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Cancer nanomedicines: closing the translational gap

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The 2014 update from the International Agency for Research on Cancer¹ is a sombre reminder of the burden of morbidity and mortality resulting from cancer worldwide. Many cancer therapeutics are small, hydrophobic molecules, characterised by poor water solubility, rapid biodegradation, non-specific biodistribution, and off-target toxicities. As a result, these agents often show problematic dose-limiting toxicities, narrow therapeutic indices, and provide limited clinical benefit. These shortcomings underscore the need for alternative drug delivery systems that can offer advantages over traditional formulations and overcome such obstacles.

Nanomedicines in cancer use nanometre-scale drug delivery systems (eg, liposomes, dendrimers, polymers, or inorganic particles; figure) that can improve solubility and drug pharmacokinetic profiles, protect therapeutic payloads from premature degradation, enhance drug delivery to diseased tissue, and control rates of drug release, often resulting in reduced toxicities.^{2,3} They can also enhance transport across biological barriers and overcome drug-resistance mechanisms.⁴ The leaky nature of the tumour neovasculature and the lack of effective lymphatic drainage allow systemically injected nanomedicines to accumulate and be retained in tumour tissues. This enhanced permeability and retention effect is believed to be responsible for the successful delivery of nano-formulated drugs;⁴ although how pronounced and homogeneous this effect is within individual tumours and across different tumour types is unclear.⁵ Nanoparticles have also been designed to interrogate the molecular signatures of different cancers to probe specific cell-surface and intracellular targets, and to provide direct activity readouts.^{6,7}

In principle, the versatility of nanomedicine platforms could allow active targeted and multi-targeted approaches, codelivery of synergistic agents, theranostics (ie, codelivery of a therapeutic and a diagnostic agent in the same nanoparticle), and development of effective immunotherapies relying on antigen delivery vehicles for cancer vaccines and artificial antigen-presenting cells.⁸

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PEGylated liposomal doxorubicin (Doxil), liposomal daunorubicin (DaunoXome), liposomal cytarabine (DepoCyt), liposomal vincristine (Marqibo), and albumin-bound paclitaxel (Abraxane) are the only US Food and Drug Administration-approved members of this relatively new class of drugs.⁹ However, several other nanomedicines are currently in development with the aim of increasing the clinical potential of a broad range of cytotoxic drugs and biologicals. More than 50 of such nanomedicines are in clinical trials.⁹

Despite the promise of nanomedicines, substantial obstacles need to be overcome before they can enter mainstream cancer-care settings.² These problems include the technical challenges of manufacturing, the high cost of development, modification of regulations on manufacturing standards and process control requirements, and mitigation of the high risk of reduced market penetration as a consequence of pricing and reimbursement. Non-specific uptake of nanomaterials by the mononuclear phagocyte system might hinder therapeutic potential or result in unwanted toxicities. Surface charges of these materials could also potentially affect biological outcomes in the body given their tendency to bind a range of plasma proteins. The delivery of nanomedicines to tumours, their cellular internalisation, and mechanisms of release are complex and vary within and among tumour types.⁵ Analytical and pharmacological methods to improve product characterisation, or monitor the biological fate of nanomedicines and their metabolic products, might require customised development and validation. The importance of the enhanced permeability and retention effect in various tumours, effectiveness of active targeting, and ability to control endosomal escape of the nanoparticle payload need to be understood further to achieve optimised biological effects of nanomedicines.

Standardised preclinical models to evaluate and predict the efficacy, safety, and toxicity of nanomedicines in humans are scarce.¹⁰ Thus, studies of nanomedicine candidates should adapt established preclinical models of solid tumours in patients to validate disease-associated biomarkers, assess target engagement, study associations between target distribution and biological response, and assess efficacy. Standards are needed for the choice of tumour model and to individualise imaging protocols, the latter providing non-invasive readouts of particle accumulation, distribution, EPR activity, and efficacy.

Nanomedicines will allow for tailored drug selection and delivery to stratified subpopulations of patients.¹¹ The ability to predict the clearance and biodistribution of nanomedicines by radiolabelling particles with PET-emitters or measuring mononuclear phagocyte system function could individualise and optimise cancer therapy. Ideally, candidates for nanomedicines would be assessed with at least one imaging approach, and subsequently selected for treatment based on observation of successful particle localisation to the tumour.¹² Dynamic contrast-enhanced MRI or CT might complement PET approaches,⁷ and provide tumour perfusion and permeability estimates that give indices of enhanced permeability and retention activity. Standardisation of clinical trial designs incorporating informative and quantitative analytical approaches, biological assays, and imaging modalities could maximise the amount of information that will link particle, payload, and patient characteristics to successful clinical outcomes, and advance the field of cancer nanomedicine.

Nanomedicines have the potential to become an innovative class of therapeutics for cancer. Their inherent versatile and modular design capabilities, and improved biological and therapeutic properties as compared with conventional anticancer agents, they could lead to improved outcomes for patients with cancer.

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Figure. Developing a nanomedicine

Nanomaterials with functionalised surfaces are adapted to deliver therapeutic agents and imaging labels. Adapted from Kamaly N and colleagues, 2012.³ Reproduced with permission of The Royal Society of Chemistry. NPs=nanoparticles.