NANOTECHNOLOGY – A WONDER IN CANCER TREATMENT

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Abstract

In this review, we summarize the recent advances in nanotechnology applied for theranostic use, distinguishing between passive and active targeting of these vehicles. Finally, we focus on two types of nanoparticles used to stimulate an anticancer immune response: Exo carried with A Disintegrin And Metalloprotease-10 inhibitors and NP loaded with aminobisphosphonates. The former would reduce the release of decoy ligands that impair tumor cell recognition, while the latter would activate the peculiar anti-tumor response exerted by T cells, creating a bridge between innate and adaptive immunity. Nanotechnology anticancer new treatment appears to be powerful in effectively using nanodrugs to enhance the immune response. The coupling of these interventions with other therapies, such as photothermal or cancer vaccine treatment, can result in an improved antitumor result. Thus, the direction of antiproliferative therapies strives to increase the efficacy of the use of different therapies in a complementary approach rather than independently.

INTRODUCTION

As the research progress ,in the same way, treatment of many diseases can be achieved with great success whether it about vaccines or insulin and the use of anesthesia in surgery these are some of the major medical developments.[1] But unfortunately, cancer has still become a major cause of death worldwide.

There are three standard strategies for treating cancer: Surgery, radiotherapy, and chemotherapy. surgery and radiotherapy are considered effective to cure any cancerous tumor, but they are not limited to low-stage tumors and are not suitable for high-stage tumors.[2,3] Therefore, the final treatment for malignant tumors requires a new design of drugs and combination therapies to maximize the anti-cancer effect.

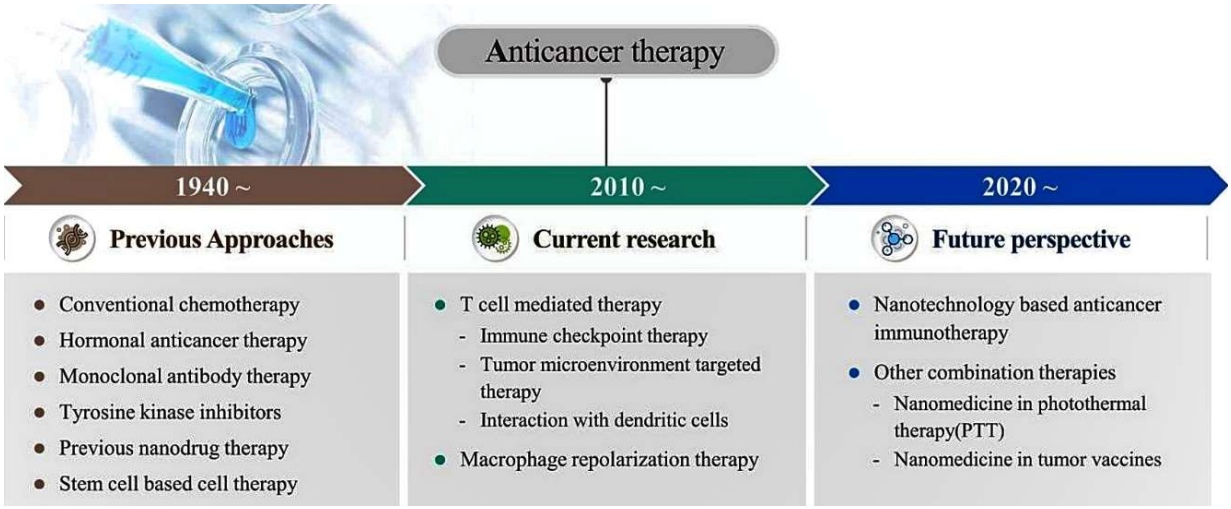


Figure1 Previous, contemporary, and future anticancer therapies. (A) Original techniques to cancer therapeutic strategies. Although almost all these strategies are indeed efficacious, they have constraints and are therefore not most beneficial in targeting malignant cells. (B) Current research in cancer treatment. Cancer immunotherapy, which include T cell-mediated medication and macrophage repolarization, is by far the most plausible. (C) Long term perception of cancer treatment. The future of cancer therapeutics rests in nanotechnology-based antitumor immunotherapeutic and certain combination therapies.

The help of new target-based anti-cancer drugs allows the selection of complete removal of cancer cells. However, most strategies that destroy the tumor cell adversely affect normal cells during chemotherapy.[4] Therefore, targeted drug delivery in cancer treatment not only targets malignant tumor cells but also inactivates the cancerous activity that affects non-tumor cells. Therefore, rapid growth of targeted based anticancer drugs has the potential to select tumor cells in tissues.[5,6]

Previous cancer treatments:

Conventional chemotherapy: Although the use of traditional anti-cancer chemotherapeutic drugs causes serious side effects, the use of these drugs is still widespread. Conventional chemotherapy inhibits DNA synthesis and mitosis, thereby preventing the proliferation of cancer cells.[7] Some cancer cells develop resistance to chemotherapeutic drugs by repairing DNA, inactivating cancer drugs, or rapidly expelling drugs to prevent cytosol accumulation.[8]

Hormone cancer treatment: The development of tamoxifen to cure breast cancer completely changed the landscape of cancer treatment, beginning in the era of "target cancer treatment". Hormone therapy uses the endocrine system to attack hormone-responsive tumor tissues. However, this has some drawbacks. [9] Since estrogen receptors are naturally present not only in breast cells but also in tissues throughout the human body, they activate estrogen receptors in the endometrium and cause side effects in bone and adipose tissue. It should be noted that despite the many side effects and limitations of tamoxifen as a hormone anticancer therapy, research has begun in targeted treatment.[10]

Monoclonal antibody therapy: Use of monoclonal antibodies (MOBs), receptor-specific antibodies (MOBS), which detect high-stress receptors in tumor cells and select malignant cells, is the earliest, most widespread, and most effective approach to targeted tumor treatment [11] monoclonal antibodies are more effective than previous chemotherapies because they are selected with high-pressure cancer membrane

receptors, thereby reducing damage to normal cells but often trigger immune-related dermatological problems.[12]

Tyrosine kinase inhibitor therapy: Tyrosine kinase is an enzyme involved in the activation of many proteins in tumor signaling. By blocking this enzyme, TKIs activate signaling mechanisms that lead to tumor formation and proliferation. [13] TKIs are very effective anticancer drugs, they still have some clinical limitations. First, they are only effective in treating specific cancers that express target proteins. For example, Trastuzumab is only effective against breast cancer.[14] Unfortunately, this drug does not work well for other tumors, such as lung or lung cancer. Also, these types of drugs can destroy normal cells that contain the same type of receptors for drugs.[15] Although their cytotoxicity is very limited compared to traditional anticancer chemotherapy, they still get serious side effects. Therefore, future cancer therapies should focus on treating advanced tumors and overcoming the side effects associated with mAbs and TKIs.[13]

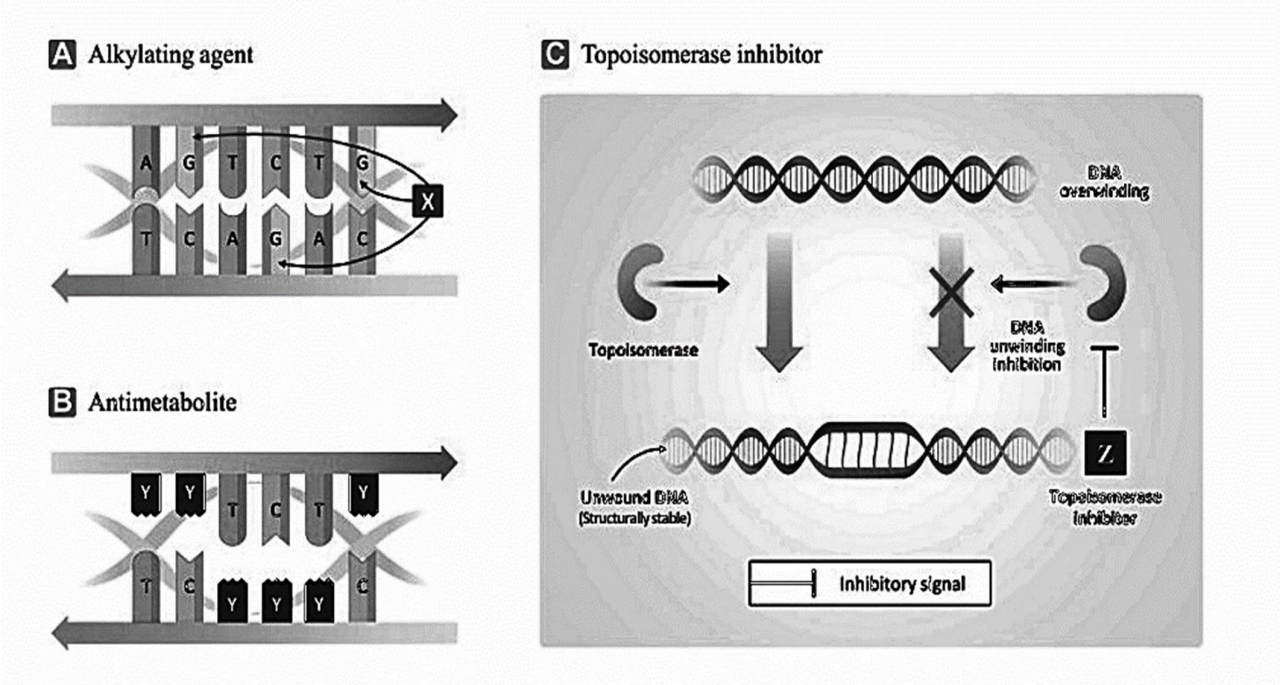


Figure 2: Conventional chemotherapy. (A) Alkylating agents. A = adenosine, T = tyrosine, G = guanine, C = cytosine, X = alkylating agent. Alkylating agents react with the N7 of guanine, resulting in abnormal base pairing, which leads to miscoding and strand breakage. (B) Antimetabolites. Y = Antimetabolite. Antimetabolites are structurally like endogenous compounds and destroy cancer cells by posing as purines or pyrimidines, which are building blocks of DNA. In B, the antimetabolite is masquerading as a purine. (C) Topoisomerase inhibitors. Z = Topoisomerase inhibitor. Topoisomerases normally decrease the torsion of the DNA. When this process is stopped by topoisomerase inhibitors, the torsion of the DNA strand increases and causes DNA breakage. [15]

Establishment of Approaches in Nano drug Therapy: A new type of anticancer drug has been discovered that not only effectively reaches the tumor site, but also makes it easier to capture by tumor cells. [16-17] By carefully designing the unique physicochemical properties of nano drugs, in addition to their anticancer efficacy, nano drugs can bypass cancer efflux pumps and optimize intracellular endosomal drug delivery, allowing nanodrugs to select the cancer cell. [18] However, the major drawbacks of nano-drug delivery for the clinical application of nanodrugs are toxicity and clearance issues. Despite various attempts to increase the ability to target the tumor and reduce clearance problems, the toxicity of the nano-drugs prevented them

from becoming the ultimate cure for cancer.[17-20] However, nanotechnology research has shown that changes in nanoparticle (NP) shape, size, and material can affect their biodistribution and improve their cellular carrying capacity.[19-21]

The main limitation of conventional nanodrugs is that they can reduce RES accumulation in the reticuloendothelial system (RES), a group of important immune organs, rather than specific tumors to which they are intended to join.[21-23] Nanodrugs in the blood, which increase the interaction time between nanodrugs and immune cells. Therefore, to maximize targeted nano-drug delivery, it is essential to determine the optimal blood circulation time. One strategy for adjusting the optimal blood circulation time of nano drugs is to control their polyethylene glycol (PEG) / polylactic acid (PLA) ratio by changing the molecular weight ratios of PEG and PLA.[24] In some cases, drugs needs to be delivered not only to the target tissue but also to the specific part in tumor cell. [23-26]As mentioned above, nanodrugs have shown great results for tumor targeting, but have shown clearance problems and immunosuppression, which further impairs the use of nanodrugs to destroy cancer cells.[25]

Stem cell-based cell therapy: Among the anticancer treatments currently in use, stem cell therapy is one of the best strategies. Stem cell therapy is primarily based on the natural ability of mesenchymal stem cells to inhibit cancer cells.[24,26,27] Treatment of malignant tumors, brain, pancreatic, and small-cell lung cancers (SCLC). However, stem cell therapy still has some drawbacks. The use of genetically engineered MSCs (mesenchymal stem cells) with increased anticancer potential mediated by the secretion of therapeutic protein secretion or the expression of suicide-inducing enzymes has resulted in some unexpected long-term side effects, such as shorter lifespan and lower delivery drug delivery ability and resistance to treatment.by some large cancer cell population. [26-28]To overcome such limitations, the combination of nanomedicine and MSC therapy has shown enormous potential to effectively target tumors.[29]

Current Immuno-Anticancer Therapy

T cell-mediated therapy: T lymphocytes, which play a major role in the adaptive immune system, can destroy cancer cells naturally by detecting cancer antigens expressed by the tumors and responding specifically to the tumors. Activate the immune system to boost the innate immune response. By doing so, natural, and adaptive immune systems combine to fight cancer. [30-32]

Macrophage repolarization therapy: Like T cells, macrophages also play a key role in TME and can destroy cancer cells. TAMs are generally classified as M2-type macrophages, which, unlike M1-type macrophages, exhibit anti-inflammatory capabilities. M2-type macrophages suppress antitumor immune responses and promote tumor growth, whereas M1-type macrophages do the opposite. Because of these features, researchers have attempted to re-validate macrophages from M2 to M1-type.[31,33,34]

However, the TAM strategy is still at a very early stage of development, and differences between human and mouse macrophages make the clinical application of laboratory results difficult. Therefore, to effectively formulate a macrophage-repolarization strategy, the interaction between the human immune system and TME needs to be further investigated and explained.[34-37]

Future Anticancer Therapy: The future of anticancer therapy will involve a combination of existing strategies. Therefore, to obtain the greatest anticancer effect, it is essential to determine which strategies work together well in a combined manner.[35] By understanding the exact mechanisms by which drugs destroy tumors, the ultimate combination therapy to treat cancer can be designed. Until now, the most promising anticancer strategy is NP immunotherapy. Indeed, the field of nanotechnology can be exploited to boost the anticancer efficacy of conventional immunotherapy. [38]

Nano drug-based anticancer immunotherapy: Although the clinical application of traditional anticancer nanodrugs has not been successful, nanomedical cancer treatment is still considered a good approach. Nano

drug therapy approaches direct attack on cancer cells or transport of cytotoxic drugs into cancer cells. [39] However, due to its benefits in metastasis and recurrence prevention, immunotherapy using NPs can only be considered as a natural way of transmitting anticancer drugs into cancer cells. Also, nano-drug anticancer immunotherapy is expected to overcome limitations of current immunotherapy in terms of efficacy and cytotoxic side effects. [40]

Other combination therapies: As mentioned earlier, the future of cancer treatment lies in a combination of different methods already in place to effectively kill cancer cells. The use of monoclonal antibodies is more effective in the treatment of cancer when combined with conventional chemotherapy rather than alone.[41]

Nanomedicine in photothermal therapy (PTT)

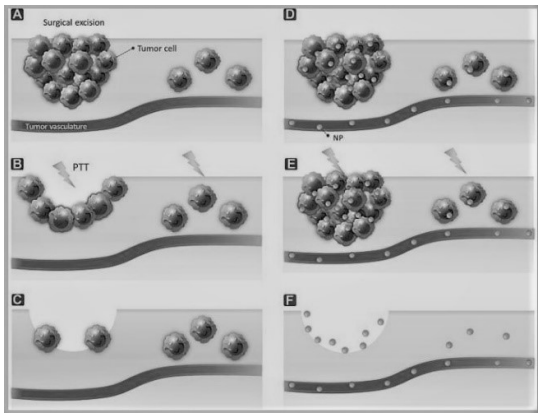
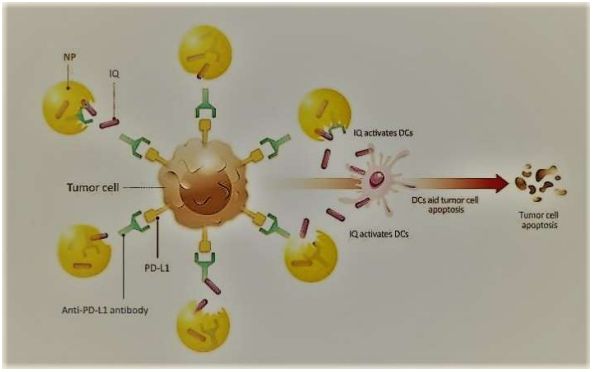


Figure 1 **Nanomedicine in photothermal therapy (PTT)**

Use of the NPS in photothermal therapy (PTT) is beneficial PTT is a form of PDT that utilizes heat produced by radiation (Fig1). Thermal stimulation of cancerous cells using PTT is a possible therapeutic treatment approach of localized, solid tumors. However, it can only be used as adjunctive therapy upon tumor excision and is not appropriate to malignant tumors. Hyperthermia may trigger cancer cells to release antigens and pro-inflammatory cytokines, that may detrimentally increase tumor cell interaction. [42-45]

Nanomedicine in tumor vaccines: Chronic recurrent immunosuppressive tumor vaccines are also in development. For long-term recurrence prevention of tumors, immunohistochemical testing center immuno-modified NPs are used to activate immunity in TME.[47-49] Auxiliary-loaded NPs are made by inserting the immune response helper imiquimod (IQ) into photo-responsive polydopamine NPs (IQ / PNs) and modifying them with the PD-L1 AB-IQ / PNL. Anti-PD-L1 antibodies on IQ / PNs overexpression of PT-L1, attacking them and preventing tumor recurrence Increased NP binding to CT26 cancer cells.[50] Therefore, the next generation of cancer therapy would rely on a combination of nanomedicine and immunotherapy to control the immune response against the cancer cells and thereby destroy them more effectively. By using this approach in combination with other proven therapies mentioned above, the effectiveness of the treatment can be further enhanced.[51-52]



Discussion

The primary objective of anti-cancer science is its implementation in the treatment center; considerable research in this field is continuing, as the established anti-cancer framework is neither comprehensive nor adequate for patient outcomes. Chemotherapy drugs has definite dosage constraints, therefore more efficacious medical treatments are still under investigation. While target receptor-based interventions were just useful to certain tumor cells that overexpress the relevant receptors and are therefore inactive in management of many groups of cancers.[49] Reconfiguration of the physicochemical characteristics of

nanodrugs has indeed been investigated for about twenty years, however this route was also widely abandoned for cancer therapy thanks to its toxicity and relative inefficiency.[45] By modulating immune mechanism to initiate a T-cell assault, we will reach the acceptable level of cancer treatment. Immune checkpoint repression can disrupt the inhibiting factors that prevent T cells from attacking cancer cells, thus employing our own immune system to attack cancers.[52] The mixing of immunotherapy strategies may be more comprehensive relative to single immunotherapy strategies. As a practice, the next wave of cancer therapies will primarily rely on the convergence of nanomedicine and immunotherapy to regulate the immune response to cancer cells and thereby kill them more effectively.[35] In end, a hybrid treatment incorporating cancer-immunology and nanodrug delivery strategies will be the two keywords of future anticancer strategies. Conversely, existing nano-therapeutic anticancer efficacy will significantly increase with the combination of proven immunotherapy. [41]

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87–108.
2. Dans M, Smith T, Back A, et al. NCCN guidelines insights: palliative care, version 2.2017. *J Natl Compr Canc Netw*. 2017;15(8):989–997.
3. Saxena G, Kumar N, Goswami R, Sameul A. Effects of *Mangifera indica* & *Punica granatum* extracts on semen after cryopreservation. Pharma Innovation 2019;8; 1:114-117.
4. Sawyers C. Targeted cancer therapy. *Nature*. 2004;432(7015):294–297.
5. Pritchard KI. Combining endocrine agents with chemotherapy: which patients and what sequence? *Cancer*. 2008;112(3 Suppl):718–722.
6. Jordan VC, Assikis VJ. Endometrial carcinoma and tamoxifen: clearing up a controversy. *Clin Cancer Res*. 1995;1(5):467–472.
7. Rajewsky K. The advent and rise of monoclonal antibodies. *Nature*. 2019;575(7781)
8. Blume-Jensen P, Hunter T. Oncogenic kinase signaling. *Nature*. 2001;411(6835):355–365.
9. Sudhir Kumar, Gaurav Saxena and Anjali Sudha Significant breakthrough in the field of anticonvulsant natural remedies J Mah S R Univ; 2021; 55 ;1;209-215.
10. Brown JB, Pai RK, Burgess MA, Chennai J, Zureikat AH. Pathologic complete response in a large gastric GIST: using molecular markers to achieve maximal response to neoadjuvant imatinib. *J Natl Compr Canc Netw*. 2018;16(12):1424–1428.
11. Hirsch FR, Scagliotti GV, Mulshine JL, et al. Lung cancer: current therapies and new targeted treatments. *Lancet*. 2017;389(10066):299–311.
12. Bjornmalm M, Thurecht KJ, Michael M, Scott AM, Caruso F. Bridging bio-nano science and cancer nanomedicine. *ACS Nano*. 2017;11(10):9594–9613.
13. Hartshorn CM, Bradbury MS, Lanza GM, et al. Nanotechnology strategies to advance outcomes in clinical cancer care. *ACS Nano*. 2018;12(1):24–43.
14. Markman JL, Rekechenetskiy A, Holler E, Ljubimova JY. Nanomedicine therapeutic approaches to overcome cancer drug resistance. *Adv Drug Deliv Rev*. 2013;65(13–14):1866–1879.
15. Tiwari, R, Verma, A, Nutan & Saxena, G A Descriptive Analysis of Phytochemical Agonists of PPAR-g. W J Res, 2020; 13; 51; 49-62
16. Zang X, Zhao X, Hu H, Qiao M, Deng Y, Chen D. Nanoparticles for tumor immunotherapy. *Eur J Pharm Biopharm*. 2017; 115:243–256.

17. Kim SW, Park JY, Lee S, Kim SH, Khang D. Destroying deep lung tumor tissue through lung-selective accumulation and by activation of caveolin uptake channels using a specific width of carbon nanodrug. *ACS Appl Mater Interfaces*. 2018;10(5):4419–4428.
18. Zhao J, Castranova V. Toxicology of nanomaterials used in nanomedicine. *J Toxicol Environ Health B Crit Rev*. 2011;14(8):593–632.
19. Kim SW, Khang D. Multiple cues on the physiochemical, mesenchymal, and intracellular trafficking interactions with nanocarriers to maximize tumor target efficiency. *Int J Nanomedicine*. 2015; 10:3989–4008.
20. Toy R, Peiris PM, Ghaghada KB, Karathanasis E. Shaping cancer nanomedicine: the effect of particle shape on the in vivo journey of nanoparticles. *Nanomedicine (Lond)*. 2014;9(1):121–134.
21. Hoshyar N, Gray S, Han H, Bao G. The effect of nanoparticle size on in vivo pharmacokinetics and cellular interaction. *Nanomedicine (Lond)*. 2016;11(6):673–692.
22. Li SD, Huang L. Pharmacokinetics and biodistribution of nanoparticles. *Mol Pharm*. 2008;5(4):496–504.
23. Saxena G, Singh H, Kumar N, Seliya M, Nutan "*In-Vivo* Shielding Effects of *Semecarpus anacardium* Extract in Presenile Dementia". Intl J Pharm Res 2020,12.
24. Verma SK, et al. Mechanistic insight into the rapid one-step facile biofabrication of antibacterial silver nanoparticles from bacterial release and their biogenicity and concentration-dependent in vitro cytotoxicity to colon cells. *RSC Adv*. 2017;7(64):40034–40045.
25. Nie S. Understanding and overcoming major barriers in cancer nanomedicine. *Nanomedicine (Lond)*. 2010;5(4):523–528.
26. Kim SW, Kyung Lee Y, Yeon Lee J, Hee Hong J, Khang D. PEGylated anticancer-carbon nanotubes complex targeting mitochondria of lung cancer cells. *Nanotechnology*. 2017;28(46):465102.
27. Saxena G, Mishra S, Nutan Physiological consequences of a diabetic retina &
innovative medical care prospects, a review. Think India Journal 2019; l22; 14.
28. Kim SW, Kyung Lee Y, Yeon Lee J, Hee Hong J, Khang D. PEGylated anticancer-carbon nanotubes complex targeting mitochondria of lung cancer cells. *Nanotechnology*. 2017;28(46):465102.
29. Gao P, Pan W, Li N, Tang B. Boosting cancer therapy with organelle-targeted nanomaterials. *ACS Appl Mater Interfaces*. 2019;11(30):26529–26558.
30. Fortuni B, Inose T, Ricci M, et al. Polymeric engineering of nanoparticles for highly efficient multifunctional drug delivery systems. *Sci Rep*. 2019;9(1):2666.
31. Blau HM, Daley GQ. Stem cells in the treatment of disease. *N Engl J Med*. 2019;380(18):1748–1760.
32. Clarke MF. Clinical and therapeutic implications of cancer stem cells. *N Engl J Med*. 2019;380(23):2237–2245.
33. Ridge SM, Sullivan FJ, Glynn SA. Mesenchymal stem cells: key players in cancer progression. *Mol Cancer*. 2017;16(1):31.
34. Saxena G., Mittal A., Siddiqui A. Evaluation of preliminary phytochemical screening,
acute toxicity & antioxidant profile of *Ocimum kilimandscharicum*. J D D T. 2019;9; 2; 372-375.
35. Murphy KM, Reiner SL. The lineage decisions of helper T cells. *Nat Rev Immunol*. 2002;2(12):933–944.
36. Paul WE. Bridging innate and adaptive immunity. *Cell*. 2011;147(6):1212–1215.
37. Pathria P, Louis TL, Varner JA. Targeting tumor-associated macrophages in cancer. *Trends Immunol*. 2019;40(4):310–327.

38. Murray PJ. Macrophage Polarization. *Annu Rev Physiol*. 2017; 79:541–566.
39. Gotwals P, Cameron S, Cipolletta D, et al. Prospects for combining targeted and conventional cancer therapy with immunotherapy. *Nat Rev Cancer*. 2017;17(5):286–301.
40. Mahoney KM, Rennert PD, Freeman GJ. Combination cancer immunotherapy and new immunomodulatory targets. *Nat Rev Drug Discov*. 2015;14(8):561–584.
41. Musetti S, Huang L. Nanoparticle-mediated remodeling of the tumor microenvironment to enhance immunotherapy. *ACS Nano*. 2018;12(12):11740–11755.
42. Yoon HY, Selvan ST, Yang Y, et al. Engineering nanoparticle strategies for effective cancer immunotherapy. *Biomaterials*. 2018; 178:597–607.
43. Fontana F, Liu D, Hirvonen J, Santos HA. Delivery of therapeutics with nanoparticles: what's new in cancer immunotherapy? *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2017;9(1).
44. Parhi P, Mohanty C, Sahoo SK. Nanotechnology-based combinational drug delivery: an emerging approach for cancer therapy. *Drug Discov Today*. 2012;17(17–18):1044–1052.
45. Zhuang J, Holay M, Park JH, Fang RH, Zhang J, Zhang L. Nanoparticle delivery of immunostimulatory agents for cancer immunotherapy. *Theranostics*. 2019;9(25):7826–7848.
46. Park W, Heo YJ, Han DK. New opportunities for nanoparticles in cancer immunotherapy. *Biomater Res*. 2018; 22:24.
47. Nutan, Das M, Saxena G, Kumar, N. To perform phytochemical screening & study the antioxidant potential of isolated compound from *Hemidesmus indicus*. JDDT 2019; 9; 2; 188-191.
48. Nam J, Son S, Ochyl LJ, Kuai R, Schwendeman A, Moon JJ. Chemo-photothermal therapy combination elicits anti-tumor immunity against advanced metastatic cancer. *Nat Commun*. 2018;9(1):1074.
49. Banchereau J, Palucka K. Immunotherapy: cancer vaccines on the move. *Nat Rev Clin Oncol*. 2018;15(1):9–10.
50. Kwon S, Yoo KH, Sym SJ, Khang D. Mesenchymal stem cell therapy assisted by nanotechnology: a possible combinational treatment for brain tumor and central nerve regeneration. *Int J Nanomedicine*. 2019; 14:5925–5942.
51. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252–264.
52. Pelaz B, Alexiou C, Alvarez-Puebla RA, et al. Diverse applications of nanomedicine. ACS Nano. 2017;11(3):2313–2381.