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Mini Review

Using Nanomedicine to Drive Advances in Cancer Immunotherapy: A Mini Review

Ghizlane Choukrani[1,2], Jimena Álvarez Freile[1,2], Edwin Bremer[2] and Lars Dähne[1]*

[1]*Surflay Nanotec GmbH, Germany*

[2]*Department of Haematology, University Medical Center Groningen, University of Groningen, The Netherlands*

***Corresponding author:** Lars Dähne, Surflay Nanotec GmbH, Max-Planck-Str.3, 12489 Berlin, Tel: 0049-30-63921764 Germany.

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Abstract

Immunotherapy has shown remarkable clinical success and holds tremendous promise for enhancing cancer treatment Outcome. However, therapeutic complete responses are limited to a subset of patients selected cancers and treatment outcome can trigger severe toxicity due to systemic activation of the immune system. Here, we discuss the opportunities to overcome these drawbacks by combining immunotherapy with nanomedicine using tailor-made nanoparticles (NPs) to increase cancer selectivity and minimize toxicity. Further, we provide directions on requirements and discuss advantageous characteristics of using calcium carbonate as core component of such NPs.

Keywords: Nanoparticles, Cancer Immunotherapy, Drug delivery

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In recent years, immunotherapy with so-called checkpoint inhibitors that (re)activate tumour-directed T cell responses has induced complete remissions in a subset of patients, conclusively demonstrating the significant potential of immunotherapy in cancer [1,2]. One of the major challenges for such immunotherapy is the ubiquitous immune-related side-effects and limited intrinsic selectivity for cancer [3]. This challenge is starting to be addressed by an emerging field of research that combines immunotherapy with nanotechnological design of tailored carrier materials. Hereby, systemic exposure of active therapeutics is prevented and accumulation as well as selective release of immunotherapeutics in so-called tumour micro-environment is achieved. Due to their unique properties, nanoparticles accumulate selectively at the tumor by the so-called enhanced permeability and retention effect (EPR). Their surface can be modified to increase their blood circulation time by a stealth effect and to actively target the tumor micro-environment with precision, increasing both safety and therapeutic efficacy [4].

Various articles providing proof of concept for this use of NPs have emerged in recent years. For instance, Li Tang et al. used protein nanogels (NGs) to selectively deliver and release supporting protein drug (i.e IL-2 and TGF-β receptor-I inhibitor) on T cells in response to T cell receptor activation at 8-fold higher doses of administered cytokines, without toxicity and a 16-fold expansion of T cells in tumors. Several other nanoparticle designs have been developed for cancer immunotherapy applications, of which some key examples are summarized in Table 1. However, there are still major challenges associated with the design of these delivery systems, such as sub-optimal drug-loading. Further, a lack of regulation of drug release, which is often mediated by spontaneous leakage from the nanoparticles. In addition, degradation, undesired release or chemical modification of the loaded molecules during storage or blood circulation requires new design of nanoparticles-based drug delivery systems that can address these challenges.

The first consideration when choosing the NP type is its ability to achieve high loading of the immunotherapeutics without altering their biological properties and. Ideally, degradable NPs at the site of the tumor. Porous templates with tuneable parameters including pore size, pore volume have gained considerable attention due to

their large surface area and the ability to load different sizes of molecules [5]. There are several candidate materials known. E.g. mesoporous silica (MPS) has been most intensively investigated due to its stable and rigid framework with excellent chemical, thermal and mechanical stability. The biomolecules are loaded to the particle's pores, which are then modified with a 'gatekeeper' that responds to an internal or external stimulus such as pH [6], redox reaction [7], temperature [8] and antibodies [9]. However, silica cannot be exploited directly for controlled drug delivery and further modifications are required making an approval by the FDA difficult.

Another potential candidate for therapeutic biomolecule delivery is vaterite, a polymorph of calcium carbonate (CaCO3), which is formed by the direct mixing of soluble salts containing Ca2+ and CO32-. Vaterite has been gaining increasing popularity due to its low cost, biocompatibility and high porosity, which enables efficient protein encapsulation. Perhaps most importantly, vaterite is pH sensitive, an intrinsic feature that may allow for selective drug release in the acidic tumor micro-environment due to its selective dissolution [10]. Vaterite particles can also be produced in a precisely defined size, ranging from several micrometres to a few hundred nanometres. Particles and their pore size strongly depend on the experimental conditions such as salt type used, their concentration, pH, temperature, mixing rate and the agitation intensity of the reaction mixture. Controlling these various parameters enables the synthesis with defined vaterite particles of small size dispersion. Herewith, one can for instance tailor the size of NPs to meet specific needs, e.g. for optimal passive tumor targeting using the EPR effect [10-12], or tailor pore size to meet loading needs [13].

Another important consideration for immunotherapeutic NPs is the loading strategy of the biomolecule. This step should be carefully chosen to achieve optimal loading, while at the same retaining bioactivity. Biomolecules can be loaded to vaterite either by physical adsorption/pore diffusion or by coprecipitation. In the first strategy, pH is a decisive factor of the loading efficiency when dealing with charged macromolecules, whereas for uncharged macromolecules the molecular weight is a crucial factor [14]. The second loading approach is coprecipitation, and it is based on the inclusion of the biomolecules inside vaterite particles during the process of growth from the mixture of aqueous salt solutions. This strategy typically leads to a higher loading efficiency, e.g. with a 5-fold increase in loading for coprecipitation compared to physical absorption using alpha-chymotrypsin [15]. Achieving high protein loading to a particulate delivery system is advantageous for drug delivery, but it is also crucial to preserve the activity of the biotherapeutic upon encapsulation. This step presents a major challenge when formulation conditions are far away from the physiological environment. Biomolecules such as proteins are most stable and have maximum activity at their optimum pH, but stability and activity decreases as the pH value incrementally increases/decreases from this value. In this respect, alpha-chymotrypsin retained 56% activity by adsorption into synthesized vaterite particle at pH 5.0. Conversely, residual activity was only 12% when encapsulation was performed via the coprecipitation process. This lower activity might be due to the high pH of sodium carbonate during synthesis. Therefore, when attempting coprecipitation, it is pivotal to choose solutions and salts that has a pH in the activity range of the therapeutic molecule during the process. Rational selection of salts e.g. sodium hydrogen carbonate, calcium chloride, $CaCl_2$, or calcium nitrate, $Ca(NO_3)_2$ can be used for achieving reaction conditions close to physiological once [16-21].

Although many technical challenges are faced in nanoparticle design for immunotherapy, of which we here have discussed the choice and design of the nanoparticle, the future of these 'magic bullets' continues to expand. Indeed, exciting proof-of-concept studies highlight the promise of combining immunotherapy with nanomedicine. The next few years are expected to provide substantial breakthroughs and insight into a new era of next-generation immunotherapy (Table 1).

Table 1. Examples of Nanoparticles and their application in Cancer Immunotherapy.

Nano particle	Mechanism	Outcome	Citation
PLGA	Deliver TSP to APCs and improve the efficacy of αPD-1 treatment.	20% cure rate compared with 0% without nanoparticles system	17
IONPs	Stimulate a tumors specific CD8+ cytotoxic T cell response by Hsp70-SPIONs	Delayed tumor progression and an increased overall survival.	18
Zinc Oxide	Carcinoembryonic antigen delivery into dendritic cells	Delayed tumour growth enhanced survival.	19
Liposome	immune cell-recruiting liposomal system (FN-nps)	Assisting anti-PD-1 antibody immunotherapy	20
LPG	Liposomal polymeric gels of drug-complexed cyclodextrins and cytokine-encapsulating biodegradable polymers	Increased activity of NK and intratumoral-activated CD8+ T-cell infiltration	21

PLGA: Poly Lactic-co-Glycolic Acid, TSP: Tumour-Specific Proteins, APCs: Antigen-Presenting Cells, IONPs: Iron Oxide Nanoparticles, LPG: Liposomal Polymeric Gel

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