astrocytes, are suggested to play an important role in the development and maintenance of chronic pain in the central nervous system (CNS) [11,12]. Following an external damage leading to a pathological condition, these cells can pass towards a reactive status participating in the processes with consequent occurrence of neurological diseases.

Interestingly, microglia cells are characterized by a phenotypical signature similar to macrophages, on which the inhibitory effect of BPs, especially if encapsulated into nanovectors, is well known [10]. On the other hand, long circulating nanovectors can be used to deliver drugs to CNS when the permeability of blood brain barrier is altered [13]. Thus, we use PEGylated liposomes to deliver ZOL in CNS in an animal model of neuropathic pain, for which an alteration of BBB has been reported [14]. In our study, the presence of liposomes encapsulating ZOL in the spinal cord was revealed in injured animals, but not in healthy animals [15]. More interestingly, a significant reduction of mechanical hypersensitivity after nerve injury was found;

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in the same experimental model, no effect was found in animals treated with free ZOL [15]. Interestingly, in this study, the analgesic effect of ZOL-encapsulating PEGylated liposomes occurred together with the restoration of normal glial architecture of the dorsal horn of spinal cord in the same experiment, free ZOL was not able to induce any restoring effect [15].

Taken together, all these data demonstrate that “old” drugs, such as bisphosphonates, have an unexplored therapeutic potential due to their biodistribution. Our studies demonstrated that BPs can have new therapeutic indications by using formulations, i.e. based on nanotechnologies; the use of this formulations is able to reduce drug accumulation into the bone, thus, increasing drug level in extra-skeletal tissues. Until now, powerful anticancer activity and an interesting ability to treat neuropathic pain of ZOL, the most powerful BP, have been demonstrated. From a general point of view, our experience confirms the importance of the formulation when evaluating the translation of drug from *in vitro* to *in vivo* applications.

References

1. Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, et al. (2004) A systematic review of the role of bisphosphonates in metastatic disease. *NIHR Health Technology Assessment* 8: 1-176.
2. Widler L, Jahnke W, Green JR (2012) The chemistry of bisphosphonates: from antiscaling agents to clinical therapeutics. *Anticancer Agents Med Chem* 12: 95-101.
3. Caraglia M, Santini D, Marra M, Vincenzi B, Tonini G, et al. (2006) Emerging anti-cancer molecular mechanisms of aminobisphosphonates. *Endocr Relat Cancer* 13: 7-26.
4. Dunford JE, Thompson K, Coxon FP, Luckman SP, Hahn FM, et al. (2001) Structure-activity relationships for inhibition of farnesyl diphosphate synthase *in vitro* and inhibition of bone resorption *in vivo* by nitrogen-containing bisphosphonates. *J Pharmacol Exp Ther* 296: 235-242.
5. Chen T, Berenson J, Vescio R, Swift R, Glichick A (2002) Pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases. *J Clin Pharmacol* 42: 1228-1236.
6. Shmeeda H, Amitay Y, Gorin J, Tzemach D, Mak L, et al. (2010) Delivery of zoledronic acid encapsulated in folate-targeted liposome results in potent *in vitro* cytotoxic activity on tumor cells. *J Control Release* 146: 76-83.
7. Marra M, Salzano G, Leonetti C, Tassone P, Scarsella M, et al. (2011) Nanotechnologies to use bisphosphonates as potent anticancer agents: the effects of zoledronic acid encapsulated into liposomes. *Nanomedicine* 7: 955-964.
8. Salzano G, Marra M, Porru M, Zappavigna S, Abbruzzese A, et al. (2011) Self-assembly nanoparticles for the delivery of bisphosphonates into tumors. *Int J Pharm* 403: 292-297.
9. Marra M, Salzano G, Leonetti C, Porru M, Franco R, et al. (2012) New self-assembly nanoparticles and stealth liposomes for the delivery of zoledronic acid: a comparative study. *Biotechnol Adv* 30: 302-309.
10. De Rosa G, Misso G, Salzano G, Caraglia M (2013) Bisphosphonates and cancer: what opportunities from nanotechnology? *J Drug Deliv* 2013: 637976.
11. Rossi DJ, Brady JD, Mohr C (2007) Astrocyte metabolism and signaling during brain ischemia. *Nat Neurosci* 10: 1377-1386.
12. Hanisch UK, Kettenmann H (2007) Microglia: active sensor and versatile effector cells in the normal and pathologic brain. *Nat Neurosci* 10: 1387-1394.
13. De Rosa G, Salzano G, Caraglia M, Abbruzzese A (2012) Nanotechnologies: a strategy to overcome blood-brain barrier. *Curr Drug Metab* 13: 61-69.
14. Echeverry S, Shi XQ, Rivest S, Zhang J (2011) Peripheral nerve injury alters blood-spinal cord barrier functional and molecular integrity through a selective inflammatory pathway. *J Neurosci* 31: 10819-10828.
15. Caraglia M, Luongo L, Salzano G, Zappavigna S, Marra M, et al. (2013) Stealth liposomes encapsulating zoledronic acid: a new opportunity to treat neuropathic pain. *Mol Pharm* 10: 1111-1118.

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