Nanorobotics: A Promising Medical Frontier

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Today, a cancer diagnosis is a grim and life-changing sentence for a patient. Even amidst a treatable prognosis, those who undergo cancer therapy often experience diminished quality of life due to the harmful side effects and lengthy recovery period involved. The current standard of care for these patients includes chemotherapy, radiation therapy, and surgery, and while none of these procedures is entirely effective, each threatens substantial risks to patients. Chemotherapy, for example, takes advantage of one distinguishing feature of cancerous cells—that they exhibit rapid and uncontrolled division. Chemotherapeutics non-specifically target cells undergoing rapid division, and though this mechanism works to eliminate the cancerous mass, these powerful drugs also target the other rapidly dividing of cells in our body that are found in bone-marrow and hair follicles (9). Effectively, patients endure diminished wellbeing as they contest with hair loss and immune suppression throughout treatment (9). According to Brannon-Peppas et al., improving the quality of life after therapy depends on that treatment's ability to target tumor cells alone (8). But amidst the current chemotherapeutic options, such selectivity is limited to those drugs that tend to affect one type of cancer cell over healthy cells, and this is no guarantee (8). Surgery and radiation also threaten to harm a patient's healthy cells, and these methods are limited to small, accessible tumors. As such, there remains a need for an effective, selective, and non-invasive cancer therapeutic to increase patient outcomes during and after intervention.

Nanorobotics offers a promising solution to the shortcomings of cancer treatment today. Defined on a scale between 1 to 100 nm in size, nanotechnology poses unique advantages to medicine because it operates on the scale of viruses, proteins, and other natural-occurring cellular machinery (3). Furthermore, nanoparticles could be especially useful for cancer treatment; unlike radiation therapy and surgery, nanorobots can be injected into the blood stream and specifically target tumor cells. This selectivity would leave a patient's healthy cells untouched, vastly improving wellbeing and life expectancy beyond chemotherapy (1). In the past two decades, nanoparticles have been developed to provide an impressive variety in therapeutic techniques; first, the tiny structures can be loaded with cancer-treating drugs and delivered on site of the tumor (4). Additionally, nanoparticles can function to heat-shock tumor cells in a treatment called photothermal therapy, which converts irradiated light into heat (5). Nanoparticles have also been developed to function as imaging agents to illuminate tumors under PET and MRI scans (6). All together, nanotechnology is a captivating solution for progressing cancer therapy as individualized and noninvasive.

But the promise of nanorobotics in cancer therapy is not without challenges—it must overcome a number of obstacles before it can function as an improved cancer therapeutic. The first barrier is stability *in vivo*; interaction with blood and lipoproteins can cause dissociation of the nanoparticles if they are not stable to resist degradation (7). Additionally, the nanoparticles must be small enough to clear the body and resist aggregation in the liver and spleen, and they must be safe and biologically compatible to perform predictably *in vivo* without toxicity (7). The organic and inorganic nanoparticles developed in recent years have not yet met this demand (7). The inorganic varieties, such as semiconductor quantum dots and gold-based nanomaterials, have not been demonstrated as safe for the long-term use (7). Similarly, organic nanoparticles, including PTX-loaded polymeric micelles and liposomal doxorubicin, tend to be limited to drug-carrying functions are lack properties necessary for light absorption useful for imaging and photothermal therapy (7). In order to replace the current standard in cancer treatment, this new technology must be developed as safe, stable, biologically compatible, and versatile.

This summer, Li et al. introduced a newly designed organic nanoparticle that may just meet that demand. The molecule, called PEG-Por_4CA_4, is an amphiphilic polymer containing a hydrophilic head and a long hydrophobic hydrocarbon tail. It is composed of polyethylene glycol (PEG), 4 groups of pyropheophorbide-a (Por), and 4 groups of porphyrin/cholic acid (CA) (7), (Fig 1).

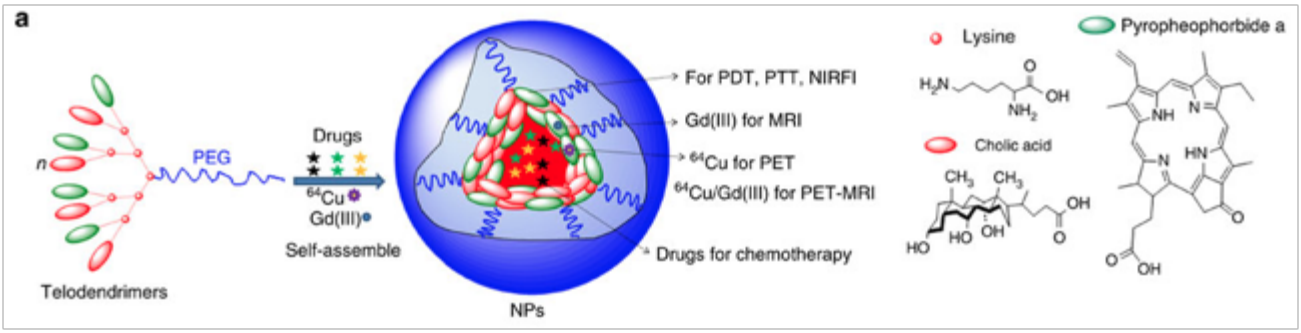

Fig. 1 Depiction of a self-assembling nanoparticle (NP), PEG-Por_4CA_4 (7). The NP is formed by amphiphilic polymers called telodendrimers, containing polyethylene glycol (PEG), as well as cholic acid (CA) and pyropheophorbide-a (Por) (7). These subunits are identified and illustrated to the right of the figure. In an aqueous environment, the subunits aggregate spontaneously to form a micelle (NP), with a hydrophobic interior and hydrophilic exterior (7). Additionally, when hydrophobic drugs are introduced the NPs, they arrange on the inside of the particle due to hydrophobic interactions with water (7). Metal ions (CU, Gd(III)) may also chelate to Por within the NP for diagnostic imaging purposes (7). Arrows on the NP structure indicate the various functions of different subunits in the NP, ranging from imaging: near-infra red florescent imaging (NIRFI), positron emission tomography (PET), and magnetic resonance imaging (MRI) to therapeutic: including photodynamic therapy (PDT), photothermal therapy (PTT), and drugs for chemotherapy (7).

Importantly, each of these organic groups is safe for *in vivo* application; the components are naturally occurring and biologically compatible molecules. PEG- Por_4CA_4 is also 21± nm in size, and so it is small enough to avoid aggregation in the liver and spleen (7). The last *in vivo* barrier that this nanoparticle overcomes is structural integrity in contact with blood; the research group modified the particle by crosslinking it with disulphide bonds. This formed CNPs, or disulphide-crosslinked nanoparticles, and they exhibit increased stability and circulation in blood over the standard NPs (7). Such stability is essential to improving the quality imaging diagnostics and also controlled drug release.

CNPs function to serve a variety of clinical applications. They can be loaded with organic chemotherapeutics (such as doxorubicin, or DOX) to deliver on site of a tumor, and drug release can be triggered by irradiation or exposure to the reducing agent glutathione (7). CNPs also conduct photothermal therapy—in the presence of phosphate-buffered saline, they convert irradiated light to heat and essentially heat-shock tumor cells, as well as photodynamic therapy (PDT), where light triggers the release of singlet oxygen to destroy tumor tissue (7). Effectively, these therapies dramatically lower tumor cell viability over time (Fig. 2).

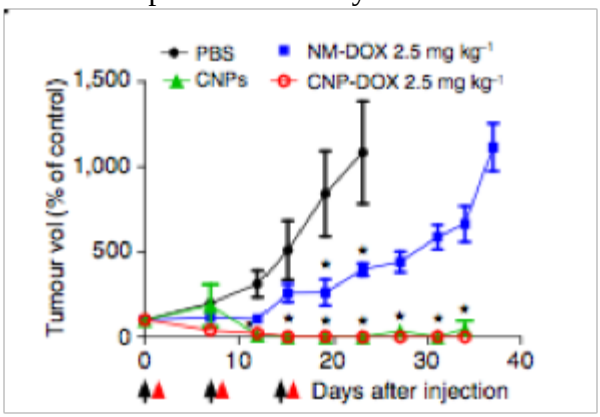

Fig. 2 Tumor volume change over time in mice with mammary cancer that have been injected with CNPs, CNP-DOX (drug-loaded CNPs), NM-DOX (standard micelles without porphyrin), and the control group PBS (phosphate buffered saline) as indicated by the black arrow (7). This injection was followed by light irradiation to trigger photothermal therapy, as indicated by the red arrow-head. The experimental groups containing CNP nanoparticles, including CNP-DOX and CNPs, display the greatest decline in tumor volume over time (7). This effect should be contrasted to that of the non-CNP nanoparticle (NM-DOX) and the solution of PBS, which both display tumor volume increase over time (7).

Diagnostically, CNPs also increase tumor visibility for MRI, NIRFI, and PET scans. When they are exposed to sodium

dodecyl sulfate, the florescent properties of the nanoparticles illuminate tumor cells for early and accurate diagnosis (7), (Fig. 3).

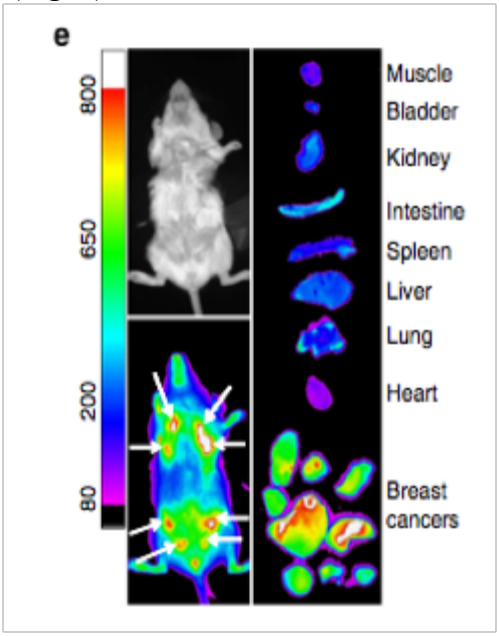

Fig. 3 *In vivo* and *ex vivo* near-infrared florescence imaging (NIRF) of a mouse with mammary cancer, 24 hours after injection with CNPs (7). The light spectrum on the left of the image shows the range of light wavelengths appearing on the imaging scan, from the ultraviolet at 80 wavelengths of light, to the infra-red, at 800 wavelengths of light. CNPs will fluoresce in the near infrared, and so NIRF imaging of the mouse abdomen shows aggregation of the CNPs at the site of mammary tumors, as indicated by the near-infrared florescence (from 650 to 800 wavelengths). The white arrows show the location of tumor sites on the mouse mammary glands (7). To the right of the mouse images are depictions of the isolated organs fluorescing at varying wavelengths. The organs shown emitting 80-200 wavelengths of light, including the muscle, bladder, and kidney, do not exhibit aggregation of CNPs. The breast cancers, however, fluoresce at 650 to 800 wavelengths of light, display high concentration of CNP aggregation (7).

This newly developed nanoparticle succeeds where its precursors fell flat: it is biologically compatible, stable, and versatile (7). Further, CNPs increase health outcomes for patients by allowing for early tumor diagnosis through enhanced imaging and minimal harm to healthy cells (7). Together, these advantages increase the chance of patient survival and quality of life after treatment. This technology takes a great stride towards personalized and precise medicine that minimizes harm, and addresses one of the most significant contributors to mortality in the developed world. Armed with this nanotechnology, the future of cancer treatment does not look so grim.

It is worthwhile to ponder where nanorobotics will bring medicine and biology hundreds of years down the line. The almost unnoticeable presence and biological compatibility of these particles in our system makes them available for a variety of clinical functions. With the right chemical modifications, nanotechnology may be used to deliver DNA, RNA, proteins, and enzymes (7). Labs are beginning to develop RNA nanoparticles, where non-coding RNA, such as siRNA and miRNA, as therapeutic agents to correct the often malfunctioning RNA in cancerous cells (10, 12). Additionally, nanoparticles show promise to enhance cancer fighting immune function by boosting antitumor-efficacy (11). Further imagination towards the future hybrid system of humans and nanotechnology affords nothing short from extraordinary; Bhat considers the future for nanorobotics as a groundbreaker for human evolution, when we become internally “robotically enhanced organisms” (1). It may even be possible that one day, nanoparticles will relay vital signs to medical monitoring systems, turning the tales of science fiction into reality (1). Whatever the outcome, nanorobotics is a frontier that inspires extraordinary possibilities for the future of medicine and human biology.

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