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Antibody based drug delivery to target prostate cancer cells

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Abstract

To determine if the activation process affected the mAbs' immunoreactivity, we used PC3 human prostate cancer cells samples. Compared to IC50 values for There was a significant difference between the concentrations of free DTXL (6.79 µg/ml) and unconjugated DTXL-NPs (4.7 µg/ml) and mAb conjugated TMB-DTXL-NPs (2.2 µg/ml). decreasing the immunogenicity of the generated protein corona; and targeting stem-like cells, breast cancer cells, and lung adenocarcinoma cells. The method involves making a matrix that, when introduced to water, will self-assemble into SLN via electrohydrodynamic processes. Trials of *in vitro* cytotoxicity on PC3 prostate cancer cells were made possible by successfully linking the A3 batch with the TMB monoclonal antibody by thiolation.

Keywords: Antibody, drug, prostate, cancer and medicinal

Introduction

The neutral polymer dextran is often thought to have been the very first noteworthy instance of microbial exopolysaccharides used in medicinal therapy. Because it is safe, biodegradable, and has no adverse effects on people, dextran is an excellent choice for medical applications. By selectively targeting cancer cells, photodynamic therapy is able to eradicate them used for NIR and MR imaging. Thanks to the "of/on" conduct of the fluorescent signal's redox cellular reaction shown by nanoparticles, accurate tumor imaging was accomplished. The effectiveness of improved photodynamic treatment was further supported by the superior magnetic targeting ability demonstrated as well as in living organisms. The C6 mouse was used by Hong *et al*. glioma cells or theragnostic nanoparticles to prepare their study.

decreasing the immunogenicity of the generated protein corona; and targeting stem-like cells, breast cancer cells, and lung adenocarcinoma cells. In relation to other hand, building drug delivery systems with ligands attached is a labor-intensive process that requires many targeting designs that include physiological aspects like transport of blood, state of illness, and structure of tissues. Not only that, but their absorption process is still a mystery, and there have been very few investigations into how nanocarriers with ligands attached interact with cell membranes. In addition, it is well-known that cells can uptake nanoparticles through either phagocytic or non-phagocytic pathways (e.g., clathrinid-mediated endocytosis, cavernosal endocytosis, among others.

This suggests that these nanoparticles may be useful in treating depression. In addition, Román *et al*. developed alginate microcapsules that bind epidermal growth factor to the surface of non-small cell lung cancer cells, allowing them to be targeted selectively. The nanoparticles were also loaded with cisplatin, a chemical that causes cancer. Incorporating EGF into carrier systems greatly improved their selectivity and demonstrated cell killing kinetics (Within the H460 lung cancer subtype at a faster rate than the unrestricted remedy.

The scientists state that contaminated blood samples may be selectively separated from Hep G2 hepatocellular cancer cells by attaching an anti-GPC3-antibody to the nanoplatform. The regulated and/or prolonged release of medicinal compounds is another area where QDs may be useful. To produce this behavior with regulated release, one

may use environmental factors, such as radiation, temperature, magnetic fields, or radio waves. The theragnostic system created by Olerile *et al.* is a lipid nanostructured parenteral multifunctional system carrier to co-load anti-cancer drugs with quantum dots.

Literature Review

Karishma Barthwal *et al.* (2023) [1] This article focusses on the disease's features that provide opportunities for drug delivery systems to target cancer this term. Though tailored medicine delivery based on chemotherapy has been the topic of considerable study, A lot of people are interested in the most promising method that can bypass. Incorporating the current upsurge in the usage of targeted delivery methods including small molecule chemotherapies employing various nanocarriers was also a part of this investigation with cancer therapy. This article also touches on the challenges of employing a personalized medicine delivery system to treat cancer.

Michael J. Mitchell *et al.* (2021) [2] There has been a proliferation of new therapeutic uses for nanoparticles in the last few years. To get around the problems with free therapies and the many biological hurdles that patients with different illnesses and conditions face, scientists have created nanoparticles. These nanoparticles can traverse systemic, microenvironmental, and cellular barriers. Precision therapies, which use tailored treatments to improve treatment success, has also helped overcome this patient heterogeneity. The optimization of progress in nanoparticle development mostly focused on creating delivery platforms with a one-size-fits-all approach. Nanoparticles made of lipids, polymers, and inorganic materials can be manufactured with ever-greater accuracy.

Gen Zhang *et al.* (2013) [3] Investigations into Nanomaterials combined with cancer drugs might improve the delivery and effectiveness of anti-cancer treatments by lowering tumor size therapies. Nanomedicine has made great strides thanks to the challenge of getting drugs to diseased regions. We provide a synopsis of encouraging results concerning nano-drug delivery vector-based cancer therapies. Nanoparticles that are not coated are not suitable for human usage due to their high toxicity. Many methods have concentrated on encasing nanoparticles in in order to reduce their toxicity, biocompatible materials are used. Efficient delivery of high-dose cancer treatments has been achieved by the engineering of nanoparticles that contain bilayer molecules. systems.

Vicky V. Mody *et al.* (2014) [4] Dysregulated vasculature creates unique hypoxic microenvironments in tumours that are absent in healthy tissues, a condition known as tumor hypoxia, which means low oxygen concentration. classic cancer treatments that target tumours by inhibiting cell division are ineffective in hypoxic zones, and many classic anti-cancer drugs cannot reach these zones. Because of their versatility, ease of synthesis, and potential to be modified for particular biological uses, magnetic.

Jayanta Kumar Patra, *et al.* (2018) [5] Two emerging but rapidly growing areas of study, Applications in nanomedicine and nano delivery systems include the controlled administration of medicinal substances to particular sites or the use of materials in the nanoscale range as diagnostic instruments. The targeted and site-specific distribution of precise medications is one of the many ways in which nanotechnology might improve the long-term management of human illnesses. Chemotherapeutic medications, biological agents, immunotherapeutic agents, and many more have lately found impressive applications in nanomedicine in the management of several illnesses, among many others.

Research Methodology

The method involves making a matrix that, when introduced to water, will self-assemble into SLN via electrohydrodynamic processes. Polyvinylpyrrolidone (PVP) and glyceryl Tri stearate (GTS) form the basis of the drug-loaded matrix. The strong interactions between the C=O bond of the PVP matrix and water will lead the formulations to absorb water, which is a necessary condition for self-assembly of SLN. Because of these interactions, the fibers and microparticles inflate, which makes it possible for the building blocks within the structures to move about. The polymer will then break down and dissolve, allowing the medicine and GTS to combine creating hybrid nanoparticles that will reduce the amount of contact between the hydrophobic species and the water. The self-assembly of the SLNs is believed to be dependent on the PVP polymer's strong hygroscopicity and hydrophilicity, we can see a simplified diagram of the procedure.

Data Analysis

To determine if the empty nanoparticles were harmful to the cells, the SRB approach was used to PC3 human prostate cancer cells. Figure 1 shows that the use of empty nanoparticles did not result in any toxicity to the cells, since the measured inhibition of the control was more than 1000 µg/ml.

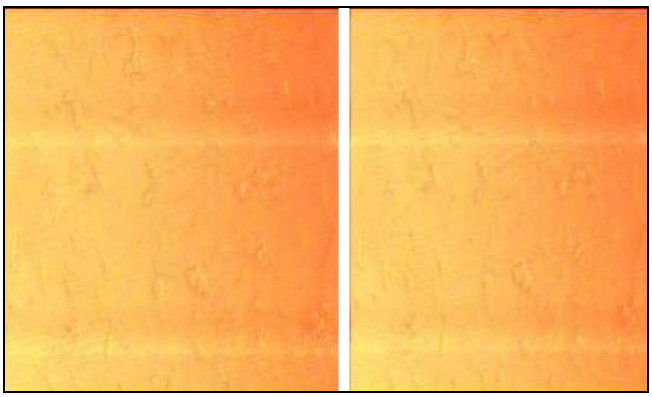

Fig 1: Histocompatibility assay of NPs; a) Normal cell as control, b) with empty NPs

Below, in a methodical fashion, was detailed the characterization of TMB-DTXL-NPs and surface mAb detection on NPs:

First, FTIR measurements were used to assess the coupling of trastuzumab mAbs to NPs. Figure 1 shows a comparison between the spectra of nanoparticles and the trastuzumab monoclonal antibody. that were either drug-loaded or paired with a monoclonal antibody. In order to confirm that trastuzumab is present in the nanoparticles, the spectral peak associated with trastuzumab emerged nanoparticles (188–189).

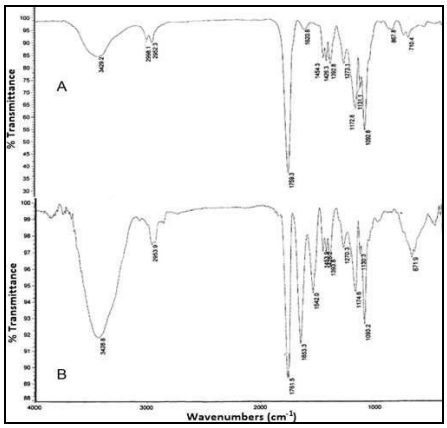

Fig 2: FT-IR spectrum of mAb conjugated docetaxel nanoparticles; a) DTXL-NPs b) TMB-DTXL-NPs

(II) Particle Size and zeta potential

Table 1 displays the findings of the assessed the prepared DTXL-NPs and TMB-DTXL-NPs for particle size and zeta potential. How a medication is released from a particle is greatly affected by its size. distribution pattern. There was just a little rise in the formulation's polydispersity index (PDI). Surface charges on the items may influence the stability of the nanoparticulate formulation's particles via significant electrostatic repulsion, which is shown by the zeta potential, which in turn indicates the formulation's physical stability. It is possible that the negative charges and shielding action carboxylic groups that are present on the surface of the nanoparticles containing monoclonal antibodies explain why the zeta potential of these particles was lowered. Figure 2 shows that there was an increase after TMB mAb conjugation.

Table 1: Physicochemical characterization of TMB monoclonal antibody conjugated docetaxel nanoparticles.

Formulation	Particle Diameter (nm)	Polydispersity Y Index (PDI)	Zeta Potential (mV)	Loading Efficiency y (%)	Drug Encapsulation N (%)
Empty-NPs	152.4± 2.47	0.170± 0.08	-18.7±1.22	-	-
DTXL-NPs	179.2±2.8	0.264±0.07	- 14.8±0.24	15.78±2.11	66.79±2.84
TMB-DTXL-NPs	249.28± 15.8	0.290± 0.05	-12.1± 1.08	14.94± 0.67	68.76± 1.23

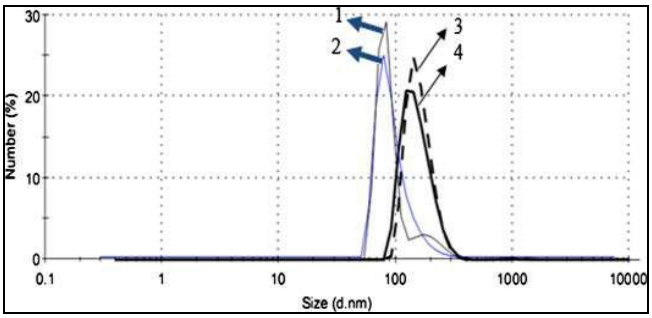

Fig 3: Figures 1 and 2 show the DTXL-NPs before TMB conjugation, and TMB-DTXL-NPs after TMB conjugation, demonstrating an increase in particle size of NPs

The scanning electron microscopy picture of the trastuzumab linked nanoparticles' form and surface morphology is presented in figure 3. A razor blade was used to crack apart a suitable specimen of TMB-DTXL-NPs fixed on metal (aluminum) rods by means of double-sided adhesive carbon tape. The samples were sputtered with palladium or gold for 120 seconds at 14 mA in an argon atmosphere to get them ready for secondary electron emissive scanning microscopy (SEM). Next, the samples' morphology was analyzed using an acceleration voltage of 15 kV.

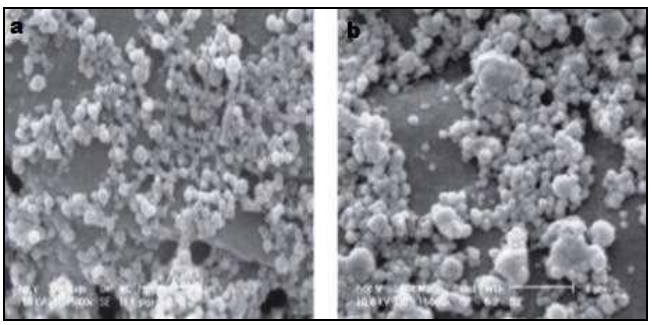

Fig 4: SEM images of TMB conjugated NPs

To couple with the surface of docetaxel nanoparticles, a thiol-activated trastuzumab monoclonal antibody was used. Byproducts such as trastuzumab oligomers may be obtained during the coupling process, which carries the danger of bridge formation of oxidized sulphydric. This waste product is not desired since it may interfere with biological processes (190). There was no discernible difference in activity between the unconjugated and conjugated trastuzumab monoclonal antibodies when tested on HER2 overexpressed PC3 prostate cancer cells and HER2 negative Vero cells.

Use to find out how much trastuzumab was attached to the surface of the NPs by using the Bradford test. We preserved two controls: one to examine the effect of adsorbed trastuzumab and another to evaluate the contribution of uncoated nanoparticles utilized without a linker, as we were unable to distinguish between the two types of trastuzumab binding to bovine serum albumin. The results of the comparison were given in figure 4, which shows the standard curve for a solution of bovine serum albumin (BSA) at 1.1 mg/ml.

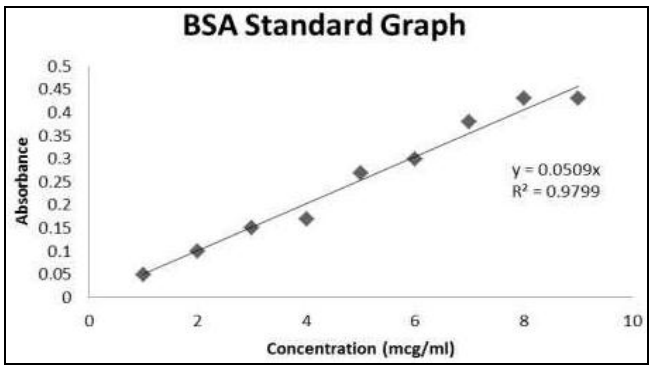

Fig 5: Standard graph of bovine serum albumin (BSA).

In order to confirm that TMB mAb is covalently attached to nanoparticles:

The fluorescence intensity of monoclonal antibody-linked nanoparticles and uncoupled NPs was measured using an anti-human antibody labelled with FITC coupled to a monoclonal antibody. Evidence of trastuzumab coupling on NP surfaces was shown by an increase in fluorescence intensity for mAb linked NPs.

negative for HER2 The cellular uptake of linked nanoparticles was studied using Vero cells and HER2 overexpressing PC3 prostate cancer cells. The results were compared employing a confocal microscope and free trastuzumab, as seen in figure 5. As compared to Vero cells, PC3 cells with prostate cancer show the highest absorption of TMB-DTXL-NPs. that uptake was blue in the nucleus and green in the cytoplasm. Furthermore, FACS analysis corroborated these findings, indicating that linked nanoparticles had quicker uptake to nanoparticles that are not linked.

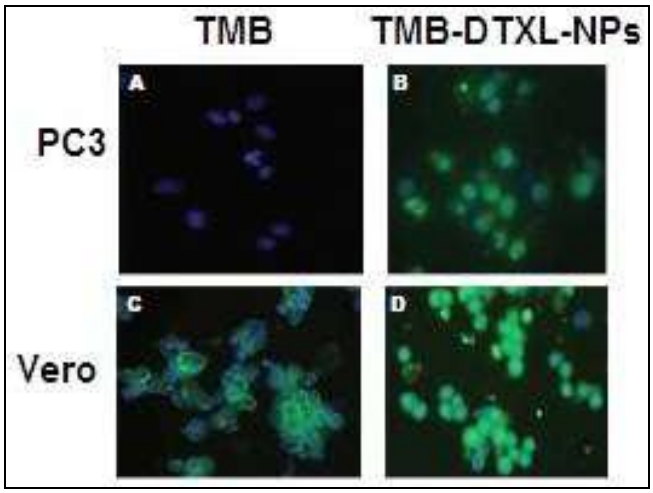

Fig 6: Fluorescence microscope image. (a-b) HER2- over expressing PC3; and (c-d) HER2-negative Vero cells

Using The cytotoxicity of several NP formulations, including free DTXL, DTXL-NPs, TMB-DTXL-NPs, and generated empty NPs, was examined on Vero and PC3 cells using the MTT test. Whereas PC3 cell lines are HER2 overexpressing positive, Vero cell lines are HER2 negative. The PC3 cell line has an overexpression of the HER2 antigen, which is characteristic of human prostate cancer (193). Both the tabular and graphical representations of the predicted IC50 values for free DTXL and its formulations are available.

Both the empty-NPs and free mAb were determined to be nontoxic, with IC50 values of 186.17 ± 0.62 µg/ml and 771.50 ± 2.55 and 272.42 ± 1.96 µg/ml, respectively, for free DTXL. For HER2 negative Vero cell lines, the IC50 values of DTXL-NPs were 625.58 ±0.95 and TMB-DTXL-NPs were 564.38 ±0.64 µg/ml, as shown in figure 6 and table 2.

Table 2: Cytotoxicity assay of different NPs in HER2 negative Vero cells

S. No.	Samples	HER2 Negative Vero Cell Lines		Conc. (µg/ml)	IC50 (µg/ml)
		Normal	50% toxic		
1	Empty NPs			1250 625 312 156 78 39	771.50 ± 2.55
2	TMB			500 250 125 62.5 31.25	272.42 ±1.96
3	Free DTXL			625 312.5 156.25 78.12 39.06 19.53 9.76	186.17 ±0.62
4	DTXL NPs			625 312.5 156.25 78.12 39.06 19.53 9.76	625.58 ±0.95
5	TMB-DTXL-NPs			625 312.5 156.25 78.12 39.06 19.53 9.76	564.38 ±0.64

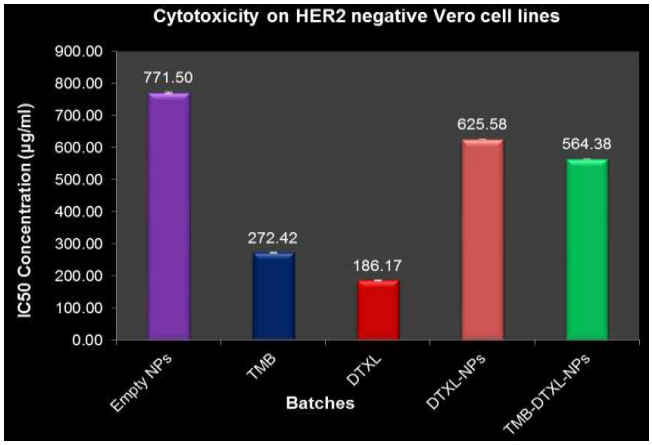

Fig 7: IC_{50} of NPs on HER2 negative Vero cell lines.

Figure 7 shows that cells were not harmful to empty NPs and TMB in the cytotoxicity investigation. The IC50 value of free DTXL was 6.79 ± in the PC3 cell line that was

overexpressed and had HER2 positive, 2.38 µg/ml. The graph does not include empty NPs and free TMB mAb since they posed no danger. The concentrations at which DTXL-NPs, Free TMB, and TMB-DTXL-NPs where 50% effective were 28.56 ± 0.43 and 12.68 ± 0.57 µg/ml, respectively. Table 3. summarizes the results of the test, which were run three times.

The combined effects of the nanoparticles' size and the EPR impact on passive targeting allow for the delivery of docetaxel encapsulated in nanoparticles at high concentrations (194). Figure 7 shows that nanoparticles paired with the monoclonal antibody trastuzumab had a lower IC50 and were more effective in treating prostate cancer.

Table 3: Cytotoxicity assay of different NPs in HER2 over expressed PC3 cells

		Normal	50% toxic		
3	Free DTXL			625 312.5 156.25 78.12 39.06 19.53 9.76	6.79 ± 2.38
4	DTXL-NPs			625 312.5 156.25 78.12 39.06 19.53 9.76	28.56 ±0.43
5	TMB-DTXL-NPs			625 312.5 156.25 78.12 39.06 19.53 9.76	12.68 ± 0.57

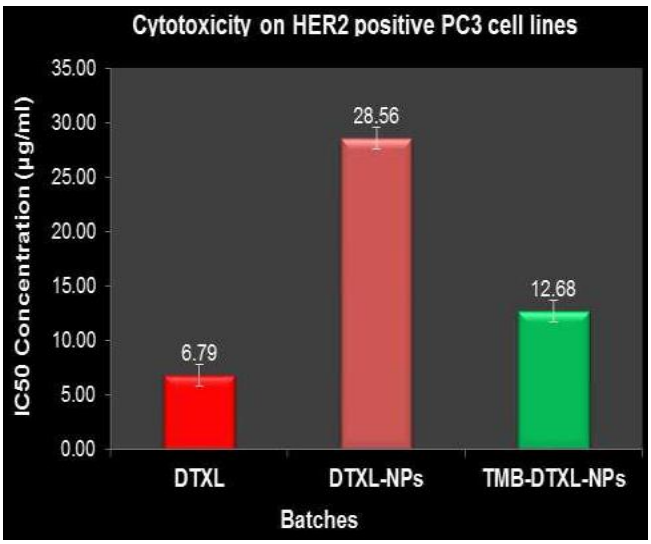

Fig 8: IC_{50} of NPs on HER2 overexpressed PC3 cells

Compared to The IC50 of trastuzumab linked TMB-DTXL-NPs (12.68 µg/ml) was found to be lower than both free DTXL (6.79 µg/ml) and uncoupled DTXL-NPs (28.56 µg/ml). The expected average drug content for DTXL-NPs was 4.7 µg/ml, whereas for TMB-DTXL-NPs it was 2.2 µg/ml.

Conclusion

Trials of *in vitro* cytotoxicity on PC3 prostate cancer cells were made possible by successfully linking the A3 batch with the TMB monoclonal antibody by thiolation. overexpressed with HER2. d. Cancerous cells may have taken advantage of the particles' weak negative charge, which gave them a longer half-life and decreased phagocytic absorption. The strong interactions between the C=O bond of the PVP matrix and water will lead the formulations to absorb water, which is a necessary condition for self-assembly of SLN. By selectively targeting cancer cells, photodynamic therapy is able to eradicate them used for NIR and MR imaging to determine if the activation process affected the mAbs' immunoreactivity, we used PC3 human prostate cancer cells samples

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