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Revolutionizing nanoparticle-mediated cancer immunotherapy through genetic engineering advances

Aman Chandrakar

*Corresponding author. Assistant Professor, Department of Pharmacy, Kalinga University, Naya Raipur, Chhattisgarh, India. E-mail address: ku.amanchandrakar@kalingauniversity.ac.in

Hemlata Dewangan

Assistant Professor Department of Pharmacy, Kalinga University, Naya Raipur, Chhattisgarh, India. E-mail address: ku.hemlatadewangan@kalingauniversity.ac.in

Abstract

Objectives

The immune system has meticulously adjusted itself to become a powerful protection mechanism against infectious pathogens in the process of evolution. A fundamental aspect of its functionality lies in the ability to discern between self and nonself, crucial for triggering immune responses. However, cancer disrupts this equilibrium, characterized by aberrations in the DNA code that empower cells to proliferate uncontrollably while evading immune surveillance. Immunotherapy emerges as a promising method, seeking to boost the immune system to identify and eradicate these rogue cancer cells, thereby presenting a novel strategy in the battle against cancer. Although immune checkpoint inhibitors have shown to be beneficial in treating several forms of advanced cancer, the overall response rate in patients receiving these therapies remains at about thirty percent. Recognizing the need for advancements, recent research delves into nanoparticle-based approaches aimed at enhancing cancer therapies and vaccinations.

Materials and methods

The focus centers on developing biotechnology that employs durable artificial nanoparticles to transform cancerous cells into tumor-based Antigen-Presenting Cells (APCs). This transformative process involves stimulating coexpression of costimulatory molecules and immunostimulatory cytokines. What distinguishes this nanomedicine is its capacity to induce a generalized tumor-specific and cell-mediated immune response without assuming specific antigens expressed by tumors.

Results

At t = 67 days, a considerable percentage of the animals in the nanoparticle's subgroup had successfully removed the malignancy and remained free of illness.

Conclusions

This innovation holds tremendous potential for advancement in translational medicine, offering a versatile and adaptive solution to the challenges posed by cancer immunotherapies. By leveraging the capabilities of artificial nanoparticles, researchers aspire to elevate the efficacy of cancer treatments and propel the field towards a new era of more targeted and potent interventions. In conclusion, the intricate interplay between the immune system and cancer underscores the necessity for innovative therapeutic approaches. The exploration of nanoparticle-based strategies represents a frontier in cancer research, holding the promise of refining immunotherapies and ushering in a new era of precision medicine for the benefit of patients grappling with this complex and formidable disease.

Keywords: Cancer, Genetic Engineering, Immunotherapy, Nanoparticle.

Paper Type: Research Paper.

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Introduction

The onset of cancer is an intricate and diverse process driven by a multitude of variables. A significant factor is genetic mutations, which may be either inherited or acquired over the course of an individual's lifespan (Bray et al. 2021). Alterations in certain genes, such as genes that limit tumor development or genes that promote tumor growth, may disturb regular cellular processes

and result in unregulated cell proliferation. Environmental factors are significant contributors, since they expose individuals to carcinogens such as tobacco smoke, UV radiation, and certain chemicals, hence elevating the likelihood of developing cancer. Various lifestyle decisions, such as dietary habits, level of physical activity, and alcohol use, might also influence an individual's vulnerability to cancer. Persistent infections caused by certain viruses, such as Human Papilloma Virus (HPV) and hepatitis B or C, may have a role in the formation of particular types of cancer. Age is a crucial determinant, since the likelihood of developing cancer normally rises with age owing to the accumulation of genetic alterations and prolonged exposure to environmental variables. Gaining a comprehensive understanding of the many factors that contribute to the development of cancer is crucial for the successful implementation of preventive measures and early detection tactics.

The conventional remedies for cancer have not improved much, even though the capacity to identify and appreciate the sickness has significantly progressed. Conventional treatments such as radiation therapy, chemotherapy medication, and surgical excision can fail on occasion (Lichter 2021). They result in the recurrence of the tumor or the spread of the cancer to other parts of the body. In these kinds of situations, a fresh approach is necessary. Immunotherapy for cancer has emerged as an essential component of cancer treatment (Duffy et al. 2021). A cancer immunotherapy medicine, in its most basic form, encourages the immune system to fight cancer more efficiently. This is accomplished by generating a network of tumor-specific T cells that can lyse tumor cells and eliminate malignancies (Sušac et al. 2022). Despite this, the overall response rates for patients who receive treatment with the most widely used immunization-based cancer therapies are less than thirty percent (Li et al. 2023). As a consequence of this, the existing cancer immunotherapies demand immediate enhancement.

To lay the groundwork for the research, the study will examine relevant research from various studies and then describe the most recent efforts to advance cancer immunotherapy via nanomaterial-based techniques. Nanotechnology enables the fabrication of nanoparticles that can perform a variety of functions, including the following: (1) delivering materials to specific tissue, organs, and cellular structures; (2) delivering antigenic compounds and ingredients to Antigen-Presenting Cells (APCs) for robust resistant triggering (Darragh and Karam 2022); (3) delivering treatments to malignant cells in a surgical and stimuli-responsive behavior; and (4) providing a secure and readily biodegradable framework for mixture immunotherapy was administered.

When altering an individual's native APCs to better this interaction, one of the most prominent difficulties is the considerable costs and safety dangers associated with ex vivo cell modification (Marofi et al. 2021). The technological restrictions of targeted in situ APC modification impose additional challenges. It is still essential to manipulate cells outside of live

creatures to use artificial APCs (a-APCs), and it is wasteful to build antigens (Isser et al. 2021): The combinations specific to tumors and sufferers to generate a-APCs. Although biomimetic synthetic particles constitute most a-APCs, their use requires cell manipulation using genetic engineering. Identifying tumor neoantigens remains a significant challenge, and their availability to patients is restricted.

The ideal antigens to use in a particular circumstance are not readily apparent, vary from patient to cautious, and need prior knowledge before administering treatment (Yang et al. 2021). Cancer cells use various strategies to avoid being detected by the immune system. These include the creation of immunosuppressive signals by cancer cells and alterations in tumor antigen production that are often unforeseen. The use of APCs for targeting specific tumor-associated antigens or the administration of vaccinations that include particular antigens associated with tumors are rendered ineffectual due to the unique characteristics of the tumor microenvironment (Deng et al. 2022). The study believes that nanotechnology presents unique opportunities for improving cancer immunotherapy using genetic engineering.

The following sections are organized in the given manner: section 2 discusses the literature survey and analysis. Section 3 analyses nanoparticle-based cancer immunotherapy through genetic engineering advances and its outcomes. Section 4 concludes the discussion and findings of the research.

Cancer immunotherapy and related research articles are discussed in this section. The recent techniques and the associated surveys are deeply discussed below.

Targeting macrophages offers several advantages, and this article provides a summary of their role in the immunotherapies that are currently being used (Duan and Luo 2021). The first step of the study was to collect data on the characteristics of these cells, including their development and distinction, categories, typical markers, and roles. This was done so that readers better grasp these cells and put them to greater use. When it comes to cancer therapy, therapeutic techniques that depend on monocytes or act in conjunction with them might potentially improve the success of the treatments.

New generations of cytotoxic T cells that include synthetic or modified genetic antigens are now the subject of clinical research that is currently being conducted (Raskov et al. 2021). Combinatory schedules might reduce the severity of adverse effects while simultaneously increasing the effectiveness of treatment. This article summarizes the current understanding of cytotoxic T cells, which are the immunological effects of most significant importance in tumor and tumor immunotherapy. The research discusses the possible ramifications that might arise regarding prospective cancer therapies.

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Nanomaterials might be purposefully created to affect tumor microbial environments, increase T-cell proliferation, and overcome complex physical hurdles (Gong et al. 2021). This would allow for the circumvention of these impediments. This article's purpose is to summarize the expanding field of cancer immunology and nanomaterial designs and to provide specifics on how nanomaterials have assisted in removing clinical barriers to T-cell-based immune therapies.

The primary emphasis is on recent discoveries in the field of immunobiology about tired T cells. These discoveries provide a more nuanced comprehension than stating that this hypofunctional status is undesirable (Chow et al. 2022). The research studies the idea that T-cell weariness results from inefficient tumor management and reflects that ineffectiveness. The study hypothesizes that the fatigue process would be disrupted in specific circumstances involving extended antigen stimulation, reducing T cells' survival rate.

Natural Killer (NK) cells are specialized immune effector cells that play a significant role in the body's defense against abnormal cells (Liu et al. 2021). This activity is an essential component of the immune system's response. Immunotherapy for cancer that uses NK cells is a relatively young field undergoing extensive investigation and advancement. This article presents the current knowledge of NK cell biology and function, the recent pre-clinical clinical trials of NK cell-based treatments, and the advances, challenges, and future perspectives on this subject.

Overexpressing Clustering of Differentiation 64 (CD64), which is a typical collector of the Fragmentation Crystallized (FC) polymeric of Immunoglobulin G (IgG), resulted in the creation of the antigen delivery vehicle. The disruption of the immune-suppressive signaling axis was done to improve the elimination of tumors that were dependent on T cells (Li et al. 2021). Through the twofold augmentation of the proliferation of T cells, it is possible to limit the formation of tumors, increase the standard of life, and prolong the mortality period in mice carrying tumors.

Bioengineering stem cells allow the production of available cellular goods "off the shelf," eliminating the necessity for a tailored and patient-specific good, a problem with the autologous cell treatments now in use (Li et al. 2021). The research explores the usefulness, impact, potential, and limitations of biological engineering, which assists translational or clinical studies. The research provides a summary of the most recent advancement that has been made in stem cell-engineered cancer therapy. Stem cells have the potential to be designed to express several anticancer drugs in a stable manner, which would allow them to overcome the lack of standard PBMC-derived medicines.

The research achieved synergistic anti-tumor activity by modifying tumor cells into manufacturers to remodel Tumor-Associated Monocytes (TAMs) in situ by combining CD47 inhibition with an immune-activating cytokine (Lin et al. 2022). The study paves the way for a

novel approach to programming cancerous cells in situ via the simultaneous use of CRISPR-mediated CD47 deletion and release to design an efficient immunization for tumors.

This section summarizes the articles on cancer immunotherapy and the recent techniques available to detect and treat cancer. This necessitates improved cancer immunotherapy with nanoparticles, which will be discussed in the following section.

Materials and Methods

Animal Study: The Institutional Animal Control & Use Commission (IACUC) of the College of Southern California approved all animal treatments. Female NSG mice six to eight weeks old were bought from the Jackson Testing and kept in sterile kennels to conduct tests on effectiveness and T cell penetration.

Molecular Cloning and SMART-Exos: The anti-human Epidermal Growth Factor Receptor 3 (anti-HER3) and anti-cluster of Differentiation (anti-CD2) were made using synthetic genomes from Integrated DNA Sciences. The anti-HER3 genome was taken using anti-HER3 trastuzumab, while the anti-CD2 gene originated from anti-CD2 autoantibodies. The anti-HER3 comprised a 228-peptide linkage that divided the trastuzumab's lighter chain changeable domain at the N-terminus from its strong chain changeable domain at the C-terminus. A flexibility linker linked the two ends of the anti-CD2 antibody—the N-terminal lighting chain changeable region and the C-terminal large chain changeable region—to form the anti-CD2. Crossover extensions Polymerase Chain Reaction (PCR) was used to create portions of genes that encode anti-CD2 and anti-HER3. The anti-HER3 or anti-CD3 were connected using a flexible linkage. To create SMART-Exos (S-Ex) production structures, antibody Transmembrane Domain (TMD) of adult Platelet-Derived Growth Factor Receptor (PDGFR) protein fusions were generated by cloning solitary and dual-gene segments into a Display vector amid restricted enzyme domains. The intended protein fusions have a tag attached to their N-terminus. The genome sequencing services validated the expression plasmids that were produced. Transfected into Expi293 cells was carried out using ExpiFect-amine 283 transfected kits, according to the producer's recommendations.

***In Vitro* Transfection of Cells:** The incredible donation of murine melanoma samples and murine colonic tumor cells were kept at less than 80% density and cultivated in a complete medium for development with 10% fetal bovine serum and 1% penicillin. Before the transfer, tissues were placed in flat-bottom 96-well cells with 100 μL of complete development medium, with 5×10^3 cells in each well. To create nanoparticles on the first day of transmission, a mixture was prepared by reducing the plasmid DNA encoding a green luminescent protein, which was bought from Clontech and enhanced, and a variety of PBAE plastics in 25 mM potassium acetate

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as the buffers, pH 5. The mixture was then left to self-assemble. Nanoparticles were introduced to the cells in complete growth media after 10 minutes, with levels of DNA varying between 150 to 450 μg/mL and PBAE levels reaching 5 μg/mL. The cells were exposed to nanomaterials for 2 hours at 37 °C with 5% CO_2. After that, 100 μL of new complete development medium was added to each well to replace the old media (Das et al. 2023). The metabolic rate of cells was measured using a test twenty-eight hours after transfected to evaluate the harmful effects of the nanomaterials. Using a 1× Phosphate-Buffered Saltwater (PBS) as a buffering, the infection effectiveness was assessed by flowing cytometry 48 hours after transfected.

Design, Generation, and Characterization of S-Ex: The study hypothesized that the S-Ex could stimulate robust defenses against HER3-positive breast tumors by refocusing and activating naturally occurring damaging effector cells so that target cancer cells convey the HER3 recipient. This protein is often overproduced in human breast tumors. For this purpose, the study genetically displayed functional monoclonal antigens on the surface of exosomes by fusing them with the person's PDGFR transmembrane domains. Active molecules on exosome membranes and mammal cell membranes have been shown and expressed via the transmembrane domain of phosphoglycerate kinase. The study fused just one polypeptide storing in-tandem parameter against people CD2 and HER3 sensors with the TMD to guarantee co-expression of a CD2 and HER3+ antigens on identical exosome tiny particles and reduce reduced affinity for binding caused by interest steric obstacles caused by two antibodies scaffolding. In the middle of the two antigens was a stretchy linkage. The S-Ex were created by attaching anti-human CD2 antibodies to the N or C terminator of the anti-human HER3 treatment. This was done given the position of the distinct antigens that can impact the biological, physical, and chemical properties capabilities of the created S-Ex. S-Ex has been generated by independently engaging the corresponding autoantibodies with the TMD. Hemagglutinin (HA) antigen tags were attached to the N-terminal of every fusion product. The produced S-Ex were isolated from medically specified culture conditions devoid of fetal bovine saline using a combination of differential centrifugation and ultrasound after cells were transfected with the expression plasmids. Asymmetric ultracentrifugation yields intermediate recoveries with medium presence, making it a commonly utilized approach for isolating vesicles from other cells. The total produced S-Ex per 30 mL of transfection cell suspension was about 72 mg or around 5.2×10^8 particles. Several exosomal indicators were detected using immunoblot examination, including antibody TMD protein fusions. Using an enzyme-linked immunosorbent test, the study looked at the binding of S-Ex to female HER3+ coated on a plate. It was found that a CD2 S-Ex did not bind to HER3.

Results and Discussion

Fig. 1 shows the Binding vs. Fluorescence intensity analysis of different nanomaterials. Fig. 2 illustrates the Binding vs. Concentration analysis of various nanomaterials, and Fig. 3 depicts the Cell number ratio analysis of other nanomaterials.

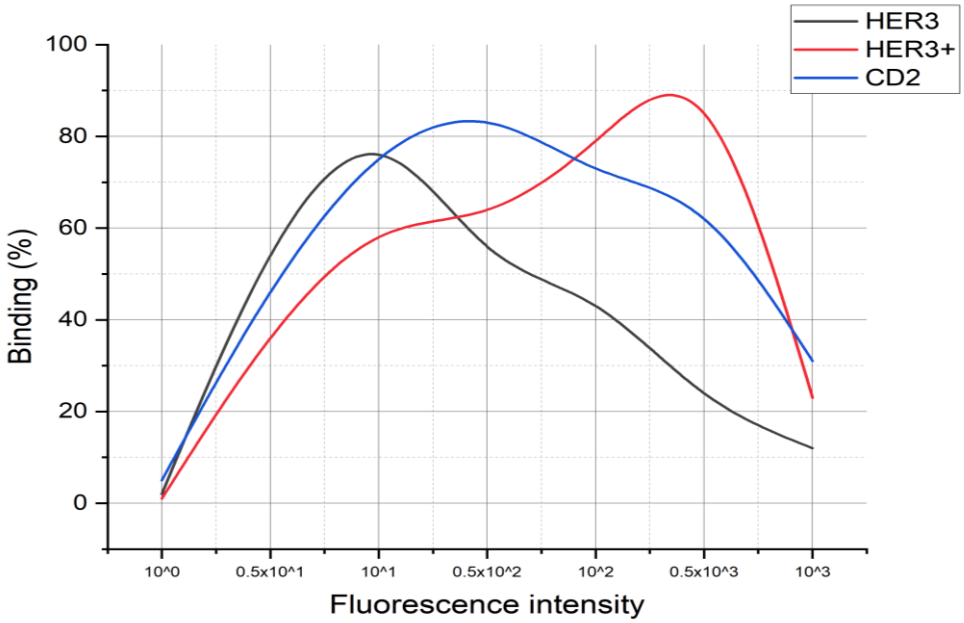

Figure 1. Binding vs. fluorescence intensity analysis of different nanomaterials

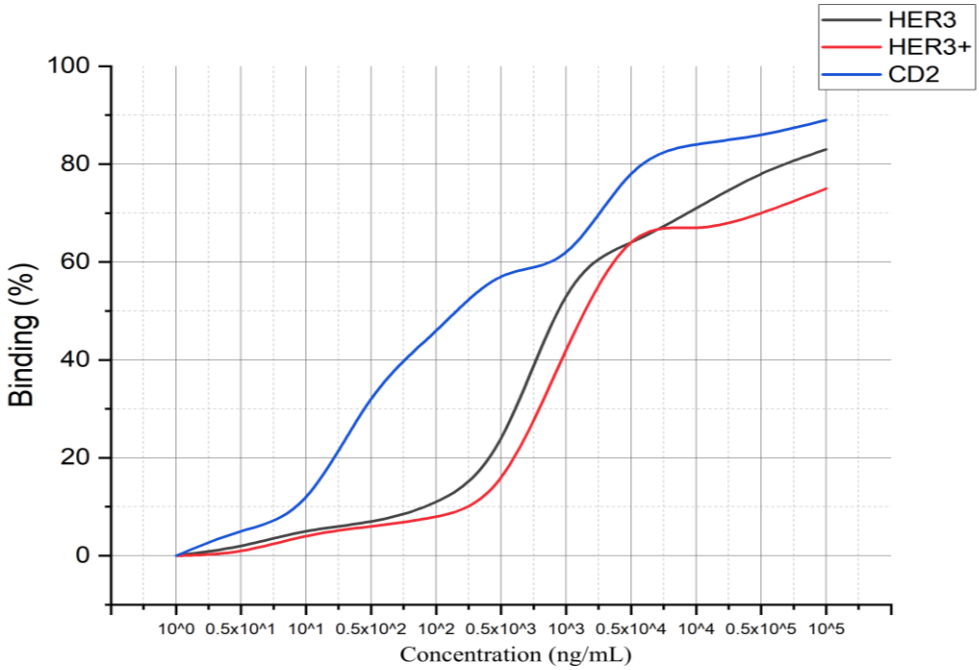

Figure 2. Binding vs. concentration analysis of different nanomaterials

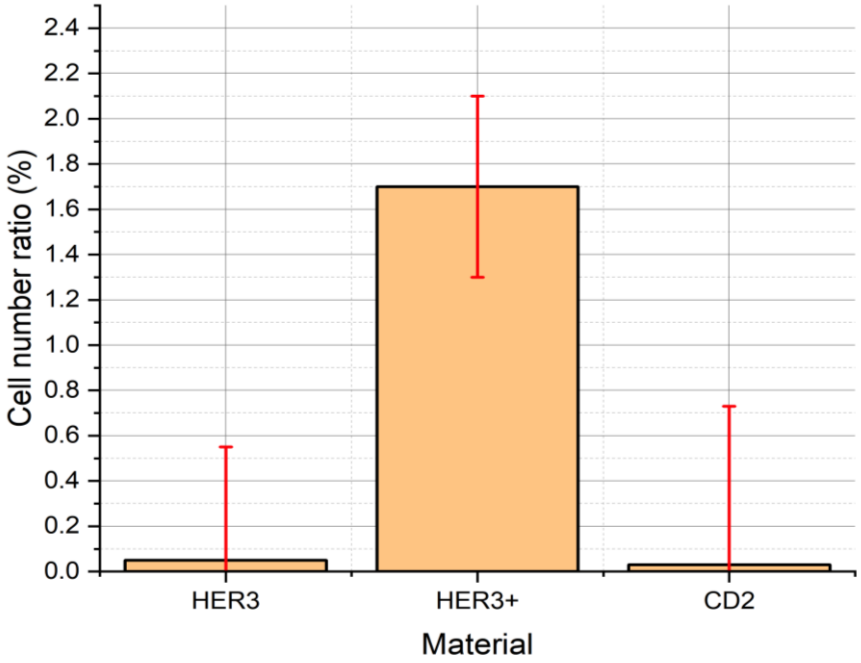

Figure 3. Cell Number Ratio Analysis of Different nanomaterials

This flow cytometric evaluation also showed that the S-Ex bound tightly to the CD2 and HER3+ cell types but weakly to the cells, indicating the functional show of multifaceted antigens on their exterior aimed at cells conveying both CD2 and HER3. Based on the findings of the ELISA, the S-Ex were selected for additional in vitro and in vivo testing because they showed a greater binding capacity to the CD2 and HER3+ cell types compared to the S-Ex. The size range of S-Ex peaked at 129 nm in width, in agreement with earlier research, as shown by the Nanoparticles Tracing Assessment (NTA). The antibody-TMD fused proteins on the outer layer were verified by Transmitted Electron Microscope (TEM) examination of S-Ex immunogold labeled with antibodies. The study investigated S-Ex-mediated cell-cell relationships using confocal microscopes to determine if S-Ex might direct T cells toward HER3-expressing tumor cells. Considerable crosslinking of cells occurred in the context of S-Ex; however, no crosslinking occurred in lines. When native exosomes or a combination of CD2 or HER3, S-Ex were present. Confocal microscopy examination showed that cells uptake the labeled S-Ex and cell-cell bridging generated by these exons. These findings indicate that S-Ex promotes cell interaction and imply that S-Ex might be used for shipping therapy payloads to cell targets.

In-Situ Genetic Reprogramming for Tumour Immunotherapy: Somatic tumor cells were injected subcutaneously into the flanks of C57BL/6 animals. On days 7 and 9, anti-PD-2 polyclonal antibodies antibody were given via the abdomen, and on dates 7, 9, and 11 following

tumor vaccination, DNA nanomaterials were delivered intravenously. On the fourteenth day, three days after the last nanoparticle therapy, tumors receiving signaling two and three nanomaterials had their γ levels evaluated in the Tumor Intermittent Flow (TIF) using enzyme-linked immunosorbent assay. The findings were consistent with what was seen in the lab, showing that cells had a more significant impact and that the highest level of γ secretion was elicited by combining signals 2 and 3. Curiously, while the production of γ could not be induced just by administering anti-PD-2, combining nanomaterials and anti-PD-2 resulted in higher γ levels in the TIF in animals both ways than in animals administered with nanomaterials alone. Fig. 4 shows the density analysis of nanoparticles with different plasmid ratios, and Fig. 5 shows the secretion analysis of nanoparticles with varying doses of plasmid.

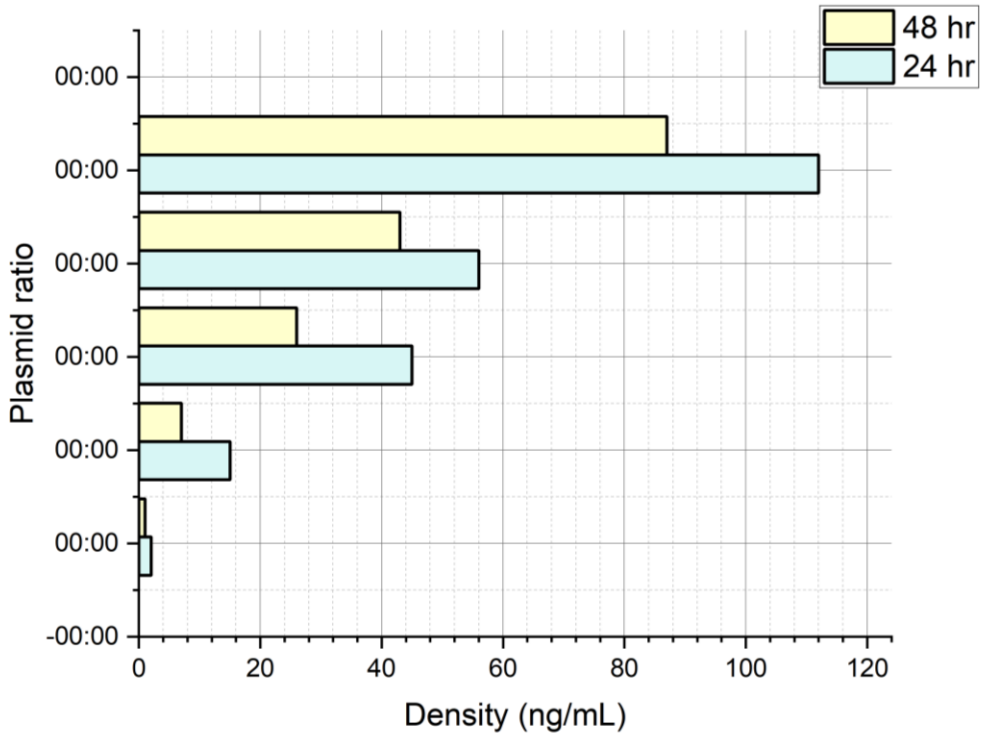

Figure 4. Density analysis of nanoparticles with different plasmid ratio

Tumor growth in mice administered with anti-PD-2 and control nanomaterials was comparable to that in animals administered with controlling nanomaterials alone, with no significant variations. Tumor development was considerably slower in mice receiving nanoparticles than oversight, and this impact was more critical in animals with ten small particles, between mice with anti-PD-2, typical immune therapy for terminal melanoma.

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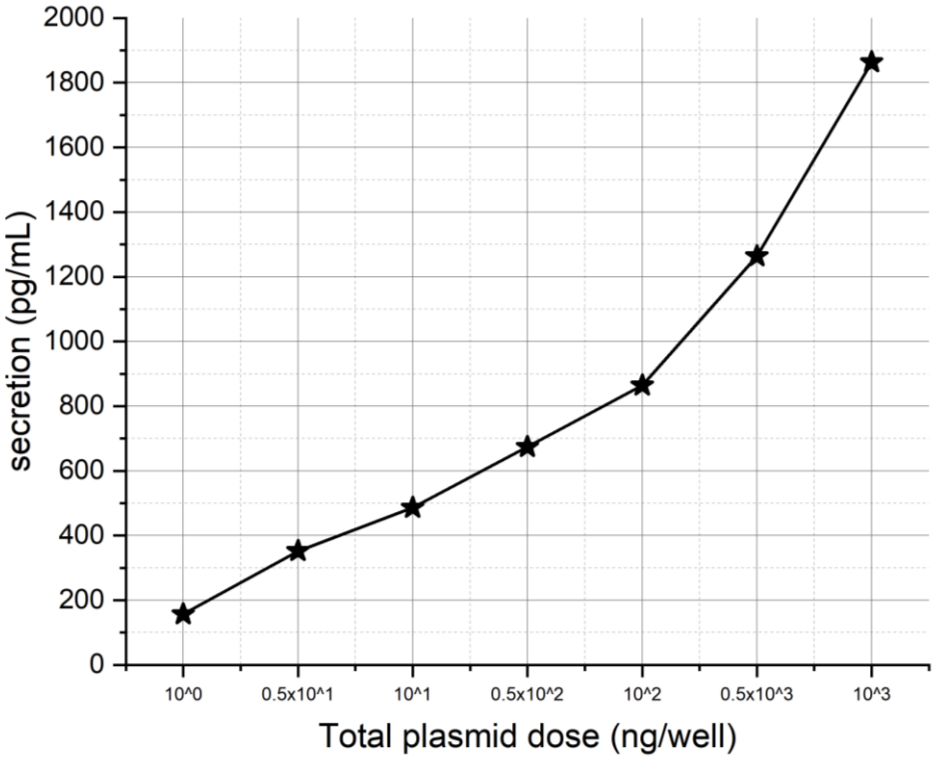

Figure 5. Secretion analysis of nanoparticles with different plasmid dose

Although there was no discernible difference in cancer development rates between the control and nanomaterials across the period under consideration, this seems to be attributable to the high degree of heterogeneity in response rates in this group. As shown in the lifespan curve, a small percentage of mice in the nanoparticle grouping outlived the animals in the control group by a significant margin. Among these mice, one managed to eradicate its flank cancer and showed no signs of discomfort even 65 days after the first tumor procedure. Mean survival was 36 days in the ten-nanotechnology population and 38 days in the nanoparticles category; this was considerably higher than the untreated control group's 24-day median survival, a 40–60% rise. At t = 67 days, a considerable percentage of the animals in the nanoparticle's subgroup had successfully removed the malignancy and remained free of illness. Fig. 6 shows the tumor area analysis, and Fig. 7 displays the survival rate analysis over time.

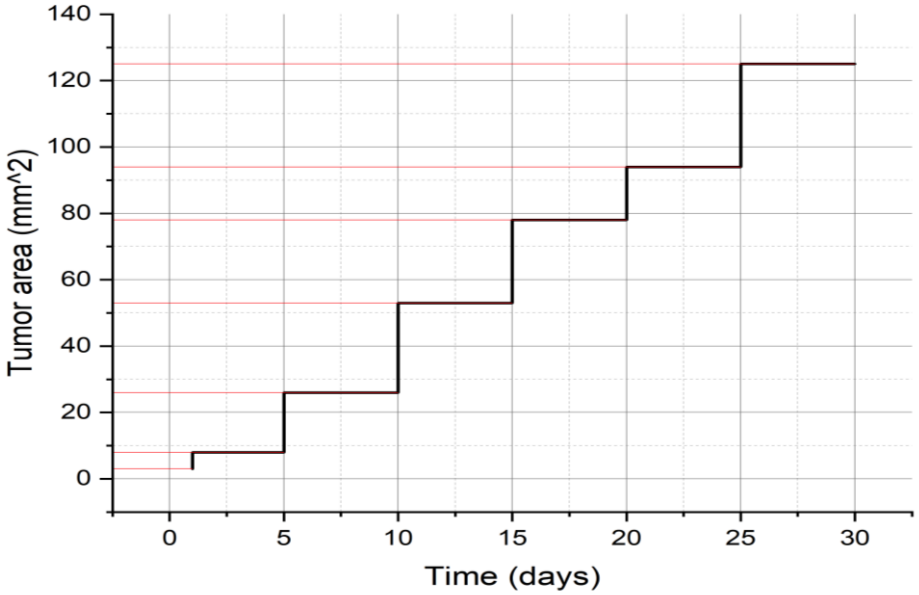

Figure 6. Tumor area analysis over time

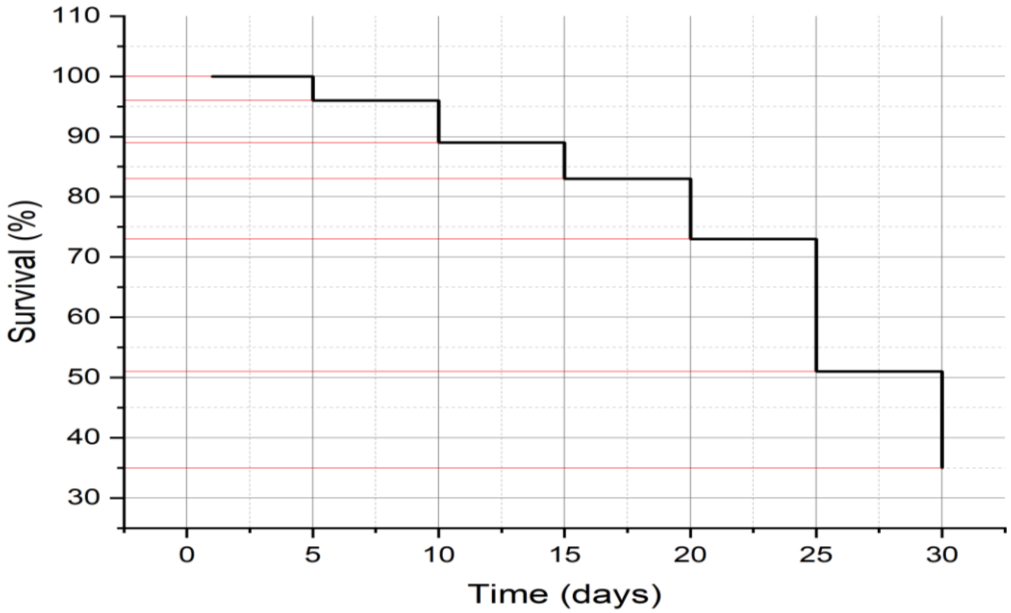

Figure 7. Survival rate analysis over time

The study developed Genetic engineering that uses durable artificial nanoparticles to change cancerous cells into tumor-based APCs. This is accomplished by stimulating a costimulatory molecule expression and an immunostimulatory cytokine. The analysis shows the impact of nanoparticles in tumor detection and treatment.

One thing that all of these immune therapies have in common is nanotechnologies, which have several benefits. One possible use for Nanomaterials is as a foundation for conjunction-

resistant treatment; another is the targeted administration of cargo content to particular cells, organs, and tissues. Nanomaterials can also be delivered to APCs for powerful stimulation of the immune system, and they provide treatments to cells with cancer in a nonsurgical and stimuli-responsive way. While nano vaccines utilize antigens to enhance the immune response of cancer antigens and boost reactions from anticancer T cells, nano vaccines are based on entire cancer cells displaying payloads in their original form.

Conclusions: Cancer immunotherapy has shown encouraging results in both experimental and clinical scenarios. Still, the effectiveness and safety of these therapies, as well as their affordability and regulatory weight, require significant investment in research and development. The study demonstrations that nonviral nanotechnology transports immunostimulatory proteins to cancer and obtains comparably high outcomes in a second animal paradigm employing colorectal cancer. The study used the complex animal melanoma model to illustrate this potential. Solid tumors are the primary target of the technique due to the nanoparticle delivery approach. For dependable tumor individuals whose lesions are needle-or catheter-accessible but not readily operated, this approach has therapeutic utility. The findings indicate that the administration of nanoparticles locally triggers an extensive and long-lasting immune reaction. This finding suggests a potential strategy for directing the body's defenses to attack cancerous cells or metastasis. This method does not involve manipulating cells outside the living organism to stimulate an endogenous biological reaction. The engineered nanoparticles provide exciting new avenues for advanced immunotherapy against cancer. The translation rate of nanotechnology into treatments for tumor immunotherapy will be influenced by nanoparticle synthesis, production, and evaluation advancements. The nanomaterial's structure is another factor. Translating marketing and patient access to therapies should be prioritized. While innovation is necessary, the study must not lose sight of the need to enhance current nanoparticle systems and incorporate these challenges into future nanoparticle-based chemotherapy for cancer.

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امان چاندراکار

*نویسنده مسئول. استادیار، گروه داروسازی، دانشگاه کالینگا، نایا رایپور، چاتیسگار، هند. ایمیل: ku.amanchandrakar@kalingauniversity.ac.in

هملاتا دوانگان

استادیار گروه داروسازی، دانشگاه کالینگا، نایا رایپور، چاتیسگار، هند. ایمیل: ku.hemlatadewangan@kalingauniversity.ac.in

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چکیده

هدف: سیستم ایمنی بدن خود را به دقت تنظیم کرده است تا به یک مکانیسم حفاظتی قدرتمند در برابر پاتوژن‌های عفونی در فرآیند تکامل تبدیل شود. یک جنبه اساسی از عملکرد آن در توانایی تشخیص بین خود و غیر خود نهفته است که برای تحریک پاسخ‌های ایمنی بسیار مهم است. اما، سرطان که با انحراف در کد DNA مشخص می‌شود این تعادل را مختل می‌کند، لذا سلول‌ها را قادر می‌سازد تا به طور غیرقابل کنترلی تکثیر شوند و در عین حال از نظارت ایمنی فرار کنند. ایمونوتراپی به عنوان یک روش امیدوارکننده ظاهر می‌شود و به دنبال تقویت سیستم ایمنی برای شناسایی و ریشه‌کن کردن این سلول‌های سرطانی سرکش است و در نتیجه یک استراتژی جدید در نبرد با سرطان ارائه می‌کند. اگرچه مهارکننده‌های ایمنی بازرس نشان داده‌اند که در درمان چندین نوع سرطان پیشرفته مفید هستند، اما نرخ پاسخ کلی در بیمارانی که این درمان‌ها را دریافت می‌کنند در حدود ۳۰ درصد باقی می‌ماند. با درک نیاز به پیشرفت‌ها، پژوهش حاضر به رویکردهای مبتنی بر نانوذرات با هدف افزایش درمان‌ها و واکسیناسیون‌های سرطان می‌پردازد.

مواد و روش‌ها: تمرکز بر روی توسعه بیوتکنولوژی است که از نانوذرات مصنوعی بادوام برای تبدیل سلول‌های سرطانی به سلول‌های ارائه‌دهنده آنتی‌ژن مبتنی بر تومور (APCs) استفاده می‌کند. این فرآیند تبدیلی شامل تحریک بیان همزمان مولکول‌های تحریک کننده و سیتوکین‌های ایمنی تحریک کننده است. چیزی که این نانودارو را متمایز می کند، ظرفیت آن برای القای پاسخ ایمنی عمومی اختصاصی تومور و سلولی بدون فرض آنتی ژن‌های خاص بیان شده توسط تومورها است.

نتایج: در روز t = ۶۷، درصد قابل توجهی از حیوانات در زیر گروه نانوذرات با موفقیت بدخیمی را حذف کرده و عاری از بیماری باقی ماندند.

نتیجه‌گیری: این نوآوری دارای پتانسیل فوق العاده‌ای برای پیشرفت در پزشکی ترجمه است و راه حلی همه کاره و سازگار برای چالش های ناشی از ایمنی درمانی سرطان ارائه می‌دهد. با بهره‌گیری از قابلیت‌های نانوذرات مصنوعی، محققان در آرزوی ارتقای اثربخشی درمان‌های سرطان و سوق دادن این حوزه به سمت عصر جدیدی از مداخلات هدفمندتر و قوی‌تر هستند. در نتیجه، تعامل پیچیده بین سیستم ایمنی و سرطان بر ضرورت رویکردهای درمانی نوآورانه تاکید می‌کند. اکتشاف استراتژی‌های مبتنی بر نانوذرات نشان‌دهنده مرزی در تحقیقات سرطان است که نویدبخش بهبود درمان‌های ایمنی و آغاز دوره جدیدی از پزشکی دقیق به نفع بیمارانی است که با این بیماری پیچیده و وحشتناک دست و پنجه نرم می‌کنند.

کلیدواژه‌ها: سرطان، مهندسی ژنتیک، ایمونوتراپی، نانوذرات

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