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Theranostic Nanoparticles in Cancer Imaging

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Editorial

Nowadays, multiple imagine techniques hold a substantial role in all stages of cancer management: prognosis, screening, biopsy guidance, staging and detection of metastasis, therapy, surgical guidance and recurrence. In current clinical practice, cancer imaging includes non-invasive imaging modalities, such as Computed Tomography (CT) Scans, Magnetic Resonance (MR) Imaging Scans, Positron Emission Tomography (PET) Scans, Single Photon emission CT (SPECT), Ultrasound (US) Scans and optical imaging for macroscopically visualising tumours [1]. However, molecular imaging offers new insights to fight cancer in microscopic level, for the detection of cancer- specific bio molecules and signalling pathways in order to diagnose cancer metastasis at early stages and to design drug systems focused on cancerous tissues towards an era of personalized medicine [2].

The last two decades various nanoparticles (NPs) have been described and few of them have been suggested for their use in nanodiagnostics and/or nanotherapeutics. Recently, there is a growing interest for theranostic NPs, which combine therapy and diagnosis in a single biocompatible and biodegradable nanosystem. However, none of the so far described nanosystems are incorporated in clinical practice, except for iron oxide NPs (IONPs), particularly due to the lack of reproducibility, suitable bio distribution and pharmacokinetics [3].

Several NPs have been successfully combined with imaging modalities, because of their beneficial properties as fluorescent probes (controllable emission wavelengths, sharp emission profiles, robust signal strength and the use of a single excitation source) and their potential for fictionalization with peptides, antibodies and various drugs such as chemotherapeutics [4]. Most studies suggest that NPs systems based on passive targeting of tumor sites, can be more effective for targeting solid, primary tumors with fairly large size (at least 2mm) and well developed vasculatory system. However, early stage primary tumors and micro-metastases do not demand robust blood supply and are not detectable via passive targeting. Therefore, tumor-specific detection via active targeting is still a challenge of great significance [5, 6]. The combination of the existing imaging technology with theragnostic NPs, gives a great advantage for high-resolution *in vivo* cancer imaging, drug monitoring and drug delivery in a specific mode of action. So far, FDA has approved 35 imaging or/ and therapeutic NPs for clinical trials among them, IONPs, gold nanocages and nanoshells, biodegraded polymeric NPs, silica and silica-gold NPs. However, the incorporation of NPs in molecular imaging still needs a lot of progress since such nanomaterials are characterized by pharmacokinetic properties that cannot be easily controlled [3, 7].

NPs can be easily combined with MRI, optical imaging and photo acoustic imaging. When appropriately functionalized with imaging probes they can be incorporated in nearly all imaging modalities. SPECT, PET and even more multimodal imaging techniques like PET/SPECT, MRI, CT, NIRF combined with NPs, allow high sensitivity with minimized background noise, measurement quantification and non-invasive procedures, creating an indispensable tool for targeted *in vivo* molecular imaging [8, 9]. There are various theragnostic NPs and delivery strategies used, depending on the imaging modality combined with. Their size has a range of 10 to 100nm, manufactured from soluble or colloidal polymeric materials and functionalized with an imaging probe (encapsulated in the core or conjugated on the surface) and another probe on the surface that recognizes the tumor in a specific way [9, 10] (e.g targeting the folate receptor, integrin $\alpha_v\beta_3$, VEGF, PSMA that are up regulated in different cancer types) [11-14]. The desired nanosystem should be non-toxic, non-immunogenic and active only in the tissue of interest and not in bloodstream. PEG polymer (polyethylene glycol) is approved by the FDA and conjugated to several drugs such as, Oncaspar (asparaginase), Neulasta (granulocyte colony stimulating factor), Peg-Intron (a-interferon 2b). Monoclonal antibodies and recombinant DNA are used to reduce immunogenic reaction, enhance the stability of the nanosystem and thus prolong half-life in bloodstream, while conjugated linkers responsive to specific stimuli release the encapsulated drug only in specific environments (eg. pH sensitive, thermo sensitive) [3, 4, 7].

Polymeric micelles, liposomes and dendrimers are usually combined with molecular imaging technology in order to study pharmacokinetics, targeted drug delivery, drug release and therapeutic efficacy. Xiao *et al.* [15], demonstrated that multifunctional unimolecular micelles showed passive and active tumor-targeting abilities via c-RGD peptides for integrin $\alpha_v\beta_3$ targeting, with pH-controlled drug release and PET imaging capabilities for cancer-targeted drug delivery. The anti-cancer drug, doxorubicin (DOX) was covalently conjugated to the arms of a hyper branched amphiphilic block copolymer, in order to study its release and target efficacy to the tumor. Tagami *et al.* [16], created a liposomal nanosystem encapsulated with an MRI gadolinium-based agent (Gd-DTPA) and DOX, which is simultaneously released in a locally heated tumor (HaT: Hyperthermia-activated-cytoToxic), to predict the anti-tumor efficacy and release of DOX in a standard pharmacological response model. In two other studies [17, 18], theragnostic nanoparticles were developed, to follow up tumor size in real time in relation to drug uptake. Kaida *et al.* [17], used a mouse model with human pancreatic tumor to evaluate the effect of platinum anticancer drugs, in a polymeric micelle conjugated with gadolinium-based agent, while

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Phillips *et al.* [18], developed a radionuclide (rhenium 186) liposome for enhanced contrast MRI scan, to study the efficacy of brachytherapy in a glioma rat model, with outsanding results regarding the tumor size. Another interesting approach is the binding of siRNA anti-tumor small drugs in solid lipid NPs or iron oxide NPs (IOs), with the possibility of co-encapsulation of other chemotherapeutic drugs like paclitaxel for synergistic chemotherapy and imaging at the same time [19-21].

Consequently, drug delivery and imaging nanosystems exhibit many advantages regarding the access in cancerous sites and the vasculatory system of the tumor, the prolonged circulation, the encapsulation of various drugs and imaging agents. Thus, theragnostic NPs are suitable for imaging liver, spleen, lymph nodes, organs that simultaneously take up NPs and interesting candidates for the development of a drug delivery nanosystem for imaging-guided interventions regarding cancer management [22, 23].

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