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Bridging cancer biology and the patients' needs with nanotechnology-based approaches

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ABSTRACT

Cancer remains as stressful condition and a leading cause of death in the western world. Actual cornerstone treatments of cancer disease rest as an elusive alternative, offering limited efficacy with extensive secondary effects as a result of severe cytotoxic effects in healthy tissues. The advent of nanotechnology brought the promise to revolutionize many fields including oncology, proposing advanced systems for cancer treatment. Drug delivery systems rest among the most successful examples of nanotechnology. Throughout time they have been able to evolve as a function of an increased understanding from cancer biology and the tumor microenvironment. Marketing of Doxil® unleashed a remarkable impulse in the development of drug delivery systems. Since then, several nanocarriers have been introduced, with aspirations to overrule previous technologies, demonstrating increased therapeutic efficacy besides decreased toxicity. Spatial and temporal targeting to cancer cells has been explored, as well as the use of drug combinations co-encapsulated in the same particle as a mean to take advantage of synergistic interactions *in vivo*. Importantly, targeted delivery of siRNA for gene silencing therapy has made its way to the clinic for a "first in man" trial using lipid-polymeric-based particles. Focusing in state-of-the-art technology, this review will provide an insightful vision on nanotechnology-based strategies for cancer treatment, approaching them from a tumor biology-driven perspective, since their early EPR-based dawn to the ones that have truly the potential to address unmet medical needs in the field of oncology, upon targeting key cell subpopulations from the tumor microenvironment.

Cancer disease, the cornerstone treatments and nanotechnology as new driving force in cancer treatment

Cancer remains as stressful condition in the western world, having surpassed heart diseases in 1999 as the leading cause of death [1]. Globally, lung cancer stands as the leading cause of death amongst the respiratory system cancers, whereas colon cancer stands out in digestive diseases [2]. Nevertheless, if one accounts for gender, a substantially different reality emerges, revealing breast cancer as the leading cause of death, accounting for 23% of all cancer cases among women whereas lung cancer is the leading diagnosed cancer in men, accounting for 17% of newer cancer cases [2]. However, the reality may change when looking to US only, where lung cancer is the main cause of death, whereas prostate and breast cancers are responsible for 28% and 29% of newly diagnosed cancers in men and women, respectively [3]. Over the years, such scenarios have unleashed a tremendous effort from the international scientific community in order to cope with this enormous health problem.

Drug development has led the way by delivering a vast set of molecules capable to tackle the disease, from which some still remain as the cornerstone treatment of several cancer conditions. They act upon interfering with cell cycle progression by impairing correct DNA synthesis or repair (like alkylating agents), inhibiting mitotic spindle formation (as vinca alkaloids) [4], stabilizing microtubule (like taxanes) [5] or inhibiting topoisomerase II (typical of anthracyclines) [6]. Ultimately, each of the mentioned examples triggers cell death, either programmed or not. Supporting such rationale is tumor biology and the intrinsic features of tumor cells. Those features, named *hallmarks of cancer*, were summarized by Hanahan and Weinberg in 2000 [7], and further updated recently [8]. Drugs of the aforementioned classes interfere with DNA

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processing, inducing cell cycle arrest, an event that ultimately prompts for apoptosis in highly proliferating cells, including neoplastic and healthy [9]. This is the reason why these drugs are not voided of severe side effects, which arise from the accumulation of chemotherapeutics in cells of the bone marrow, gastrointestinal tract or hair follicles [6], which represent a true limitation of their clinical use. In order to overcome this bottleneck, several research groups, both from academia and industry, have dedicated their efforts to develop strategies to simultaneously circumvent side effects and increase the efficacy of chemotherapeutic agents.

The advent of nanotechnology brought the promise to revolutionize many fields in science by introducing the possibility to manipulate different materials at the nanoscale size rendering a variety of structures with different applications in areas such as cell-based therapies or cancer therapy and diagnosis. At the nanoscale size (between 1 and 100 nm), materials present unique physical, chemical and biological features which differ significantly from bulk materials [10]. In particular, several biocompatible nanocarriers, have been long-making their way through the nanotechnology field, holding the promise to keep revolutionize cancer treatment [11,12].

In the present review, an insight into the most prominent nanotechnology-based strategies for drug delivery in cancer therapy will be provided, either in clinical use or in development, conveying an evolution perspective based on their mechanism of action, and how this can be translated into the patients benefit.

Advanced drug delivery for cancer treatment: from tumor biology to nanotechnology

Several nanomedicines have been developed over the years as drug delivery entities, including carbon nanotubes, polymer therapeutics, dendrimers, liposomes, metal particles, like nanoshells, among others [11,13]. Based on the intrinsic properties of the tumor microenvironment, such nanoparticles are being developed to provide increased stability of the entrapped drug, by preventing early degradation, and modify and control the pharmacokinetics, an essential feature to circumvent toxicity and enhancing the biodistribution profile towards the tumor [11]. In this respect, liposomes and polymeric nanoparticles stand so far in the leading edge of nanocarrier development.

Enhanced permeability and retention effect – the foundation of nanopharmaceutical tissue targeting

Lipid-based nanoparticles

Liposomes: the 1st generation. The development of innovative systems for drug delivery started long ago as a mean to solve the toxicity profile of a leading edge antitumor agent, doxorubicin (DXR). This potent drug has a broad spectrum activity against many solid tumors, as well as leukemias [6]. However, its clinical use in humans is associated with severe dose-limiting cardiotoxicity [6]. In early days, the "first generation" of liposomes viewed their most successful iteration with the encapsulation of doxorubicin by Gabizon et al. in 1982. The authors demonstrated that neutral and negatively charged liposomes (termed OLV-DOX) were able to retain doxorubicin and decrease the accumulation in cardiac tissues, thus minimizing cardiotoxicity [14]. However, a series of drawbacks culminated with the demonstration that the OLV-DOX liposome technology had poor pharmacokinetic parameters in humans, setting forth extended drug leakage from the particle, which potentially could result in undesired cardiotoxicity [15]. In addition, classical liposomes faced extensive clearance by the mononuclear phagocytic system (MPS) [13], following adsorption of opsonins [16]. Such shortcomings diminished the expectations of the successful application of liposomes into the clinics at that time [17]. Nonetheless, some years later, confidence was once regained upon the introduction of a technological innovation that would change that scenario.

PEGylated liposomes: The key for successful EPR. From the studies regarding nanomedicine-mediated drug delivery, namely liposomes, it has been established that longer blood circulation times translate to an increase in the accumulation of the nanoparticles into solid tumors. Such fundamental principle inherently dictates that, upon encapsulation of a drug, it is possible to alter its pharmacokinetics and biodistribution profiles, which are closely related to the physico-chemical properties of the nanoplatform. Such fine tuning renders an increase in safety for the clinical utilization of otherwise extremely toxic chemotherapeutics. However, needless to say that concomitantly to that rationalization was the technological development protagonized by PEG [poly(ethylene)glycol polymer] and the concomitant approval of Doxil® by the US Food and Drug Administration (FDA) in 1995.

It introduced a revolution into the field, but, above all, brought a boost of confidence into liposome technology for medical applications. Doxil® belongs to the "2nd generation" of liposomes, featuring long blood circulation times, an accomplishment attained by modulation of the lipid composition, especially by the engraftment of PEG. It was reasoned that the hydrophilic cloud around the liposomes enabled by PEG, minimizes opsonization and the blood clearance by the MPS system [18–20]. The resulting extended half-lives in the blood led to increased drug accumulation in solid tumors, while reducing toxicity in non-target organs. This passive tumor targeting was conceptualized by Maeda as the *enhanced permeability and retention* (EPR) effect (Fig. 1). The specific tumor structure presents an extensive network of dysfunctional and leaky blood vessels, resulting from persistently activated angiogenesis, a process that conveys the formation of new blood vessels from the existing ones. The leaky vessel structure (with fenestrae up to 600 nm) combined with poor tumor lymphatic drainage originates the EPR effect, enabling the passive accumulation of nanosystems (either lipid-based or polymeric) at the tumor site [21–23]. Additionally, those modifications led to dose-independent drug accumulation in the different tissues, contrary to classical liposomes, enabling accurate *in vivo* prediction of drug levels [20,18,24,25]. Many of the existing nanomedicines explore the features described above and are considered the basis of drug delivery development [13,11,26].

Eventually, Doxil® entered a "first in man" study revealing similar pharmacokinetics to preclinical studies, with extended half-lives, slow plasma clearance and efficient drug retention [25], culminating with the approval by FDA in 1995. Initial indication included Kaposi's sarcoma, followed by recurrent ovarian cancer, metastatic breast cancer and multiple myeloma [17]. Indeed, Doxil® demonstrated similar efficacy against metastatic breast cancer when compared to free doxorubicin, but with significantly lower side effects [27].

The combined use of PEGylated liposomal doxorubicin with other drugs is also being explored as a mean to increase treatment efficacy. Recently, Doxil® combined with carboplatin demonstrated better therapeutic index with less toxicity than the combination of paclitaxel and carboplatin for the treatment of ovarian cancer in elderly [28]. In another trial, a modified combination of bortezomib, dexamethasone and PEGylated liposomal doxorubicin demonstrated improved tolerability while maintaining a good response in the treatment of multiple myeloma when compared to standard therapy [29].

Recently developed, a PEGylated formulation employing (Nanoliposomal CPT-11) an innovative irinotecan stabilization strategy