

REVIEW OF ALBUMIN AS A CARRIER IN NANODRUG DELIVERY

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ABSTRACT

Albumin is an interesting carrier in the nanomedicine field due to its unique properties. First, it is the most abundant protein in plasma and has high biodegradability, biocompatibility, non-immunogenicity and safety in clinical use. Second, the chemical structure and conformation of albumin allow it to interact with a wide range of different drugs, potentially protecting them from elimination and metabolism in the body and thus increasing their efficacy. Pharmacokinetics. Finally, albumin can interact with receptors overexpressed in tissues and cells and provide specific functions for activation of disease sites without the need for the addition of specific ligands for the nano- carriers. This article highlights the power of endogenous proteins such as albumin as drug carriers, highlights the importance of drug carriers in biological processes and suggests possible future developments in the use of this drug.

I. INTRODUCTION

Nanotechnology shows great potential in medicine, especially in drug delivery. Drugs that are poorly soluble in body fluids target cells and intracellular targets such as proteins and gene therapy. ^{3,4} In fact, in some cases, nanoparticles with various chemical structures, including lipids, polymers and inorganic nanocarriers, have been shown to be effective in controlling the bio distribution of one or more released substances. There are many drugs that can be used to treat and overcome biological problems in order to deliver targeted drugs to the infected area. However, nanocarriers, depending on their structure, have shortcomings that limit their effective drug delivery, such as non-specific drug uptake by phagocytes, dispersion of the target, lack of immune system and inadequate control of drugs.

Hydrophobic vs. Hydrophilic Drugs have relatively long half-lives, have specific targets for the inflammation site and appear to have minimal toxicity and immunogenicity.

Because it plays a role in maintaining intravascular colloid osmotic pressure, neutralizing toxins and transporting doctors. In addition to the binding affinity of various drugs to albumin, the possibility of binding drugs to albumin nanoparticles has been investigated for many organizations. In addition, the surface of albumin-based nanoparticles can be functionalized with ligands due to the presence of functional groups that can bind different types of linkages or spacers. This substance, recognized by the gp60 receptor and the secreted protein, acidic and cysteine-rich (SPARC) pathway, can provide active targets without the need for other ligands. Albumin nanoparticles have been the subject of many positive reviews to date.

II. CHARACTERISTICS OF ALBUMIN FROM DIFFERENT SPECIES

Albumin is the most abundant protein in plasma, accounting for 60% of all proteins in the blood. It is a highly water-soluble, small globular protein with a molecular weight of 67 kDa and an average half-life of 19 days. Heating for 10 hours. It can be obtained from a variety of sources, including human blood (human serum albumin, HAS) bovine serum (bovine serum albumin, BSA), rat serum (rat serum albumin, RSA).) and albumin (ovalbumin, OVA), but the two most commonly used for drug delivery are HSA10 and BSA. The main function of this protein is to control the osmotic pressure in the blood. As the main function of hydrophobic molecules such as fatty acids and hormones, makes it the best candidate for drug delivery. Lipophilicity is one of the limitations of its applications. Therefore, it is important to find a non-toxic, widely available and portable material that can improve the separation and transport of drugs. Each domain consists of two subdomains containing 4 and 6 α -helices, respectively. The most important human serum albumin binding sites for hydrophobic compounds (especially neutral and negatively charged hydrophobic compounds) are Sudlow domain I and Sudlow domain II, 12 very long hydrophobic pockets with highly valuable lysine and arginine residues in domains IIA and IIIA, respectively. It is called the warfarin site because drugs such as azacetone, phenylbutazone, and warfarin Human bind here. Site II is also known as the benzodiazepine site because compounds such as diazepam,

ibuprofen, and tryptophan bind here. Thanks to this, various drugs such as paclitaxel and docetaxel can be combined and delivered to the tumor site.

1. Human serum Albumin

Human serum albumin has a chain of 585 amino acids. Its secondary structure is flexible and is characterized by 67% α -helices and 17 6-turn disulfide bridges that serve as linkages to three homologous domains. . Although albumin is the most abundant plasma protein, most albumin is not in the blood.

Up to 60% of albumin is stored in the intercellular space. Although its biological half-life is 19 days, it lasts only 16-18 hours in the circulation. Constant plasma protein concentration. Its products are regulated according to the needs of the body. In particular, synthesis is stimulated by conditions such as insulin, thyroxine and cortisol or hypoalbuminemia, while synthesis is inhibited by potassium and the greater osmotic pressure of hepatocytes. In addition, the basis of albumin production is adequate nutrition. In fact, poor absorption can reduce the liver's ability to produce protein. Albumin degradation can occur in any tissue, but occurs most frequently in the liver and kidneys. The balance between albumin production, degradation, and movement in the bloodstream and central nervous system determines the effectiveness of plasma albumin concentration.

Albumin is responsible for maintaining blood osmotic pressure, supporting tissue fluidity, and transporting hormones, vitamins, drugs, and divalent cations (such as calcium and zinc) throughout the body medical treatment. In fact, hypoalbuminemia can lead to coagulopathy.

The first category includes all substances found in the body, such as bilirubin, fatty acids, cations, free radicals, vitamins, and hormones. The second category includes drugs that enter the body from the outside, such as antibiotics, anti-inflammatory drugs, antibacterial drugs, antiviral drugs, heart and kidney drugs, drugs that affect the central nervous system, and hypoglycemic drugs. Amino acid residues have a charge of ± 17 mV at body pH. Therefore, sodium ions and other cations are attracted to albumin. Sodium's preference for albumin draws water into the blood vessels (1 gram of albumin can hold 18 mL of water in the blood vessels). When conditions affect liver production, albumin levels can fall, protein breakdown can increase, protein loss from the kidneys can increase, and the volume of fluid in the blood (plasma) can increase, diluting the blood. Conditions that can alter albumin levels include severe liver disease and kidney disease. One of the kidney's primary functions is to control plasma proteins (such as albumin) and prevent them from being excreted in the urine as waste products. If the kidneys are damaged, such as with diabetes, high blood pressure, or nephrotic syndrome, they lose their ability to maintain plasma protein levels, and albumin levels fall.

2. Serum Albumin from other species

Bovine serum albumin is derived from bovine serum and is similar to HAS. It has a molecular weight of 69.323 kDa and an isoelectric point (pI) in water (25 $^{\circ}$ C) of 4.7, making it negatively charged at neutral pH and positively charged at acidic pH > 22. The presence of two amino acids, both negative and positive, in BSA can lead to the binding of positive and negative species. It is widely used as a carrier for drug delivery in materials due to its low cost and ease of cleaning and handling. It also has a high loading capacity and is water soluble, allowing it to bind both hydrophilic and hydrophobic substances, making it a versatile carrier. The only drawback would be the potential for immunogenicity in humans²³ and mice²⁴. Human serum albumin and BSA have 80% homology; A major difference is the number of tryptophan (Trp) residues. Human serum albumin has one Trp, while BSA has two. Tryptophan is responsible for the fluorescence of the protein and thus allows human serum albumin and bovine serum albumin to be distinguished by fluorescence spectrophotometry. Antibodies to BSA have been discovered in animal models and the protein has been used as a model protein to study immune responses to milk and meat as well as vaccines and drugs. In 2005, a quantitative radioimmunoassay was developed to measure anti-BSA IgG antibodies in healthy patients and cancer patients. Increased levels of BSA, but not anti-BSA antibodies, have not been associated with clinical events in healthy or cancer patients. In another study, three types of rabbits were injected with BSA. Some rabbits do not respond even to stimulation. This unresponsiveness may be genetic or related to the nature of the antigen. It has also been shown that the immunogenicity of BSA is related to its molecular state. The lack of immunogenicity of BSA in some rabbits may be due to its resemblance to rabbit serum albumin, which shares some structural similarities with BSA. Ovalbumin(OVA) is the main protein of egg white and constitutes 55% of

the total protein content. It belongs to the serpin family and is a globular acidic glycoprotein with a polypeptide chain of 386 amino acids with a molecular weight of 42-47 kDa. HAS and BSA are similar. However, OVA is often chosen as one of the most popular model antigens due to its immunogenicity. In addition, its isoelectric point is 5.7. When the amino acid composition of RSA and HAS is compared, it is clear that RSA contains more tyrosine and less lysine, cystine and leucine. The obtained albumin conjugates, which are used as protein carriers in many immunotherapies, have been tested in heterologous tumor models. Research or Considering the high homology of albumins from different species in terms of amino acid sequence, all serum albumins should have similar binding sites to HAS analysis. However, different opinions have been expressed in recent years. Panjehshahnin et al. 33, I and II, respectively. Conducted a comparative study on six animal serum albumins using warfarin and dansyl cosine as fluorescent markers for the sites and thus measured binding in multiple conditions. The results showed that all serum albumins, except RSA, had similar binding sites for HAS. In particular, the displacement of warfarin by phenylbutazone on mouse serum albumin is lower than all others, providing a binding site for warfarin on a different albumin structure. On the other hand, only a small difference was observed in binding site II. In another study, Schmidt and Janchen³⁴ reported differences in the ligand binding sites for other acidic compounds of RSA compared to HAS. Massolini et al.³⁵ evaluated the differences between HAS, RSA and rabbit serum albumin; they showed that the stereoselectivity of subprofen and ketoprofen was evaluated between HAS and rabbit serum albumin Combined but not in RSA. Also Aubrey et al. The binding properties of RSA and rabbit serum albumin for HAS showed some differences. The sites have many similarities. A few years later, Kosa et al.³⁷ showed that in order to allow the characterization of drug binding sites in animals and humans, the properties of the drug binding site and the binding site of the drug in previous studies should be specified in detail. Comparison of drug interactions between proteins. They tried to use drugs binding to canonical site I (warfarin and phenylbutazone) and drugs binding to canonical site II (ibuprofen and diazepam) through a strict competition.

Their studies showed that the binding site I drug for rabbit serum albumin, RSA and BSA were similar to HAS. However, the negative correlation for dog albumin was smaller than that for human albumin.

III. THE PROPERTIES OF ALBUMIN AS A NANOCARRIER IN DRUG TARGETING

Albumin's natural ability to target cancer and other pro-angiogenic sites. The well-known enhanced permeability and retention (EPR) effect in tumors, together with the high permeability of blood vessels and impaired lymphatic fluid, has been proposed as a mechanism responsible for passive targeting of more nanocarriers to the tissue (Fig. 2). However, the decisive role of the EPR effect, which is responsible for the negative activity of nanocarriers in tumors even in preclinical animal models, has recently been questioned. Since the amount extracted is very large, nanoparticles are transported to the tumor. Less to explain the accumulation of nanoparticles in tumors. Dilation increases vascular permeability, improves the EPR effect and temporarily eliminates the problem of drug deficiency in the tumor in the blood, which limits its use. For this purpose, Kinoshita et al. The combination of albumin-based drug delivery (nab-paclitaxel) and SNO-HAS dimer increased the efficacy and showed greater tumor growth inhibition than drug delivery systems alone (although in tumors with low vascular permeability). One of the unique properties that makes albumin such a powerful and effective drug is its ability to bind to receptors expressed by tumors. The main pathway by which albumin internalization in tumors relies is receptor-mediated endothelial transcytosis (Figure 2). Albumin binds with high affinity to the gp60 receptor, a 60 kDa glycoprotein (albondin). It binds to caveolin-1, an intracellular protein that causes the invagination of the cell membrane, resulting in the formation of transcytotic vesicles (caveolae) that transport albumin in the tumor. In addition, SPARC (secreted acidic cysteine-rich protein), also known as the anti-adhesin, osteonectin, BM-40, and 43K protein, is overexpressed in many tumor types but absent in normal cells. Tissues attract albumin and contribute to its accumulation in tumors. These two important mechanisms cause the protein to be actively folded by the tumor. Among the albumin receptors, in addition to gp60, there are also gp18 and gp30, which are cell surface glycoproteins with molecular weights of 18 and 30 kDa, respectively. Cell membrane and peritoneal macrophages. They are scavenger receptors with high affinity for damaged albumin.

Modification of albumin for active drug targets. In addition to the natural receptors with which albumin interacts, additional steps have been taken to improve the targeting ability of albumin by covalently targeting

the surfaces of albumin nanoparticles with specific targets or by not adding isocovalent modification. High specificity and low immunogenicity.

Stealth albumin nanoparticles. Attempts have been made to treat nanoparticles with antibacterial agents such as polyethylene oxide (PEO) or polyethylene glycol (PEG), which render the particles “invisible.” Drinking alcohol is one of the most effective and well-studied ways to improve the pharmacokinetics of drugs.

IV. PREPARATION METHODS OF ALBUMIN NANOPARTICLES

There are various production methods to produce albumin-based nanoparticles. These are divided into chemical-based methods, which use chemical additives such as ethanol, cottonseed oil or β -mercaptoethanol to form nanoparticles, and physical-based methods, which use physical factors such as heat or high pressure to form nanoparticles. Nanospray drying, thermal gelation and the NAB process, which will be discussed later, are all physical processes. Repeatability is an important feature to achieve, and all production processes should aim to produce nanoparticles with high yield and repeatability.

1. Desolvation (coacervation)

Desolvation is a widely used method to prepare albumin nanoparticles. This is done by adding a solvent such as ethanol or acetone to the albumin solution and continuously stirring the solution until it becomes cloudy. The gradual change in the tertiary structure of the albumin causes protein phase separation and aggregation. In effect, a homogeneous solution separates into two phases, one of which is mostly solvent and the other is dissolved albumin, forming submicron aggregates. Often the formulation is not sufficiently stable and requires the use of cross-linking agents such as glutaraldehyde to stabilize the morphology of the resulting nanoparticles and increase adhesion. The properties of the resulting formulation depend on process parameters such as pH, protein concentration, cross-linker concentration, desolvation level, ionic strength and stirring speed.

2. Emulsification

The emulsification process involves adding the non-aqueous solution (oil phase) to the albumin solution (aqueous phase) with stirring to form a rough emulsion. Homogenize using a pressure homogenizer. There are then two ways to stabilize the nanoparticles; heat (temperature $>120\text{ }^{\circ}\text{C}$) or chemical treatment using a binding agent (such as glutaraldehyde).

3. Self-assembly method

Self-assembly is based on the formation of albumin nanoparticles resulting from the use of primary amines to increase the hydrophobicity of the protein or the cleavage of disulfide bonds caused by the use of β -mercaptoethanol. The addition of lipophilic compounds forms the 66th group of the protein.

4. Thermal gelation

As can be seen from the 3D image, thermal gelation is characterized by protein modifications and unfolding, followed by protein-protein interactions such as the formation of electrostatic hydrogen bonds, hydrophobic interactions, and disulfide-sulfhydryl exchange reactions.

5. Nano spray drying

Nano spray drying is a versatile technique widely used to produce dry powders from liquid phases. One of the advantages of this method is that the product is dried in a continuous, single-step process. The process involves different steps such as atomization of the food into the spray, contact of the spray with air, spray drying and separation of the dry material from the dry air. Contact with dry air to ensure evaporation of moisture. This contact occurs in the drying chamber containing the aqueous albumin. As the water evaporates, dry particles are formed and collected by the electrostatic particle collector. Optimizing nano spray drying parameters allows the properties of nanoparticles to be tuned to suit specific applications.

technique	advantages	disadvantages
desolvation	robustness, reproducibility, absence of toxic organic solvents, simplicity, possibility to obtain smaller size nanoparticles	use of toxic cross-linkers, demand for strict purification steps and removal of unreacted cross-linker, not appropriate for highly water-soluble drugs
emulsification	higher drug entrapment efficiency	use of toxic chlorinated solvents, use of toxic cross-linkers or thermal stabilization, demand for removal of both the surfactants and oily residues, harmful to heat-sensitive drugs (if thermal stabilization is used), high energy requirement in homogenization, larger size nanoparticles, difficulty of controlling the albumin particles' size
self-assembly	high loading of poorly water-soluble drugs	use of only lipophilic drugs, difficulties in scaling-up the technology, insufficient storage stability, different solubility protocols for different drugs
thermal gelation	possible fabrication of nanoscale hydrogels	encapsulation only of drugs that are not heat sensitive
nanospray drying	single-step continuous and scalable process, versatile technique, useful for heat-sensitive samples, control for particle size	production of larger particles
microfluidic mixing	tunable size, structure, and surface, narrow size distribution, controlled release profile, high versatility and reproducibility, smaller size nanoparticle, low reagent consumption, better mixing, better drug loading capability	risk of fouling and channel clogging, complex device design, not fully automated, labor-intensive, sometimes requiring special equipment, such as cleanroom facilities
NAB-technology	ideal for encapsulating lipophilic drugs, safe and suitable for intravenous usage of poorly soluble drugs, no requirements for surfactants or polymeric materials for preparation, disulfide formation induced by homogenization does not substantially denature HAS, higher drug content, smaller size	demand for high pressure, use of hydrophobic drugs only

V. DRUG INCORPORATION IN ALBUMIN NANOCARRIERS

Albumin can bind drugs in two main ways: through covalent binding or non-covalent interactions. Reversible, non-covalent binding of drugs to albumin is based primarily on electrostatic/hydrophobic interactions. This type of interaction is often preferred because it allows for faster delivery and release of the drug at the time and place where it is needed. However, some studies have also provided evidence for albumin's ability to engage in covalent interactions. A single helical albumin binding site with nanomolar affinity showed a 32-fold increase in plasma elimination half-life in rats. IL-1ra (an interleukin 1 receptor antagonist) has a plasma elimination half-life of 2 minutes and 4.3 hours after binding to the albumin binding molecule. The half-life of IFN- α 2 (Interferon α -2) when placed in the bloodstream is 1.2 hours and its residence time in the blood when transported with albumin is 22.6 hours. In addition, the reversible non-covalent interaction with albumin can ensure rapid separation of biotherapeutics, facilitating their interaction with target sites and allowing their release to penetrate and expand more rapidly into areas that do not allow the entry of larger molecules.

VI. NANOPARTICLE ALBUMIN-BOUND (NAB) TECHNOLOGY

The NAB method is one of the most used and popular types of association with albumin. It is a modification of the previously described cosmetic product. NAB-Technology is a nanotechnology-based drug delivery system that uses the valuable properties of albumin to achieve selectivity and efficacy of hydrophobic drugs without the use of toxic solvents. To solve the problems arising from the traditional formulation of this drug. Paclitaxel (Paclitaxel 78 based on polyoxyethylene alcohol) and Taxotere (docetaxel based on polysorbate 80-ethanol) have been shown to be toxic, including neuropathy and allergic reactions, partly due to the use of milk Cremophor and ethanol, the former and the latter formula is polysorbate 80 and ethanol.

• Nab-paclitaxel (Abraxane)

Paclitaxel is an antibiotic belonging to the taxane family and a microtubule stabilizer. They bind to β -tubulin chains and increase polymerization, inhibiting mitosis, motility and intracellular dynamics, causing cell death (apoptosis). The simple formula of paclitaxel is C₄₇H₅₁N₀O₁₄ and its molecular weight is 853.91 g/mol. Nab-Paclitaxel (Abraxane for Injectable Suspension, ABI-007 manufactured by Abraxis bioscience) is a formula containing paclitaxel-loaded albumin-based nanoparticles obtained from NAB Technology.

VII. CROSS LINKING OF ALBUMIN BASED NANOPARTICLES

In general, albumin-based nanoparticles are prepared by coagulation, emulsification, or thermal gelation methods, followed by cross-linking of the particle with aldehyde-containing reagents (e.g., glutaraldehyde) to stabilize and cap the degradation rate and hydration capacity of the resulting nanoparticles. Abraxane is an albumin-bound paclitaxel formulation approved for the treatment of various cancers. However, comparison of conjugated and unconjugated albumin-bound paclitaxel nanoparticles is important to determine which nanoparticles are more effective. To address this issue, Li et al. 102 compared the in vitro stability,

pharmacokinetics, biodistribution, and efficacy of both unconjugated and conjugated paclitaxel-loaded albumin nanoparticle formulations. The linkages had no effect on the distribution size. Both formulations have a mean particle size of approximately 130 nm, a narrow size distribution, and a polydispersity Index (PDI) <0.1. Overall, more drug was found in the tumor compared to non-crosslinked nanoparticles, while less drug was found in other organs.

VIII. ALBUMIN-BASED FORMULATIONS FOR THE DELIVERY OF OTHER THERAPEUTIC AGENTS

• **Docetaxel**

Docetaxel is an FDA-approved antibiotic derived from the taxanes that promotes microtubule stabilization, resulting in cell cycle arrest and death. It can be used as monotherapy or in combination with other chemotherapy drugs to treat non-small cell lung cancer, gastric cancer, breast cancer, breast cancer, and ovarian cancer.

• **Doxorubicin**

Doxorubicin¹⁹ is an anthracycline antibiotic with antibacterial properties that is widely used in the treatment of breast cancer, as well as soft tissue sarcoma, colon cancer, and osteosarcoma. Doxorubicin has two main mechanisms of action in cancer cells. First, it enters DNA and affects topoisomerase II-mediated DNA repair; Second, it produces free radicals that damage cell membranes.

• **Other therapeutic agents**

Due to the versatility of the carrier and its conjugation with many different drugs, many albumin-based nanoparticles have been developed. Cabazitaxel (Cbz) is a chemotherapy drug for the treatment of taxanereliant metastatic castration-resistant prostate cancer (mCRPC). Polymerization of tubulin causes cell death. It exhibits better antiinflammatory activity against cancer cells than docetaxel and has better anti-inflammatory properties in vivo. The formula of retinoic acid (ATRA), a derivative of retinoic acid called tretinoin, was studied by Li et al. ATRA is a potent drug involved in many signaling pathways for stem cell maintenance. It activates retinoic acid receptors, regulates gene transcription, and induces stem cell differentiation.

IX. ALBUMIN-BASED DRUG FORMULATIONS CURRENTLY IN CLINICAL TRIALS

Several albumin-based anticancer agents are currently in clinical trials and are being tested against various types of cancer. Albumin-based anticancer therapies can be divided into micro- or nano-albumin-based particles, albumin-drug covalent conjugates, and gene fusions.

FORMULATION	COMPOUND	CLINICAL STATUS
Abraxane(ABI-007)	Paclitaxel	FDA-approved (phase 4)
ABI-008(Nabdocetaxel)	Docetaxel	Phase 1/2
INNO-206	Aldoxorubicin	Phase 3
MTX-HSA	Methotrexate	Phase 2
ABI-009 (Nab-rapamycin)	Rapamycin	Phase 1/2

X. PROTEIN CORONA

Albumin, in addition to being important in assembling nanoparticles and acting as a matrix, can also alter the delivery and targeting of other drug delivery systems by forming coronas on the surface of nanoparticles. Nanoparticles in the biological environment are adsorbed by proteins on their surface, forming a “protein corona”. This shell or halo will inevitably cover the original nanoparticle and make the biological surface visible. This phenomenon is characterized by the initiation of more proteins (soft corona) and interaction with proteins that bind to the substance with greater affinity (hard corona).

Important factors to consider include concentration, composition of adsorbed protein, and type of interaction with the nanoparticle surface. Uncontrolled plasma protein adsorption is a major factor in the rapid elimination and toxicity of nanoparticles. Therefore, scientists thought of using good proteins to interact with nanoparticles and form a pure protein corona first.

XI. FUTURE PERSPECTIVES

Up to now, the great potential of albumin has been widely demonstrated in various medical and therapeutic studies. Although gp60 and SPARC are thought to be responsible for the internalization of albumin in tumors and soft tissues, many studies have investigated gp30 and gp18 and their cooperation to interact with albumin nanocarriers. It will also be important to confirm that the binding of ligands to albumin affects its function. Preparation and action process of albumin

XII. CONCLUSION

The nanomedicine business has become very attractive because it offers effective and smart solutions for the treatment of cancer, inflammatory diseases and other diseases. In the past few years, the great potential of albumin as a drug carrier has attracted the attention of many researchers due to its biocompatibility, biodegradability, non-immunogenicity and nontoxicity. It is not a foreign substance; it is not stopped by the immune system as it is the most abundant protein in plasma, which makes it more beautiful. Its high affinity for hydrophobic substances, the possibility of surface modification and high loading capacity allow us to overcome the difficult problems arising from the properties of various compounds in today's market. It is a versatile drug that can be used not only for the delivery of medical drugs but also for imaging and gene therapy. In addition, the association with specific receptors of endothelial cells and other cells in diseased tissue allows albumin formulations to be recognized from the target to an important target and specific. This is the most important and unique feature that makes albumin different and unique from other nanocarriers. This feature may inspire the use of albumin as a preformed carrier for various nanodelivery systems. Since many albumin-based formulations are currently in clinical trials and the currently approved Abraxane formulation has shown excellent results in cancer patients, albumin nanoformulations are safe and have a good potential for the formulation of various drugs. Existing and emerging drugs.

XIII. REFERENCES

- [1] Liu, D.; Zhang, H.; Fontana, F.; et al. Microfluidic-assisted Fabrication of carriers for controlled drug delivery. *Lab Chip* 2017, 17 (11).
- [2] Dinarvand, R.; Taheri; Rabbani; Khorramizadeh; Taheri Borougeni, A; Mansoori; Atyabi, F.; et al. Use of biotin targeted Methotrexate-human serum albumin conjugated nanoparticles to Enhance methotrexate antitumor efficacy. *Int. J. Nanomed.* 2011, 6.
- [3] Wiedenmann, N.; Valdecanas, D.; Hunter, N.; et al. 130-nm Albumin-bound paclitaxel enhances tumor radiocurability and Therapeutic gain. *Clin. Cancer Res.* 20