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# Nanomedicines in Cancer Therapy

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Nanoparticulate drug delivery has become an area of extensive research as these systems enable bioavailability improvement of poorly water-soluble compounds as well as targeted delivery of active pharmaceutical ingredients to various tissues and organs. Generally, nanoparticles in drug delivery are defined as submicron colloidal particles ranging from 10 to 1000 nm[3]. The US Patent and Trademark Office, however, define nanotechnology using a scale from only 1 to 100 nm and slightly larger.

As one of the more important challenges to overcome in cancer therapy is the administration of the required therapeutic active compound concentration at the tumor site for a convenient period of time, nanotechnology arises as a promising tool.

Targeted drug delivery to solid tumors would allow achieving optimum therapeutic outcomes minimizing at the same time adverse effects related to the chemotherapeutic drug; because of this, it is currently asked to develop innovative dosage forms that can either passively or actively target cancerous cells. Nanopharmaceutics fulfil with most of the required features that an appropriate targeted drug delivery system should present; additionally and because of their mean size, nanoparticles have demonstrated to increase cellular uptake and interaction with biological tissues.

The tumor vasculature is highly heterogeneous in distribution and also in permeability. Another characteristic of neoplastic tissues is the impaired lymphatic drainage which contributes to increased interstitial fluid pressure. This limites extravasation and transvascular transport of macromolecules, inhibiting the transport of molecules in tumor interstitial space. High tumor cell density and dense tumor stroma are other factors that hamper the movement of active compounds within tumors. These conditions are known as the "enhanced permeability and retention effect" (EPR) in the tumor microenvironment, which could be favourably used when administering nanoparticles that also exhibit long half life.

Nanocarriers can be used as a passive targeting tool which can exploit EPR effect because they can extravasate into the tumor tissues via the leaky vessels, and then they can localize and accumulate in the tumor microenvironment. The junctions between the cancerous cells ranging from 100 to 600 nm; therefore, the optimal size of nanoparticles was thought to be between 10 and 100 nm but particle clearance and circulation times should be considered in targeting studies. The optimal size of a nanoparticle for active targeting to tumor cells *in vivo* remains an unanswered question. Host and tumor factors including size, stage, and location of the tumor may also impact the efficacy of targeted nanoparticles for anti-cancer applications and should be more carefully considered as well.

Targeting molecules, such as antibodies, small molecular weight ligands, or aptamers, attached to the surface of nanocarriers contribute to drug delivery to the tumors, thus allowing specific binding to tumoral cells by the nanocarriers. However, the need of additional structures which are necessary for the stealth effect so as to exhibit selective tumor distribution along with the binding of targeting molecules for the targeting effect become the nanocarrier design in a highly challenging task. The three most studied types of nanoparticles for active targeting in cancer treatment are liposomes, lipid and polymer-based nanoparticles, and micelles. The advantage of actively (cancer cell) targeted nanomedicines over passively targeted formulations is that they are taken up by cancer cells much more efficiently, but it is necessary to remark that they need to penetrate several cell layers before being able to bind to cancer cells. Despite the significant progress that has been made with regard to better understanding the patho-physiological principles of drug targeting to tumors, several important pitfalls has been identified, such as insufficient incorporation of nanomedicine formulations in clinically relevant combination regimens. Another problem is that clinical practices require treatment for metastasis and not to solid tumor. It is well-known that patients with locally confined tumors can often be curatively treated with surgery and/or radiotherapy, and chemotherapy is only given in an adjuvant setting, to prevent and treat metastasis.

It is currently asked for a rational formulation design, based on standard criteria for acceptable safety and efficacy, and desirable pharmaceutical characteristics (e.g. stability, ease of administration, etc.); a detailed physicochemical characterization as well as functional tests in order to support highly reproducible manufacturing processes are also recommendable. The minimum set of nanoparticle characteristics that should be measured and reported include size, morphology, state of dispersion, physical and chemical properties, surface area, and surface chemistry as they significantly contribute to the biologic activity of ligand targeted nanoparticles *in vivo*.

There are some critical features that an ideal nanomedicine should meet to have good potentiality not only for clinical but also for technology transfer purposes; 1) knowing of critical components along with understanding of their interactions; 2) identification of key characteristics and their relation to performance; 3) reproducibility under industrial production; 4) capability of sterile form production; 5) appropriate pharmacokinetics and ability to target and/or accumulate in cancerous tissues by an adequate period of time after overcoming the biological barriers; 6) acceptable characteristics of stability, storing and administration.

Proper formulation design is critically important to achieve antitumor efficacy *in vivo* and in patients. As opposed to in animal models, in patients, nanomedicine formulations often fail to demonstrate significant therapeutic benefit. They are generally much

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better tolerated, and tend to have less (and other) side effects, but their ability to improve response rates and survival times is limited. It is considered that more time and effort should be invested in selecting and generating animal models which are physiologically and clinically more relevant and able to more confidently predict treatment efficacy in patients.

The fact that biodistribution and targeting must be considered and that systemic therapies using nanocarriers require methods that can overcome non specific uptake by mononuclear phagocytic cells and by non-targeted cells add considerable complexity to a task that is challenging indeed from the very beginning.

It is also necessary to remark once more that the particular complexity and multicomponent nature of nanomedicines introduce large number of additional variables that may substantially increase the level of difficulty in controlling processes and predictability of behaviour in a biological system.

Through the large number of clinical trials performed up to date, formulations have been combined with other treatment modalities, such as standard chemotherapy and/or radiotherapy, becoming clear that tumor-targeted nanomedicines – as do standard chemotherapeutic drugs – perform particularly well when integrated in combined modality anticancer therapy. Therefore, in the years to come efforts should also focus on establishing rational combination regimens, in order to better exploit the biocompatibility and the beneficial biodistribution of nanomedicines.