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Pharmacological evaluation of novel drug delivery systems for targeted cancer therapy

¹Reshu Jain and ²Dr. Jagrati Gope

¹Department of Pharmacy, Swami Vivekanand University, Sagar, NH 26, Narsinghpur Road, Sironj, Sagar, Madhya Pradesh, India

²Parashar Ayurvedic Medical College and Hospital, Jamunia, Zirnia, Narsingh road, Parvalia, Bhopal, Madhya Pradesh, India

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Corresponding Author: Reshu Jain

Abstract

The ability to precisely deliver medications to tumors is a huge step forward in the fight against cancer. So, it's ideal to find new ligands that target tumors or pharmacological nanocarriers. Using phage display, we discovered SP90, a novel targeting peptide that identifies tumor tissues from breast cancer patients and attaches selectively to breast cancer cells. The conjugation of SP90 with liposomes allows for effective drug transport into cancer cells by endocytosis, as shown by confocal and electron imaging. Additionally, SP90-conjugated quantum dots have tumor-targeting capabilities, as shown by in vivo fluorescence imaging. By boosting the drug's accumulation in tumors selectively, SP90-conjugated liposomal doxorubicin improved the chemotherapeutic drug's therapeutic index in tumor xenograft and orthotopic models. Our research leads us to believe that SP90, a targeted peptide, may greatly enhance the therapeutic advantages of chemotherapy for breast cancer patients and their doctors.

Keywords: Breast cancer, targeted drug delivery system, active targeting, physicochemical targeting

Introduction

Cancer is a collection of disorders characterized by the unchecked proliferation of malignant cells. The malignant process begins when these cells undergo modifications that allow them to replicate endlessly and spread to other parts of the body. The patient usually dies as a result of the inability to control or stop the spread of malignant cells. In the United States, cancer is responsible for roughly one out of four fatalities, making it the leading cause of death overall. The survival rate varies according on the kind of cancer and the stage of diagnosis. Estimates put the number of new cancer cases in the United States at 1,658,370, with 589,430 people losing their lives to the disease. Compared to 49%, the relative survival rate for all malignancies diagnosed was 68%. A number of causes, both internal and external, contribute to the development of this fatal illness. Some external causes include germs, food, pesticides, environmental pollutants, and tobacco; some internal factors include hormones, immunological disorders, and inherited

genetic abnormalities. All of these things may contribute to cancer, either alone or in a chain reaction. Cancer often progresses through phases that are defined by the size of the tumor, the area of the main tumor, and the capacity of the tumor to spread to lymph nodes or other organs in the vicinity. Initiating treatment requires a diagnosis and staging. Radiation therapy, chemotherapy, and surgery are the mainstays of traditional cancer treatment.

Malignant treatment is a multidisciplinary endeavor due to several variations between normal and malignant biology. It has been very difficult to develop tumor-specific targeted therapies that are both effective and safe. Some malignancies have not responded well to targeted treatment. In an effort to find a more comprehensive method of categorization, the cancer genome atlas (TCGA) was established. The researchers at the TCGA proposed a multiplatform study of 12 different cancer types to reveal how comparable cancers are based on molecular biology and genetics. Using cell origin instead of tissue location, our

approach reclassified around 10% of cancers. It is worth noting that the 12 different cancer types were united into 11 primary subtypes by TCGA's integrative study. Based on mutational data from 3281 tumors, eleven major cancer types were identified: LUAD, LUSC, BRCA, UCEC, GBM, HNSC, COAD, READ, BLCA, KIRC, OV, and AML. When it comes to global public health, cancer is among the top causes. Major obstacles persist in cancer treatment. New diagnostic and therapeutic approaches have been made possible by the enormous promise of NDDS in cancer treatment.

The specific method of medication delivery may significantly impact its efficacy. Some drugs have an optimal concentration range where they work best; going too high or too low might have negative side effects or fail to induce the desired therapeutic effect. Two primary requirements should be met by advanced drug delivery carriers. First, shipping costs should be determined by the rate. Finally, it has to be tailored to each individual location. Traditional medicine does not conform to any of these requirements. NDDS are categorized into many groups. 1) A method for the controlled release of medication. 2) A method for the controlled release of drugs. The goal of developing a drug delivery system was to create a therapeutic impact that would take place at a later, more gradual time. A strong yet non-lethal steady-state blood level should be achieved as the primary goal of therapy for a long time.

Literature Review

Martin, Johnes & Taqa, Amer. (2016) [1]. The study aims to develop innovative drug delivery methods for targeted cancer treatment, enhancing the effectiveness of anticancer drugs while minimizing adverse effects. It uses nanotechnology-based techniques like liposomes, micelles, and nanoparticles to control drug release and improve tumor accumulation. Active targeting techniques, such as ligands or antibodies, minimize off-target effects. Stimuli-responsive medication delivery devices and nanocarriers are also explored. The study also explores the use of advanced imaging modalities for real-time therapeutic response and drug distribution tracking. The research also explores the potential of combining multiple treatment drugs through a single delivery method.

Moghtaderi, Maryam. (2022) [2]. Nanotechnology has revolutionized medicine by providing unique therapeutic tools for disease diagnosis and treatment. Customized medicine aims to minimize treatment-related negative effects while maintaining medication efficacy. Niosome vesicles, polymeric nanoparticles, have desirable properties for targeted drug delivery, including excellent absorption and biocompatibility. This review examines features of niosome vesicles, in-silico tools for design, prediction, and optimization, and their size and formation. The study also explores the use of niosome-delivered anticancer medicines and their potential for developing treatment plans.

Dai, Liangliang & Liu. (2016) [3]. This review explores the potential of targeted drug delivery systems (TDDSs) as a treatment for tumors, focusing on both passive and active targeting mechanisms. It examines active targeting techniques for organelles and tumor cytomembranes, and highlights contemporary TDDSs being evaluated in clinical

and preclinical studies. These TDDSs have shown promising clinical promise as an alternative approach to tumor therapy. Further research is needed to achieve highly effective tumor treatment with acceptable biosafety.

Nankya, Winniefred & University VIII, Kampala International. (2024) [4]. This research aims to improve specificity and reduce toxicity in cancer treatment by investigating the function of nanoparticles in cancer medication delivery systems. Nanoparticles like polymeric nanoparticles, dendrimers, and liposomes are used to concentrate therapeutic medicines within tumors while reducing systemic exposure. Controlled release techniques and passive and active targeting mechanisms enhance medication effectiveness. The research highlights the revolutionary potential of nanomedicine, but also addresses issues like manufacturing scalability, biocompatibility, and ethical concerns. It examines current and prospective nanoparticle formulations for cancer therapy, focusing on the clinical and future implications of nanotechnology in oncology.

Kolte, Nikita & Shinde, Yogita. (2024) [5]. Drug carriers are essential for delivering drugs to specific tissues, organs, and cells, but issues like poor solubility, limited bioavailability, drug degradation, and adverse effects from conventional dose forms affect patient compliance. To improve medication effectiveness, there is a growing need for innovative delivery methods. Pharmaceutical research has seen technical innovation in the last decade, including microsponges, microneedles, microcapsules, nanoparticles, microchips, liposomes, and niosomes. Some methods cross physical barriers, like the blood-brain barrier, to maximize efficacy. The market for these innovative drug delivery systems is growing due to the desire for efficient pharmaceutical products.

Research Methodology

Cell Lines and Cultures

The American Type Culture Collection provided the breast cancer cell lines BT483, MDA-MB-231, MD1-MB-361, MCF-7, and SK-BR-3. 20 mM L-glutamine was added to the BT483 cells' growth media, which was DMEM (Invitrogen). DMEM/F12 (Invitrogen), Leibovitz's L-15 (Invitrogen), and McCoy's 5A (Sigma-Aldrich) were the media used for the cultivation of MDA-MB-231, MD1-MB-361, and SK-BR-3 cells, respectively. Cultivated in DMEM, the human normal nasal mucosal epithelial (NNM) cells originated from a nasal polyp [36]. The Mammary Epithelial Cell Medium was used to cultivate normal mammary epithelial cells (HMEpiC), which were procured from ScienCell Research Laboratories. In a humidified incubator with 5% CO₂ at 37°C, all cell lines were grown in a medium that included 10% fetal bovine serum (Invitrogen) and 100 µg/ml penicillin/streptomycin.

Phage Display Bio panning Procedures

The BT483 breast cancer cell line was cultured with an insertless phage that had been treated with ultraviolet light to render it inactive. The phage-displayed peptide library from New England BioLabs was subsequently supplemented with 5×10^4 plaque-forming units (pfu). A lysis solution containing 150 mM NaCl, 50 mM Tris-HCl, 1 mM EDTA, 1% NP-40, 0.5% sodium deoxycholate, 0.1%

SDS, and pH 7.4 was used to elute the bound phages after washing. The reaction was performed on ice. The phage pool that was eluted was cultured on an Escherichia coli ER2738 medium (New England BioLabs) and then titered. We proceeded with the next round of panning using the recovered phages, just as detailed before.

Identification of Phage Clones using Cellular Enzyme-linked Immunosorbent Assay (ELISA)

Cancer cells or human normal nasal mucosal epithelial (NNM) control cells were put into 96-well ELISA plates. The cell-coated plates were treated with a horseradish peroxidase (HRP)-conjugated mouse anti-M13 monoclonal antibody from GE Healthcare, and then incubated with the peroxidase substrate o-phenylenediamine dihydrochloride from Sigma-Aldrich. After that, individual phage particles were introduced to the plates. After stopping the reaction, an ELISA reader was used to detect absorbance at 490 nm.

Sequencing of Recovered Phages

Next, the phage clones that passed the first screening were sequenced using the 5'-CCCTCATAGTTAGCGTAACG-3' primer that matches the pIII gene sequence. A peptide sequence known as QNIYAGVPMISF, EATNSHGSRTMG, TVSWSTTGRIPL, QLEFYTQLAHLI, and SMDPFLFQLQL were presented, respectively, by phage clones PC34, PC65, PC73, and PC90, which exhibited greater BT483-binding activities. The GenBank entry codes for the peptide sequences of PC34, PC65, PC73, PC82, and PC90 are KC802225, KC802226, KC802227, KC802228, and KC802229, in that order.

Flow Cytometry Analysis

Collecting the breast cancer cell lines or control cells was done using PBS that included 10 mM EDTA. Following that, the cells were treated at 4 °C for 1 hour with 1×10¹⁰ pfu/mL PC90 phages or insert-less control phages. Incubation of the phage-bound cells with anti-M13 mAbs (GE Healthcare) at 4 °C for 1 hour followed by treatment with PE-conjugated goat anti-mouse IgG antibody at 4°C for 30 minutes followed by washing. After cell washing, the data were collected using a flow cytometer (Becton Dickinson).

Peptide Synthesis

Academia Sinica used reverse-phase high-performance liquid chromatography to achieve a 95% purity level in the synthesis and purification of the synthetic targeting peptide SP90 (SMDPFLFQLQL) and control peptide (MP5-2, TDSILRSYDGGG).

In vivo Homing Experiments and Tissue Distribution of Phages

1 × 10¹ BT483 cells were administered subcutaneously to the dorsolateral flank of SCID mice. Intravenously administered 109 pfu of either the targeted phage or control phage was given to animals that had breast cancer xenografts of a similar size (around 300 mm³). Once the phage had circulated for eight minutes, the mice were killed and 50 ml of PBS was administered to remove any unbound phage. After that, the xenograft tumors and the organs from

the mice were taken apart and mixed together. Placing ER2738 bacteria on IPTG/X-Gal agar plates allowed for the recovery of the phages attached to the various tissue samples. The phages were injected with 100 µg of synthesized targeting peptide in the studies of peptide competitive inhibition. Using Bouin's solution (Sigma-Aldrich), the organs and tumor masses were fixed. Following fixation, the specimens were set in paraffin blocks. Following deparaffinization and rehydration, the paraffin slices were immunostained with the mouse anti-M13 mAb.

Immunohistochemistry Staining for Human Surgical Specimens

A study at National Taiwan University Hospital (NTUH) involved 20 cases of infiltrating breast ductal carcinoma. The tissue was incubated with PC90 or control phages to determine the binding site. The phages were combined with control peptides or synthetic SP90 for a peptide competitive inhibition experiment. Anti-M13 mouse mAb was applied to sections for 1 hour, and immunoreactivity was detected using a Biogenex biotin-free highly sensitive polymer-HRP detection system. The slides were mounted with Aquatex, counterstained with hematoxylin, and viewed under a light microscope. A medical pathologist from NTUH measured the proportion of cells that stained positively and assessed the section's labeling index (LI).

Preparation of SP90-conjugated Liposomal Nanoparticles

The doxorubicin (Sigma-Aldrich) or sulforhodamine B-DSPE (Avanti) was encapsulated or added to PEGylated liposomes made of distearoylphosphatidylcholine, cholesterol, and PEG-DSPE using a lipid film hydration process. Following their manufacture, the liposomes exhibited a particle size between 65 and 75 nm in diameter and contained 110 to 130 µg doxorubicin for every µmol phospholipid. Then, pre-formed liposomes were co-incubated with SP90-PEG-DSPE for 1 hour with moderate shaking at 60°C, which is the transition temperature of the lipid bilayer. Approximately 500 peptide molecules were visible on the surface of each liposome after incubation. The liberated free drug, unconjugated peptides, and unincorporated conjugates were removed using Sepharose 4B gel filtration chromatography, manufactured by GE Healthcare. The concentrations of doxorubicin in the eluent fractions were found by using a spectrofluorometer (Spectra Max M5, Molecular Devices) to measure fluorescence at λEx/Em=485/590 nm.

Results and Analysis

Identification of Novel Peptides that Bind to Breast Cancer Cells

Here, we isolated phages capable of binding to BT483 breast cancer cells by using a phage-displayed random peptide library. The bound phage titer grew by as much as 60-fold after four rounds of affinity selection, also known as biopanning (Fig. 1a). Five phage clones (PC34, PC65, PC73, PC82, and PC90) were found to have distinct peptide sequences that bind to BT483, but not to control normal nasal mucosal (NNM) epithelial cells, according to ELISA screening and DNA sequencing (Fig. 1b). The

QNIYAGVPMISF, EATNSHGSRTMG,
TVSWSTTGRIPL, QLEFYTQLAHLI, and
SMDPFLFQLQL peptide sequences were shown,

respectively, by phage clones PC34, PC65, PC73, PC82, and PC90, which had increased BT483-binding activities.

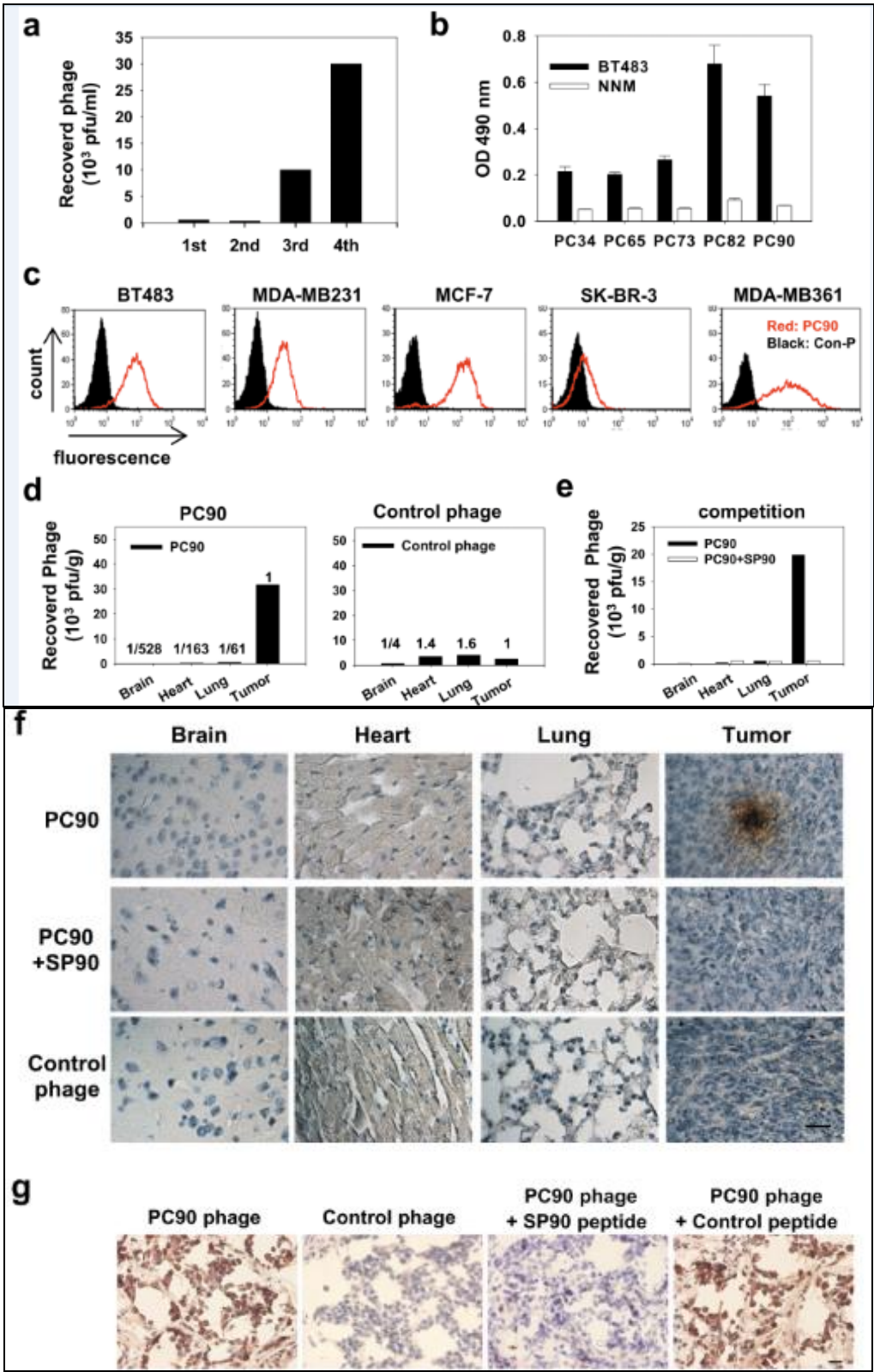


Fig 1: Identification of breast cancer cell-targeting peptides using *in vitro* phage display.

The study investigated the surface binding activity of five phage clones to determine their potential effectiveness against breast cancer cells. PC90 showed the highest level of reactivity when bound to BT483 cells, and did not attach

to HMEpiC or normal human mammary epithelial cells. The binding capacity of PC90 to five breast cancer cell lines was analyzed using flow cytometry, showing minor changes in SK-BR-3 cells' fluorescence and significant positive shifts

in BT483, MDA-MB-231, MCF-7, and MDA-MB-361. In vivo, mouse carrying BT483-derived tumor xenografts were injected with each phage clone, revealing tumor-homing capacity. The most effective PC90 was found in tumor masses at concentrations 61 times greater than in the control

organs and targeted tumors most effectively. PC90's specificity to human breast cancer surgical samples was determined through PC90 immunohistochemical staining on breast infiltrating ductal carcinoma tissue sections.

Table 1: Detection of human breast cancer surgical specimens by PC90 phages using immunohistochemistry

(a)					
	Labeling Index	3+	2+	1+	N
	Cases	12	5	1	2
(b)					
	Diagnosis	Tumor size	Tumor grading	Nodal involvement	PC90 immunoreactivity
1	Infiltrating ductal carcinoma	pT3, 5.5 x 4.5 x 3.5 cm	Grade III, Nottingham Score: 3+2+3 points	25/32	3+
2	Infiltrating ductal carcinoma	pT2, 2.5 x 2.3 x 2.0 cm.	Grade I, Nottingham Score: 3+1+1 points	1/9	3+
3	Infiltrating ductal carcinoma	pT2, 4 x 3 x 2 cm	Grade II, Nottingham Score: 3+3+1 points	9/21	3+
4	Infiltrating ductal carcinoma	pT2, 3 x 2.5 x 2.5 cm.	Grade III, Nottingham Score: 3+3+3 points	0/43	3+
5	Infiltrating ductal carcinoma	pT1c, 2.6 x 2.1 x 1.9 cm.	Grade II, Nottingham Score: 2+2+2 points	1/24	3+
6	Infiltrating ductal carcinoma	pT4b, 5.9 x 4.9 x 3.8 cm	Grade II, Nottingham Score: 3+2+1 points	7/21	3+
7	Infiltrating ductal carcinoma	pT1c, 2 x1.7 x 1.5 cm	Grade II, Nottingham Score:: 2+3+1 points	0/25	3+
8	Infiltrating ductal carcinoma	pT2, 3 x 2.5 x 2 cm.	Grade II, Nottingham Score: 3+2+1 points	5/29	3+
9	Infiltrating ductal carcinoma	pT3, 8 x 4 x 2.5 cm	Grade II, Nottingham Score: 3+2+1 points	23/25	2+
10	Infiltrating ductal carcinoma	pT3, 5 x 3 x 3 cm	Grade II, Nottingham Score: 3+2+1 points	8/30	2+
11	Infiltrating ductal carcinoma	pT3, 5 x 4.5 x 2 cm	Grade II, Nottingham Score: 3+2+2 points	7/22	N
12	Infiltrating ductal carcinoma	pT2, 2 x 1.8 x 1.5 cm	Grade III, Nottingham Score: 3+3+2 points	0/12	3+
13	Infiltrating ductal carcinoma	pT2, 3.2 x 2.5 x 2 cm	Grade II, Nottingham Score: 3+2+1 points	5/29	2+
14	Infiltrating ductal carcinoma	pT2, 4.2 x 3.4 x 1 cm	Grade I, Nottingham Score: 1+2+1 points	10/25	3+
15	Infiltrating ductal carcinoma	pT2, 2.8 x 2.5 x 2.5 cm	Grade III, Nottingham Score: 3+3+3 points	0/43	3+
16	Infiltrating ductal carcinoma	pT3 7.5 x 5.3 x 2.2 cm	Grade I, Nottingham Score: 1+1+1 points	5/15	2+
17	Infiltrating ductal carcinoma	pT3, 5 x 3 x 2 cm	Grade III, Nottingham Score: 3+3+2 points	0/1	N
18	Infiltrating ductal carcinoma	pT2, 2.5 x 2.2 x 0.8 cm	Grade II, Nottingham Score: 3+2+2 points	3/9	1+
19	Infiltrating ductal carcinoma	pT2, 2.1x 2 x 1.9 cm	Grade II, Nottingham Score: 3+2+1 points	Cannot be assessed	3+
20	Infiltrating ductal carcinoma	pT2, 2.2 x 1.8 x 1.8 cm	Grade II, Nottingham Score: 2+3+1 points	1/28	2+

P90-conjugated Liposomes Exhibit Enhanced Drug Intracellular Delivery and Cytotoxicity

The study aimed to investigate the potential of conjugating SP90 to NHS-PEG-DSPE to improve liposomal medication delivery to human breast cancer cells. The researchers attached liposomal nanoparticles to the PEGylated SP90 conjugates, which contained either doxorubicin or sulforhodamine B. Tricine-SDS-PAGE and MALDI-TOF MS were used to confirm the PEGylation effectiveness of SP90. The internalization ability of the targeting ligand is crucial for successful tumor-targeted liposomal drug delivery. The study found that SP90-conjugated liposomal SRB (SP90-LD) effectively internalized SRB in tumor cells, enhancing intracellular SRB uptake by cancer cells. To verify internalization of SP90-conjugated liposomes through receptor-mediated endocytosis, transmission electron microscopy (TEM) was used to analyze the endosomes of tumor cells treated with either SP90-conjugated liposomal doxorubicin (SP90-LD) or control peptide-conjugated liposomal doxorubicin (CP-LD) at 37°C for 5 minutes. As shown in Figure 2a the results showed that SP90-LD accumulated in the endosomes of cancer cells to a much greater extent than CP-LD, with endocytosed liposomes observed in 90% of cells treated with SP90-LD, but only in 51% (Fig. 2b) of cells treated with CP-LD. (Fig. 2c).

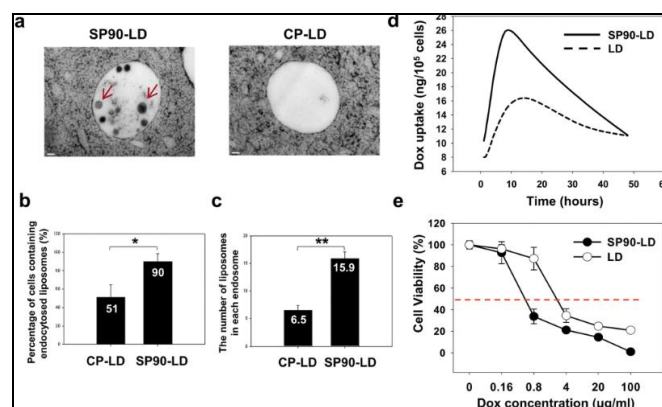


Fig 2: SP90-conjugated liposomes enhanced drug delivery and cytotoxicity towards cancer cells, through increased endocytosis

The small-molecule chemotherapeutic drug doxorubicin has a long and storied history of use in breast cancer therapy. We administered BT483 cells the same doses of LD or SP90-LD to find out whether SP90-conjugated liposomes may improve doxorubicin delivery. Quantitative measurements of doxorubicin uptake were made using fluorescence intensities recorded at several time periods (Fig. 2d). Treatment of BT483 cells with SP90-LD increased their cellular absorption of doxorubicin. Between

LD and SP90-LD, the AUC₀₋₄₈ hour in breast cancer cells was 2.36 times higher. We conducted *in vitro* cytotoxicity experiments for SP90-LD in BT483 cells to see whether SP90-conjugation enhanced the therapeutic potential of LD. Figure 2e shows that SP90-LD led to a 4.9-fold reduction in the half maximum inhibitory concentration (IC₅₀) in BT483 cells and a remarkably lower viability of cancer cells when compared with LD. A dose-dependent competitive reduction of SP90-LD's enhanced cytotoxic impact was seen when it was co-treated with free SP90 peptides (Fig. 2a). Treatment with SP90 peptides alone had no effect on the cell survival of BT483 cells (Fig. 2b).

SP90-conjugated Liposomes Improved Drug Delivery *in vivo*

By injecting SCID mice harboring BT483 xenografts with FD, LD, control peptide-conjugated LD (CP-LD), or SP90-LD, we investigated drug accumulation in tumor tissues and the processes leading to the improved inhibitory effects of SP90-conjugated liposomal medicines. Figure 3a shows that compared to the FD, LD, and CP-LD groups, the SP90-LD group had a mean intra-tumor doxorubicin concentration that was 12.0, 2.2, and 2.6 times greater, respectively. We ran the same experiment again excluding PBS perfusion since it's conceivable that heavy perfusion removed LD from the tumor tissues. When compared to FD (9.4-fold) and non-conjugated LD (1.5-fold), SP90-LD accumulation in tumors remained much greater. Using fluorescence microscopy, we analyzed the intracellular absorption of doxorubicin in tumor tissues to assess the drug delivery profile of the three doxorubicin formulations. Fig. 3b shows that in tumors treated with SP90-LD, regions containing detectable doxorubicin were greater in the nucleus compared to tumors treated with LD. In contrast, tumors treated with FD did not contain any detectable doxorubicin. Based on the results of these investigations, it can be concluded that SP90 may improve the tumor-target drug delivery and penetration, leading to drug accumulation at the intracellular target site and an enhanced therapeutic impact.

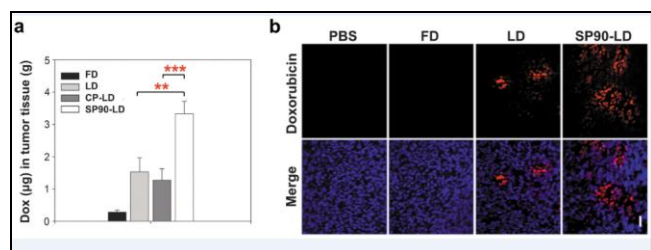


Fig 3: SP90-conjugated liposomes enhanced drug delivery to tumor.

Conclusion

Finally, we found many new peptides, SP90 included, that could attach to the surface of breast cancer cells in both laboratory and living organism settings. By increasing tumor apoptosis and decreasing tumor angiogenesis, the treatment effectiveness was boosted in mice with human breast cancer xenografts when SP90 was linked to liposomes carrying doxorubicin. The imaging and quantification of doxorubicin levels also showed that the drug concentrations in the tumor tissues that the liposome

targeted were higher, demonstrating that the medication was better delivered and penetrated into the tumor. Our findings pave the way for the potential use of the SP90 peptide in breast cancer diagnostics and therapy via the ability to target tumor cells specifically.

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