

# Nanomedicine - the future of cancer treatment: a review

## Abstract

Conventional cancer therapies are limited to surgery, radiation, and chemotherapy. Conventional treatments come with significant adverse effects. Modern cancer treatments focus on precise drug delivery to the cancer tissues and minimize adverse effects on healthy cells. Researchers have been working on an improved technique for delivering chemotherapeutic agents precisely at the molecular level in the tumor tissue. It has led to the use of nanotechnology in cancer treatment. Nanotechnology is the science and engineering of controlling matter, at the molecular scale, to create devices with novel chemical, physical and biological properties. Nanoscale objects are used themselves or as part of larger devices containing multiple nanoscale objects. Almost every field of Biosciences uses nanotechnology and all of which have an impact on biomedicine. It has the potential to change the current methods to diagnose and treat cancer. There has been real progress in translating nano-based cancer therapies and diagnostics into the clinic, and much more are in development. Nanoparticles are mainly used as nanocarriers to deliver the cytotoxic drugs to the tumor tissue. Use of nanoparticles is based on different concepts of pharmacology. Nanomedicine also is utilized to deliver multiple drugs at the cancer site at the same time for a better cytotoxic effect. CytImmune Sciences is a developing field of nanomedicine for targeted chemotherapy method. They selectively deliver the drug at the cancer site because of the increased permeability of the blood vessels at the tumor site. This article reviews various nanomedicine-based cancer therapeutics.

**Keywords:** immunotherapy, adoptive cell transfer, nanocarriers, nanoshell, PSMA, phototherapy, PDT

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**Abbreviations:** FDA, food and drug administration; PMSA, prostate-specific membrane antigen; siRNA, small interfering RNA; FSC, feedback system control (FSC); TNF- $\alpha$ , tumor necrosis factor alpha; PEG-THIOL: thiol-derivatized polyethylene glycol

## Conventional cancer treatment

Conventional cancer therapies are limited to surgery, radiation, and chemotherapy. All three methods cause damage to healthy tissues or incomplete eradication of cancer. Conventional chemotherapy suffers the lack of aqueous solubility of the drugs, lack of selectivity for the cancer cells and multidrug resistance developed after repeated administration of the same drug.<sup>1</sup> Nanotherapeutics is a rapidly progressing field of cancer research aimed to solve several limitations of conventional drug delivery systems. The nonspecific target of cancer chemotherapy leads to the damage of rapidly proliferating normal cells. These adverse effects can be significantly reduced through the administration folate and transferrin-mediated nanotherapeutics which are aimed to target cancerous cells.<sup>2</sup> Multidrug resistance is a challenge in cancer chemotherapy that can be managed effectively by using solid lipid nanoparticles, mesoporous silica nanoparticles, nanoparticulated chemosensitizer, nanoparticulated poloxamer, polymeric nanoparticles, and magnetic nanoparticles.<sup>3</sup> Chemotherapeutic drugs are hydrophobic, and that leads to poor aqueous solubility and low bioavailability. It can be overcome by nanocrystals, albumin-based nanoparticles, liposomal formulation, polymeric micelles, cyclodextrin and chitosan-based nanoparticles.<sup>1</sup> Nanotherapeutics help to overcome the lack of selectivity, multidrug resistance and lack of aqueous solubility of conventional cancer chemotherapy. Nanotechnology provides nanoparticles that target

chemotherapies directly and specifically to cancerous cells and neoplasms, guides in surgical resection of tumors, and enhances the therapeutic efficacy of radiation-based and other anti-cancer treatment modalities. Use of nanotechnology-based therapeutic agent's leads to a decreased risk to the patient and an improved survival rate.<sup>4</sup> The use of nanotechnology in cancer treatment increased the possibility of destroying cancer tissues with minimal damage to healthy tissue and organs, detection of cancer and elimination of cancer cells before they form tumors. As the field of chemotherapy gradually integrates nanoparticles to deliver multiple chemotherapeutic agents with different targets, a non-conventional dosing will be necessary. Medical conditions vary from patient to patient so that the phenotypic personalized medicine will be required. Also, these issues create a parameter space that is too large to be individually tested and can result in an arbitrary dosing scenario.

## Modern cancer treatment

The immune system has significant natural capacity to identify and destroy abnormal cells. This may prevent the development of many cancers but not all cancers. Some cancer cells escape the anticancer effect of the natural immune system by reducing the expression of tumor antigens on their surface, inactivating the immune cells by expression of certain proteins, or modifying the cells in the surrounding microenvironment to release substances to suppress the immune response. Immunotherapies either stimulate the activities of specific components of the immune system or counteract signals produced by cancer cells that suppress immune responses.<sup>5</sup> The author discusses some important immunotherapy methods below.

## Immune checkpoint modulators

There are certain natural proteins called immune checkpoint proteins that normally keep immune responses in check by preventing intense responses that might damage normal cells as well as abnormal cells. Blocking the activity of immune checkpoint proteins stimulate the immune system and increase its ability to destroy cancer cells. Several immune checkpoint inhibitors have been approved by the Food and Drug Administration (FDA). The first FDA approved drug was ipilimumab for the treatment of advanced melanoma, blocks the activity of a checkpoint protein known as CTLA4, which is expressed on the surface of activated cytotoxic T lymphocytes.<sup>6</sup> CTLA4 inactivate these T cells, thereby reducing the strength of immune responses; ipilimumab binds to CTLA4 and prevents it from sending its inhibitory signal.

## Adoptive cell transfer (ACT)

Infiltrated T-cells from a patient's tumor are collected from samples of the tumor. The T-cells that show the greatest recognition of the patient's tumor cells in laboratory tests are selected, and large populations of these cells are grown in the laboratory. The cells are then activated by treatment with immune system signaling proteins called cytokines and infused into the patient's bloodstream.<sup>7</sup>

## Therapeutic antibodies and cancer treatment vaccines

Therapeutic antibodies are made in the laboratory that are designed to destroy the cancer cells.<sup>5</sup> One class of therapeutic antibodies, called antibody–drug conjugates (ADCs), has proven to be particularly effective to kill cancer cells. ADCs are created by chemically linking antibodies, or fragments of antibodies, to a cytotoxic substance. The antibody portion of the ADC allows it to bind to a target molecule that is expressed on the surface of cancer cells. The toxic substance can be a poison, such as a bacterial toxin; a small-molecule drug; or a radioactive compound. Once an ADC binds to a cancer cell, it is taken up by the cell and the toxic substance kills the cell.<sup>8</sup> Cancer treatment vaccines are usually prepared from a patient's own tumor cells or from substances produced by tumor cells.<sup>5</sup> They are designed to treat already developed cancers by strengthening the body's natural defenses against the cancer.<sup>9</sup>

## Chimeric antigen receptor T-cell therapy (CAR-T cell therapy)

It is an advanced version of Adoptive Cell Transfer techniques. After collection, the T cells are genetically engineered to produce special receptors on their surface called chimeric antigen receptors (CARs). CARs are proteins that allow the T cells to recognize a specific protein (antigen) on tumor cells [10]. These engineered CAR-T cells are then grown in the laboratory until they expand their population in billions. The expanded population of CAR T-cells is then infused into the patient. After the infusion, the T cells multiply in the patient's body and, with guidance from their engineered receptor, recognize and kill cancer cells that harbor the antigen on their surfaces.<sup>10</sup> Despite the promising clinical results, CAR-T cell therapy also involves several deleterious types of toxicity due to the inability to control T cell activity and some tumor-associated antigens that are presented by both diseased and healthy tissue. The prominent toxicity of CAR-T cell therapy involves cytokine release syndrome (CRS) and “on-target, off-tumor” toxicity.<sup>11</sup>

## Stem cell transplant

The types of stem cell transplant includes autologous (stem cells collected from the donor before initiating high dose chemotherapy)

allogeneic (stem cells from a donor is used), and syngeneic (stem cells collected from an identical sibling). The harvested marrow is filtered, stored in a special solution in bags, and then frozen. When the marrow is to be used, it's thawed and then put into the patient's blood through a vein, just like a blood transfusion. The stem cells travel to the bone marrow, where they engraft and start to make blood cells. Signs of the new blood cells usually can be measured in the patient's blood tests in about two to four weeks.<sup>12</sup>

## Principles of nanotechnology in cancer treatment

### Nanocarriers

Conventional chemotherapy utilizes drugs that are able to kill cancer cells effectively. But these cytotoxic drugs destroy healthy cells in addition to tumor cells, leading to many unintended adverse side effects. Nanoparticles are used as drug carriers for chemotherapeutics to deliver medication directly to the tumor while sparing healthy tissue. Nanocarriers have several advantages over conventional chemotherapy.<sup>13</sup> Nanomaterials offer manifold advantages as drug carriers.<sup>4</sup> Evidently, the drug particles that are large cannot reach the remote, secluded areas of the body. Because of the small size of the cell, the particles should be small enough with nanoscale dimensions to penetrate and cross the cell boundary.<sup>14</sup> The tiny capillaries have 5-6 micron diameter, and most of the microparticles cannot pass through them. So nanoparticles are more suitable than microparticles for intravenous delivery. For systemic circulation, the particle diameters should lie in the range of 10-100nm to have access to various parts of the body.<sup>14</sup> Secondly, nanomaterials raise the drug effectiveness since they are consumed by cells efficiently than comparatively larger micromolecules. The drug is integrated into a matrix of nanoparticle or attached to the particle surface. As nanoparticles possess very high surface to volume ratio, the dissolution rate is increased. For example, when formulated as nanosuspensions, poorly soluble drugs like paclitaxel, cyclosporine, or amphotericin B exhibit an increased rate of dissolution and absorption in the gastrointestinal tract. Thirdly, nanomaterials improve the uptake of a poorly soluble drug through targeted drug delivery at the particular disease site.<sup>15</sup> Nanoparticles are formulated to adsorb preferentially on organs or tissues depending on the particle charge, surface properties, and relative hydrophobicity, fourthly, nanomaterials help in the lessening of undesirable side effects by a controlled release.<sup>16</sup> Nanosphere encapsulation of the drug safeguards against degradation and prolongs exposure of the drug by restricted release, a preferred quality of any chemotherapeutic agents.<sup>14</sup> Therefore, use of nanomaterials in the pharmaceutical sector improves therapeutic index, providing solutions for delivery problems. Nanomaterial-based drug carriers can protect drugs from being degraded in the body before they reach their target, and increase bioavailability to obtain the best effect from it.<sup>17</sup> It also enhances the absorption of drugs into tumors, and the cancerous cells themselves thus prevent drugs from interacting with normal cells and avoids side effects.

### Passive targeting

Because of their size and surface properties, certain nanoparticles can escape through blood vessel walls into tissues. Nanoparticles accumulate in tumors since tumors have leaky blood vessels and defective lymphatic drainage.<sup>18</sup> This feature enables concentrating the attached cytotoxic drug where it's needed, protecting healthy tissue and significantly reducing adverse side effects. Examples of such diseases where passive targeting of can be achieved are the tumor tissues and inflamed tissues. There are several nanocarrier-based

drugs in the market, which rely on passive targeting through a process known as enhanced permeability and retention.<sup>19</sup> Because of their size and surface properties, certain nanoparticles can escape through blood vessel walls into tissues.

### Active targeting

Active targeting is based on the molecules expressed by cancerous cells on their surfaces and the selective targeting by nanoparticles. Attaching a molecule to a nanoparticle enables targeting of the molecule to a cell that expresses a particular receptor. Active targeting principle is used to deliver drugs into the cancerous cell, by inducing the cell to absorb the nanocarrier.<sup>14</sup> Active targeting can be combined with passive targeting to reduce further the interaction of carried drugs with healthy tissue. Nanotechnology-enabled targeting can also increase the efficacy of a chemotherapeutic, achieving greater tumor reduction with lower doses of the drug.<sup>4</sup>

### Destruction from inside the cell

Nanoshells are a form of nanoparticles that are used in the laboratory to destroy tumors from the inside by its thermal properties. Nanoshells can be designed to absorb light of different frequencies, generating heat (hyperthermia).<sup>20</sup> The multifunctional gold nanoshells could be a more efficient cancer treatment because of its ability to target cancer cells specifically and spare healthy cells. After the nanoshells get into the cancer cells (via active targeting), scientists apply near-infrared light that is absorbed by the nanoshells. It creates an intense heat inside the cancer tissue that selectively kills the tumor cells without disturbing neighboring healthy cells.<sup>21</sup>

Newer targeted magnetic nanoparticles that are in development will be visible through Magnetic Resonance Imaging (MRI) and can destroy cells by hyperthermia.<sup>22</sup> Features of improved targeting ability, guiding the nanoshells to specific cancer cells and attaching to markers on the surface of the cells are attributed to the small peptides situated on the surface of the nanoshells.<sup>23</sup> Cancer cells maintain an acidic environment, and that triggers the offloading of the anticancer drugs. The specific nanostructure of the gold nanoshells could also allow near-infrared light to be absorbed and converted into heat whereby cancer cells are exposed to slightly higher temperatures than usual to destroy them.<sup>21</sup> Some studies have demonstrated the use of iron oxide gold-shell nanoparticles that are MRI-visible photothermal sensitizers during laser irradiation of pancreatic cancer cells.<sup>24</sup> Exposure to iron oxide gold-shell nanoparticles followed by laser irradiation led to significant improvement in the management of pancreatic cancer cell.<sup>24</sup> There are some major disadvantages for nanoshell therapy such as drug toxicity and tumor resistance. Toxicity can cause significant complications, such as neutropenia or heart failure that necessitate cessation of treatment. The tissue damage inflicted by some nanoshell therapies can even be fatal.

In spite of all disadvantages, there are many significant benefits of the nanoshell therapy too. Nanotechnology-based therapeutics have exhibited clear advantages compared to unmodified drugs, including improved half-lives, retention, and targeting efficiency, and fewer patient side effects.<sup>25</sup> Many nanomedicine compounds are in various stages of trials or already approved by the U.S. Food and Drug Administration (FDA). Studies showed that nanoparticles- combined chemotherapeutic drug with prostate-specific membrane antigen (PSMA) has shown to reduce lung and tonsillar lesions with greater efficacy compared with the conventional chemotherapeutic drug alone, and at substantially lower doses.<sup>26</sup>

### Simultaneous delivery of two drugs

Researchers recently reported the efficacy of multidrug delivery using nanoparticles in effectively mediating resistance in relapsing cancers and to improve triple-negative breast cancer treatment.<sup>27</sup> For example, delivery of layer-by-layer small interfering RNA (siRNA) and doxorubicin for breast cancer therapy. Others include simultaneous loading of siRNA and tumor-penetrating peptides against ovarian cancer, and sequential administration of multiple types of nanoparticles for pancreatic cancer treatment.<sup>28</sup>

For chemotherapies modified using nanotechnology to change hematological and oncological practice, the application of engineered nanomedicines must be paired with emerging strategies to design rationally nanotherapeutic combinations. This is crucial because combinatorial therapy is widely used in treating cancer and infectious diseases, and is an efficient way to simultaneously address the barriers to treatment success.

### Nanotechnology-based therapeutic agents in cancer treatment

Current clinical methodologies for combinatorial drug design will be replaced as the field of chemotherapy accepts the use of nanoparticles that deliver multiple compounds with different targets, and avoids the additive dosing. Medical conditions vary from patient to patient so that the phenotypic personalized medicine will be required. Also, these issues create a parameter space that is too large to be individually tested and can result in an arbitrary dosing scenario.

Nanomedicines need to be paired with advanced strategies to determine dosing conditions that can simultaneously optimize for efficacy and safety to enable long-term permanent disease management. One promising route is the field of feedback system control (FSC), which relies on phenotypic responses instead of interrogating cellular pathways, their individual protein components, or a spectrum of genotypic responses.<sup>28</sup> FSC utilizes outcomes to suggest new possible combinations before rapid convergence toward an optimal combinatorial dose, pharmacokinetics, and pharmacodynamics. FSC also will help personalized nanomedicine dosing on a case-by-case basis as combinations will vary from patient to patient.

### Nanomedicines of future

CytImmune is one of the major companies doing research on nanomedicines in cancer treatment. CytImmune founded in 1988, has transitioned from a successful diagnostics company into a clinical stage nanomedicine company with a core focus on the discovery, development and commercialization of multifunctional, tumor-targeted therapies. It is a global leader in the field of nanomedicine with the successful completion of a Phase I clinical trial of CYT-6091- the first in a series of products based on the CytImmune's Aurimmune nanomedicine platform (cytimmune.com). It utilizes colloidal gold nanoparticles to deliver drugs directly to cancer tumors. CytImmune uses a combination of techniques to target the nanoparticle to cancer tumors. First, the nanoparticle is designed to be too big to exit most healthy blood vessels. However, some blood vessels located at the site of tumors are leaky, allowing the nanoparticle to leave the blood vessel at the tumor site [29]. They also attach molecules of tumor necrosis factor alpha (TNF- $\alpha$ ) - a tumor-killing agent, to the nanoparticle, as well as molecules of Thiol-derivatized polyethylene glycol (PEG-THIOL). PEG-THIOL hides the TNF- $\alpha$  bearing nanoparticle from the immune system allowing the nanoparticle to flow through the blood stream without being attacked. Once the nanoparticle is in the region

of a cancer tumor TNF molecule, bind the nanoparticle to cancer cells. CytImmune's patented technology is based on colloidal gold particles that carry specific drugs to targets such as cancer cells.<sup>29</sup> The particles allow the drugs to be safely transported through the blood stream and

directed to their specific cellular targets. There are few other targeted chemotherapy treatment and nanomedicines under development. The following Table 1 lists some important therapeutic agents.<sup>30</sup>

**Table 1** Nanomedicines<sup>30</sup>

Name of the nanoparticle/ agent	Name of trial drug/ mechanism of action	Developing organization
CRLX101	Targeted chemotherapy	Cerulean Pharma
AuroShells	Thermal destruction	Nanospectra
CriPec®	Delivers Docetaxel to tumors	Cristal Therapeutics
IPA-3	Infrared light to trigger release of two cancer drugs	Massachusetts General Hospital
Dendrimers	Reduce growth of prostate cancer cells	University of Georgia
Graphene strips(non-nano)	Deliver nucleic acids that suppress tumors to liver cancer tumors	University of Texas Southwestern Medical Center
Two different nano particles	Enters the cell and delivers the second drug to the cell nucleus.	
Iron-oxide nano particles	The first nanoparticle removes material on the exterior of the cancer cells that block the entry of chemotherapy drugs; the second nanoparticle carries the chemotherapy drug	UCLA
Hydrogel containing Herceptin	Heat up cancer tumors and stimulate immune system	No name/ Independent Researcher
Polymer nanoparticles carrying Docetaxel	Decrease tumour size	Institute of Bioengineering and Nanotechnology and IBM
Nanodiamonds	Increasing the rate of delivery of the chemotherapy drug to the tumors	BID Biosciences
Nanotrain(Connected DNA strands)	Combination with chemotherapy drugs stays in tumor for longer	No name /Independent Researchers
Nano particle with Camptothecin and Herceptin	Deliver chemotherapy drugs to cancer cells	No name /Independent Researchers
Staurosporine in liposome nanoparticles	Targets breast cancer cells	No name /Independent Researchers
Nanoparticles containing a radioactive core	Suppress tumors without side effects	UC San Diego
Photosensitizing agent to enhance the ability of drug carrying nanoparticles	Attach to lymphoma cells	No name /Independent Researchers
Bismuth nanoparticles	The photosensitizing agent causes the blood vessels in the tumor to be more porous.	No name /Independent Researchers
Gold nanoparticles (topical)	Concentrate radiation used in radiation therapy to treat cancer tumors	No name /Independent Researchers
Micelles	Penetrate the skin and the RNA attaches to a cancer-related gene	No name /Independent Researchers
Auroshell	Delivers Paclitaxel to bladder	No name /Independent Researchers
Nanotubes	Accumulate at the tumor the AuroShell™ nanoparticles are used to concentrate the heat from infrared light	Nanospectra Biosciences
nbtxr3	Infrared light from a laser is absorbed by the nanotubes and produces heat that incinerates the tumor	
Nanoparticles containing interleukins	when activated by x-rays, generate electrons that cause the destruction of cancer tumors to which they have attached	Nanobiotix
Polymer nanoparticles	When the T-cells reach a tumor the nanoparticles release the drug molecules, which cause the T-cells to reproduce	No name /Independent Researchers
	Deliver JSI-124 molecule to cancer cells, degrades their ability to suppress immune system	No name /Independent Researchers

## Nanomedicine in early cancer detection

Nanoparticles are not just used only to treat cancer, but are also useful for early detection of cancer. Sensors based on nanoparticles or nanowires can detect proteins related to specific types of cancer cells in blood samples.<sup>31</sup> It allows early detection of cancer. T2 Biosystems uses superparamagnetic nanoparticles that bind to cancer indicating protein and cluster together. These clusters provide a magnetic resonance signal showing the presence of the cancer-related protein.<sup>32</sup> One of the studies used quantum dots and molecules that emit a fluorescent glow to detect DNA strands that are early indicators of cancer.<sup>33</sup>

## Conclusion

Cancer Nanomedicine possesses the versatility required to overcome some of the most challenging impediments to treatment success while using conventional chemotherapeutic agents. Designing appropriate nanotherapeutic combinations using rapid convergence solutions such as Feedback System Control (FSC) represents a promising pathway from cancer management towards cancer elimination. Research should focus on identifying the appropriate nanoparticles that work well with certain chemotherapeutic agents for the drug's cytotoxic effect or the cytotoxic effect of the nanoparticles itself after activating with a suitable form of electromagnetic energy. Studies also should be encouraged to identify and formulate nanoparticle-based tests

for early identification of cancer. Cancer studies need to hasten the clinical trials, and FDA approval to enable clinicians to use these tests in the clinics conveniently as a preventive measure.

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## Conflicts of interests

The authors declare that there is no conflict of interest.

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