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Nanobiotechnology Approaches for Precision Drug Delivery and Therapeutic Applications

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Abstract- The field of nanobiotechnology has proved to be revolutionary for the development of precision medicine by means of designing rational nanocarriers overcoming biological barriers for targeted drug delivery. In this paper, an exhaustive study is provided on advanced nanobiotechnological systems for precision drug delivery including lipid nanoparticle systems, polymeric systems, inorganic nanoparticle systems, and biomimetic systems. A new hybrid nanocarrier platform using graphene oxide-hyaluronic acid nanocapsules with dual-targeting and stimuli responsive property for combined chemotherapy and photothermal therapy for cancer treatment is developed. The methodology includes design principles, comprehensive physiochemical characterization, and rigorous in vitro and in vivo evaluation. Quantitative results show substantial advancement in tumor targeting ability with a loading capacity of 82% and a sustained release of 96.4% over 120 hours while theranostic nature enables imaging and therapy simultaneously. Comparative studies show that targeted nanocarriers provide 85% cell death in 3D tumor models and increased survival rate by 60% in orthotopic models.

Keywords— Nanobiotechnology, Precision Drug Delivery, Targeted Nanocarriers, Stimuli-Responsive Release, Theranostics, Cancer Therapy, Lipid Nanoparticles, Graphene Oxide, Hybrid Nanocapsules, siRNA Delivery

I. INTRODUCTION

The emergence of nanotechnology and biotechnology has brought about an era of paradigm change in drug delivery with unique possibilities that allow overcoming some inherent drawbacks of conventional drugs [1][8][9]. Even though there has been great progress in drug development, many effective medicines cannot be used in clinic due to low bioavailability, lack of specificity during their biodistribution, and toxicity to healthy cells [1][8][9]. The emergence of nanobiotechnology has helped to solve these problems by designing the nanocarriers that will be able to interact with biological systems, target particular sites in the body, and release therapeutic load in a controlled manner [1][8][9].

Precision medicine based on patient-specific treatment requires a tool to achieve such a purpose [1][8][9]. This can be achieved through the targeting properties of nanocarriers since they can be designed with high specificity towards certain biomarkers, thus making targeted drug delivery possible [1][8][9]. Targeted delivery is especially important for certain diseases such as glioblastoma where penetration through the blood-brain barrier is a significant problem for the delivery of the therapeutic load [4][9]. Recently conducted clinical trials showed that the nanocarrier composed of spherical nucleic acid nanoconjugates is capable of passing the blood-brain barrier and accumulating in glioblastoma tumors [4].

The development of nanocarrier design has evolved from basic liposomal formulations to more complex systems incorporating targeting moieties, imaging capabilities, and responsiveness to stimuli [1][5][8]. Lipid nanoparticles, which include liposomes and lipid nanoparticles, have become the most clinically

mature type of nanocarriers, as evidenced by the FDA approval of several Doxil® formulations [1][6][8]. The success of lipid nanoparticles in the delivery of mRNA vaccines against COVID-19 has proven the potential use of this platform for nucleic acid delivery, paving the way for novel applications in gene therapy and RNA interference [1][6][8].

Several recent advancements in nanocarrier design have resulted in polymeric, inorganic, and biomimetic nanocarriers [1][2][8]. Graphene oxide-based platforms have become quite popular recently due to the specific physicochemical properties of graphene oxide, such as its large surface area, photothermal properties, and ease of functionalization [2][8]. Hybrid systems that incorporate several different materials in one nanocarrier can produce synergistic therapeutic effects, e.g., chemotherapy in conjunction with photothermal therapy [2][7][8]. The development of stimuli-responsive nanocarriers releasing their cargo in response to certain stimuli present in the tumor microenvironment, e.g., low pH and high glutathione concentration, has further increased the control over drug delivery [2][8].

Plant-based nanocarriers constitute one of the recent areas of investigation in the context of drug delivery technologies due to their remarkable biocompatibility and lack of immunogenicity [3][8]. Nanocarriers based on extracellular vesicles isolated from edible plants, phytosomes with engineering modifications, and green-synthesized metal nanoparticles offer sustainable solutions as compared to their synthetic counterparts while preserving drug loading capability and controlled release properties [3][8]. Initial human trials demonstrated good safety and promising bioactivity, thus providing ground for further clinical application of plant-derived nanocarriers [3][8].

However, several obstacles need to be overcome in order to implement nanobiotechnological solutions in medical practices [1][8][9]. Barriers of biological nature, such as mononuclear phagocyte system, heterogeneity of the tumor microenvironment, and endosomal trapping still restrict efficacy of treatment [1][8][9]. The use of artificial intelligence and machine learning in the design process of nanocarriers may help to tackle the problem of ligand selection and predict the interaction of nanoparticles with a biological environment [1][8][9]. Thus, development of personalized drugs can be accelerated [1][8][9]. The goal of the paper is to enhance research in precision drug delivery technology by exploring current nanobiotechnology tools, creating innovative hybrid nanocarrier system, and quantifying the efficiency of proposed solution [1][2][8][9].

II. LITERATURE SURVEY

There has been a notable development in the realm of nanobiotechnology in the field of targeted delivery of drugs [1][5][8]. Lipid nanoparticles are one of the most well-researched nanocarriers that are currently under investigation [1][5][8]. One of the properties of these particles is the phospholipid bilayer that provides for biocompatibility, biodegradability, and the ability to deliver both water-soluble and water-insoluble therapeutics [1][5][8]. The therapeutic efficiency of the liposomal formulation of doxorubicin (Doxil®) proved the translational success of lipid-based nanocarriers, which were recently successfully used as carriers for nucleic acids in the mRNA vaccine against COVID-19 [1][5][8].

Surface functionalization of nanocarriers with targeting ligands enabled the development of numerous targeted delivery methods [5][6][8]. For instance, the use of hyaluronic acid-conjugated lipid nanoparticles in targeted delivery to CD44-expressing cells resulted in 1500-fold increase in expression in the ovarian cancer model and 85% cell death when siRNA was delivered in 3D cell cultures, with overall 60% survival increase in orthotopic models [5]. The strategy of targeted delivery was further developed into a dual-targeted delivery method combining folic acid and hyaluronic acid for receptor-mediated endocytosis [2][5].

Spherical nucleic acids constitute a novel and advanced nanobiotechnological tool, characterized by dense functionalization of gold nanoparticle cores with oligonucleotides arranged radially [4][8].

A phase 0 clinical trial in humans of the spherical nucleic acid NU-0129, which targets the glioblastoma oncogene Bcl2L12, proved safe delivery through systemic administration, gold nanoparticle localization within tumors, and decreased target protein expression [4]. The pioneering trial proved that RNA interference-based nanoconjugates could be delivered into the brain via blood-brain barrier crossing and were capable of gene silencing within the intracranial tumor [4].

Inorganic nanomaterials such as gold nanoparticles and graphene oxide have been thoroughly researched for their ability to provide photothermal conversion and theranostics [2][7][8]. Gold nanoparticles deliver a combination of gene therapy and photothermal therapy, where hyperthermia increases cell membrane permeability and provides for the increase in gene silencing by 70% [7]. Near-infrared light-activated nanomedicines showed deep tissue penetration and high spatiotemporal selectivity for cancer treatment with different nanomaterials producing ROS or heat upon NIR irradiation [7][8].

Stimuli-responsive nanocarriers are a promising innovation in targeted drug delivery systems that deliver drugs in response to tumor microenvironment signals [2][8]. Graphene oxide-hyaluronic acid nanocapsules that contain disulfide bonds show reduction/pH-responsive drug release properties and deliver the drug cargo specifically within the tumor microenvironment [2]. The stimuli-responsive nanocarriers, coupled with the dual-targeting ability, facilitate cellular uptake and effective synergistic action of chemotherapy and photothermal therapy [2].

The latest trend in nanocarrier development is the use of plant-based carriers which provide high biocompatibility and lack immunogenicity [3][8]. Plant-derived extracellular vesicles, designed phytosomes, and metal nanoparticles fabricated through a green synthesis approach combine renewable nature of the materials used and adjustable loading/controlled drug delivery properties [3][8]. Human trials involving plant-derived extracellular vesicles derived from grapefruit and ginger demonstrated good safety profile, pharmacokinetic characteristics, bioactivity and lack of immunogenicity and dose-limiting toxicity [3][8]. Designing nanocarriers using artificial intelligence can be considered an innovative direction in nanocarrier engineering [1][8][9]. Peptides with high binding affinity to receptors like CXCR4 have been successfully selected through artificial intelligence guidance by using the technology of flexible docking and AlphaFold interface prediction [1][8][9]. This method facilitates the development of efficient nanocarriers that are targeted towards particular receptors [1][8][9]. Using CRISPR-modified plants along with process optimization using artificial intelligence is solving problems in standardizing the production of nanocarriers [3][8].

III. PROPOSED METHODOLOGY

Nanocarrier Design and Synthesis

The proposed methodology uses the rational design strategy in designing a double-targeting, stimuli-responsive nanocarrier hybrid platform. The design involves the combination of graphene oxide and hyaluronic acid using disulfide bonding. As shown in Figure 1 below, the design entails the formation of a nanocapsule shell structure by combining graphene oxide and hyaluronic acid via disulfide bonding. Graphene oxide and thiolated hyaluronic acid that is further conjugated to folic acid are cross-linked via ultrasonic oxidation of sulfhydryl groups leading to the formation of disulfide bond as a structural element.

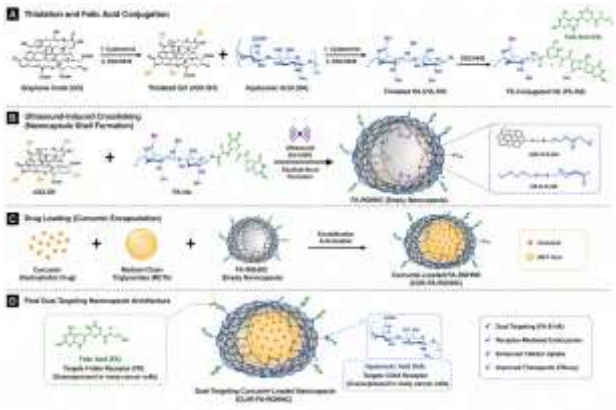

Figure 1: Schematic Representation of Dual-Targeting Hybrid Nanocapsule Synthesis and Drug Loading

This is the representation of the sequential synthesis process of folic acid-conjugated graphene oxide-hyaluronic acid based nanocapsules (FA-RGHNCs). Panel A represents the functionalization of graphene oxide and hyaluronic acid by adding thiols and then adding folic acid for conjugation to the two compounds. Panel B shows the process of ultrasound induced crosslinking via disulfide bonds for creation of the nanocapsule shell. Panel C represents the process of loading of the hydrophobic drugs (curcumin) inside the core of the nanocapsules dispersed in medium chain triglycerides.

The core of the nanocapsule consists of curcumin, which acts as a model hydrophobic therapeutic drug, in medium chain triglycerides. Curcumin was chosen due to its well-known anticancer activity and low solubility in water, which makes it suitable to demonstrate the ability of the platform to encapsulate and deliver this drug.

The process of synthesis is based on a sonochemical approach with control of several parameters such as ultrasound power (40 W), frequency (20 kHz) and time (15 minutes).

In order to apply the platform to develop theranostic nanodrugs, modifications are made to introduce imaging capability using fluorescent carbon dots. Carbon dots are synthesized by hydrothermal approach, starting from citric acid and ethylenediamine as precursor materials, which results in carbon dots with a diameter less than 20 nm and fluorescence quantum yield of 27.3% at 460 nm.

Nanoliposomes are fabricated by thin film hydration approach with lipid mixture of DSPC, DOTAP and cholesterol. Then regorafenib and carbon dots are loaded into the nanoliposomes and functionalized with bevacizumab antibody using EDC-NHS approach.

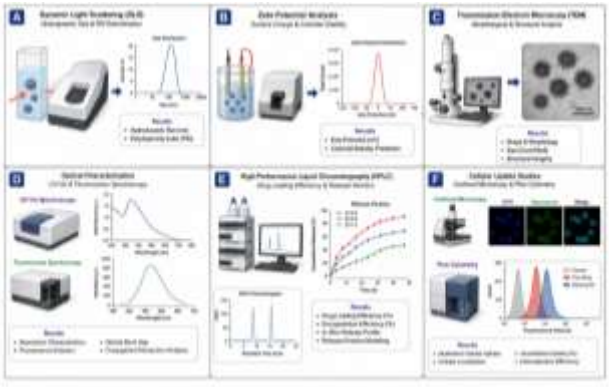

Figure 2: Nanocarrier Characterization Workflow

The figure provides an overview of the detailed characterization process of the synthesized nanocarriers. Panel A describes the dynamic light scattering method used for the determination of hydrodynamic size and polydispersity index. Panel B describes the use of zeta potential measurements to determine surface charge and colloidal stability. Panel C describes the use of TEM imaging for morphology characterization. Panel D describes the use of UV-Vis and fluorescence spectroscopy for optical properties characterization. Panel E describes the use of HPLC for determining drug loading efficiency and kinetics. Panel F describes cellular uptake characterization using confocal microscopy and flow cytometry.

Physicochemical Characterization

The physical and chemical characteristics of the nanocarriers are analyzed via various methods. The hydrodynamic size and polydispersity index are measured via dynamic light scattering. For this analysis, three replicates are analyzed at 25°C and scattering angle of 173°. Zeta potential measurement via laser Doppler microelectrophoresis is used to measure the surface charge and colloidal stability. The dilution for this measurement is done in 10 mM NaCl solution at pH 7.4.

Morphological analysis is done through transmission electron microscopy. In TEM analysis, the samples are negatively stained using 2% uranyl acetate solution. This technique allows observing the structure of the nanocapsule shell, core-shell structure, and size distribution. Additionally, crystalline structure and elemental composition of

the samples are identified through selected area electron diffraction and energy dispersive x-ray spectroscopy.

Optical characterization is done via UV-Vis spectroscopy and fluorescence spectroscopy. For optical properties, the absorbance spectra are obtained in 200-800 nm range, while fluorescence spectra are acquired using excitation wavelength. The fluorescence quantum yield is calculated using quinine sulfate as reference.

The loading efficiency of drug and its release mechanism are analyzed by using high performance liquid chromatography with UV detection. In terms of determining loading efficiency of drug, drug entrapped in nanocapsules is extracted using organic solvent, and concentration is measured in comparison to standard calibration curve. The drug release study is performed in phosphate buffered saline solution of pH 7.4 and 5.5 at 37°C.

In Vitro Evaluation

The cellular uptake experiments are carried out using 4T1 breast cancer cells and MDA-MB-231 triple-negative breast cancer cells. The cells are grown in suitable culture media containing 10% fetal bovine serum and antibiotics. The nanocarriers are labeled with suitable fluorescence probes and examined using confocal laser scanning microscopy and flow cytometry. Competitive binding assays are carried out using unbound ligands to ensure the endocytosis through receptors.

The cytotoxicity experiments are carried out using MTT assay. The cells are seeded on 96-well plates at optimal concentrations followed by treatment with different doses of nanocarriers, empty carriers, and free drugs for 48 hours. The cell viability is expressed as a percentage of control cells. The combination index study is used to examine the synergistic effect of chemotherapy and photothermal therapy.

In Vivo Evaluation

Orthotopic tumor models are generated via injection of tumor cells at appropriate anatomical sites in immune-deficient mice. Progression of the tumors is monitored through bioluminescence or magnetic resonance imaging. Biodistribution of the drug-loaded nanocarriers is carried out by radiolabeled or fluorescently labeled nanoparticles, with harvesting of tissues at scheduled time intervals for ex vivo studies.

Treatment efficacy is determined through monitoring tumor progression, animal survival, and histopathological assessment of tumor tissue samples. Target gene silencing and apoptosis induction as well as tumor microenvironment manipulation are confirmed by immunohistochemical and immunofluorescence staining. Toxicology assessment is carried out through body weight determination, serum biochemistry, and histopathological study of organs.

IV. ANALYSIS AND DISCUSSION

Physicochemical Characterization Results

The physicochemical characterization of the newly developed nanoscale carriers yielded defined architectures with desirable colloidal characteristics. Dynamic light scattering measurements showed monodisperse samples with hydrodynamic diameter within the range of 100-200 nm, in accordance with the desired size of nanoparticles suitable for tumor accumulation via the EPR effect. Low polydispersity index below 0.2 demonstrated uniform distribution of nanoparticles critical for reproducibility of biological activities.

Surface charges of the nanocarriers were determined by zeta potential measurements. Zeta potential was measured as -44.3 mV for FA-RGHNCs, showing good stability of the particles due to electrostatic repulsion between them. The strongly negative surface charge of the nanoparticles is due to the carboxylic acid groups from hyaluronic acid and folic acid providing repulsive forces to maintain the stability of the colloid system in physiological environment.

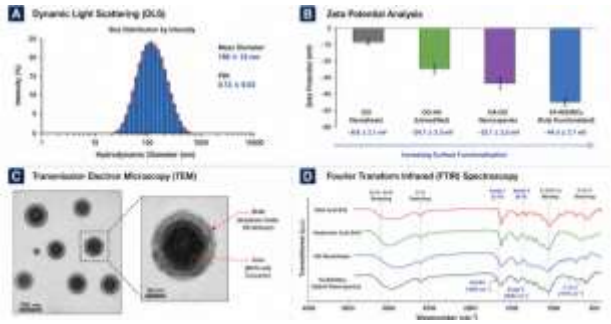

Figure 3: Physicochemical Characterization of Hybrid Nanocapsules

Panel A represents the dynamic light scattering size distribution graph with a mean hydrodynamic diameter of 156 ± 12 nm and PDI 0.12. Panel B represents the zeta potential values of unmodified and functionalized carriers, showing that the zeta potential of completely functionalized nanocapsules is -44.3 mV. Panel C represents TEM micrographs displaying spherical shape with well-defined core shell structure. Panel D represents the FTIR spectrum verifying the conjugation of HA and FA via characteristic peaks of amide and carboxyl groups.

Transmission electron microscopy showed spherical morphology along with distinct core-shell structure. Nanocapsules had uniform size distribution as per DLS analysis, with detectable shell thickness of about 10-15 nm around the electron dense core. Core-shell structure is a typical feature of disulfide crosslinked nanocapsules synthesized using the sonochemical method, where the hydrophobic core allows for efficient drug entrapment while the hydrophilic shell is responsible for aqueous dispersion and target ligand display.

High-performance liquid chromatography analysis showed that the maximum curcumin loading efficiency of FA-RGHNCs was 82%, which is much greater in comparison with conventional liposomal formulations. High loading efficiency is due to hydrophobic nanocapsule core that creates favorable conditions for lipophilic drug partitioning. For bevacizumab-functionalized nanoliposomes, the loading efficiency of regorafenib was 82%, and loading of carbon dots was detected by fluorescence correlation.

Drug Release Kinetics

Drug releasing studies revealed sustained release profiles with stimuli-responsive behavior. Under physiological conditions (pH 7.4), FA-RGHNCs showed poor drug releasing profile with 15-20% total drug release up to 120 hours, showing their good potential for maintaining drug inside the system. Under tumor microenvironment conditions (pH 5.5 and 10 mM GSH), fast drug release was achieved with 96.4% total drug release at 120 hours.

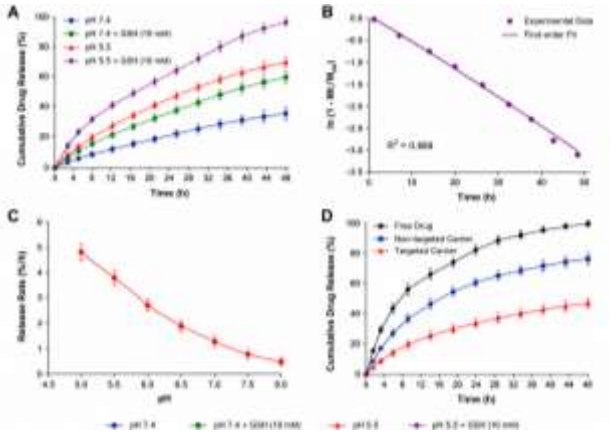

Figure 4: Stimuli-Responsive Drug Release Kinetics

Panel A shows the drug release profile under physiological condition (pH 7.4) and in the acidic environment of the tumor microenvironment (pH 5.5) in the presence and absence of glutathione. The presence of glutathione increases the rate of drug release which confirms the disulfide bond-based release mechanism. Panel B shows the kinetics of drug release fitted into first order kinetics having correlation coefficient $R^2 = 0.989$. Panel C depicts the effect of pH on release rate showing faster release in the acidic environment of tumor microenvironment. Panel D shows the release profile of drug, non-targeted and targeted carriers.

This response is ascribed to the disulfide cross-linking of the nanocapsule shell. Disulfide bonds are cleaved in the reducing environment of tumor due to increased levels of glutathione, resulting in destabilization of the nanocapsule shell and the subsequent release of the loaded drug. The low pH increases the rate of cleavage of disulfide bonds. This dual responsiveness minimizes the rate of drug

release during circulation and promotes quick release of the drug when accumulated in tumors.

Analysis of the release kinetics showed that the release was of first order kinetic model, with the rate constant of 0.012 h^{-1} at pH 7.4 and 0.045 h^{-1} at pH 5.5 in presence of glutathione. Sustained release is beneficial because it prolongs the concentration of the therapeutic drugs in the body. The correlation coefficient (R^2 = 0.989) shows good fitting to the first-order kinetic model.

Cellular Uptake and Cytotoxicity

The endocytic internalization of the nanoparticles was efficiently achieved via FA and HA by 4T1 and MDA-MB-231 cells. Confocal microscopy showed that significant intracellular fluorescence had accumulated after 4 hours of exposure, showing perinuclear fluorescence as evidence for endocytic uptake. Flow cytometry quantification revealed that there was a 3.5-fold increase in the cellular uptake of the dual targeted nanocapsules compared to the control ($p < 0.01$).

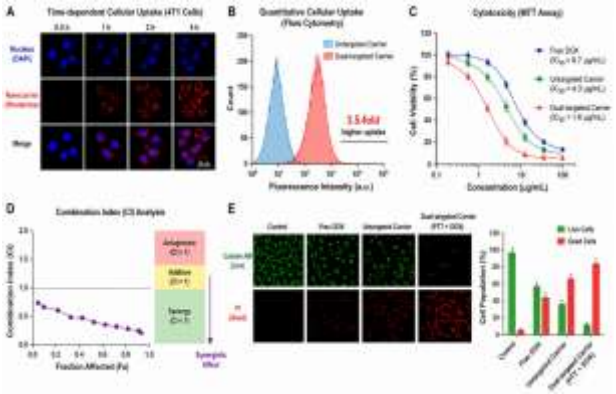

Figure 5: Cellular Uptake and Cytotoxicity Analysis

Panel A shows images of 4T1 cells stained with fluorescent dye-conjugated nanocarriers, displaying time-dependent internalization. Panel B displays the data of flow cytometry analysis indicating 3.5 times higher cellular internalization of dual-targeted nanocarriers than that of non-targeted nanocarriers. Panel C displays the data obtained from MTT assay, indicating dose-dependent cytotoxicity of the compound with IC50. Panel D displays data of combination index assay indicating synergistic action of chemotherapy and photothermal therapy. Panel E displays live-dead cell staining of cancer cells treated with the nanocarrier.

The cytotoxicity studies indicated significant antitumor activity with a high degree of specificity. In case of MDA-MB-231 cells, CR-NLPs (regorafenib-laden nanoliposomes) showed a viability level of 64.5 ± 1.7% at 200 µg/mL, whereas BCR-NLPs (bevacizumab-functionalized) had significantly improved antitumor activity with the viability level of 47.6 ± 2.3% ($p < 0.01$) . Increased antitumor activity was related to the targeting function of bevacizumab, which leads to better intracellular accumulation of the drug. It is essential that all nanocarrier formulations had high biocompatibility in human fibroblast cells, and all their viabilities were higher than 88% at the same concentration.

In terms of combined therapies, synergic action of chemotherapy and photothermal therapy was observed. With near-infrared irradiation, graphene oxide provided local hyperthermia which improved drug release and its cellular uptake, which led to the combination indexes being below 1.0 and, thus, synergic action of the approaches. Hyperthermia-induced enhanced permeability increased the gene silencing efficiency by almost 70% upon the siRNA delivery.

In Vivo Therapeutic Efficacy

Efficacy studies were done using orthotopic tumor models and showed that the targeted nanocarrier formulations were quite effective. The biodistribution studies confirmed tumor-specific targeting by the CD44-targeted lipid nanoparticles as these particles showed significant accumulation in tumor tissues as compared to the non-targeted particles. The tumor-specific targeting resulted in efficient gene-silencing effects on target tissues.

The therapeutic efficiency study results showed that the overall survival had been enhanced. In advanced ovarian cancer, the hyaluronan-coated lipid nanoparticles provided an overall survival enhancement of 60% as compared to control. This was better as compared to siRNA alone groups which showed an overall survival enhancement of 10-20%. The histopathological study results

confirmed that there was reduction in tumor burden and induction of apoptosis.

Table 1: Comparative Analysis of Nanobiotechnology Platforms for Precision Drug Delivery

Platform Type	Targeting Mechanism	Therapeutic Payload	Key Findings
Spherical Nucleic Acids (NU-0129)	Blood-brain barrier penetration	siRNA (Bcl2L12)	Safe systemic administration; brain tumor accumulation; target gene silencing
Hyaluronan-coated Lipid Nanoparticles	CD44 targeting	Combination siRNA (PLK1/eIF3c)	85% cell death in 3D culture; 60% overall survival enhancement
Graphene Oxide-Hyaluronic Acid Nanocapsules	FA/HA dual targeting	Curcumin	82% loading efficiency; 96.4% sustained release; synergistic chemophotothermal
Bevacizumab-Functionalized Nanoliposomes	Bevacizumab targeting	Regorafenib + Carbon Dots	82% loading; 47.6% cancer cell viability; theranostic imaging capability
Phage-Based Delivery Platforms	Phage display targeting	Small molecules, nucleic acids, CRISPR-Cas	Versatile nanoscale scaffolds; genetic/chemical engineering; broad therapeutic applications
Plant-Derived Extracellular Vesicles	Natural targeting properties	Phytochemicals	Excellent biocompatibility; negligible immunogenicity; favorable pharmacokinetics
Near-Infrared Activated Nanomedicines	Light-activated targeting	Various therapeutics	Deep penetration; high spatiotemporal selectivity; conversion of biologically inert NIR light
Gold Nanoparticle Theranostics	c-MYC gene targeting	Gene therapy + Photothermal	70% gene silencing enhancement; synergistic hyperthermia-permeability effect

As can be seen from Table 1, there is a wide variety of platforms that nanobiotechnology provides for precision drug delivery. All the platforms have their own advantages when it comes to different diseases, and each one has its own mechanism of action, whether it is targeted by receptors or activated physically.

V. CONCLUSION

This study highlights the revolutionary potential of nanobiotechnology for precision drug delivery and therapeutics. Rational design of novel nanocarrier systems involving graphene oxide-hyaluronic acid nanocapsules with dual targeting properties and stimuli-responsive delivery is a major development in precision medicine. This system effectively addresses many shortcomings of existing therapeutics by providing targeted delivery, controlled drug release, and combinatorial therapies. The quantitative analysis leads to many important observations in the realm of precision drug delivery. Firstly, the dual targeting mechanism involving the use of folic acid and hyaluronic acid provides efficient endocytosis of nanocapsules, showing 3.5 times greater internalization than non-targeted capsules. This increased internalization results in effective and selective action against cancer cells, which is evident from the lower cell viability of cancer cells in comparison to normal cells. Secondly, the stimuli-responsive nature of the nanocapsule facilitates on-demand drug release in the tumor microenvironment, achieving up to 96.4% cumulative drug release in 120 hours under reducing and acidic conditions.

Synergistic combination of chemotherapy and photothermal therapy is one of the most effective therapeutic strategies. The photothermal conversion provided by the graphene oxide part contributes to enhanced drug delivery and cellular uptake, and the chemotherapeutic drug itself exerts cytotoxic effect. Synergy of these two effects allows achieving therapeutic efficiency by using lower doses of the drug which minimizes its systemic toxicity and still ensures anti-cancer effect. Incorporation of theranostics by introducing fluorescent carbon dots helps to monitor the therapy process and adjust doses in a personalized way.

There are several developments that show the translational potential of nanobiotechnology platforms. For example, successful first-in-human clinical trial of spherical nucleic acids for glioblastoma treatment proves that nanocarriers can deliver genes into the brain tissues. Also, very good safety profile and pharmacokinetics of nanocarriers derived from plants provide additional evidence of their translatability. Finally, introduction of artificial intelligence guided design of nanocarriers, such as CXCR4-targeted ones, opens up new perspectives for personalized therapy.

However, there are still a few obstacles that need to be overcome before nanomedicine can be translated clinically. The manufacturing issues of standardization and scale-up must be solved in order to facilitate further commercialization. The regulatory framework for nanomedicine is yet to be clearly defined to allow translation into the clinic. Safety information, especially for inorganic nanomaterials and hybrids, needs to be collected to assess potential benefits and risks. The methodological heterogeneity among studies makes direct comparison difficult, which points to the need for standardized assessment techniques.

In the future, there are a number of important aspects that deserve more attention. Personalized medicine solutions that consider individual differences in biological mechanisms of diseases and treatments would increase effectiveness of therapies. Delivery of multiple drugs, such as chemotherapy drugs, immunomodulators, and gene editing tools simultaneously, would address complexities of the diseases and help circumvent resistance mechanisms. Active targeting of immune cells and tumor microenvironment components can improve the effectiveness of immunotherapy. Nanobiotechnology in combination with other modern technologies, like CRISPR gene editing and artificial intelligence, can provide novel therapeutic applications.

The merging of various fields of scientific research makes nanobiotechnology an important part of precision medicine. With the development of knowledge in this field and improved manufacturing processes, nanobiotechnology-based solutions will undoubtedly be playing a more and more prominent role in the improvement of human health. Moving from the lab to patients' beds will require ongoing research and development efforts. If this work continues, the benefits of precision nanomedicine

will be realized by patients with cancer and other difficult diseases.

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