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REVIEW

Albumin-based nanocarriers: Singularities, synthesis methods, clinical relevance and targeting strategies in cancer

Edgar Pérez-Herrero[a,*], Alberto Fernández-Medarde[b], Juan M. Irache[c,*]

[a]*ENCAPBIO-ULL Research Group, Departamento de Ingeniería Química y Tecnología Farmacéutica, Universidad de La Laguna, San Cristóbal de La Laguna 38206, Spain*
[b]*Centro de Investigación del Cáncer-Instituto de Biología Molecular y Celular del Cáncer (CSIC-Universidad de Salamanca) y CIBERONC, Salamanca 37007, Spain*
[c]*NANO-VAC Research Group, Departamento de Ciencias Farmacéuticas, Universidad de Navarra, Pamplona 31008, Spain*

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Abstract Proteins have emerged as highly promising biomaterials for the design of drug-loaded nanocarriers due to their biocompatibility, biodegradability and reduced immunogenicity. Among them, albumin stands out as the most widely used due to its unique physicochemical and biological properties, high affinity to important cell surface receptors, structural stability, long circulation time and intrinsic binding capacities. This review provides an overview of the advantages and limitations of the main proteins that have been proposed as biomaterials for nanoparticle fabrication, with a specific focus on albumin-based systems. It explores the physicochemical characteristics of these nanosystems, receptor binding affinity and functionalization strategies for both passive and active tumor targeting. The main synthesis methods and functionalization strategies are discussed, highlighting their relevance in cancer therapy. Their clinical relevance is stressed by the US Food and Drug Administration (FDA)-approved formulations and the additional albumin-bound drugs in ongoing trials. Despite promising preclinical data and numerous active targeting approaches reported, clinical translation remains limited. This review provides the necessary information to develop improved strategies and cover the gap between preclinical research and clinical application and outlines future perspectives for enhancing the therapeutic efficacy and specificity of albumin-based drug delivery nanosystems in oncology.

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*Corresponding authors.
E-mail addresses: eperezhe@ull.edu.es (Edgar Pérez-Herrero), jmirache@unav.es (Juan M. Irache).
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1. Introduction

Proteins can be considered one of the best biomaterials for the synthesis of drug carriers for biomedical applications due to their outstanding biocompatibility, absence of toxicity, reduced immunogenicity and extraordinary biodegradability, being degraded *in vivo* by proteolytic enzymes into innocuous bioproducts. The primary structure of proteins and their amphiphilic nature provides the nanocarriers unique binding characteristics that facilitate their surface modification for active targeting, but also enable their interaction with multiple drugs, providing high encapsulation capabilities[1−3]. Furthermore, it should be noted that when proteins are part of delivery systems, their limitations can be overcome, increasing their circulation time, stability and cellular uptake[4]. These bioinspired carriers are usually fabricated using naturally occurring proteins from animals and plants, which are abundant and renewable but are usually designed as heterogeneous mixtures with very different molecular weights, generating in most cases batch-to-batch variability. To solve this problem, some authors are reporting the use of recombinant proteins or chemically synthesized proteins or polypeptides[5−8]. Nevertheless, in this review, we describe the key properties of the main natural proteins obtained from plants (zein and gliadin) or animals (gelatin, collagen, elastin and milk-derived), which make them appropriate raw materials for carrier manufacturing (an extensive description of these is included as Supporting Information), making a comparative discussion of these with albumin, on which this article is focused due to its unique properties. In fact, although multiple examples of carriers made with many proteins obtained from biological sources can be found in the literature, translation to the clinic has only been achieved with those based on albumin from human serum. In this manuscript, we have included the current status of their clinical development (US Food and Drug Administration (FDA) or FDA-approved formulations and ongoing clinical trials), which is still limited. There is no doubt that the gap between preclinical research and clinical practice can be filled in the near future by improving the current synthesis methodology and redefining the targeting strategies. Thus, in this article the main conventional methods of synthesis have been detailed, along with the novel approaches that preclude harsh conditions, as well as the main passive and active targeting approaches related to their application in cancer.

2. Naturally occurring proteins as base biomaterials for drug delivery systems

Among the most promising animal- and plant-derived proteins for the development of NPs for drug delivery applications are prolamins, albumins, collagen and gelatin, casein, silk fibroin, elastin-like polypeptides (ELPs) and ferritin. Their affinity for hydrophilic or lipophilic compounds generally depends on their nature, with the proteins of a hydrophilic nature (*e.g.*, albumins, collagen, gelatin or casein) having a more limited capacity to encapsulate lipophilic compounds. However, this capacity can be increased using alternative techniques, such as protein modification by forming conjugates with cholesterol or other lipophilic compounds, drug encapsulation *via* complexes with cyclodextrins or co-encapsulation/adsorption of certain excipients (polyethylene glycol or PEG, glycerol, etc.).

2.1. Plant-based proteins

Prolamins (particularly gliadin and zein) are plant-based proteins characterized by a high content of proline and glutamine residues and a distinctly hydrophobic nature[9,10]. Their lipophilic properties contribute to a notable resistance to enzymatic degradation[11] and an excellent capacity for encapsulating lipophilic drugs[12,13]. **Zein**, derived from corn, is considered non-toxic and is classified as a GRAS (generally recognized as safe) material[14]. It has the ability to encapsulate both small molecules[13,15] and macromolecules such as DNA[16] and proteins[17,18]. However, due to its lipophilic nature, zein-based nanoparticles are prone to aggregation, requiring the use of stabilizers to mitigate colloidal instability in aqueous media[19,20]. **Gliadin**, obtained from wheat, forms NPs with strong mucoadhesive properties[21] and prolonged gastrointestinal residence time[22]. Nevertheless, it can trigger immune responses in sensitive individuals (*e.g.*, those with celiac disease)[23,24] and its commercial forms are often of lower purity, which limits its pharmaceutical applicability. Due to their hydrophobic nature[10] and mucoadhesive properties[21,25], prolamins are administered by the enteral route and show low loading efficiencies for hydrophilic drugs (up to 5%[16,22,26]), and up to 15% for hydrophobic compounds[27,28].

2.2. Animal-based proteins

As animal-based proteins, collagen, gelatin and casein are particularly noteworthy. **Collagen** provides mechanical strength but presents significant limitations for nanoparticle formulation due to its poor solubility in water and other physiologically acceptable solvents[29]. In contrast, gelatin (the hydrolysed form of collagen) is water-soluble, biocompatible and widely used as pharmaceutical excipient in a variety of dosage forms[30]. **Gelatin** NPs efficiently load hydrophilic drugs (with loading efficiencies up to 10%)[31-33] and nucleic acids[34,35] and offer targeting potential *via* RGD (arginine-glycine-aspartic acid) motifs[36,37]. However, they are limited by low mechanical stability[38], relatively large particle size[39] and low loading capacity of hydrophobic compounds (up to 3%)[40]. From a regulatory point of view, the route of administration of the gelatin-based NPs is enteral, showing mucoadhesive properties[41]. **Casein**, an amphiphilic milk protein also classified as GRAS[42], forms micellar nanoparticles with pH-dependent behavior[43]. It has been proposed as a mucoadhesive[44] carrier for the oral delivery[45,46] of hydrophilic drugs (loading capacity: up to 9%)[47] and, to a lesser extent, hydrophobic compounds (drug loading up to 3%)[44,48]. Nevertheless, a major limitation of casein-based NPs is their potential to trigger allergic reactions[49].

Other alternatives, such as **silk fibroin** and **elastin-like polypeptides (ELPs)**, offer several promising advantages, such as their

mucoadhesivity[50,51], but also present certain challenges for clinical application, such as allowing only enteral administration. While it is known the biocompatibility and structural robustness of the amphiphilic silk fibroin[52], their formulations have relatively low drug-loading efficiency for hydrophilic molecules (up to 6%)[53-55], with slightly better values for hydrophobic drugs (up to 10%)[56,57], and faces issues related with batch-to-batch variability[58] and complex purification processes[59]. ELPs are recombinant amphiphilic biopolymers characterized by thermoresponsive behavior[60], making them attractive candidates for stimuli-responsive drug delivery, especially for lipophilic compounds[61,62] reaching values of up to 20%[63]. However, their phase transition behaviour can be inconsistent under physiological conditions[64,65] and their clinical translation is hindered by regulatory and manufacturing challenges[66].

A special case is **ferritin**, a protein that, in addition to animals, can be widely found also in plants and bacteria, and that can form self-assembling nanostructures responsive to pH changes[67] with ideal capabilities to load hydrophilic[68] and metal-based drugs[69]. It also offers tumour targeting through transferrin receptor binding[70,71] and has been explored for antigen delivery in vaccine development[72], which allows their administration route to be parenteral and has resulted in their entry into clinical trials, as detailed in section 3.4. However, ferritin nanoparticles still face significant limitations, including poor loading efficiency for hydrophobic drugs and complex manufacturing processes that hinder large-scale production[73].

2.3. *Albumin-based proteins*

Although all the natural animal- and plant-based proteins described above have characteristics that make them promising base materials for the synthesis of drug delivery nanosystems, the formulations based on **Human Serum Albumin (HSA)** are the only ones that have entered the market, as described in Section 3, and albumins (*i.e.*, HSA and **Bovine Serum Albumin or BSA**) remain the most widely used proteins for carrier fabrication as evidenced by the literature on the field in the last ten years, with the articles published on albumin-based nanocarriers being around 20% of the reports on protein-based nanocarriers (the next most commonly used proteins are gelatin or collagen-based, 5% or 7%−8% respectively, and zein-based, 2%−3%) (source: PubMed).

Albumin is an ionic, globular and water-soluble small protein that comprise 3 repeated helical domains (I, II and III), which are composed of 2 subdomains (A and B), 17 disulfide bridges and a highly helical tertiary structure, with a 67% alpha-helix, 23% random coils and 10% turns[74,75]. This animal-based protein can be easily isolated in large quantities from blood plasma in vertebrates, accounting for around a 60% of serum proteins, which allows the possibility of administering high amounts of this protein into the body with reduced side effects[2,7]. The great abundance of albumins and its easy and cheap production process are very important advantages for their pharmaceutical use as lower prices are required to make drugs affordable for hospitals and patients. Moreover, this protein shows a long time of circulation in blood of up to 19 days and is very stable, maintaining the activity in organic solvents and under a wide range of pH values (4−9) and temperatures (60 °C for up to 10 h)[2,76], which makes this protein a very favorable base material for synthesizing nanocarriers. In addition, albumins are not glycosylated, which is crucial for its low immunogenicity. The special affinity of albumin for some cell surface receptors, such as the secreted protein acidic and rich in cysteine (SPARC/osteonectin) and the glycoprotein 60 (GP60/albondin), provide nanocarriers made with this protein with passive targeting capabilities. In fact, GP60 is overexpressed on endothelial cells and SPARC is widely expressed in the tumor tissue, making the albumin-based carriers themselves powerful tools for delivering drugs to cancer cells[77]. Nevertheless, the binding capacity of albumin to SPARC can be exploited beyond cancer to deliver bioactive molecules to inflamed tissues (*e.g.*, intestinal inflammation[78]) or to cross the blood brain barrier (*e.g.*, brain tumors[79] or neurodegenerative diseases[80,81]). Moreover, the presence of multiple reactive groups (amino, carboxyl and thiol) on the surface of the albumin-based NPs allows for their easy functionalization by covalent binding to induce active targeting capabilities[76]. The surface of all the nanocarriers based on naturally occurring proteins can be "camouflaged" through adsorption of hydrophilic compounds (*e.g.*, PEG or dextrans) or covalent binding of ligands, enhancing their *in vivo* properties, particularly their biodistribution, but only HSA- or ferritin-based NPs can be used for parenteral administration, without raising regulatory concerns.

The high content of charged amino acids (arginine, aspartate, glutamate and lysine) in albumin facilitates the entrapment of charged bioactive molecules (synthetic nucleic acids, cationic antimicrobial peptides, berberrubine, etc.) by electrostatic interaction[2,76,82]. Besides, it has long been shown that albumin is able to bind and transport several drugs, such as aspirin[83], penicillin[84] or sulphonamides[85], and albumin-based NPs show a high capacity to incorporate both hydrophilic[86,87] and hydrophobic[88] molecules, with drug loadings of up to 13% and 15%, respectively.

All the unique characteristics of albumin described above, which differentiate it from the rest of the natural proteins, explain why most protein nanocarriers that have been achieved clinical translation are those based on albumin, as it is described in Section 3, and justify this article being focused on these particular carriers. Thus, the main methods of synthesis and the passive and active targeting strategies of albumin-based nanocarriers are described in detail in section 4. Nevertheless, when talking about albumin, it should be noted that there are different types depending on the extraction source, with those obtained from human or bovine serum (HSA or BSA) being the most commonly used for drug delivery purposes. In this regard, although BSA and HSA share around 80% of sequence homology, HSA is commonly used in clinical studies because of its total absence of immunogenicity and undesired interactions with serum after their intravenous administration[5,82,89], and BSA in preclinical research due to its lower cost and ease of purification[7]. Anyhow, albumins are not glycosylated, which is crucial for its low immunogenicity. In any case, although BSA and HSA share analogous biological functions, like the preservation of osmotic pressure or the transportation of small molecules and metabolites (free fatty acids, metal ions, bilirubin, etc.), they differ in thermal stability, hydrophobicity, molecular weight, length (585 or 583 amino acids for HSA or BSA)[75] and significantly in their sequence (number of tryptophan and aromatic residues, subdomain IB, etc.)[90].

3. Current status in the clinical development of protein-based nanocarriers

As previously mentioned, the clinical translation of protein nanocarriers has been accomplished mainly with those based on

albumin, particularly HSA, due to its unique properties, resulting in several products on the market, such as Abraxane® and Sirolimus®, as well as some ongoing clinical trials.

3.1. Abraxane® (albumin-bound paclitaxel)

Paclitaxel, also known as Taxol, is a taxane derivative first isolated from the pacific Yew more than fifty years ago[91]. It binds to microtubules and blocks their polymerization/depolymerization dynamics, thus inhibiting mitosis[92]. Since its isolation, it was clear that paclitaxel could be used as a therapeutic tool in cancer[91], but due to the lack of interest at the initial stages by the scientific community, its approval by the FDA took more than twenty years[93]. Paclitaxel is highly insoluble in aqueous solutions and, for this reason, for many years it was dissolved in a 1:1 (*v*/*v*) mixture of ethanol and polyoxyethylated castor oil (Cremophor EL), but this formulation has several vehicle-related side effects[94,95]. To address this toxicity, several approaches have been used, including lipid, glucidic and protein encapsulation. In 1993, Kumar et al.[96] showed that paclitaxel spontaneously binds to serum albumin. Using this knowledge and to reduce toxicity of Cremophor EL, while keeping water solubility, Paál et al.[97] bound paclitaxel to albumin. Later that year, in a milestone on the synthesis of protein NPs and their clinical use, results from the first clinical trial using albumin-bound paclitaxel NPs (NP−albumin-bound or nab® paclitaxel) were published by Damascelli and colleagues (2001)[98]. This formulation showed advantages over free paclitaxel: it avoided the serious side effects of Cremophor EL, eliminated the requirement for premedication to reduce the risks of anaphylactic reaction and allowed a higher dose, reducing the infusion time[99]. The positive results achieved during this phase I study led to successful phase II and III studies[100,101] and, subsequently, in January 2005, to FDA approval for *"the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within six months of adjuvant chemotherapy"*, becoming the first protein nanoparticulate formulation approved for cancer treatment[102]. In Fig. 1 is included the timeline of nab® paclitaxel in cancer from generation to tumor drug release after systemic administration of the nanoformulation.

This was a landmark in the use of protein-based NPs for drug delivery, showing the feasibility of this approach. Thus, subsequently, Abraxane®, the commercial name of nab®-paclitaxel, in combination with carboplatin, was authorized by FDA in 2012 for the treatment of locally disseminated or metastatic unresectable Non-Small Cell Lung Cancer (NSCLC). Moreover, in 2013, this formulation, in combination with gemcitabine, was approved for the treatment of advanced pancreatic adenocarcinoma (FDA: Drugs@FDA, https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021660s037lbl.pdf). Despite the lack of new approvals in the last ten years, Abraxane® is still the chemotherapeutic option used as a first-line treatment for NSCLC and advanced adenocarcinoma of the pancreas and for the treatment of non-responsive metastatic breast cancer. In addition, there are more than 1500 on-going or starting clinical trials with Abraxane® for many conditions and combinations, with 25 active trials in phase III (see Table 1).

Although this encapsulation technology has been a success, improving paclitaxel efficacy and reducing its toxicity, this formulation still has a low percentage of serious side effects, such as neutropenia or neuropathy[100,101], that also include sepsis or respiratory problems when combined with gemcitabine[103,104]. In addition, even though Abraxane® treatment achieved better response rates (33% *vs* 19% for breast cancer) and longer time to tumor progression (23.0 *vs* 16.9) than the non-encapsulated formulation[100], new approaches are being tested to reduce toxicity and improve the efficacy of Paclitaxel, and encapsulation with liposomal (NCT01994031) or micellar (NCT06301165, NCT06752811) nanoparticles is being tested in clinical trials to this effect (https://www.clinicaltrials.gov).

3.2. Sirolimus®/Fyarro® (albumin-bound rapamycin or sirolimus)

To the best of our knowledge, apart from Abraxane® there is only other protein-based platform approved for human use, the application of the nab® technology to the delivery of sirolimus (nab®-sirolimus). This drug, originally known as rapamycin, is an antifungal antibody isolated from a bacteria from Rapa Nui, *Streptomyces hygroscopicus*[105]. Two years after its discovery, its immunosuppressive bioactivity was described[106] and unencapsulated sirolimus (Rapamune) was approved by FDA in 1999 as an immuno-suppressor for prophylaxis of organ rejection after renal transplantation[107]. In 2007, Temsirolimus (Torisel), a new sirolimus derived prodrug, was approved as first-line treatment for advanced renal cell carcinoma by the FDA[108]. Both Sirolimus and Temsirolimus are potent inhibitors of mTOR signaling, a crucial pathway in metabolic and protein synthesis regulation[109]. For this reason, treatment with these drugs is linked to a high rate of adverse reactions, and several groups have worked on their encapsulation in nanoparticles[110]. Among all the delivery approaches reported, to date only the nab® technology has reached clinical trials, being Fyarro® (nab®-Sirolimus) approved for the treatment of malignant perivascular epithelioid cell tumors (PEComa) in 2021[111−113]. Fyarro® is the first (and to date only) drug approved for the treatment of malignant PEComa, with an overall response rate of 38.7% and a median overall survival of 53.2 months at the end of the Phase II clinical trial, being an important step for the treatment of this rare and aggressive cancer[113]. During treatment of PEComa patients with Fyarro®, the most common (>60%) side effects were stomatitis, fatigue and rash, but also a low percentage of life-threatening adverse effects, which together with the high rate of non-respondents[113], indicate the need for further research on new formulations to improve PEComa treatment.

3.3. Albumin-bound docetaxel (nab®-docetaxel)

The third albumin-bound formulation in terms of clinical development is the nab®-docetaxel (also known as ABI008 or HB1801). Nab®-docetaxel is a nanoparticulated albumin bound formulation developed by Su and co-workers (2023)[114], who aimed to achieve the success shown by Abraxane, that is being tested on patients with head and neck squamous cell carcinoma (NCT05027204), ovarian cancer (NCT05325229) and gastric cancer (NCT05705635) (https://www.clinicaltrials.gov). New studies are planned to include pancreatic cancer (NCT05616494/NCT06492941), breast cancer (NCT06747338/NCT05838066), NSCLC (NCT06525350, NCT05863325 and NCT06319313) and upper digestive tract tumors (NCT06136988 and NCT06296706) (https://www.clinicaltrials.gov). Moreover, other approaches using nab®-docetaxel have been developed to include additional components. For example, CPO-100 is a nanoparticulate formulation in which albumin is conjugated to polylactide (PLA) containing docetaxel. It was developed to avoid the use of Polysorbate-80, a

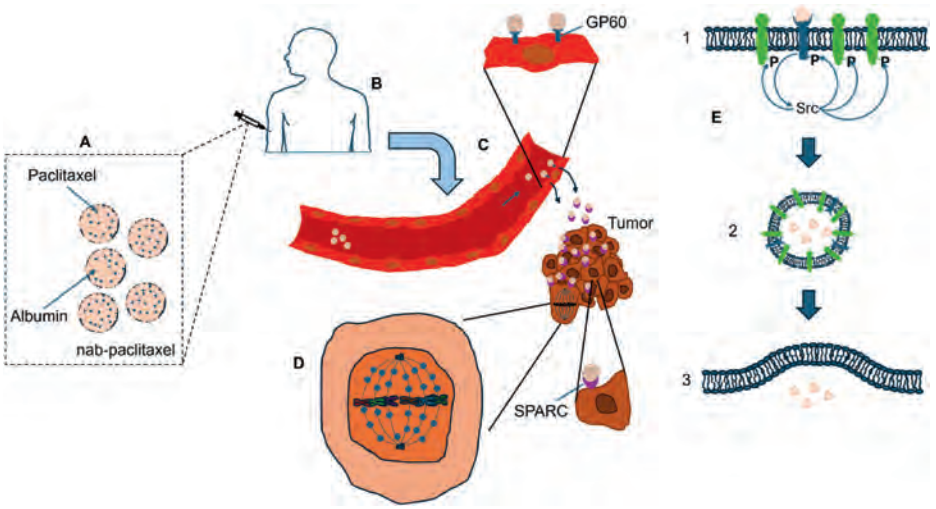

Figure 1 Recreation of the timeline in nab-paclitaxel generation and delivery. (A) Paclitaxel is encapsulated in albumin NPs to generate Abraxane®. (B) Abraxane® is administered intravenously to the patients. (C) Albumin NPs travel in the bloodstream, bind to the endothelial GP60 receptors and are transported by transcytosis to organs and tissues. (D) When the NPs reach the tumor, they bind SPARC who helps their association with the tumor cells membrane. Then, paclitaxel is gradually released and the drug binds to β-tubulin in the microtubules, blocking their depolymerization and cell division. (E) Mechanism of transport of NPs through the vascular endothelium. 1. Albumin binds to its receptor GP60, this leads to Src tyrosine kinase activation, which phosphorylates both GP60 and caveolin, inducing endocytosis. 2. After endocytosis, the GP60 receptors, caveolin and other membrane components are recycled. 3. The vesicle binds to the external membrane of the endothelium and releases its content to the extracellular media.

common component in docetaxel formulations that produce severe side effects, such as anaphylactic reactions or thrombophlebitis[115] and remove the use of steroids before infusion that are used to prevent hypersensitivity. There is an active phase I clinical trial using CPO-100 aiming for dose determination (NCT04931823). It started in 2021, but no results have been posted to date.

3.4. Other developments and challenges in clinical practice

Another formulation that uses the nab® technology has reached clinical trials, the ABI-011/IDN 5404, a nanoparticle bound to albumin, containing a dimer of thiocolchicine, an inhibitor of both microtubule polymerization and Topoisomerase I. It was tested in one phase I clinical trial (NCT01163071) but it was terminated early (and another clinical trial was not even started, https://www.clinicaltrials.gov). Besides, there are two active phase I clinical trials with the GP350-Ferritin NP vaccine (NCT04645147/NCT05683834), where its security and antigenicity are being tested. This nanoparticle formulation consists of the Epstein−Barr virus glycoprotein GP350 with a saponin adjuvant linked to ferritin and used as a vaccine against the Epstein−Barr virus, which has been associated with several types of cancer, including Hodgkin's and non-Hodgkin's lymphomas, other lymphomas and nasopharyngeal carcinoma[116].

Nevertheless, to date there are still only two albumin-based formulations on the market, Abraxane® and Fyarro®, but despite their successful development, their efficiency is still low due to several factors, such as the appearance of resistance mechanisms. For example, overexpression of the ABCB1 transporter has been shown to lower intracellular accumulation of nab® paclitaxel[117]. To overcome this, new drugs targeting the transporter have been developed and could be used in the future in a combinatory therapy[118]. Other mechanisms of resistance to Abraxane® include alterations in microtubule binding proteins, overexpression of anti-apoptotic proteins or alterations in cytokine or growth factor signaling pathways[119]. In addition to the molecular changes that produce drug resistance after initial treatment, other factors are responsible for the low percentage of therapeutical success. Thus, low expression of the GP60 and SPARC has been also linked to low efficacy of nab® paclitaxel[120]. This limitation could be overcome with targeted NPs, which leads to accumulation of the NPs specifically to the tumor area (see Section 4.3). Other causes of failure can include low accumulation of the NPs in specific tumors or relapse due to the cancer stem cells, a niche of cells responsible for tumor initiation that can remain quiescent and resistant to chemotherapeutic drugs but can induce tumor regrowth after treatment termination[121]. Moreover, the failure of Abraxane® can be found in some patients with a too advanced stage of the illness, in which cancer cells have spread to vital organs.

Some of the reasons described above to explain the low efficiency of Abraxane® could be applied for the resistance to or low efficiency of other drugs loaded into albumin NPs. However, there are no studies analyzing the reasons behind the low efficiency of Fyarro® or other NPs that failed to show enhanced efficiency in clinical trials. Due to this, it is believed that augmenting the efficiency of these NPs will require the use of combinatory treatments as well as modifications for targeted delivery.

4. Albumin-based nanoparticles as targeted delivery systems

Even though albumin has proven to be one of the ideal materials for the generation of drug delivery systems due to its exceptional and distinctive properties, which were described in Section 2, there are challenges that need to be addressed to release the full potential of the albumin-based nanocarriers and advance its clinical translation. In this regard, although there are multiple established methods in the literature for synthesizing these

Table 1 Active (non-recruiting) clinical trials in Phase III using Abraxane® for cancer treatment.

Cancer type/condition	Combination drugs	Starting date	CT. ID.
Breast cancer: Triple negative recurrent or metastatic	Toripalimab	2018-12-21	NCT04085276
Breast cancer: Triple negative with PIK3CA mutation or PTEN loss	Alpelisib	2020-06-08	NCT04251533
High-grade epithelial ovarian, primary peritoneal, or fallopian-tube cancers: Advanced, platinum-resistant	Relacorilant	2022-06-29	NCT05257408
Advanced biliary tract cancer: newly diagnosed.	Gemcitabine hydrochloride and cisplatin	2019-02-07	NCT03768414
Breast cancer: HR^+ or $HER2^-$ locally recurrent inoperable or metastatic	Pembrolizumab	2021-06-18	NCT04895358
NSCLC: Metastatic	Pembrolizumab or vibostolimab	2022-03-24	NCT05226598
NSCLC	Retifanlimab	2020-09-11	NCT04205812
NSCLC: Metastatic	Pembrolizumab, olaparib	2019-06-28	NCT03976362
NSCLC: Squamous or non-squamous metastatic	Pembrolizumab, cisplatin or carboplatin, pemetrexed	2021-08-05	NCT04956692
NSCLC: Stage IIIB, IIIC or IV	HLX-10, carboplatin	2019-08-14	NCT04033354
NSCLC: Advanced	Pembrolizumab, radiotherapy	2018-01-24	NCT03774732
NSCLC: Metastatic	Zimberelimab, domvanalimab, cisplatin or carboplatin, pemetrexed *vs.* pembrolizumab, cisplatin or carboplatin, pemetrexed	2022-10-12	NCT05502237
Nasopharyngeal carcinoma: anti-PD-1 resistant recurrent or metastatic	Cadonilimab, cisplatin, and capecitabine	2024-10-21	NCT06664983
NSCLC: Stage III or IV	N-803, carboplatin, pembrolizumab	2018-05-18	NCT03520686
NSCLC: Previously untreated locally advanced or metastatic non-squamous and squamous	Canakinumab, pembrolizumab, cisplatin or carboplatin, pemetrexed	2018-12-21	NCT03631199
NSCLC: Metastatic	Pembrolizumab, berahyaluronidase alfa, cisplatin or carboplatin, pemetrexed, filgrastim or pegylated filgrastim	2023-06-13/2023-02-14	NCT06212752 & NCT05722015
Breast cancer: HR^+ or $HER2^+$ metastatic	Pertuzumab, trastuzumab	2015-09	NCT02344472
NSCLC: Resectable stage II, IIIA or select IIIB	Atezolizumab, carboplatin	2018-04-24	NCT03456063
PDAC: Advanced	KN046, gemcitabine	2022-01-20	NCT05149326
PDAC: Resectable or borderline resectable	Cisplatin, gemcitabine, capecitabine	2020-11-03	NCT04793932

NSCLC: non-small cell lung cancer; PDAC: pancreatic ductal adenocarcinoma; HER2: human epidermal growth factor receptor 2.

nanocarriers, the most common of which are described below, these require conditions, such as high-shear mixing, high temperatures or potentially toxic compounds and organic solvents, that could affect the encapsulated drugs and compromise the unique properties of albumin. Hence, this section also includes new and alternative approaches that do not use harsh conditions in the synthesis process. On the other hand, despite the fact that albumin-based nanocarriers have entered the clinic, as discussed in section 3, they can be improved by implementing passive and active targeting strategies, the main ones being discussed in this section, particularly those designed for cancer treatment.

4.1. Main methods of synthesis

Several physicochemical techniques have been proposed for easily synthesizing albumin nanoparticles, including desolvation or coacervation, emulsification, thermal gelation, self-assembly methods and biomineralization. The selection of a specific method is usually dependent on factors such as the intended application, drug properties and scalability requirements. Freshly synthesized albumin-based nanoparticles often display poor stability, requiring an additional stabilization step to harden the particle arrangement and, thus, extend their shelf-life. After this, and before freeze-drying for preservation, the particles may be purified by dialysis, gel permeation chromatography, tangential filtration or, more frequently, subsequent centrifugations[82,89]. Fig. 2 shows a schematic representation of the main methods for the preparation of albumin nanoparticles.

4.1.1. Desolvation/coacervation

This method is the most commonly used for synthesizing albumin-based NPs. It is based on the dehydration of an albumin aqueous solution by the continuous dropwise addition of a desolvating agent, such as ethanol or acetone while stirring, until turbidity appears. With the incorporation of ethanol to the aqueous albumin solution, this protein loses its solubility and its tertiary structure

changes from a stretched to a coiled conformation, being phase separated and aggregated into submicronic particles. In order to avoid redissolution of the generated nanoparticles when redispersed, the formed coacervates need to be hardened by crosslinking agents, mainly glutaraldehyde[82,89,122–124].

This is a simple, reproducible and rapid method with no requirement for surfactants that allows the encapsulation of hydrophobic and hydrophilic molecules. In this synthesis approach, the rate of addition of ethanol and the concentration and pH of the albumin solution are the main variables which influence the physicochemical properties of the generated particles, with the size and the polydispersity generally being larger than with other synthesis methods (*e.g.*, self-assembly). However, the main drawbacks of this approach are the use of organic solvents and crosslinker agents, which can lead to systemic toxicity and alter the native protein structure with a loss of their biological properties and an increase of the immunogenicity[3,82,124,125]. Table 2[125-142] contains some examples of the use of the desolvation method to synthesize albumin-based NPs as carriers of different drugs. The use of *N*-(3-dimethylaminopropyl)-*N*-ethyl carbodiimide hydrochloride (EDC) has been reported as an alternative to glutaraldehyde, reducing the time of preparation, from overnight to 3 h, and diminishing the toxic effects since it can be easily removed by centrifugation unlike glutaraldehyde which remains retained in the structure of the generated particles[128,129]. Other approaches to avoid the toxicity of glutaraldehyde may be the use of glucose with and without UV radiation[137–139], sorbitol, ascorbic acid, citric acid or tannic acid[138,139].

4.1.2. Emulsification

In this technique, an aqueous solution of the protein is dispersed into a lipophilic phase (*i.e.*, vegetal oils or, more frequently, an organic solvent). To obtain an adequate dispersion of the two non-miscible phases, the phases are mixed by using energetic stirring techniques and/or in the presence of high concentrations of surfactants[89]. In recent years, to simplify the technique and facilitate the purification stage of the obtained NPs, there has been a trend towards avoiding the use of vegetable oils and minimizing the use of surfactants. Instead, the use of organic solvents and ultrasonication techniques is preferred. Ultrasonication also enables the formation of more homogeneous emulsions with smaller particle sizes[143,144]. Once the emulsion is obtained, the albumin

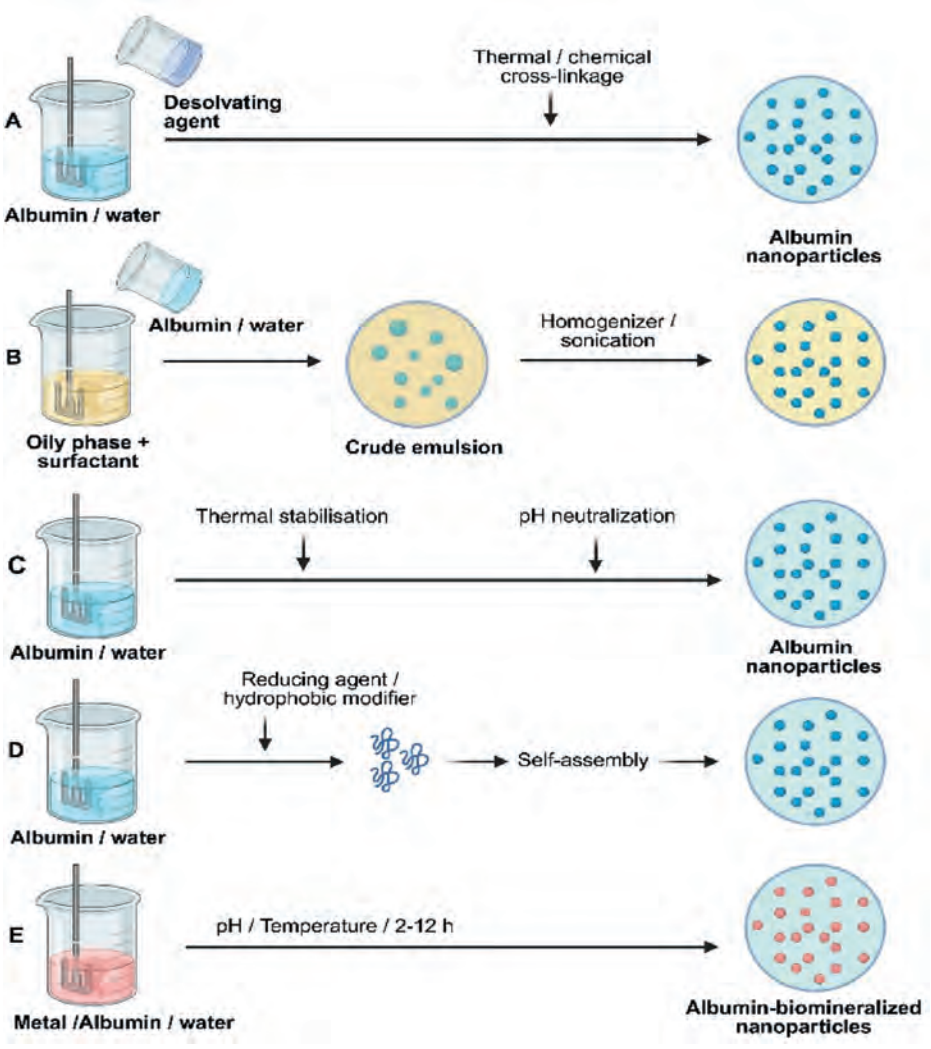

Figure 2 Main methods used for the synthesis of albumin-based nanoparticles. (A) Desolvation; (B) emulsification; (C) thermal gelation; (D) self-assembly; (E) biomineralization. Figure created using Biorender.

droplets are solidified. For this purpose, the following methods have been proposed: (i) chemical crosslinking with glutaraldehyde[145], (ii) mechanical treatment with a high-pressure homogenizer[146] and (iii) thermal stabilization at temperatures higher than 110 °C for periods of time ranging from 10 to 30 min[147]. Finally, the organic solvents are removed and the NPs collected or freeze-dried. In any case, the characteristics of the final NPs are significantly influenced by parameters such as the mixing intensity, the volume ratio of the aqueous and lipophilic phases and the type and concentration of surfactants employed[123,148].

Overall, this emulsification approach is considered simple and particularly suitable for incorporating hydrophobic drugs. On the contrary, the emulsification process also presents some challenges, including the destruction of NPs due to excessive shear force and high pressure, the use of chlorinated organic solvents and the low encapsulation efficiency of hydrophilic drugs[124,149]. Table 3[143,144,146,147,150-153] includes some examples of albumin NPs prepared by emulsification. An interesting variation of the typical emulsification method is the nab® technology[154] employed to obtain Abraxane® (nab-paclitaxel)[155]. It involves the formation of a crude emulsion by adding the lipophilic drug to the aqueous albumin solution before subjecting the mixture to high-pressure jet processing. This approach facilitates the generation of NPs with mean particle sizes typically ranging from 100 to 200 nm[156]. However, the main advantage of this approach is the elimination of solubilizers and emulsifiers, particularly, for intravenous applications[156,157].

4.1.3. Thermal gelation and self-assembly

Thermal gelation is a technique used to produce albumin NPs by inducing protein aggregation through heat exposure. The process involves a structural change in albumin, where heating induces a transition from an α-helix to a β-sheet configuration. These β-sheets then interact through non-covalent weak forces (*i.e.*, hydrogen, electrostatic and hydrophobic bonds), as well as disulfide-sulfhydryl exchange reactions, leading to NPs formation[89,158]. The procedure is simple and involves the heating of an aqueous solution of albumin to temperatures above 60 °C for a defined time[82]. Afterward, the solution is cooled, its pH adjusted toward neutral and stirred continuously to allow the NPs to form[159,160]. This method is appreciated for its simplicity, elimination of chemical cross-linkers and the production of relatively stable NPs[76,161]. However, it is not appropriate for incorporating unstable drugs at high temperatures.

The self-assembly approach relies on enhancing the hydrophobic nature of albumin to trigger intermolecular interactions between protein molecules[89]. This typically involves adding specific agents to an aqueous albumin solution to either disrupt disulfide linkages[162], reduce the availability of free primary amine groups[163] or increase the hydrophobic domains of the protein[164]. In the first case, reducing agents, such as glutathione, β-mercaptoethanol or cysteine are commonly used[165,166]. In the second, hydrophobic modifiers (*e.g.*, cholesterol) can be introduced to chemically block amine functionalities[167,168]. Alternatively, incorporating hydrophobic drugs, like paclitaxel, doxorubicin or quercetin, directly into the system can also promote NPs self-assembly[89,164,169-171]. Moreover, the self-assembly approach also appears to be the most suitable method for preparing NPs based on albumin conjugates, obtained by the covalent binding of hydrophilic ligands, such as cholesterol[167], maltose[171] or PEG and its derivatives[172,173], to the protein backbone. In any case, this method offers significant advantages, including efficient drug loading and compatibility with biological systems; but it also presents some drawbacks, such as the necessity for chemical alterations to boost self-assembly interactions and the possibility of protein denaturation or loss of activity during the process[89].

Table 4[161,167,170,171,173-177] gives examples of albumin NPs prepared by thermal gelation and self-assembly approaches.

4.1.4. Biomineralization

Biomineralization of albumin is an emerging bioinspired strategy that mimics natural mineralization processes to produce inorganic−organic hybrid NPs, using albumin as a template or stabilizer[178]. In this approach, albumin molecules serve as scaffolds, templates or nucleation sites to guide the formation of inorganic nanomaterials under mild, aqueous and often physiological conditions, offering a scalable and biocompatible method for nanoparticle synthesis[179,180]. The process is based on the capability of albumin to chelate various metal ions, including Ca^{2+}[181], Mn^{2+}[182], Fe^{3+}[183], Ce^{3+}[184] and Au^{3+}[185]. These metal ions nucleate and aggregate into inorganic cores within or around the albumin structure, whereas albumin acts as a structural agent, controlling size, shape and dispersion characteristics[180]. Key synthesis variables (*i.e.*, pH, incubation time, temperature and metal ions-to-albumin ratio) can be adjusted to finely control the morphology and physicochemical properties of the resulting NPs[183,186].

4.2. Novel synthetic approaches that avoid harsh conditions

As described above, the conventional methods used to synthesize albumin-based NPs employ conditions that can generate toxicity (crosslinkers, reducing/denaturant agents, organic solvents, etc.) or seriously damage the protein and/or encapsulated material (high-shear homogenization, high temperatures, …).

Regarding the techniques that require additional stabilization steps, although different alternatives have been proposed, glutaraldehyde remains the most commonly used due to its ability to provide a superior thermal and chemical stability compared to other cross-linkers[187] since it reacts with the free albumin amino groups (mainly of lysine and arginine) forming bridges that stabilize the nanostructure[188]. In addition, other chemical cross-linking agents have been proposed, including 2,3-butadione[189], oxidized dextran derivatives modified with methyl polyethylene glycol[190] or *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide (EDC)[129]. Unfortunately, these chemical reagents face similar drawbacks to glutaraldehyde, such as the presence of toxic residues or their potential reactivity with the functional groups of the loaded drug[89], but as mentioned above, EDC can be easily removed by centrifugation[126,127]. In order to avoid the use of chemicals, safer alternatives have been proposed, including stabilization through ultraviolet irradiation[128], ultrasonication[191] or enzymatic cross-linking with genipin[192]. Additionally, stabilization without covalent bonding can be achieved by coating the NPs with polymers by hydrophobic/electrostatic interactions or hydrogen bonds, among others. This strategy has yielded promising results with different compounds, including polyethylenimine (PEI)[193], Gantrez® ES-425[194], PEG 35,000[86] or dextran[195]. In this regard, it is worth mentioning the use of **chitosan** to stabilize albumin-based NPs synthesized by the desolvation technique. Based on the results obtained by the group of Uludag[193,196] using PEI and PEI-PEG, several authors have reported the coating of albumin-based NPs with chitosan, a mucoadhesive biopolymer that can facilitate the interaction with

Table 2 Some examples of albumin-based nanoparticles prepared by desolvation.

Protein	Drug	Desolvation	Stabilization	Purification	Variable with effect	Physicochemical characteristic	Ref.
HSA	–	Ethanol	Glutaraldehyde	Centrifug.	HSA pH/conc., solvent flow rate, crosslinker amount	PS: *c.a.* 100–300 nm; PDI: 0.010–0.100; ZP: −40 to +38 mV	125,126
HSA	–	Acetone or EtOH or MeOH/water, EtOH/MeOH	Glutaraldehyde	Centrifug.	Stirring time, solvent used & amount/conc./addition	PS: *c.a.* 50–500 nm; PDI: 0.020–0.400; ZP: −58.9 to −68.5 mV	127
HSA/BSA	–	EtOH	EDC	Centrifug.	BSA/HSA conc., solvent flow rate, crosslinker amount	PS: *c.a.* 100 nm; PDI: *c.a.* <0.2; ZP: *c.a.* −30 mV	128,129
HSA	Anthracycline derivatives (DXR, DNR, THP, ACR)	EtOH, MeOH, 2-propanol	Glutaraldehyde	Centrifug.	HSA pH/conc., desolvation agent, drug	PS: 104–153 nm; PDI: 0.030–0.160; ZP: −24 to −49 mV; EE (%): 95.7 (DXR), 97.1 (DNR), 87.8 (THP), 29.7 (ACR)	130,131
HSA	Sulforhodamine B sodium salt	EtOH	Glutaraldehyde	Vacuum evap. & Centrifug.	–	PS: 230–250 nm; PDI: *c.a.* 0.060–0.110; ZP: −44 to −47 mV; EE: 65%	132
BSA	Ganciclovir	EtOH	Glutaraldehyde	Centrifug.	Drug/crosslinker, solvent & crosslinker volume	PS: 225–320 nm; ZP: −22.4 to −27.8 mV; EE: 12.5%–40.6 %	133
BSA	DXR	EtOH	Glutaraldehyde	Centrifug.	BSA pH/conc., mass of DXR, amount of crosslinker	PS: 128–645 nm; ZP: −1.7 to −39.7 mV; EE: 23.3%–83.6%	134
BSA	–/Tetrandrine	EtOH	Glutaraldehyde	Centrifug.	BSA conc./pH, temperat., solvent volume & flow rate, volume of crosslinker	PS: *c.a.* 60–500 nm; PDI: 0.020–0.590; ZP: −24 to −52 mV; EE: >95%	135,136
BSA	Docetaxel/–/–	EtOH or acetone	Glucose	Centrifug.	Crosslinker, BSA conc./pH, temperat., solvent	PS: *c.a.* 125–200 nm; PDI: 0.03–0.163; ZP: c.a. −15 to −33 mV	137,138,139
BSA	DXM	EtOH	Glutaraldehyde	Rotary evap. & filtration	–	PS: *c.a.* 250–270 nm; PDI: 0.115–0.165; ZP: − 20 to −40 mV; EE: 84%	140
BSA	Ipriflavone	EtOH	Glutaraldehyde	Centrifug.	Amount of drug	PS: 109–668 nm; PDI: 0.067–0.527; ZP: −19.6 to −24.7 mV; EE: 31.6%–82.6%	141
BSA	Celastrol	EtOH	Glutaraldehyde	Centrifug.	–	PS: 118 nm, PDI: 0.167; ZP: −2.5 mV; EE: 75.6%	142

HSA/BSA: human/bovine serum albumin; DXR: doxorubicin; DNR: daunorubicin; THP: pirarubicin; ACR: aclarubicin; DXM: dexamethasone; EtOH: ethanol; MeOH: methanol; EDC: *N*-(3-Dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride; Conc.: concentration; Centrifug.: centrifugation; PS: mean particle size; ZP: zeta potential; PDI: polydispersity index; EE: encapsulation efficiency.

Table 3 Some examples of drug-loaded albumin nanoparticles prepared by the emulsification method.

Drug	Hydrophilic phase	Lipophilic phase	Emulsification technique	Stabilization procedure	Purification procedure	Physico-chemical characteristic	Ref.
Paclitaxel (PTX)	HSA in water	PTX in chloroform/ ethanol	Homogenizer	High pressure homog. (12 cycles/20000 psi)	Rotary evaporation under vacuum	Size: 170 nm; ZP: −17.4 mV; yield: 93%; EE: 82%	146
Camptothecin (HC)	BSA in 0.04 mol/L NaOH + HC	Castor oil/Span 80	Agitator 9000 rpm, 10 min	Heat 140 ± 5 °C	Petroleum ether	Size: ∼600 nm; ZP: 19.3 mV; yield: 91%; DL: 2.2%; EE: 57.5%	147
Camptothecin (HC)	BSA in water	Chloroform/ Ethanol/HC	Ultrasonication (60%/8 min)		Rotary evaporation under vacuum	Size: ∼260 nm; ZP: −17 mV; DL: 2.9%; EE: 78%	144
Flurbiprofen	BSA in water (pH 5.6−5.9) with citric acid	Chloroform/ Flurbiprofen	Magnetic stirring	High shear homog. (15,000 rpm/ 5 min)	Centrifugation	Size: 172 nm; PDI: 0.35; ZP: −6 mV %; DL: 18.1%; EE: 90.4%	150
MPT0B291	HSA in water	MPT0B291, soybean lecithin in chloroform/ ethanol	Sonication	High-pressure homog. (20,000 psi/up to 40 cycles)	Rotary evaporation under vacuum	Size: 136 nm; PDI: 0.24; ZP: −1.87 mV; yield: 95%; DL: 6%; EE: 92%	151
Farnesylthiosalicylic acid (FTS)	BSA in water	FTS, soybean oil, ethyl acetate, dichloromethane	Ultrasonication (330 W/8 min)		Rotary evaporation under vacuum	Size ∼ 100 nm; PDI: 0.24; ZP: 18.99 mV; DL: 2.3%; EE 98.6%	143
Resveratrol	FA-HSA conjugate in water	RES in methanol/ chloroform	Speed homogenizer Stirrer	Ultrahigh-pressure nanometer high-efficient device	Rotary evaporation under vacuum	Size: 102 nm; PDI: 0.001; DL: 14.7%; EE: 98.4%	152
Tacrolimus (TAC)	BSA in water	TAC, cholesterol in chloroform/ ethanol	Ultrasonication	High-pressure homog. (90−100 Mpa/8 cycles)	Rotary evaporation under vacuum	Size: 190 nm; PDI:0.23; ZP: −20.9 mV; EE: 85%; DL: 1.7%	153

HSA/BSA: human/bovine serum albumin; FA-HSA: folic-acid-HSA conjugate; Homog.: homogenization; ZP: zeta potential; PDI: polydispersity index; DL: drug loading; EE: encapsulation efficiency.

Table 4 Some examples of drug-loaded albumin nanoparticles prepared by thermal gelation and self-assembly.

Protein	Drug	Method	Preparation strategy	Physicochemical characteristic	Ref.
BSA-FA functionalized amylopectin copolymer conjugate	Curcumin in ethanol	Thermal gelation	Heat (80 °C)	PS: *c.a.* 90 nm; ZP: −24 mV; EE: *c.a.* 100%	161
BSA	−	Thermal gelation	Heat (70 °C/2 h)	PS: 120 nm; PZ: −4 mV; PDI: 0.45; yield: 90%	174
HSA	Paclitaxel in ethanol	Self-assembly	B-mercaptoethanol	PS: 120 nm; PDI<0.1; ZP: 24.6 mV; DL: 12%; EE: 98%	175
HSA	Curcumin in ethanol	Self-assembly	Dithiothreitol	PS: 100 nm; DL: 4%; EE: 92%	176
Chol-BSA conjugate	Paclitaxel in ethanol	Self-assembly	Cholesterol	PS: 148 nm; PDI: 0.08; ZP: −20.5 mV; DL: 38%; EE: 95%	167
BSA	Paclitaxel in ethanol	Self-assembly	−	PS: 110 nm; yield: 89%; DL: 7%	170
BSA	Curcumin in ethanol	Self-assembly	Glutathione	PS: 141 nm; PDI: 0.08; ZP: 19.2 mV; DL: 9.3%; EE: 83%	177
Maltose−BSA conjugate	Doxorubicin	Self-assembly	Glutathione	PS: 167 nm; PDI: 0.21; ZP: −9.3 mV; DL: 8.5%; EE: 93%	171
PEG_{20kDa}−HSA conjugate	Paclitaxel + ICG in methanol	Self-assembly	−	PS: 201 nm; PDI: 0.217; ZP: −4 mV; PTX DL: 8.2%; EE: 55%; ICG DL: 2.9%; EE: 72%	173

HSA/BSA: human/bovine serum albumin; FA: folic acid; Chol: cholesterol; ICG: indocyanine green; PS: mean particle size; ZP: zeta potential; PDI: polydispersity index; DL: drug loading; EE: encapsulation efficiency.

mucosal barriers and reduce the drug release rates. The stabilizing coating is formed by the electrostatic interaction between the negatively charged surface of the albumin NPs and the positively charged chitosan. This formulation was perfectly integrated in different systems that induced a dual release process of drugs such us vancomycin and dexamethasone[197], bone morphogenetic protein-2 (BMP-2) and dexamethasone[198], abaloparatide and acetylsalicylic acid[199] or BMP-2 together with inorganic osteoinductive and antibacterial nanomaterials[200,201], for bone regeneration purposes. Similarly, Li et al.[202] included the osteogenic growth factor NELL-1 within this type of chitosan-stabilized albumin NPs. In all these cases, the surface charge of the NPs, logically, moved from negative values (*c.a.* −30 mV) before the coating process to positive values (*c.a.* +30 mV) after the stabilization with the polymer. The particle size increased depending on the thickness of the coating (from *c.a.* 250 to 270−390 nm), with no effects on the PDI values. Moreover, regardless of the drug used, entrapment efficiencies around 90% or greater were achieved. Logically, this mild technique has also been used to synthesize albumin-based nanocarriers for the delivery of cytotoxic drugs in the field of cancer. For example, Esim et al.[203] reported the entrapment of methotrexate, a toxic low-solubility drug, within chitosan-coated BSA nanocarriers for the treatment of breast cancer. Similar to the previous cases, the surface charge of the BSA NPs changed from negative (−25.5 mV) to positive (38.7 to 53.3 mV) when chitosan was included. Depending on the amount of chitosan added, the authors observed a large variation in the size (234.1 to 733.1 nm), polydispersity (0.294 to 0.583) and encapsulation efficiency (22.2% to 45.4%) of the nanocarriers. Apart from avoiding toxicity, the authors demonstrate that replacing glutaraldehyde with chitosan as a stabilizer is very beneficial *in vitro* for the cellular uptake of the drug and the induction of cytotoxic and apoptotic effects on MCF-7 breast cancer cells[203].

Although thermal gelation and self-assembly methods do not require additional chemical stabilization steps, the structure of the protein is irreversibly modified because of the use of high temperatures or the alteration of their hydrophobic nature, respectively, not to mention the effects on the trapped bioactive molecules. Because of this, some authors have proposed alternative mild approaches for the synthesis of albumin-based NPs that do not use any harsh conditions throughout the entire process. In this context, several authors have reported the use of the ion gelation method for the synthesis of albumin NPs by reacting the negatively charged protein at basic pH with chitosan in acidic conditions, which is positively charged. The group of Zhao L first used this approach to transport different drugs to tumoral cells (gefitinib[204]) and throughout the blood brain barrier (curcumin[205]) for the treatment of neurodegenerative diseases. In both cases, the mean particle size was around 140−170 nm, with a high monodispersity (PDI: 0.020−0.060), achieving encapsulation efficiency values higher than 85% and biphasic profiles of slow release during 48 h. Although the reported surface charge of the NPs was slightly negative (−10.8 mV), with this methodology and a variation of the relative proportions of both reactants this value can be tuned as the need.

Microfluidics has been also applied in recent years for the formulation of albumin-based systems. This technology achieves the mixing of phases by molecular diffusion below laminar flow within microchannels, avoiding turbulence patterns and assuring batch-to-batch reproducibility, good control of all variables, high mixing efficiency with protection of the encapsulated biomaterial and reduced volumes of reactants with high entrapment efficacies[124]. Regarding the self-assembly method, Zhao et al.[206] used a Y-shaped chip to mix glutathione-pretreated HSA with paclitaxel (PTX) in tertiary butyl alcohol (TBA) in a flow focusing pattern to obtain PTX-loaded HSA nanocarriers that were hardened by heating at 37 °C to form the disulfide bonds. With this procedure the authors were able to encapsulate 75% of the PTX used in HSA NPs of 160 nm in size. Later, Sun et al.[207] employed an inverted W-type microfluidics mixer with a flow focusing pattern for the synthesis of cabazitaxel (CTX)-loaded HSA NPs by mixing an inner fluid (emulsion) composed of CTX in ethanol with a HSA aqueous solution and two outer fluids of hot water (40−80 °C), both streams being driven in a controlled manner by syringe pumps at different flow rates/ratios. The use of this technology allowed an increase in the encapsulation efficiency of a previously reported new self-assembly method with a cooling stabilizing process[208−210] from 51.4% to 84.3%, maintaining the mean size and surface charge of the particles (*c.a.* 140 nm and −20 mV, respectively) and reducing their polydispersity from 0.193 to 0.095. More recently, Du et al.[211] reported the use of microfluidics to generate 118 nm docetaxel-loaded BSA NPs, using a novel organic solvent/surfactant-free thermal-driven (65 °C) self-assembly method, which allowed obtaining a encapsulation efficiency of almost 90%, a drug loading greater than 8% and a sustained drug release over 96 h. The authors highlighted the possibility of industrial production of the formulation due to its stability and reproducibility when using microfluidics technology. Besides, other authors have used microfluidics to improve the desolvation method and generate homogeneous albumin-based NPs, whose physicochemical characteristics are easily tuned by varying the variables of the synthesis process. In this regard, Hakala et al.[212] described the use of a microfluidic chip with a 3D co-flow design to produce celastrol-loaded HSA NPs with tunable particle size (from 100 nm to 1 μm), encapsulation efficiencies greater than 75% and a high stability, without the use of crosslinkers, by using a protein previously reduced with glutathione. Similarly, Minetti et al.[213] used a novel coaxial microcapillary-based microfluidic setup, where phases were driven by gravity, and managed to synthesize curcumin-loaded bovine alpha-lactalbumin-based NPs by the desolvation method with encapsulation efficiencies around 40%, mean sizes between 181 and 255 nm and very low polydispersity values (*c.a.* 0.12).

Another emerging approach in the development of the albumin-based nanocarriers is the incorporation of **stimuli-responsive** properties that respond to the anomalous conditions of the diseased tissues[89], such as the acidic pH of the tumor microenvironment[214], the highly reducing conditions within the tumoral tissues with high levels of glutathione (seven-fold higher than in normal tissues)[215] or the high production of hydrogen peroxide (H_2O_2) in tumor cells (with concentrations up to 100 μmol/L, being 20 nmol/L in healthy cells)[216], resulting in the release of the cargo of the NPs when reaching these conditions.

Regarding the provision of pH sensitivity, authors often resort to the inclusion within the structure of the albumin NPs of pH-sensitive compounds, such as methoxypolyethylene glycol amino (mPEGA)[217] or manganese dioxide (MnO_2)[218], which produces the disintegration of the particles and the consequent release of the encapsulated drug upon reaching the acidic pH values of the tumor microenvironment. Moreover, Yang et al.[219] and later Zheng et al.[220] demonstrated that when albumin-based NPs are synthesized by the desolvation method with glutaraldehyde stabilization, the Schiff base bonds formed between the amino groups of the lysine and arginine residues of albumin and the aldehyde groups of glutaraldehyde can be broken at acidic pH, leading to the destabilization of the NPs and, therefore, producing a pH-sensitive release of the drugs (doxorubicin and PTX). Similarly, Argitekin et al.[221] reported the generation of pH-sensitive BSA NPs by the desolvation method using tris-catechol-V(III) as crosslinker, which at acidic conditions change its coordination state from tris to bis and/or mono, generating the degradation of the NPs and releasing its cargo (doxorubicin).

On the other hand, the possibility of obtaining albumin NPs by the self-assembly approach using reducing agents, such as glutathione, to disrupt the disulfide bonds of albumin, not only stabilizes the particles without using glutaraldehyde through the disulphide−sulfhydryl interchange reaction, but also allows the incorporation of redox sensitive capacities against the reducing conditions of the tumor microenvironment[222]. Thus, Raja et al.[223] demonstrated that the use of this approach allows the synthesis of highly biocompatible and non-toxic camptothecin-loaded HSA NPs that are capable of significantly increasing the release of the encapsulated drug (from less than 30% to more than 70%) by increasing the concentration of glutathione (from 0 to 10 mmol/L), which gives them redox-responsive properties. Similarly, using the same approach, Saleh et al.[224] achieved the release of up to 70% of the curcumin contained in HSA NPs when 10 mmol/L glutathione was added (26% without redox conditions). A variation of the conventional self-assembly approach was performed by Curcio et al.[225], who applied glutathione not to the native HSA but to a conjugate composed of HSA, lipoid acid (redox sensitive) and curcumin to obtain improved redox-responsive doxorubicin-loaded HSA NPs. The particles increase their size (70 nmol/L) ten-fold when incubated with 10 mmol/L glutathione, increasing the rate and amount of drug released due to the breakage of the crosslinking bonds. A similar strategy was carried out by Brindisi et al.[226] that synthesized 120 nm doxorubicin-loaded HSA NPs with the glutathione-mediated self-assembly method but adding the reducing agent to an HSA-hyaluronic acid conjugate to provide active targeting capabilities. In this case, the mean size of the particles was increased 3-fold when the glutathione solution (10 mmol/L) was added, resulting in an increase in the cumulative drug release from 25% (normal conditions) to 85% (redox conditions) with a faster release rate.

Finally, in the design of stimuli-responsive albumin NPs, the high production of H_2O_2 in tumor cells is the least explored option at the moment. In fact, to the best of our knowledge, there is only one publication on the subject that reports the synthesis of hybrid HAS−MnO_2 nanoclusters with H_2O_2-/pH-responsive capacities, which are generated by the alkaline biomineralization of Mn^{2+}, using a modified HSA (HSA−drug conjugate) as a template and coating material[218]. This formulation is capable of generating O_2 with the endogenous tumoral H_2O_2, decreasing tumor hypoxia and diminishing the resistance to photodynamic therapies[218]. Furthermore, as mentioned above, the pH-sensitive character of MnO_2 that breaks up under acidic conditions, allows the dissociation of the HAS−MnO_2 NPs into HAS−drug complexes at acidic pH, a release process that is dramatically accelerated in the presence of H_2O_2[218].

4.3. Main passive and active targeting strategies in cancer

Drug delivery systems gain crucial importance in the context of cancer treatment. The intrinsic nature of this illness, where the own cells of the patients are the pathogenic subject, implies that the drugs used to target the cancerous cells will very frequently (if not always) have toxic side-effects on the normal, non-tumoral cells. This can be avoided through drug encapsulation and tumor targeting, which reduces the toxicity of the drug in circulation and increases its concentration at the tumor site, allowing for lower drug doses, which also reduces side-effects and costs. In addition, encapsulation increases the half-life of the drugs and allows delivery of water insoluble and/or poorly soluble biocompounds[227].

Albumin has been conjugated to several metabolites from the fifties[228] and its encapsulation has been a research tool for several purposes from the late seventies[229]. These and many other early studies opened the field for other researchers to analyze the use of this protein for the encapsulation of cytotoxic drugs. In this regard, to increase drug delivery to the tumors two different strategies have been used: passive targeting, which takes advantage of the ability of albumin to bind to different cellular receptors, and active targeting that uses several ligands attached to the albumin nanoparticle surface to direct it to the targets (Fig. 3)[227]. However, which strategy is better in cancer, passive or active targeting? In literature there is controversy about this. In the following pages, we will provide a detailed overview of the status of the topic.

4.3.1. Passive targeting strategies with albumin-based nanoparticles

As mentioned above, albumin is a natural transporter of many metabolites, and this role suggested that this protein should have cellular receptors for the delivery of those metabolites. In the eighties an albumin receptor was isolated from the Hepatitis B virus and a Streptococcal strain[230,231]. Shortly after these studies, the isolation of a eukaryotic albumin receptor was achieved by Schnitzer's group[232], who found an endothelial vascular glycoprotein of 60-kDa that binds albumin. This protein was later named as GP60, it belongs to a family of sialoglycoproteins found in the vascular endothelium and is responsible for albumin transcytosis from the blood[233,234]. Besides, later studies showed that albumin binds to other sialoglycoproteins, including gp30 and gp18 and also to a secreted protein acidic and rich in cysteine or SPARC, which is structurally related to GP60[235]. After these discoveries, several other proteins have been shown to act as albumin receptors: the neonatal Fc receptor (FcRn), megalin, cubilin and CD36[236].

However, **GP60** (or albondin) is the best characterized albumin receptor and, accordingly, its role in albumin NPs delivery in chemotherapeutic applications has been extensively studied. As a result, the first albumin-based NPs approved for cancer treatment, nab®-paclitaxel or Abraxane®, has been shown to be delivered through albumin binding to GP60[237]. As stated above, in Section 3, albumin nanocoating of paclitaxel not only reduced the toxicity of Cremophor, the solvent used to deliver the free drug but also increased tumor accumulation and the targeted delivery through its interaction with GP60[238] (Fig. 3B). Nab®-paclitaxel is the most successful example of passive targeted delivery by albumin-based NPs through their interaction with GP60, but other studies have described the development of albumin-based formulations that utilize the interaction of albumin with this glycoprotein for the transport of several chemotherapeutic drugs[239–243].

BSA-coated gold NPs loaded with cisplatin were used in a study to analyze their ability to bind the GP60 receptor and the feasibility of this approach for *in vivo* studies[242]. Similarly, cisplatin/gemcitabine-loaded PEI/BSA-coated ZnO NPs were also used for the analysis of their interaction with GP60, showing a

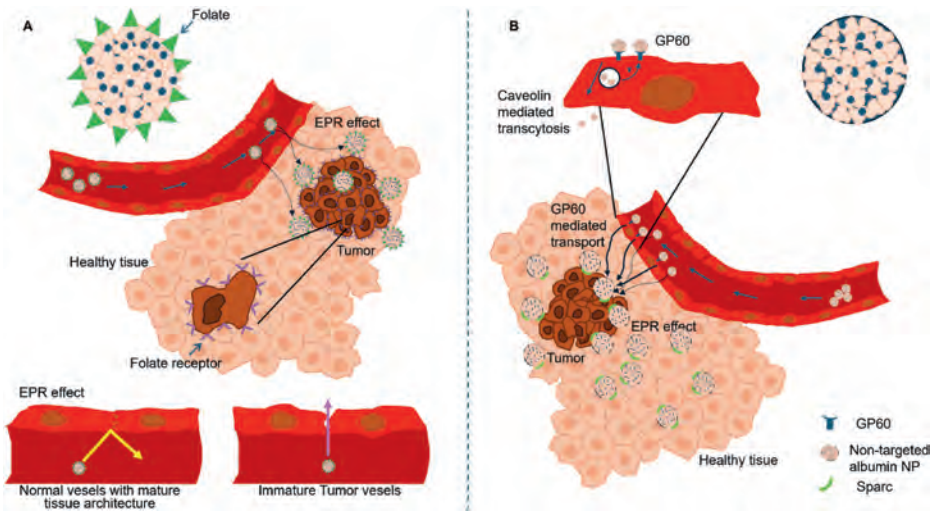

Figure 3 To target or not to target, that's the question. Targeting nanoparticles increases their specificity for the tumor cells, but this also leads to lower recognition by the albumin receptors in the endothelial cells and less efficient extravasation. (A) Targeted albumin nanoparticles with the folate receptor recognize the receptors overexpressed in tumors and the drug is specifically delivered to the tumor site, helping to reduce toxicity to non-tumoral tissue. In addition, it also increases the concentration of the NPs at the tumor site. On the contrary, folate (or other targeting molecules) binding reduces recognition by the albumin receptors, and these NPs rely mainly on the EPR effect to cross the endothelial barrier to reach the tissues. (B) Non-targeted NPs do not have the same degree of specificity for the tumor cells, but the albumin in their surface binds better to the GP60 receptors on the endothelial cells, increasing their transport by transcytosis to the tumoral environment. Then, the Sparc protein helps the attachment and uptake of the nanoparticles by the cells, although this role is not specific for the tumor cells and the drug will also enter surrounding normal tissue.

strong binding of drug-loaded PEI/BSA-coated ZnO NPs with the glycans of GP60[241]. Passive targeting of gemcitabine with albumin-based NPs have been achieved in several other studies for the treatment of pancreatic cancer[244–246], showing a better response than free gemcitabine and efficacy in treating gemcitabine resistant pancreatic cancer cell lines. Likewise, *in situ* self-assembled HSA-tannic acid NPs has been successfully tested for the dual delivery of gemcitabine and gambogic acid in the treatment of xenografts bearing tumors derived from a NSCLC cell line[247]. Furthermore, Koziol et al.[239] developed an albumin-bound fluorouracil-analog formulation to avoid non-targeted effects of this drug on healthy tissues. They tested the carrier on two breast cancer cell lines and observed that the efficiency of the formulation was dependent on the level of expression of GP60 on their surface, with better results in the cell line with higher number of receptors[239]. Another drug that has been passively delivered to tumors, using albumin-based formulations, is the anthraquinone pirarubicin. Zhou's group[240] synthesized an albumin-bound complex, HAS–pirarubicin, by the thin-film hydration method using as solubilizer polyoxyl 15 hydrostearate (Kolliphor® HS 15), for GP60 mediated delivery into breast cancer cells xenografts, observing higher pirarubicin delivery and better therapeutic effectiveness than free pirarubicin[240].

Doxorubicin, another drug of the anthraquinone family, has been used from the early sixties for the treatment of several types of cancer, including various sarcomas and cancers of the breast, ovary, bladder, thyroid, etc. Despite the observed cardiotoxicity and other side effects, this drug is still the first line treatment for many types of cancer, either alone or in combination[248,249]. To overcome this toxicity, several strategies have been followed, and liposomal doxorubicin was the first encapsulated cytotoxic drug approved by the FDA in 1995[250]. Although most of the works encapsulating doxorubicin in albumin formulations have used several active targeting strategies to specific cellular receptors (see following section), some groups have delivered this cytotoxic drug by passive targeting approaches with albumin-based formulations. An early work by Dreis et al.[251] showed the increased effect of the doxorubicin-loaded HSA nanocarriers compared to free doxorubicin in neuroblastoma cell lines. *In vivo* studies proved that doxorubicin-loaded HSA NPs have lower toxicity on a hepatocellular carcinoma mice model[252] and higher efficiency on primary tumors and metastasis in a colon cancer xenograft[161]. In a recent approach, Meng et al.[253] modified the hydrophilic amino acids in HSA (NQTY) to hydrophobic (LVF) to easily synthesize HSA NPs by the self-assembly method and efficiently entrap and deliver doxorubicin, leading to higher GP60 and SPARC interactions and increased delivery of doxorubicin to the tumors in a xenograft breast cancer model.

Another albumin interactor whose role has been analyzed in passive tumor targeting by albumin-based NPs is **SPARC**. This protein, which is structurally and functionally related to GP60[235], is a secreted protein, and early work showed a correlation between SPARC high expression in tumors and a better efficiency of nab®-paclitaxel[254]. Despite this first observation, a follow up work failed to observe a better effect of nab®-paclitaxel in the presence of higher SPARC expression levels[255]. This discrepancy could be explained because in the first work nab®-paclitaxel efficacy was associated with high levels of HER2 (human epidermal growth factor receptor 2) in the samples, meanwhile in the second study HER2 status was not considered. This controversy was also observed in two studies analyzing patient samples of NSCLC. Work by Komiya et al.[256] supported the better response to nab®-paclitaxel in NSCLC patients with high levels of SPARC. This study analyzed 200 lung cancer patients and observed a better response to Abraxane® when strong SPARC immunostaining was observed in the stroma, proposing the use of SPARC staining as a predictive marker for the response to nab®-paclitaxel. On the other hand, a work analyzing the effect of SPARC levels on response to nab®-paclitaxel of 62 NSCLC patients observed a negative correlation[257]. The differences between the data from these two studies are difficult to understand, although a different nab®-paclitaxel administration method (oral *vs* intravenous) could explain the cause for the discrepancies. Also, high SPARC levels have been linked to a better response to nab®-paclitaxel in patients with estrogen receptor-positive (ER^+) and negative for $HER2^-$ breast cancer[258], as well as to accumulation of the nanoparticulated drug in pediatric sarcomas[259].

Nevertheless, the general idea is that high levels of SPARC lead to accumulation of albumin formulations in the tumor area. In fact, this concept was used by Cohen and colleagues[260] to increase the efficacy of nab®-paclitaxel. In their work with advanced metastatic solid tumors, these authors showed that a pre-treatment with azacitidine, a drug that increases SPARC expression through demethylation of its promoter, followed by nab®-paclitaxel, led to "dramatic responses of pretreated cancer patients"[260]. This concept has also been recently explored by Zheng et al.[261], who introduced a CRISPR controlled NF-κB within albumin NPs to increase SPARC levels and achieve a better response in the treatment of subcutaneous tumors with commercial nab®-paclitaxel. In addition to the role of SPARC in the nab®-paclitaxel pharmacological properties, its interaction with albumin allows a similar role in the delivery of other chemotherapeutic drugs by albumin-based NPs. This is the case of the self-assembled nanocarriers generated from the conjugate Cellax, a carboxymethylcellulose–PEG-based polymer bound to docetaxel, that have the ability to adsorb albumin in its surface and, thus, be internalized because of the albumin and SPARC interaction, allowing a better *in vivo* delivery to SPARC-rich tumors[262]. Lapatinib is another chemotherapeutic drug bound to albumin that has been delivered to tumors using the passive targeting approach by SPARC. Zhang et al.[263] synthesized nanocarriers with a lapatinib-albumin core and a lecithin corona for the treatment of breast cancer cells and subcutaneous xenografts *in vivo*. They observed tumor accumulation and co-localization with SPARC, suggesting an albumin-mediated interaction. In addition, lapatinib-loaded HSA NPs have been also prepared and used for the treatment of triple-negative breast cancer (TNBC). In this study, the authors used a mouse model of breast cancer using 4T1 cells (a murine TNBC cells) that metastasize the lungs. Animals treated with the encapsulated lapatinib showed a reduced tumor burden and metastasis than mice treated with the commercial non encapsulated lapatinib, which the authors attributed to a high level of SPARC expression in the extracellular matrix of the tumors[264].

FCRN is another interesting albumin binding protein that has been used as a receptor for passive delivery of albumin based nanoformulations. FCRN interaction with albumin was discovered by Chaudhury's group[265], who found that the interaction prolongs albumin lifespan. The effect of FCRN expression on nab®-paclitaxel delivery was analyzed by Li et al[266]. Using FCRN knockout mice they observed that this receptor increases tissue accumulation of nab®-paclitaxel, while reducing excretion to

feces, highlighting the importance of FCRN in the efficacy of Abraxane®. **Megalin** is another receptor that binds albumin, and due to its high expression in the kidney and gallbladder has been mainly used for the treatment of kidney injury or cholecystolithiasis[267,268]. This is also true for **Cubilin**, another albumin receptor that has been proposed as a target of allopurinol-loaded albumin NPs in the treatment of hyperuricemia[269]. Despite the absence of studies on cancer for these receptors, due to their ability to bind albumin and high renal expression, both cubilin and megalin could be used in future albumin−NP formulations for the treatment of kidney cancer.

Beyond traditional passive drug delivery applications, albumin NPs have also been explored in **"hitchhiking" strategies**, which leverage serum albumin's natural trafficking to lymph nodes. This property enables the passive targeted delivery of immunological payloads to dendritic cells within these lymphoid tissues[270]. In such systems, antigens are covalently bound to albumin, forming nanostructures that function as nanovaccines. These constructs have demonstrated up to a 30-fold increase in T-cell priming, resulting in improved antitumor responses and reduced systemic toxicity as compared to the parent compounds[271]. In a related study, albumin-based nanocomplexes loaded with immunostimulatory agents (CpG oligonucleotides and SIINFEKL peptide) significantly outperformed conventional adjuvanted vaccines, eliciting approximately ten times more antigen-specific cytotoxic T lymphocytes[272]. These findings are further supported by another work showing that albumin hitchhiking nanodevices can elicit potent antitumor immune responses, leading to markedly improved survival outcomes in murine models when compared with standard therapies[273].

4.3.2. Active targeting strategies with albumin-based nanoparticles

As already shown, albumin-based NPs have the ability to bind to several receptors and factors allowing specific delivery to some tumors. In addition, the enhanced permeability and retention (EPR) of the NPs due to the immature nature of the tumor neo vasculature also favors specific delivery and reduced toxicity (Fig. 3B)[274]. Besides this passive targeting approach, a higher specific delivery can be achieved through the inclusion of ligands that bind receptors expressed in cancer cells in the surface of the particles. This strategy is called active targeting and has been extensively used for tumor drug delivery[274] (Fig. 3A). In fact, we have found more than thirty different targeting strategies to actively direct albumin NPs to specific tumor types, which we will briefly describe in the following lines.

4.3.2.1. Folate (FA) conjugation. This is probably the most frequently used strategy for achieving active targeting. The overexpression of folate receptors in cancer has been known for many years[275] and for this reason they have been used in many studies as targets for therapeutic delivery of many anticancer drugs. Folate association with albumin-based NPs (Fig. 3A) was first described in 2004 by Zhang et al.[276], who showed a high accumulation of FA-conjugated BSA NPs in an ovarian cancer cell line. This initial work led the way for many other studies using FA as a targeting modification of albumin NPs. In fact, many of the most prescribed drugs for cancer treatment have been encapsulated in FA-conjugated BSA NPs and the efficiency of these formulations has been tested. Table 5[172,210,277-307] shows a compendium of these studies. Most of these studies show specific delivery and drug accumulation in the tumor area, but only a few are used *in vivo* with mouse or rat models, and their clinical efficiency is still to be tested.

4.3.2.2. HER2 receptor targeting. HER2 belongs to epidermal growth factor receptor (EGFR) family. It is amplified in many human cancers, but it has special relevance in breast cancer, where 15% of the cases have high expression of this receptor[308]. HER2 receptors were one of the first oncoproteins used in targeted therapies in cancer. The drug trastuzumab, under the commercial name of Herceptin®, became in 1998 the second monoclonal antibody approved by the FDA for its use in humans[309]. The initial optimism created by this directed therapy for HER2 positive breast cancer patients was unfortunately hindered by the appearance of resistance mechanisms that led to relapse. However, recent work has aimed to use this monoclonal antibody to generate targeted nanoformulations loaded with chemotherapeutic agents, taking advantage of the high levels of expression of the receptor to direct the drugs to the tumor area, increasing their concentration in the tumor while protecting it after administration.

In general, trastuzumab and other monoclonal antibodies (mAb) are conjugated to the surface of albumin NPs by *N*-hydroxysuccinimide (NHS)-based strategies, particularly using the carbodiimide chemistry[310] (Fig. 4) or by the thiolation of mAb and the activation of the surface of the nanocarriers with PEG-α-maleimide-ω-NHS ester (resulting in sulfhydryl-reactive particles). Regarding the latter, Steinhauser et al.[311] bound a thiolated trastuzumab to HSA-based NPs, achieving specific binding and uptake of the particles by HER2 overexpressing cells. Using a similar strategy, Anhorn et al.[312] targeted SK-Br-3 cells overexpressing HER2 with trastuzumab-decorated HSA NPs loaded with doxorubicin, a common chemotherapeutic drug used in breast cancer management. These authors demonstrated the high specificity of the trastuzumab-modified NPs using MCF7 cells, which do not overexpress HER2, as well as a biological efficiency of the reported formulation similar to free doxorubicin. Another drug encapsulated in albumin-based NPs and delivered using trastuzumab as ligand to target HER2 positive cells is methotrexate, a dihydrofolate reductase inhibitor that blocks pyrimidine synthesis[313]. Taheri et al.[314] used trastuzumab-HSA NPs to deliver methotrexate to cells overexpressing HER2, showing the specificity of this nanoformulation to HER2 positive cells. Interestingly, trastuzumab has been also linked to albumin NPs to target HER positive cells for photothermal therapy using a novel bacterial SpyTag/SpyCatcher ligation system[315].

In addition to trastuzumab, other antibodies targeting HER2 have been used bound to albumin-based NPs. Kouchakzadeh and colleagues[316] linked a novel mAb directed against the extracellular domain of HER2 (1F2) to HSA NPs obtaining high attachment and low toxicity. Later, these authors used this system to encapsulate 5-fluorouracil, showing the specificity of the NPs towards the $HER2^+$ cell line SKBR3, with no uptake by the HER2 negative MCF-7 cells[317]. In a more recent study Zhang et al.[318] used a similar approach to encapsulate 2-methoxy-estradiol and treated the same cell lines to show specificity. Another study analyzed the use of pertuzumab as targeting antibody against HER2. The authors created a complex NPs formulation based on albumin bound MnO_2 loaded with sorafenib and decorated with pertuzumab and tested this combination *in vitro* and *in vivo* on a thyroid cancer mouse model obtained by injection of thyroid cancer cells (8305 C) in the tail vein of BALB/c female nude mice[319]. This recent work showed that this NP formulation is effective and selective of thyroid cancer cells both *in vitro*

Table 5 *In vitro* and *in vivo* **(in bold)** studies that include drug-loaded FA-conjugated BSA NPs.

Drug loaded	Other component	Cancer type	Subject of the study	Ref.
Cisplatin	–	Breast	MCF7 cells	277
Gemcitabine	–	Breast, ovary	Ovcar-5 & MCF-7 cells	278
Docetaxel	–	Liver, breast, prostate, sarcoma	MCF7, SMMC-7721 & PC-3 cells/**S180 xenografts**	279
Bexarotene	–	Breast, NSCLC	MCF7 & A549 cells	280
Tamoxifen	Alginate	Breast	MCF7 & T47D cells	281
Doxorubicin	Dextran	Liver	**–/H22 cells xenograft**	282
Ergone	–	Cervix, breast	KB & 4T1 cells	283
10-Hydroxycamptothecin	–	NSCLC, gastric	A549 & SGC7901 cells	284
Paclitaxel	–	Prostate	PC3 cells	285
Vinblastine	–	–	No *in vitro* or *in vivo* tests	286
Paclitaxel and 2-methoxyestradiol	–	Esophagus, sarcoma	EC109 cells/**S180 xenografts**	287
Doxorubicin & chlorin e6	–	Cervix	HeLa cells	288
Gemcitabine	–	Breast (TN)	MDA-MB-231 cells	289
Artemether	–	Breast	SK-BR-3 & MDA-MB-231 cells	290
Myricetin	–	Breast	MCF7 cells	291
Sorafenib	–	Liver	SMMC-7721 cells	292
Resveratrol	–	Liver	HepG2 cells/**H22 xenografts**	172
Ginsenoside Rg5	–	Breast	MCF7 cells/**xenografts**	293
Cabazitaxel	–	Cervix	HeLa cells/**xenografts**	210
Paclitaxel and di-fluorinated curcumin	–	Ovary, cervix	SKOV-3 & HeLa cells	294
Curcumin	–	Colon	**–/HT 29 xenografts**	295
Hydroxycamptothecin	–	Breast	**–/MCF7 xenografts**	296
Quetiapine	Chitosan	Prostate, pancreas, colon and breast	PC3, PANC, HT-29 and MDA-MB-231 cells	297
Fisetin	–	Cervix	HeLa cells	298
Propolis	–	Breast, NSCLC	MCF7 & A549 cells	299
Naringenin	PEG	Breast	MCF7 cells	300
Thymol	PEG	Gastric, pancreas	AGS, pancreatic cells	301
Lupine derivative (CTr)	PEG	Liver	HepG2 & BEL-7402 cells/**H22 xenografts**	302
Methyl-β-cyclodextrin	Adamantane	Liver, NSCLC	KB, A549 cells/**KB xenografts**	303
Erlotinib	–	Glioblastoma	U87MG, C6 cells/**C6 orthotopic gliomas (rats)**	304
Actinonin	–	Lung adenocarcinoma	A549 cells/**urethane induces lung adenocarcinoma**	305
Baicaln	–	Breast	MCF7 cells	306
Raloxifene	–	Breast	MCF7 & MB231 cells	307

and, for the first time also, *in vivo*. In addition to the use of antibodies for HER2 targeting, Saleh et al.[320] used an aptamer for HER2 targeting by albumin NPs in HER2 positive breast cancer cells, showing specific binding and the feasibility of this strategy as a drug delivery system. Despite the positive results shown in the previous studies, only the work by Jia et al.[319] used an *in vivo* model to analyze their efficiency in a more physiological setting. For this reason, the use of HER2 targeted albumin NPs in clinic is still a distant goal.

4.3.2.3. EGFR as a target. A similar strategy to the targeting of HER2 has been used for EGFR. This receptor is frequently mutated into several types of cancer, including breast, head and neck,

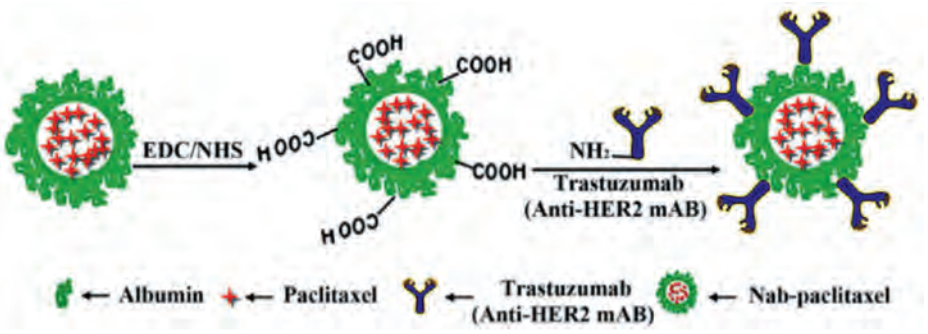

Figure 4 Synthesis of trastuzumab-conjugated nab-paclitaxel by the carbodiimide chemistry. Reprinted with permission from Xiong et al. 310 Copyright © 2018.

colorectal and non-small cell lung cancer. This makes the EGFR a bonafide therapeutic target in those types of cancer[321]. For this reason, several monoclonal antibodies have been developed to treat those malignancies, including cetuximab, panitumumab or matuzumab among others[322]. As mentioned for HER2, most of these therapeutic approaches have failed long term due to the development of resistance mechanisms, but another use for the antibodies against EGFR has emerged with their use as targeting molecules to deliver chemotherapeutic agents. Thus, Altintas et al.[323] used a fragment of an EGFR antibody, a nanobody, linked to PEGylated albumin-based nanocarriers to specifically deliver a multikinase inhibitor (17864) to cells overexpressing EGFR. Cetuximab-conjugated albumin NPs have been used for targeted delivery into colon cancer cells and mice xenografts of RKO colon cancer cells, but although it was reported a good binding of the NPs to cells expressing high amount of EGFR[324], the advantage of this strategy to deliver doxorubicin to cells and xenografts was very limited[325]. Two other works have used complex nanosystems for the targeted delivery through the EGFR interaction. For example, Hou et al.[326] prepared cetuximab-coated BSA nanocarriers loaded with a plasmid-shRNA (targeting the survivin gene) and superparamagnetic Fe_2O_3 NPs and observed better targeting/efficiency on lung cancer cells than individual treatments with either free cetuximab, non-targeted pshRNA-loaded BSA-Fe_2O_3 nanocarriers or non-magnetic cetuximab-decorated pshRNA-loaded BSA NPs. In another work, Li et al.[327] synthesized ^{131}I-labeled cetuximab-coated BSA-PCL (polycaprolactone) NPs and utilized this nanoformulation to treat mice xenografts of the U87 glioblastoma cell line, observing the accumulation of the radiolabeled NPs in the tumors. In addition to antibody-based targeting, aptamers have also been used for active targeting of EGFR expressing cells. In fact, Chen et al.[328] designed *EGFR* RNA aptamer-conjugated cisplatin-loaded albumin NPs and effectively targeted HeLa cells inhibiting EGF signaling and cell growth with a better efficiency than free cisplatin. In addition, it had good *in vivo* tolerability and therapeutic efficacy.

4.3.2.4. Other growth factor receptors. In addition to EGFR and HER2, other important growth factor receptors in cancer development have been the target of albumin formulations with linked monoclonal antibodies or small molecules that antagonize the receptors. Heukers et al.[329] used an anti-MET (hepatocyte growth factor receptor) nanobody to target albumin NPs to this receptor. The nanobody was used in this instance both as a targeting and therapeutic agent. The NPs showed specific targeting and internalization of the NPs by cells expressing the MET receptor. Due to their role in the development of the new vessels necessary for tumor growth, VEGFRs (vascular endothelial growth factor receptor) are key players in cancer development, and for this reason they have been a therapeutic target in cancer for more than twenty years. Due to their crucial role in tumor growth, these receptors are usually overexpressed in cancer and can be used to target albumin NPs containing chemotherapeutic drugs[330]. Kushwah et al.[331] used anacardic acid, a molecule that binds the VEGFRs with high affinity, to decorate albumin nanocarriers containing docetaxel and gemcitabine. These targeted NPs were tested on MCF-7 and MDA-MB-231 breast cancer cells, showing an increased apoptotic rate. In addition, *in vivo* studies showed a reduction in the toxicity of the chemotherapeutic drugs.

4.3.2.5. Carbohydrates as targeting ligands. There are some works that have used carbohydrates to target specific tumors. This is the case of galactose/galactosamine or lactose that have been used to target liver cancer cells. Shen et al.[332] reported a galactosamine-conjugated BSA NPs to deliver doxorubicin to HepG2 cells, through the interaction with asialoglycoprotein receptors, proposing the use of this formulation for liver cancer treatment. In a later work, Huang et al.[333] prepared galactosylated albumin NPs loaded with curcumin to target hepatocellular carcinoma cells, showing inhibition of cell growth and migration. Lactose has also been used to target hepatocellular carcinoma. Thao et al.[334] used lactose to decorate BSA NPs loaded with doxorubicin and paclitaxel, then they used this formulation to treat HepG2 cells and spheroids, showing high penetration and cytotoxicity. They also observed the accumulation of the NPs in the liver of ICR mice. Teran-Saavedra et al.[335,336] used a similar approach in two works, where they showed the preparation and efficiency of lactosylated BSA NPs for targeting the hepatocellular carcinoma cell line HepG2, using doxorubicin as model drug. Mannose has been also used for active targeting delivery, although this carbohydrate was used to target tumor associated macrophages (TAM) that are very important in the immunosuppressive environment of tumors and their reactivation may be an interesting therapeutic approach. In this regard, Gong et al.[337] prepared mannose-decorated HSA NPs for the delivery of a SHP2 inhibitor (SHP099), which can reactivate macrophage function in the tumor environment. They linked these NPs to photosensitizer IR820 to induce laser mediated release of SHP099 inducing the transformation of M2-TAMs (immunosuppressive) to M1 (immunoactive). Then, they used this formulation *in vitro* and *in vivo* on a mouse model bearing CT26 cell tumors, observing a high efficiency of the NPs in inhibiting tumor growth, and its ability to restore the sensibility of these tumors to anti-PD1 immunotherapy[337].

4.3.2.6. Targeting transferrin receptor (TFR). The use of TFR as a target for drug delivery has important advantages. TFRs are overexpressed in many tumors and they are present in the Blood Brain Barrier (BBB)[338]. As the low drug crossing of the BBB is a common cause for the failure of treatments against brain tumors, transferrin has been used to decorate NPs to try to overcome this problem. This idea was first tested by Ulbrich et al.[339], who used both transferrin and a TFR mAb (OX26 or R17217) conjugated to HSA NPs through a PEG-based linker to target these receptors in the BBB. The formulation was loaded with loperamide, an analgesic that does not cross the BBB, and tested in mice, showing that NPs were able to cross the BBB and induce an antinociceptive effect in the mice. This approach has been further developed more recently for the treatment of brain cancer. Zhao et al.[340] prepared dual targeting BSA NPs, containing a disulfiram/copper complex and regorafenib, to block the growth of glioma cells and induce the transformation of M2 macrophages into M1. As active targeting moieties, they used the TFR-binding peptide T12 to target the BBB, and mannose for the macrophages. This complex nanoformulation was used both *in vitro* and *in vivo*, obtaining very promising results, with a biomimetic drug delivery to mice bearing gliomas and achieving a therapeutic effect, almost doubling the life of both nude and immunocompetent mice. On the other hand, as mentioned above, TFRs are overexpressed in several types of cancer, and this has been used to direct albumin NPs loaded with different chemotherapeutic agents. Retnakumari et al.[341] used transferrin to decorate albumin NPs loaded with sorafenib and used this formulation in Chronic Myeloid Leukemia

samples. The authors isolated Patient Derived Leukemic Mononuclear Cells and treated them with the NPs, observing that the formulation efficacy was maximum when used on the more treatment-resistant patient samples. Moreover, transferrin bound to albumin NPs has been also used for targeting solid tumors. This approach was achieved by adding a PEGylated lipid bilayer to BSA NPs, which were loaded with the histone deacetylase inhibitor vorinostat and paclitaxel, and its surface was then conjugated with transferrin. This formulation was used to treat HepG2 cells and xenografts, showing good delivery, efficiency and prolonged half-life[342].

4.3.2.7. Hyaluronic acid (HA) as a targeting ligand. CD44 receptors are found overexpressed in many types of cancer[343] and this has been exploited to design NPs specifically targeted to those tumors. This receptor strongly binds to HA[344] and this has been used by many groups to develop targeted albumin-based NPs for their use on CD44 positive tumors. The first reports using this strategy loaded the albumin NPs with cytotoxic drugs, such as doxorubicin[345] (Fig. 5A), paclitaxel and Imidazoacridinone C-1375[346]. These formulations showed a marked accumulation of the drugs in ovarian carcinoma SKOV3 and A2780 cells[346], as well as in breast cancer MDA-MB-231 cells and xenografts, showing a strong anti-tumoral activity in the breast cancer model[345] (Fig. 5B and C). In a more recent study, Li et al.[347] used cationic albumin NPs decorated with HA and loaded with a differentiation agent (all-*trans*-retinoic acid) to induce differentiation of B16F10 melanoma cancer stem cells. Using this strategy, they achieved a good cell uptake and a strong reduction of cell viability. Moreover, they used the NP formulation to treat mice with tumors derived from B16F10 cells, obtaining a remarkable tumor accumulation and a strong reduction in tumor growth. Similar formulations have been used to load paclitaxel to treat ovarian cancer[348] and NSCLC[349] cell lines, or with doxorubicin for the treatment of breast cancer cells[226,350]. HA binding to albumin NPs is a recent addition to the targeting strategies used with this formulation, but the remarkable results obtained in the studies shown above should encourage other research groups to follow this line of research.

4.3.2.8. Tumor homing peptides (THP). Some studies that searched for specific methods to target cancer cells discovered this THP, which are short amino acid sequences that specifically bind to tumor cells[351]. Several THPs have been discovered, but CREKA and LyP-1 (CGNKRTRGC) were the first used for albumin NPs targeting. The authors used nab®-paclitaxel that was linked to the THPs through a sulfhydryl residue. Then, the targeted NPs were used to treat mice bearing MDA-MB-435 human

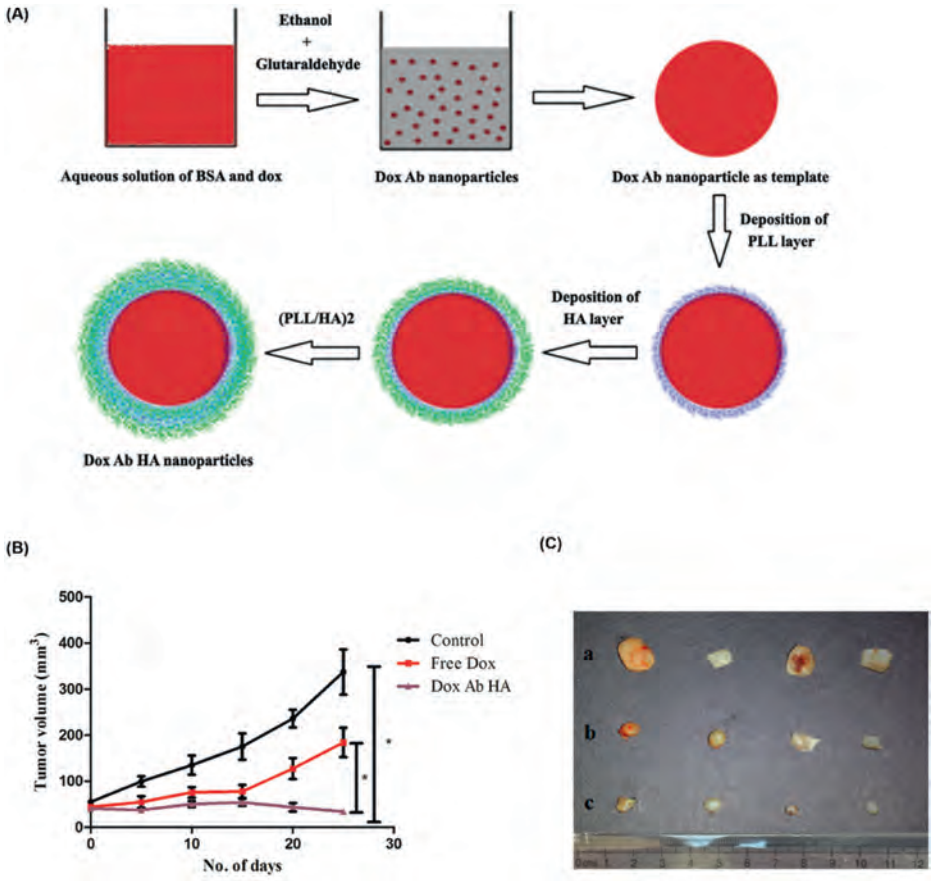

Figure 5 HA-conjugated DOX-loaded BSA NPs to target CD44 receptors and treat breast cancer tumors. (A) Scheme of synthesis of the BSA NPs and their derivatization with HA. (B) Representation of the tumor volume *vs* time (C) Image of extracted tumors (a: control mice; b: free drug; c: HA-conjugated DOX-loaded BSA NPs (Dox Ab HA NPs). Sections (B) and (C) of the figure demonstrate the strong anti-tumoral activity of the targeted nanoformulation in an MDA-MB-231 xenograft animal model. Reproduced with permission from Pulakkat et al. 345 Copyright © 2016.

cancer xenografts, achieving a good accumulation in the tumor areas and a strong reduction of tumor growth[352]. Another THP is the RGD peptide. This tripeptide has been used to direct albumin NPs to pancreatic cancer cells by binding to the integrin v3 receptor. These authors confirmed a specific targeting of the BxPC-3 cells, and an increased cytotoxic effect of gemcitabine-loaded RGD-albumin NPs compared to the free drug[353]. The tripeptide RGD has been recently used to decorate albumin NPs containing the RSPO-targeting anticancer chimeric protein, which binds to *R*-spondins and blocks the activation of Wnt signaling, a pathway very important in the development of several types of cancer. This formulation was very efficient in blocking the growth of colon cancer organoids and colon tumors *in vivo*, effectively reducing WNT signaling and cell proliferation[354].

In a different approach, Ming et al.[355] used fifteen morpholino oligonucleotides each linked to a RGD tripeptide and attached to a single albumin molecule to generate a nanoconjugate for cancer treatment. The authors hypothesized that the small size of the nanoconjugate would avoid cytotoxicity and increase distribution. Using A375/Luc705 melanoma cells, the authors observed a high accumulation of the nanoconjugate both in 2D cultured cells and in 3D tumor spheroids. Another THP that has been used to label albumin NPs for targeting cancer cells is the peptide CPTASNTSC. This peptide had been previously isolated for its ability to specifically bind TNBC cells[356]. This peptide was linked to albumin NPs, loaded with doxorubicin and its effect analyzed on TNBC cells and xenografts, showing overall better results than the free drug[357]. Furthermore, Mullapudi et al.[358] linked the CkRFYVVMWKk peptide sequence, that specifically binds the CD47 receptor, to albumin NPs loaded with gemcitabine. Then, they tested the effect of these NPs on bladder cancer cells and in a mouse orthotopic bladder cancer model. This approach reduced the gemcitabine IC_{50} ten times and was able to reduce the tumor burden in the mouse model. THPs have been also used to target the acetylcholine receptors. Zhu et al.[359] bound a CGREIRTGRAERWSEKF peptide to albumin NPs and loaded the NPs with celastrol and LY2157299 to induce the M2 to M1 transition in macrophages and block the growth of glioma cells, respectively. This formula was successful in the treatment of GL261 glioma cells with better efficiency than non-targeted NPs or treatment with free drugs. In addition, they also showed a higher survival rate and a decrease of M2 macrophages in an orthotopic glioma mouse model. The W-peptide is another THP option. This hexapeptide, with a sequence Trp−Lys−Tyr−Met−Val−D-Met, can bind the formyl peptide receptors that are overexpressed in TNBC[360]. For this reason, Liu et al.[360] bound this hexapeptide to albumin NPs loaded with paclitaxel. These NPs were then tested on MDA-MB-231 cells and on a mouse model of TNBC, showing a strong apoptotic induction and a reduced tumor burden. Also, a neuropeptide Y derivative has been conjugated to doxorubicin and loaded within albumin NPs for the treatment of breast cancer cells, which usually overexpress the neuropeptide Y receptor. The authors of this study showed that the NPs linked to the neuropeptide Y derivative selectively bind MCF7 breast cancer cells, but not to MCF10 normal mammary gland cells[361].

4.3.2.9. Chondroitin sulfate as a targeting ligand. Chondroitin sulfate is a glycosaminoglycan with high affinity for CD44 and P-Selectin receptors[362]. This, and its low toxicity makes this molecule a good candidate to label albumin NPs for targeted therapy. This approach has been used to direct doxorubicin loaded albumin NPs to breast cancer cells and showed promising results on 4T1 cells and orthotopic 4T1 tumor-bearing mice[363]. A similar formulation was used by Kudarha and Sawant[364] that loaded temozolomide within chondroitin sulfate-conjugated BSA NPs to achieve CD44 receptor mediated targeting of brain tumors. These authors showed that the NPs were able to cross the BBB and a higher accumulation of the drug in the brain. A more complex strategy was used by Luo et al.[365] that generated hybrid lipid−albumin NPs modified with chondroitin sulfate and D-α-tocopherol polyethylene 1000 glycol succinate as targeting ligands. These NPs were loaded with paclitaxel as a model drug and used for the treatment of multi-drug resistant MCF7 breast cancer cells and xenografts, obtaining very good results in terms of tumor volume reduction and survival.

4.3.2.10. Carbonic anhydrase-IX (CA-IX) as the target of acetazolamide. In most tumors, the growth of the tumoral mass leads to the appearance of areas where oxygen is lower than in the healthy tissue. In these areas of hypoxia, a higher expression of CA-IX is observed[366] and this can be used to target chemotherapeutic drugs to the tumor area. To our knowledge, only two works, from Arun's group, have used a CA-IX interactor linked to albumin NPs for targeted delivery. These authors used acetazolamide, a small ligand of CA-IX, conjugated to paclitaxel-loaded HSA NPs. With this nanoformulation they treated two TNBC cell lines: MDA-MB-468 and MDA-MB-231, finding better drug accumulation than free paclitaxel or non-targeted paclitaxel-loaded HSA NPs[367]. Moreover, these authors used acetazolamide-conjugated BSA NPs to deliver a curcumin analogue, 3,4-difluorobenzylidene curcumin. Using this combination, they showed high efficiency when treating the MDA-MB-468 and MDA-MB-231 cells, but they also employed this targeted-NPs to treat a TNBC patient derived xenograft. In this experiment, they observed a significant accumulation of the NPs in the hypoxic areas of the tumor and low levels found in the kidney or liver[368].

4.3.2.11. Glycyrrhetinic acid for liver targeting. Glycyr-Glycyrrhetinic acid is a bioactive compound found in licorice with many receptors in liver cells[369]. Thus, this ligand has been used to label albumin-based NPs for the targeted delivery of doxorubicin to HepG2 and HeLa cells, showing specificity towards the hepatic cancer cell line. In this work, the authors also analyzed the biodistribution of glycyrrhetinic acid labelled NPs in H22 liver tumor-bearing mice, finding a specific accumulation of the formulation in the liver[370]. Another study used glycyrrhetinic acid-conjugated BSA NPs loaded with curcumin to analyze their effect on hepatocellular carcinoma cells. In this study the authors observed a better blockage of cell growth and higher accumulation of curcumin inside the HepG2 cells than cells treated with non-targeted NPs or free curcumin[371].

4.3.2.12. Luteinizing hormone releasing hormone (LHRH) as a targeting agent. Due to the overexpression of its receptor in some tumors, LHRH is also a good tool for targeting several types of cancer[372]. Using this starting point, Taheri et al.[373] loaded HSA NPs with methotrexate and conjugated LHRH as a targeting moiety. They observed that this formulation was more efficient in inhibiting growth on LHRH receptor expressing cells, demonstrating the specificity of the targeting strategy. In a second work, Taheri et al.[372] analyzed the *in vivo* effect of the NPs and observed

that the targeted NPs were able to block the growth of 4T1 breast cancer tumors, in deep contrast with mice treated with non-targeted NPs.

4.3.2.13. Other active targeting strategies. In addition to the most popular targeting strategies for albumin-based NPs, other molecules have been used less frequently. All of them try to take advantage of tumor specific markers to deliver albumin-based NPs to the tumor site, but to date have been poorly studied for this purpose. We have included these less used targeting strategies in Table 6[374-385], in which the nature of the targeting molecule and the application in which it has been used are shown.

Furthermore, it is worth highlighting a targeting strategy that has recently attracted the attention of the scientific community as it enhances and improves the capabilities of albumin NPs to actively target the tumors, surpassing their well-established role as drug delivery carriers. Due to the superior biocompatibility of albumin NPs and their lack of immunity, compared to other nanomaterials, their potential as biomimetic platforms by surface modification or "camouflaging" with cellular membranes has been described. In this regard, a variety of cell membranes, derived from different cell origins, including cancer cells[386], red blood cells[387] and stem cells[388], have been explored for this purpose. Functionalizing albumin NPs with cell membranes enhances their stability and improves their ability to target tumors effectively[389]; particularly for the delivery of photodynamic agents[390,391] and immunomodulatory molecules[392,393]. For example, coating these nanoparticles with macrophage-derived membranes has been shown to significantly improve tumor-specific accumulation, cellular internalization and overall antitumor efficacy[393,394]. Similarly, decorating albumin NPs with cRGD-functionalized RBC membranes has led to enhanced tumor localization[395]. Beyond their use in oncology, the development of albumin-based nanohybrids through membrane, exosome or vesicle integration is also being investigated for therapeutic applications in inflammatory diseases[396] and neurodegenerative disorders such as Alzheimer's disease[397].

To the best of our knowledge, we have summarized in this section most of the albumin nanocarriers that have been used for drug delivery in cancer. Most of the work described shows that the use of albumin NPs to vehiculate cytotoxic compounds produces better results than the use of the free drugs, reducing toxicity while increasing the accumulation in tumors and the efficacy of the treatments. Despite this positive view obtained from these studies, few albumin nanoformulations have reached clinical trials and only two formulations have been approved for cancer treatment (see Section 3). To improve albumin-based NPs efficiency and improve its specificity, many groups have aimed to link the NPs to molecules that bind to specific markers in tumors, but this strategy still has not reached clinical trials, and the step between *in vivo* mice models and the test with patients seems to be a critical barrier for this type of formulation. Hopefully, the experience obtained from the work shown above, and the development of more complex targeting strategies will allow in the near future to break this barrier and get albumin-based NPs to the next step.

5. Conclusions and future perspectives

In recent years, the use of proteins as biomaterials for the synthesis of nanocarriers has gained increasing attention, developing versatile platforms for the delivery of therapeutic agents in oncology and other medical fields. Their inherent biocompatibility, high biodegradability, low price, structural versatility, functional tunability and ability to bind and transport a wide variety of molecules make them ideal candidates for the design of effective drug delivery systems. Moreover, their importance lies in the ability to overcome many limitations of other materials currently employed in the preparation of NPs.

Among natural proteins, albumin (particularly HSA) has demonstrated superior performance due to its stability, extended circulation time, regulatory status and natural affinity for tumor-associated receptors, such as GP60, SPARC and FCRN. These characteristics have enabled the clinical translation of albumin-based nanoformulations, like Abraxane® or Sirolimus®,

Table 6 Less used active targeting strategies in literature.

Targeting moiety	Target	Drug loaded	Cancer	System tested	Ref.
Apolipoprotein E	BBB crossing	Loperamide	Brain	*In vivo* non-tumoral model	374
Digalactosyl diacyl glycerol	Asialofetuin receptor	α-Interferon	–	Hepatocytes	375
PR81 mAb	MUC receptor	5-Fluorouracil	Breast	MCF-7 cells	376
Hematoporphyrin	LDL receptors	Doxorubicin	Liver	HepG2 cells xenograft	377
Haloperidol	Sigma 2 receptor	Doxorubicin	Lung	*In vivo* non tumoral model	378
TRAIL	Death receptors	Doxorubicin	Lung/breast	A460, MCF7 cells	379
Gelatin	MMPs overexpressing tumors	GNF-5837	Breast	Breast cancer cells	380
AS1411 aptamer	Nucleolin	Doxorubicin	Breast	MCF-7 cells	381
ATF of uPA	Urokinase-type plasminogen activator receptors uPAR	Doxorubicin	Lung/liver	H1299 cells and H22 xenografts	382
Palmitic acid	Scavenger receptor-A	Pirarubicin	Breast	4T1 cells and 4T1 orthotopic tumors in mice	383
Durvalumab	PD-L1	Docetaxel	Breast	MDA-MB-231/46 & MCF-7 cells	384
Angopep-2	LDL receptor-related protein	Carmustine	Glioblastoma	U87 cells & orthotopic GBM nude mice	385

highlighting their potential to improve therapeutic outcomes while minimizing systemic toxicity.

However, despite these promising advances, significant barriers remain. This is put in evidence by the limited number of albumin-based NPs that have reached clinical approval, underscoring the gap between preclinical success and clinical application. Critical barriers that hamper the transition from promising preclinical data to robust clinical performance include nanoparticle stability, batch-to-batch reproducibility, regulatory complexities of nanoparticle-based therapeutics and the need for scalable and reproducible manufacturing processes. Moreover, while many active targeting strategies using ligands (*e.g*., folate, HER2, EGFR, transferrin, etc.) have been proposed and evaluated in preclinical studies, very few have progressed to clinical trials, reflecting the need for better standardization and validation methods. Future efforts should focus on overcoming these translational challenges by improving nanoparticle design, refining targeting strategies and integrating responsive or stimuli-sensitive systems to achieve better control over drug release and tumor specificity. Additionally, regulatory frameworks and large-scale manufacturing protocols need to be standardized to support the clinical development of albumin-based nanocarriers. With ongoing research and interdisciplinary collaboration, it is anticipated that next-generation albumin NPs will play a pivotal role in personalized cancer therapy and open new avenues in nanomedicine.

In addition to the need to improve the clinical advancement of albumin NPs, new research should be focused on improving the success rate of these therapies. The two albumin NP formulations approved by the FDA, Abraxane® and Sirolimus®, have an overall response rate of 33%−38%, which is better than previous therapeutic options, but still too low. To improve this, a wide set of combinatorial treatments are being analyzed in clinical trials (see Table 1), which could lead to better response rates, but also, future strategies should include the design of albumin NPs containing last generation chemotherapeutical drugs, as well as the newest therapeutical approaches, such as immunotherapeutical molecules, RNA vaccines or PROTACs. Other potential future efforts and research directions may include the use of artificial intelligence and machine learning approaches to optimize nanoparticle design parameters, predict drug loading efficiencies and simulate pharmacokinetics. These technologies may also support the development of multimodal and combination therapies, enabling the incorporation of multiple therapeutic agents or the combination of drugs with imaging molecules.

Thus, while albumin-based NPs currently represent a powerful and versatile tool for targeted drug delivery in oncology, their full clinical potential is yet to be achieved. Continued interdisciplinary research, along with strategic investment in translational infrastructures, is essential to unlock their promise and revolutionize targeted cancer therapy.

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Author contributions

Pérez-Herrero E: conceptualization, supervision, methodology, validation and writing (original draft & review & editing); Irache JM: validation and writing (original draft & review & editing), Fernández-Medarde A: validation and writing (original draft & review & editing).

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supporting information

Supporting information to this article can be found online at https://doi.org/10.1016/j.apsb.2025.11.035.

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