

## THERANOSTICS USAGE OF NANO DRUG COMPLEXES IN CLINICAL PATIENTCARE

### Abstract

The extraordinary expansion in the nanomedicine with the development of new nano drug particles made surprising advancement in diagnosis and treatment. Nano drug complexes have amazing medicinal properties and clinical benefits in health care practice. That allows these to attach, absorb and deliver the nano molecule including RNA, DNA, probes and proteins at desired site in an efficient manner. Certain diagnostic agents are potential used to theranostics purpose in nano drug's formulation. Additionally the biotransformation technique used to achieve the desired clinical results and/ or pharmacological benefits. The reproducible synthesis of monodispersed nano drug particles play efficient role in healthcare system. Thus, we aimed this study to review the theranostics usage of nano drug complexes in clinical patientcare. The current scientific information used in nano drug particles; non-invasive imaging techniques; and enhanced permeability and retention are tried to incorporate to enhance the credibility of this review article. The medicinal potential of nano drug complexes can effectively be used with the interventions of modern technologies, image guided drug delivery system, antigen targeted immunotherapy and radio-guided drug distribution for individualized and poly-pharmacy practice.

**Key words:** Theranostics, Nano drug complexes, Clinical patientcare, Nanoparticles, Chemotherapy, Targeted drug delivery.

### Introduction:

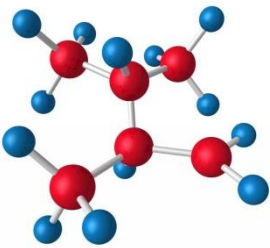

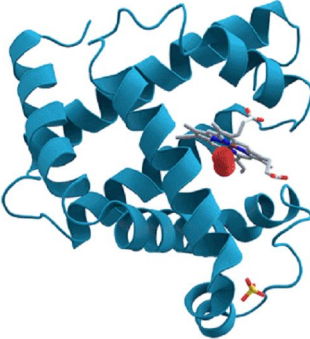


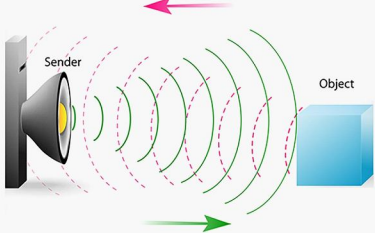
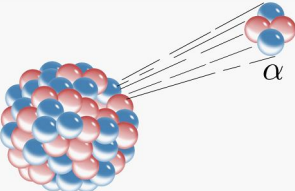

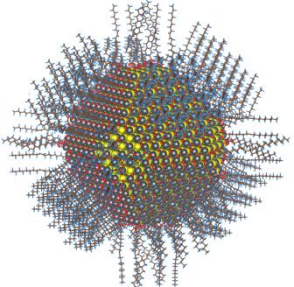
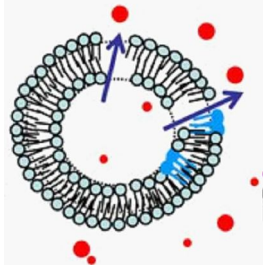
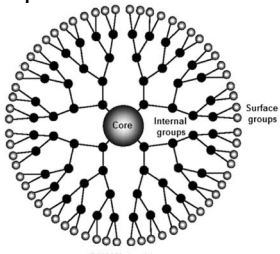
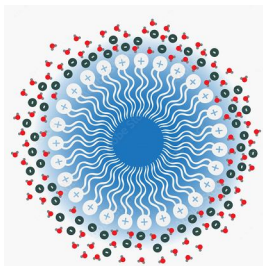
The chemotherapy, combination of surgery, radiation therapy and immunotherapy are mostly used for the treatment of critically ill patients. New scientific equipment's and research information has potentially enhanced our ability to design new methods, treatment protocols and understand the pathological complications in microenvironment. The infected cells are composed of vascular, interstitial and non-cellular compartments and predominantly different to the surrounding normal tissue. Therefore, these particular cell compartments have their own cellular characteristics and molecular features. That potentially offered difficulty challenge for scientists to delivery of drugs at desired site within the patient's body. [1]

Therefore, we aimed to write this review article with primary information covering the nanoparticles, development of nano carrier, nano drug complexes, drug delivery systems and applications of theranostics. The modern technologies of dendrimers, polymeric nano drug particles, liposomes, nano shells, inorganic nano drugs, metallic micelles and hybrid nano particles are used to improve the accuracy and efficacy of treatment. The magnetic and bacterial nano drug complexes also developed to diversify the drug and with a range of sizes, shapes, and components.[2] That allows the medicinal experts to use the techniques and tools in more efficient manner.

Though, the main objective while designing any drug delivery system is to control drug concentration, that eventually helps to achieve the primary goal therapeutical effectiveness. Additionally, we can maintain a threshold level of drug concentration; reduce cytotoxicity, minimizing the recovery period, improve the patient compliance and allows effective treatment cycles.



## Nano Theranostics

Theranostics	Diagnostics	Nano carriers
 <p>Small drugs</p>  <p>siRNA/ DNA</p>  <p>Proteins</p>	 <p>Fluorescent probe</p>  <p>Magnetic resonance imaging</p>  <p>Ultrasonic</p>  <p>Radionuclide</p>  <p>X-ray</p>	 <p>Inorganic nanoparticle</p>  <p>Liposomes</p>  <p>Dendrimer</p>  <p>Micelle</p>

**Figure 1.** The theme of the recent developments of nanoscaled theranostic systems for accurate and early diagnosis and effective treatment and/ or management of cancers.

<p><b>RNAi</b></p> <p><b>Gene Theranostics</b> is the ex-vivo, in-vivo, and in-situ gene therapy along with diagnosis of the severity and stage of particular disease.</p>	<p><b>Hyperthermia or ROS</b></p> <p><b>Cocktail Theranostics</b> is the combination of simultaneous administration of multiple therapeutic agents with molecular identification of particular tumor or pathological disorder. It is becoming important for achieving long-term prognosis and control of undesired effects.</p>	<p><b>Chemotherapeutic agent</b></p> <p><b>Diagnostic Agent</b></p> <p><b>Chemotheranostics</b> is a combination of drug (chemotherapeutic agent) and diagnostics. This term describes the usage of anticancer drugs to identify disease and deliver the active drug to treat the main or metastatic tumors.</p>
<p><b>SPECT or CT imaging</b></p> <p><b>Radio Theranostics</b> is the use of radionuclides for the paired imaging and therapy agents. Radioiodine is the classic radiotheranostic agent that has been used clinically in management of thyroid diseases for nearly 75 years.</p>	<p><b>O<sub>2</sub></b> <b>ROS</b></p> <p><b>Fluorescence imaging</b></p> <p><b>Photodynamic Theranostics</b> is the usage of photodynamic therapy, activated by light, photosensitizer or photosensitizing agent, to kill cancer cells along with determination of type and stage of disease.</p>	<p><b>Light</b> <b>Hyperthermia</b></p> <p><b>Tumor cell death, NIR imaging</b></p> <p><b>Photothermal Theranostics</b> is the utilization of photothermal therapy or physicochemical therapy for cancer treatment (optical radiation in the NIR wavelength range 700–2000 nm) along with application of techniques to identify the disease.</p>

**Figure 2.** Nano drug complexes based theranostic systems used for the treatment of different cancers.

### Clinical use and potential challenges of Nanotheranostics

Nanotheranostics is an effective usage of nanotechnology to integrate therapeutic and diagnosis together in clinical practice. [3] That helps the medical professionals to get more accurate information and optimize the clinical outcomes. However, the transformation of nanotheranostic data into understandable clinical

information still posed tremendous obstacles in actual medical practice. Therefore, we nanotheranostics system is an outstanding platform to exchange ideas and visions. [4]

The scientific community is working to overcome the challenges posed by conventional nanotechnologies including the insufficient drug deposition, uncontrolled cargo release through different smart drug delivery systems and optimization of molecular cell response. However, the controlled delivery system, clinical translation and image guided interventional has introduced considerable obstacle for clinicians to manage certain types of carcinomas. The recent development of nanotheranostics showed viable nanoplatform to provide cancer treatment with various diagnostic techniques.[5] The different kind of magnetic resonance, optical, ultrasonic and computed tomography imaging technologies can potential individualized to design more effective treatment protocols.

However, simultaneous delivery of more than one nano drug complexes at same location has got great attention because of the synergistic drug effects. Development of crosslinked polyion complex micelle of Doxorubicin and Epigallocatechin-3-O-gallate has minimized the cardiotoxicity and resistance. [6] This chemotherapeutic protocol offer synergistic antineoplastic effect along with reduction of associated heart complications. Additionally the early tumor detection is undoubtedly a vital achievement for effective neoplastic therapy. However the correct and precise diagnosis of disease in its early stage remains a difficult challenge. Therefore, an efficient, innovative, cost efficient and quick assay desired to detect a respective genetic components and molecular event that explicitly happened in prostate cancer.

### **The Nanoparticle Drug Complex**

The nano drug particles used as carriers may attach, entrap or encapsulate to the drug to protect it from destruction, denaturation or degradation. They also offer the simultaneously combination therapy against multiple disorders. The modern technologies can deliver the non-cytotoxic prodrugs i.e. administration of platinum based chemotherapeutic agents. [7]

**Table 1.** Clinical use of nanotechnology to formulate drugs targeting particular entities for the treatment of certain cancers.

Cancer type	Therapy	Target entity	Nanoformulation	Active drug
Brain Ca	Photodynamic	Epidermal Growth Factor Receptor	Peptide-targeted gold nanoparticles	Pc 4
Breast Ca	Chemotherapy	Fibrin-associated plasma proteins	CREKA-conjugated liposomes	Doxorubicin
Breast Ca	Chemotherapy	Folate receptors	PLGA polymeric nanoparticles	Doxorubicin
Breast Ca	Chemotherapy	Folate receptors	Deoxycholic acid-O-car-	Paclitaxel
Glioblastoma	Chemotherapy	IL-13R $\alpha$ 2	Liposomes	Doxorubicin
Hepatocellular Ca	Chemotherapy	Integrin receptors	RGD-modified liposomes	Paclitaxel
Epidermoid cyst	Chemotherapy	Epidermal growth factor receptor	PLGA nanoparticles	Tylocrebine
Folate receptor Ca	Photodynamic therapy	Folate receptors	Cobalt ferrite nanoparticles	Hematoporphyrin
Neuroblastoma	Chemotherapy	Transferrin receptors	PEGylated gold nanoparticles	AuNPs
Non-Small Lung Ca	Hyperthermia	Fibrin-associated plasma proteins	CREKA-conjugated dextran-coated iron oxide nanoparticles	Iron oxide NPs
Prostate Ca	Radiotherapy	LHRH receptor	Gold nanorods	Goserelin

[8,9,10,11,12,13,24]

**Table 2.** Nano-formulations, medicinal component and cancerous cell line.

Nanoformulation	Agent	Stimulant	Tested cancer cell lines
Bridged silsesquioxane nanoparticles	Plasmid DNA	Light	Human cervical HeLa cells
Chitosan derivative coated	Doxorubicin	Light/pH	Human cervical HeLa cells
Iron oxide/gold nanoparticles	DNA	AMF	Human cervical HeLa cells
Micelles	Cisplatin + cyanine dye	Light	Cisplatin-resistant lung cancer A549 cells
mPEGylated PLA-conjugated micelles	Curcumin	GSH	Human cervical HeLa cells
PEGylated, RGD-modified, and DSPEIs- functionalized gold nanorods	shRNA	GSH	Human glioblastoma U-87 MG-GFP cells

[14, 15, 16, 17, 18, 19, 20,25]

### Kinetic of the Nanoparticle Drug Complex

Nano drug particles are delivered at desired site within patient's body to cure the tumors either passively or actively. The nanoparticles are enabled to exploit the exclusive Enhanced Permeability and Retention effect of tumors in in passive delivery.[21] That enables these nano drug complexes to enter into the systemic body circulation or extravascular space, where these active drug agents can gather around the targeted

tumor cells. The nano drug complexes particles should be less than 100 nm to obtain best possible pharmacological effect in clinical setting. Distribution of nanoparticles at the particular cancerous cells may not be equal because of the heterogenic blood supply, physiological barriers and interstitial flow and density of the interstitial matrix. However, the active nanoparticles can actively attack to neoplastic cells with the help modification occur at the surface including addition of ligands, peptides synthesis, oligosaccharides, small molecules and antibodies.[22] The nanoparticle can then recognize and attach to the respective complementary target molecules located at the externally exposed or surface structural component of the of cancer cells. The target molecule may be antigen or receptor; therefore it must be in high concentration at the cancer cells but least possible level in the regular normal body tissue. That will potentially help to minimize the toxicity induces by active chemotherapeutical nanoparticles. [23,26] Once the nanoparticle drug complexes delivered to the desired body site to control the tumor, the nano drug complex must dissociate to release the drug into systemic circulation. The drugs particles are then released after binding to neoplastic cells from the respective nano drug complexes. That takes place either by diffusion from the matrix or by erosion, swelling and/ or degradation of the nano drug complexes.

### **Conclusion**

We have incorporated the most current and authentic information regarding theranostics usage of nano drug complexes in clinical settings. This exclusive attribution may potentially help the clinicians and health care professionals to explore the accurate and rational treatment plans. The potential risks posed during the adjuncts, combination and multiple therapies can be handled more skillfully. However, certain nano drug complexes are translated into new nano drug entities to develop new treatment options. Thus, interdisciplinary collaboration and knowledge exchange between scientists from various disciplines is necessary to make conclusive advancement in this growing field of pharmacotherapy.

**Conflict of interest:** The authors also declare that they are no any potential conflict of interest.

**Funding:** The authors received no direct funding for this research.

**Competing Interests:** The authors declare no potential and/ or competing conflict of interests

### **Future study**

We have incorporated the most current and authentic information regarding theranostics and nano drug complexes. Our exclusive attribution may potentially help the scientists to develop advanced pharmacotherapy protocols. However, the researchers are encouraged to develop the novel drugs carriers, therapeutic agents and imaging techniques. The nano drug complexes can be developed to produce the<sup>3</sup> ligands, multiple layers with variety of loading density. That will make these agents more suitable for angiogenesis and molecular diagnostics for extravascular targets or theranostics. Nanoparticle formulations designed to reduce excretion, prolong retention and assure the availability at desired pathological site.

**Authors' contributions:** This work was carried out in collaboration among all authors. **Taha Nazir, Saeed Ur Rasheed** and **Azharul Islam** designed the study of proposed hypothesis and compile the scientific

contents. **Nida Taha** elaborated study to make it more credible. Whereas, **Taha Nazir** managed the literature searches and citation part of the manuscript. Thus, all authors have read and approved the final manuscript for publication in this journal.

## References:

1. Janmaat VT, Steyerberg EW, van der Gaast A, et al. Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer. *Cochrane Database Syst Rev*. 2017;11(11):CD004063. Published 2017 Nov 28. doi:10.1002/14651858.CD004063.pub4
2. Woolley JL, MacGregor N. Science, technology, and innovation policy timing and nanotechnology entrepreneurship and innovation. *PLoS One*. 2022;17(3):e0264856. Published 2022 Mar 3. doi:10.1371/journal.pone.0264856
3. Sonali, Viswanadh MK, Singh RP, et al. Nanotheranostics: Emerging Strategies for Early Diagnosis and Therapy of Brain Cancer. *Nanotheranostics*. 2018;2(1):70-86. Published 2018 Jan 1. doi:10.7150/ntno.21638
4. Kumar R, Chhikara BS, Gulia K, Chhillar M. Review of nanotheranostics for molecular mechanisms underlying psychiatric disorders and commensurate nanotherapeutics for neuropsychiatry: The mind knockout. *Nanotheranostics*. 2021;5(3):288-308. Published 2021 Mar 1. doi:10.7150/ntno.49619
5. Carvalho IC, Mansur AAP, Carvalho SM, Mansur HS. Nanotheranostics through Mitochondria-targeted Delivery with Fluorescent Peptidomimetic Nanohybrids for Apoptosis Induction of Brain Cancer Cells. *Nanotheranostics*. 2021;5(2):213-239. Published 2021 Feb 8. doi:10.7150/ntno.54491
6. Almatroodi SA, Almatroudi A, Khan AA, Alhumaydhi FA, Alsahli MA, Rahmani AH. Potential Therapeutic Targets of Epigallocatechin Gallate (EGCG), the Most Abundant Catechin in Green Tea, and Its Role in the Therapy of Various Types of Cancer. *Molecules*. 2020;25(14):3146. Published 2020 Jul 9. doi:10.3390/molecules25143146
7. Deng Z, Kalin GT, Shi D, Kalinichenko VV. Nanoparticle Delivery Systems with Cell-Specific Targeting for Pulmonary Diseases. *Am J Respir Cell Mol Biol*. 2021;64(3):292-307. doi:10.1165/rcmb.2020-0306TR
8. Meyers JD, Cheng Y, Broome AM, Agnes RS, Schluchter MD, Margevicius S, Wang X, Kenney ME, Burda C, Basilion JP. Peptide-targeted gold nanoparticles for photodynamic therapy of brain cancer. *Part Part Syst Charact*. 2015;32:448-57.
9. Kirtane AR, Wong HL, Guru BR, Lis LG, Georg GI, Gurvich VJ, Panyam J. Reformulating tylocrebrine in epidermal growth factor receptor targeted polymeric nanoparticles improves its therapeutic index. *Mol Pharm*. 2015;12:2912-23.
10. Madhankumar AB, Slagle-Webb B, Mintz A, Sheehan JM, Connor JR. Interleukin-13 receptor-targeted nanovesicles are a potential therapy for glioblastoma multiforme. *Mol Cancer Ther*. 2006;5:3162-9.
11. Chen L, Liu Y, Wang W, Liu K. Effect of integrin receptor-targeted liposomal paclitaxel for hepatocellular carcinoma targeting and therapy. *Oncol Lett*. 2015;10:77-84.
12. Wolfe T, Chatterjee D, Lee J, Grant JD, Bhattarai S, Tailor R, Goodrich G, Nicolucci P, Krishnan S. Targeted gold nanoparticles enhance sensitization of prostate tumors to megavoltage radiation therapy in vivo. *Nanomedicine*. 2015;11:1277-83.

13. Liu M, Wang Z, Zong S, Chen H, Zhu D, Zhong Y, Cui Y. Remote-controlled DNA release from Fe<sub>3</sub>O<sub>4</sub>@Au nanoparticles using an alternating electromagnetic field. *J Biomed Nanotechnol.* 2015;11:979–87.
14. Cao Y, Gao M, Chen C, Fan A, Zhang J, Kong D, Wang Z, Peer D, Zhao Y. Triggered-release polymeric conjugate micelles for on-demand intracellular drug delivery. *Nanotechnology.* 2015;26:115101.
15. Fatiev Y, Croissant JG, Alsaiari S, Moosa BA, Anjum DH, Khashab NM. Photoresponsive bridged silsesquioxane nanoparticles with tunable morphology for light-triggered plasmid DNA delivery. *ACS Appl Mater Interfaces.* 2015;7(45):24993–7.
16. Li Y, Deng Y, Tian X, Ke H, Guo M, Zhu A, Yang T, Guo Z, Ge Z, Yang XL, Chen H. Multi-pronged design of light-triggered nanoparticles to overcome cisplatin resistance for efficient ablation of resistant tumor. *ACS Nano.* 2015;9(10):9626–37.
17. Qin Y, Chen J, Bi Y, Xu X, Zhou H, Gao J, Hu Y, Zhao Y, Chai Z. Near-infrared light remote-controlled intracellular anti-cancer drug delivery using thermo/pH sensitive nanovehicle. *Acta Biomater.* 2015;17:201–9.
18. Xu H, Cai C, Gou J, Sui B, Jin J, Zhang Y, Wang L, Zhai Y, Tang X. Self-assembled monomethoxy (Polyethylene Glycol)-b-P(D, L-Lactic-co-Glycolic Acid)-b-P(I-Glutamic Acid) hybrid-core nanoparticles for intracellular pH-triggered release of doxorubicin. *J Biomed Nanotechnol.* 2015;11:1354–69.
19. An J, Dai X, Wu Z, Zhao Y, Lu Z, Guo Q, Zhang X, Li C. An acid-triggered degradable and fluorescent nanoscale drug delivery system with enhanced cytotoxicity to cancer cells. *Biomacromolecules.* 2015;16:2444–54.
20. Pan J, Wu R, Dai X, Yin Y, Pan G, Meng M, Shi W, Yan Y. A hierarchical porous bowl-like PLA@MSNs-COOH composite for pH-dominated long-term controlled release of doxorubicin and integrated nanoparticle for potential second treatment. *Biomacromolecules.* 2015;16:1131–45.
21. Cheng K, Peng S, Xu C, Sun S. Porous hollow Fe<sub>3</sub>O<sub>4</sub> nano drug particles for targeted delivery and controlled release of cisplatin. *J Am Chem Soc.* 2009;131:10637-10644.
22. Brannon-Peppas L and Blanchette JO. Nanoparticle and targeted systems for cancer therapy, *Adv. Drug Delivery Rev.*, 2004; 56: 1649-1659.
23. Kunjachan S, Jayapaul J, Mertens ME, Storm G, Kiessling F, Lammers T. Theranostic systems and strategies for monitoring nanomedicine-mediated drug targeting. *Curr Pharm Biotechnol* 2012; 13: 609–22.
24. Aljamali, N. M. (2022). Designation of Macrocyclic Sulfazan and Triazan as Innovated Compounds with Their Estimation in Nano-Activities by the Scanning Microscope. *International journal of convergence in healthcare*, 2(1), 25-34.
25. Saher Mahmood J, Zainab H Al, Alaa Hamza Jaber Al. Nano- Electronic Applications in the Nanomedicine Fields. 2022- 4(2), OAJBS.ID.000407. DOI: 10.38125/OAJBS.000407
26. Nagham Mahmood A. Inventing of Macrocyclic Formazan Compounds with Their Evaluation in Nano- Behavior in the Scanning Microscope and Chromatography. *Biomedical Journal of Scientific & Technical Research*, 2022: 41(3):32783-32792. BJSTR. MS.ID.006616.; DOI:10.26717/BJSTR.2022.41.006616