Nanoparticles: Facilitating targeted delivery in cancer therapy

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PharmTech spoke to Robert Langer, Stephen Zale and Yanli Zhao about engineering nanoparticles with optimal properties for use as cancer therapies.

Robert Langer, PhD, is professor at the Massachusetts Institute of Technology and founder of BIND Biosciences.

Stephen Zale, PhD, is vice-president of development at BIND Biosciences.

Yanli Zhao, PhD, is assistant professor and national research foundation fellow at Nanyang Technological University, Singapore.

Advances in the development of nanoparticles have seen these systems being translated into clinically useful medicines, particularly in the treatment of cancer. Examples of nanoparticle-based medicines approved by EMA and FDA as cancer therapies include Doxil and Myocet (liposomal formulations of doxorubicin), DepoCyt (liposomal cytarabine), DaunoXome (liposomal daunorubicin), Abraxane (an albumin-bound formulation of paclitaxel) and Genexol-PM (a polymeric-micelle formulation of paclitaxel).

Nanomedicines in clinical evaluation

A number of nanoparticle-based formulations are in clinical development as potential treatments for cancer. NanoCarrier’s nanoplatin (NC-6004), which consists of cisplatin incorporated into micellar nanoparticles composed of polyethylene glycol (PEG) and polyglutamic acid block copolymers, is undergoing Phase II evaluation in patients with advanced or metastatic pancreatic cancer (12). Preclinical results showed that nanoplatin accumulated in cancer cells and had significantly lower nephrotoxicity and neurotoxicity (13). In a Phase I study conducted in the UK, the formulation was well tolerated in patients with solid tumors, providing sustained and prolonged release with minimal nephrotoxicity and no significant myelosuppression, ototoxicity, emesis, or neurotoxicity (14).

Cerulean’s CRLX101 consists of the topoisomerase-1 inhibitor, camptothecin, covalently conjugated to a PEG-β-cyclodextrin copolymer that self-assembles into nanoparticles of approximately 30 nm in diameter (15). Unlike camptothecin, these nanoparticles have a long circulation half-life, enabling them to accumulate in the tumors. Following uptake of CRLX101 into tumor cells, the active camptothecin is gradually released from the nanoparticles, providing a sustained concentration of the drug in tumors. It has been observed that this sustained concentration of camptothecin at the tumor site results in the inhibition of HIF-1 alpha, a hypoxia-induced transcription factor known to regulate cancer cell survival, metastasis and drug resistance. Studies have demonstrated that CRLX101 nanoparticles augment camptothecin efficacy by facilitating localisation and retention at the target tissue, increasing intracellular drug deposition, providing a sustained supply of active camptothecin and prolonging drug activity at the target site (16). CRLX101 is in Phase II evaluation for the treatment of various tumor types (15).
Nippon Kayaku’s NK105, a nanoparticle-based formulation of paclitaxel incorporated into block copolymers of PEG-polyaspartate, was developed to enhance the antitumor activity of paclitaxel while reducing adverse effects such as neurotoxicity, myelosuppression and allergic reactions (17). NK105 is currently in Phase III development and studies are being conducted to investigate if NK105 can improve progression-free survival in patients with metastatic or recurrent breast cancer.

Other examples of molecular-targeted nanoparticle-based cancer therapeutics in clinical development include BIND Biosciences’ BIND-014 (Phase I), Calando’s CALAA-01 (Phase I), Mebiopharm’s MBP-426 (Phase I/II) and SynerGene’s SGT53-01 (Phase I).

Pharmaceutical Technology Europe spoke to Robert Langer, professor at the Massachusetts Institute of Technology (MIT) and founder of BIND Biosciences; and Yanli Zhao, assistant professor and research foundation fellow at Nanyang Technological University (NTU), Singapore, about engineering nanoparticles with optimal properties for use as cancer therapies.

Building in optimal properties

PTE: What are the key considerations when designing nanoparticles for the delivery of cancer therapeutics? How do you engineer these nanoparticles to achieve targeted delivery?

Zale (BIND Biosciences): This is a complicated question because the effects of many characteristics on how nanoparticles behave in the human body are interdependent on one another. Broadly speaking though, for nanoparticles to be effective, they must be able to circulate in the bloodstream, extravasate into diseased tissues and release their therapeutic payload at a rate that provides high concentrations at the target site.

We use particles based on copolymers of polyactic acid (PLA), or copolyactic/glycolic acid (PLGA), and PEG, and attach targeting ligands to the end of the PEG chain. We have developed a particle-manufacturing process that encapsulates the drug payload in the PLA/PLGA core of the particle and orients the PEG and the targeting ligand toward the surface of the particle. PEG gives the particle a water-like corona, which disguises the particle from the systems in the body that would otherwise remove them from the bloodstream within minutes after administration. As a result, our nanoparticles display circulation half-lives of nearly 24 hours and are able to concentrate drugs in tumors at levels typically 10 times greater than when the same dose is given as a solution.

Langer (MIT and BIND Biosciences): We have used a broad range of targeting ligands, including antibodies, antibody fragments, aptamers, peptides and small molecules. We have studied a range of targets including, for example, well-established and clinically validated tumor targets such as the prostate-specific membrane antigen (PSMA) and human epidermal growth factor receptor 2 (HER2), and have discovered our own targets and “Passive targeting in itself is often not enough to eradicate the side effects of cytotoxic drugs...”

Zhao (NTU): Nanoparticles tend to aggregate as a result of their large surface-to-volume ratio in biological media. When nanoparticles agglomerate, they not only lose their intended functionality, but are quickly recognised and effectively removed by the mononuclear phagocytic cells in the reticuloendothelial system (RES) of the liver and spleen. This sequestration is often increased by the surface coating of nanoparticles with a corona of proteins that leads to opsonisation and enhanced phagocytosis by the RES.

A strategy to maintain good dispersion of drug-loaded nanoparticles in biological media is by surface modifications with PEG polymers. PEG has been known to prevent protein adsorption (opsonisation) on the nanoparticle surfaces, enhance circulation time, reduce nonspecific RES uptake and facilitate preferential accumulation at tumor sites through the EPR effect. Passive targeting in itself, however, is often not enough to eradicate the side effects of cytotoxic drugs and divert the anticancer therapy away from healthy cells to selectively target cancer cells.

To further enhance the targeting ability of drug-loaded nanoparticles, these systems must also be coupled with targeting agents that can actively bind to over-expressed antigens or receptors on the surface of cancer cells. Drug-loaded nanoparticles can be engineered to recognise and bind to cancer cells through ligand-receptor interactions and the bound nanoparticles are internalised before the loaded drug is released inside the cells. Finally, there is another concern that these drug-delivery systems should release the loaded drug rapidly upon accumulating at tumor sites and after being taken up by cancer cells.

Designing nanoparticles for selective targeting

PTE: Could you describe your research on nanoparticles as targeted drug delivery systems in cancer therapy?

Langer (MIT and BIND Biosciences): The idea of employing targeted nanoparticles to bring cancer drugs to the site of disease and increase their safety and effectiveness has been around for several decades, but...
BIND-014 has just completed a Phase I clinical trial and is advancing into Phase II. The early results for BIND-014 are very promising.

Zhao (NTU): Our multifunctional mesoporous silica nanoparticles for cancer-targeted and controlled drug delivery have three components—the mesoporous silica nanoparticle core, the amino-β-cyclodextrin, the PEG polymers functionalised with an adamantane (Ad) unit at one end and a folate (FA) unit at the other end (Ad-PEG-FA) (18).

The surface of mesoporous silica nanoparticles is firstly functionalised with amino-β-cyclodextrin rings bridged by cleavable disulfide bonds, blocking drugs inside the mesopores of the nanoparticles. The Ad-PEG-FA polymers are immobilised onto the nanoparticle surface through strong β-cyclodextrin/adamantane complexation. The multifunctional nanoparticles can be efficiently trapped by folate-receptor-rich cancer cells through receptor-mediated endocytosis, where they then rapidly release the loaded anticancer drug inside the cell when triggered by the acidic conditions prevailing in the endosome and lysosome. Importantly, the particles we developed are composed of biocompatible and biodegradable polymers that are commonly used in other pharmaceutical products such as biodegradable microspheres and PEGylated proteins.

Zale (BIND Biosciences): BIND is now using this platform to develop targeted nanoparticles called Accurins to treat cancer and other diseases. The company has set about developing Accurins for clinical evaluation. The most advanced of these nanoparticles is BIND-014, an Accurin targeted to a cell-surface receptor expressed in all major solid tumor types. BIND-014 contains the chemotherapeutic agent docetaxel, which is a blockbuster drug in its own right, with approvals in five solid tumor indications, including breast, lung and prostate.

BIND-014 has just completed a Phase I clinical trial and is advancing into Phase II. The early results for BIND-014 are very promising. We have seen that the drug behaves very differently from conventional docetaxel, including showing signs of activity at relatively low doses and in tumors where docetaxel is not normally used.

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The engineering of these functions onto the single nanoparticle entities significantly enhances the efficacy of anticancer drug delivery to cancer cells, while reducing the cytotoxic effects on healthy cells. In vivo experiments demonstrate that doxorubicin-loaded multifunctional mesoporous silica nanoparticles could effectively release doxorubicin to tumor sites resulting in significant inhibition of the tumor growth.

References
2. A. Siew et al., Mol. Pharm. 9 (1) 14-28 (2012).