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Current Opinion in Chemical Engineering

Intelligent nanoparticles for advanced drug delivery in cancer treatment

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Treatment of cancer using nanoparticle-based approaches relies on the rational design of carriers with respect to size, charge, and surface properties. Polymer-based nanomaterials, inorganic materials such as gold, iron oxide, and silica as well as carbon based materials such as carbon nanotubes and graphene are being explored extensively for cancer therapy. The challenges associated with the delivery of these nanoparticles depend greatly on the type of cancer and stage of development. This review highlights design considerations to develop nanoparticle-based approaches for overcoming physiological hurdles in cancer treatment, as well as emerging research in engineering advanced delivery systems for the treatment of primary, metastatic, and multidrug resistant cancers. A growing understanding of cancer biology will continue to foster development of intelligent nanoparticle-based therapeutics that take into account diverse physiological contexts of changing disease states to improve treatment outcomes.

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Current Opinion in Chemical Engineering 2015, **7**:84–92

This review comes from a themed issue on **Biological engineering**

Edited by **Konstantinos Konstantopoulos** and **Tatiana Segura**

For a complete overview see the Issue and the Editorial

Available online 16th January 2015

http://dx.doi.org/10.1016/j.coche.2014.12.003

Introduction

Size, charge and surface properties of nanomaterials will determine their physiological fate. In order to effectively design nanomaterials for cancer therapy; these parameters must be tailored to navigate the restrictions imposed by human and cancer physiology. While chemical synthesis and facile design procedures are widely reviewed; the precise effect of modulating these three key parameters to direct their biological fate in the context of cancer treatment is refreshed regularly.

The diverse physiological barriers presented by primary tumors, organs affected by metastasis, and tumor interstitium prevent universal design considerations. As such, nanoparticle-based therapeutics for cancer therapy face unique challenges in that they must integrate features to traverse diverse physiological barriers and cater to changing disease states, expression levels of molecular targets, and vasculature in a scalable and economical manner. Here, we present a review of recent work in the development of intelligent nanoparticles for cancer therapy with a specific focus on delivery to primary, metastatic, and multidrug resistant cancers.

Cancer physiology

Primary tumors vary in size and micro-environmental characteristics depending on progression of growth. As such, nanoscale therapeutic carriers must be designed to circumvent physiological barriers to reach the desired cellular/subcellular targets, including the circulatory system, the tumor interstitium, and the targeted cancer cells [1••]. Effective delivery of nanoscale therapeutic carriers is further complicated by metastatic cancer, due to the need for targeted delivery to multiple sites, and the possible presence of metastases in the blood or lymph. Furthermore, multidrug resistance can occur when cancer cells develop mechanisms to resist classes of chemotherapeutic agents [2••].

Nanoscale therapeutic carriers are typically administered intravenously, and spend most of their biological presence traversing through the blood circulation. Design considerations to evade circulatory clearance have received tremendous, well-deserved attention. Renal clearance occurs if the size of the nanotherapeutic is smaller than 10 nm [3]. On the other end of the scale, however, if the hydrodynamic diameter is increased beyond 200 nm, the nanoscale entity is more likely to adsorb proteins and undergo opsonization in blood flow, subsequently becoming vulnerable to uptake by macrophages and reticuloendothelial clearance [4]. Studies investigating surface charge effects show that the uptake of neutral or positively charged nanoparticles by macrophages/lymphocytes is drastically low as compared to negatively charged nanoparticles. Similarly, the influential role played by poly(ethylene glycol)

(PEG) in avoiding non-specific protein adsorption and thus improving circulation time, has driven numerous preclinical studies and engendered the widely accepted DOXIL — a PEGylated liposomal formulation of doxorubicin.

Size of nanoparticles is an important consideration post interstitial/intravenous administration, as the appropriate size can enable preferential uptake in the lymph and avoid drainage back into the blood. Experimental evidence shows that particles with size less than 10 nm are uptaken rapidly by lymph nodes, but are at higher risk of resorption back into the blood flow [5,6]. On the other hand, particles greater than 100 nm may remain accumulated at the injection site instead of being transferred into the lymphatic circulation [7,8]. In general, smaller nanoparticles have faster clearance kinetics from the blood as well as the lymphatic system.

Neutral or negatively charged nanoparticles seeking access to the lymphatics avoid electrostatic interaction with negatively charged glycosaminoglycans, and are able to enter the lymphatic system more readily. Cationic nanoparticles can form high molecular weight aggregates with interacting proteins precluding absorption from the injection site. Lymph node retention of drug delivery devices is commonly increased by using an increased size (physical filtration) or increased hydrophobicity/receptor interactions. By contrast, drainage into the lymphatics from the blood necessitates opposing properties [9].

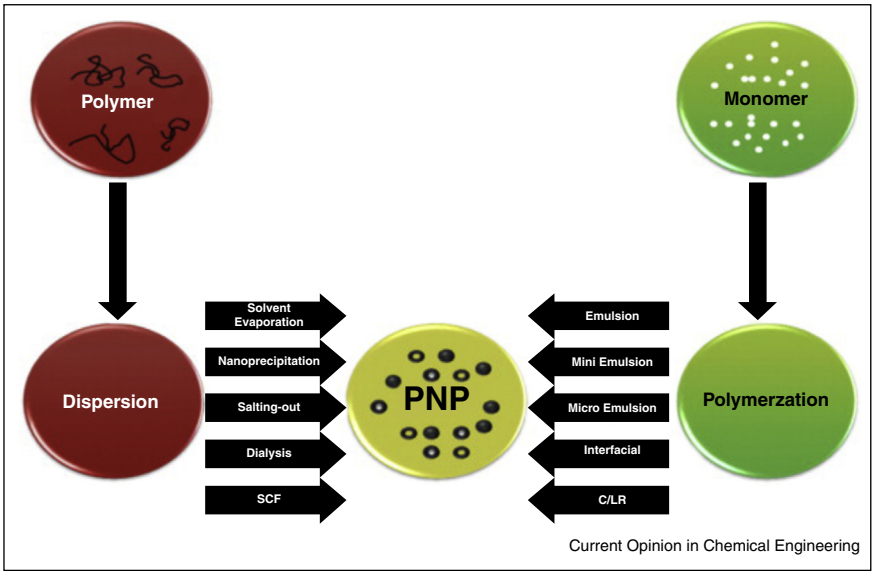
Design of intelligent nanoparticles for cancer therapy

The most commonly researched nanomaterials for cancer therapy are polymers, inorganic nanoparticles such as gold, iron oxide and mesoporous silica, and carbon based materials such as carbon nanotubes or graphene. Polymer nanoparticles have been researched extensively for drug delivery applications and have well characterized synthesis methods including solvent evaporation, nanoprecipitation, emulsion polymerization, and controlled/living radical polymerizations as shown in Figure 1 [10••,11]. Both degradable and non-degradable nanoparticles have been investigated for cancer therapies, with the most commonly employed polymeric material being poly(lactic acid-co-glycolic acid) (PLGA) due to relatively non-toxic degradation products and FDA approval [12,13]. Gold and iron oxide nanoparticles have been of great interest because of their ability to be remotely heated by IR light and magnetic fields respectively [14,15]. In the past decade, mesoporous silica based nanotherapeutics have increased in popularity because of the ability to tailor surface functionality and load drugs into pores [16–18]. Carbon based materials such as carbon nanotubes and graphene have also emerged as promising candidates for cancer therapy due to high surface area and ability to be used in photothermal therapies [19,20].

Size and shape of nanoparticles

Based upon current knowledge of cancer physiology, nanomaterials in the range of 100–200 nm have the highest chance of reaching cancerous tissues through passive targeting methods. In addition to size, nanoparticle shape plays an important role in the ability of a drug delivery system to reach cancerous tissues. A single step assembly of PLGA-lecithin-PEG nanoparticles loaded with doxorubicin and indocyanine green for a chemotherapy photothermal combination therapy for cancer by a single step

Figure 1



Schematic overview of polymer nanoparticles synthesis methods by either polymerization from monomers or preparation from preformed polymers. SCF: supercritical fluid technology, C/LR: controlled/living radical. Image taken from Rao and Geckeler [10••].