Nanotechnology as a platform for personalized cancer therapy

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Abstract

While chemotherapy has done wonders to save and prolong lives, it can cause harmful side effects in many patients and has limited efficacy in certain cancers. Newer, personalized approaches to cancer therapy look to target specific molecular characteristics of an individual's cancer cells, with the aim of improving cure rates and reducing side effects. To achieve this goal, it is vital to integrate the abundant molecular information now readily obtained from cancers—e.g., their mutational landscapes and gene expression profiles—with relevant therapeutic strategies. Nanotechnology is a powerful tool that is being studied extensively for this purpose. This article will describe key areas where nanotechnology may enable personalized approaches to cancer treatment, along with future directions and challenges in the field.

When people think of nanotechnology, they likely imagine things that are very small. However, from a molecular perspective, the nanoscale is in fact rather large. Small molecule drugs—the mainstay of medical therapy for the past 100+ years—are sub-nanometer in size: roughly 3 million ibuprofen molecules can fit into a 100 nm cube.[1] While there has been some debate over the exact size range that constitutes a nanoparticle, the FDA appears to have settled on a definition of materials with at least one dimension between 1-1000 nm.[2] Compared to traditional pharmaceuticals, nanoparticles are thus a big stepup in size, allowing for therapeutics with increased complexity and functionality. Nanoparticles can achieve this through diverse designs: shape, size, composition, and surface chemistry can all be modified to optimize performance (Figure 1).[3] In the context of cancer therapy, nanoparticles are being engineered to target and destroy tumours by delivering drugs or biologics, as well as through direct cytotoxic activity.

Chemotherapies tend to have significant toxicity in many cell types other than the cancer cells they are intended for; nanoparticle encapsulation of chemotherapy drugs can enhance tumor localization and mitigate off–target effects. The first clinically approved example of this concept was Doxil—a liposomal nanoparticle formulation of doxorubicin, first approved by the FDA in 1995.[4] Compared to free doxorubicin, Doxil has demonstrated similar overall efficacy to free doxorubicin, but greater tumor accumulation and reduced cardiotoxicity; it is approved for indications in multiple cancers including breast and ovarian.[5] Doxil is not specifically targeted to cancer cells, but relies on passive accumulation: by virtue of their size, nanoparticles have a tendency to accumulate in tumors due to the relatively high permeability of tumor vasculature coupled with poor lymphatic drainage.[6] Other nanoparticle formulations relying on passive accumulation have been approved for clinical use, including albumin–nanoparticle bound paclitaxel (Abraxane), liposomal vincristine (Marqibo), and liposomal irinotecan (Onivyde).[4] Of these, Abraxane is likely the most successful with nearly $1 billion in annual sales and approval for use in treating non–small cell lung cancer, late–stage pancreatic cancer, and metastatic breast cancer. Improved nanoparticle delivery to tumors is expected to be achieved by adding targeting ligands (e.g., antibodies) to the nanoparticle surface that recognize specific cancer markers. This concept, which is often referred to as active targeting, is being extensively researched in preclinical studies, and several targeted systems are currently being investigated in Phase I-III clinical trials.[4]

An emerging area of nanoparticle research is the delivery of delicate biological cargo. Nucleic acids are of considerable interest for cancer therapy, as they can be used to replace defective genes (via DNA or mRNA) or to silence the expression of oncogenes (e.g., via short interfering RNA). However, as drug candidates, nucleic acids suffer from several drawbacks, including rapid degradation in the blood and an inability to enter most cells. In this context, nanoparticles may act like artificial viruses that can transport nucleic acids and "infect" cancer cells to deliver a payload. The most commonly studied nanoparticles for this application are lipid–based, with several different systems now in clinical trials to treat diverse cancers.[4] Other more exotic materials are also being investigated pre–clinically, such as gold nanoparticles with dense nucleic acid shells and nanoporous silica particles.[7,8] The ultimate vision for nanoparticle gene therapy is to provide highly personalized treatments based on the patient's specific mutations (targeted by the nucleic acid) and cell surface markers (targeted by ligands attached to the nanoparticle surface).

Combining multiple drugs to target a particular cancer is a commonly used treatment strategy.[9] By packaging different therapeutics into a single nanoparticle, they can reach cancer cells at the same time at a specific ratio, irrespective of their individual pharmacokinetics. This can be important, as the precise ratio of two or more drugs can

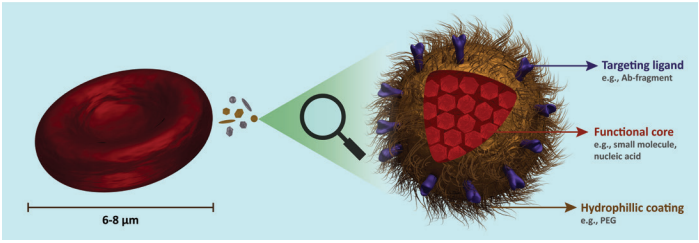

Figure 1 | Schematic illustration of biomedical nanoparticles. Nanoparticles are typically about 1/100th the diameter of a red blood cell, and can be formed with various shapes, sizes, and compositions. Nanoparticles can be made from organic and inorganic materials, with common examples being lipids, biodegradable polymers, silica, gold, and silver. The right side of the diagram shows a zoomed-in view of a typical nanoparticle design. The interior of the particle is often loaded with an active payload—for example, a small-molecule drug or nucleic acid. The outer surface of the nanoparticle is typically coated with a hydrophilic polymer layer—most often polyethylene glycol (PEG)—to improve particle stability and prolong circulation. Lastly, the outer surface of the particle may also be decorated with specific ligands to target cancer cells or other cells of interest. Examples include transferrin, folic acid, and antibodies directed against HER2.

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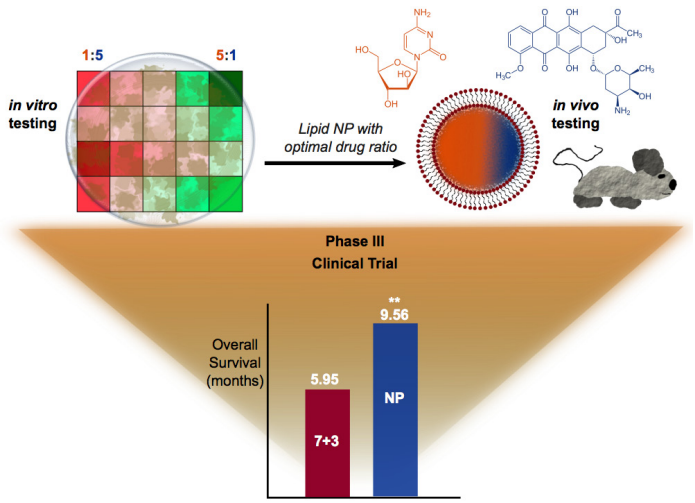

Figure 2 | Nanoparticles from bench to bedside. Drug combinations may show antagonistic, additive, or synergistic effects depending on their ratio; Celator pharmaceuticals is developing nanoparticles that deliver precise synergistic ratios of therapeutics to treat cancer.[10] The process begins by testing a given drug combination in vitro against a number of cancer cell lines (top left; red = antagonism, green = synergy). Nanoparticles are then designed to contain the optimal synergistic drug ratio to maximize effect, and are tested in animal models (top right). A recent phase III trial of the lipid nanoparticle formulation CPX-351 (Vyxeos), containing a 5:1 ratio of cytarabine and daunorubicin, showed superior efficacy compared to 7+3 (a standard regimen of the same two drugs) for the treatment of secondary acute myeloid leukemia in older patients (bottom).[11]

have a profound impact on their combined effect.[10] A recent phase III trial showed promise for using a nanoparticle formulation to co–deliver cytarabine and daunorubicin to patients aged 60-75 with high–risk acute myeloid leukemia.[11] The nanoparticle studied—called Vyxeos—contains a 5:1 ratio of the two active drugs (cytarabine and daunorubicin), which was previously shown to maximize synergy in vitro.[12] The phase III study demonstrated a significant 3.6 month improvement in overall survival, along with a superior response rate and no increased toxicity, compared to the control group receiving a standard regimen of the same two drugs (Figure 2). In addition to controlling drug ratios, preclinical data have suggested that nanoparticles can also be used to modulate the timing of drug release at the tumor site, which may further help to maximize the effect.[13,14]

Despite promising clinical and preclinical results, the vision of nanomedicines that exclusively target cancer cells remains elusive. A recent review article calculated that a median of 0.7% of administered nanoparticle doses reach solid tumors in mouse studies published over the past decade, with active particle targeting via surface ligands increasing this number to just 0.9%.[6] However, the range of efficiencies reported in the review was highly variable, and according to industry experts, tumor accumulation is thought to be upwards of 10% for the best–performing nanomedicines in humans.[15] Several barriers have been identified that impede tumor targeting: for example, upon contact with blood, proteins adsorb to the nanoparticle surface, which can both interfere with active targeting and promote phagocytosis by the mononuclear phagocyte system.[16] Nanoparticle shape, size, surface charge and chemistry all appear to play a role, and delineating the complex interplay between these factors and the biological milieu is extremely difficult. Other challenges include optimizing extravasation, tumor penetration, and particle uptake/drug release at the cancer site. Given that nanoparticles are frequently taken up by phagocytic immune cells, some researchers have suggested exploiting this property for cancer immunotherapy.[17] Other new approaches include nanoparticles that can respond to external stimuli (e.g., radiation directed at the tumor) to release their cargo or cause direct damage through heat or free radical generation. While this sounds futuristic, some of these systems have already entered clinical trials: e.g., hafnium oxide nanoparticles designed to amplify the effect of radiation therapy within tumors (NBTXR3) are being tested in a phase II/III trial for soft–tissue sarcoma.[18]

Nanotechnology currently plays a niche role in the overall landscape of cancer therapy, but there are indications that this will change. A recent analysis by scientists at the FDA showed that there has been a steady increase of drug product submissions containing nanomaterials over the past 30 years, with the largest fraction (40%) being for cancer indications.[2] Furthermore, the overall success rate for drugs containing nanomaterials—i.e., the fraction of new drug approvals relative to the number of investigational new drug submissions—is 15%, which is comparable to the success rate for biologics. It is also notable that many of the nanomedicine products currently undergoing clinical trials have been developed by startups and smaller pharmaceutical companies; if the field continues to prove itself with further success stories, larger pharmaceutical companies will likely become more involved. Continued advances in our basic understanding of the bio–nano interface are leading to improvements in rationally designed systems, and creative new designs are published nearly every day; some of these small designs will hopefully have a big impact on patient care.

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