Albumin Nanoparticles in Cancer Therapeutics: Clinical Status, Challenges, and Future Directions

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Abstract:

Cancer, a global health burden, is characterized by uncontrolled cell growth and metastasis, often resulting in debilitating treatments and mortality. While conventional therapeutic strategies have improved survival rates, they are limited by challenges such as off-target toxicity and drug resistance. With their design to enable targeted drug delivery, nanoparticles have presented a promising avenue to overcome these limitations. Protein-based nanoparticles, particularly those based on albumin, are notable for their biocompatibility, stability, and ease of modification. The approval of Abraxane, an albumin-based nanoparticle formulation of paclitaxel, for metastatic breast cancer marked a significant milestone. However, further approvals have been slow to materialize until the recent approval of Fyarro® in 2021. This mini-review highlights the potential of albumin-based nanoparticles, focusing on their advantages, their current state, and progress in clinical use as anticancer therapeutics. We also discuss challenges impeding new approvals and future directions for unlocking the full potential of this technology.

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Introduction

Cancer is a complex and multifaceted disease characterised by uncontrolled cell growth. Proliferated abnormal cells contiguously invade neighbouring cells and spread to other organs in a process called metastasis, which is the leading cause of death from cancer. (1), (2) Through a multi-stage process, normal cells transform into tumour cells to cause cancer, which usually progresses from a precancerous lesion to a malignant tumour. (3) According to the International Agency for Research on Cancer (IARC), cancer is a leading cause of death globally, with approximately 10 million cancer-related deaths in 2022. (4) Furthermore, IARC predicts 35 million new cancer cases in 2050, an increase of 77% compared with 2022. (5) This emphasizes the urgent need for sustained efforts in research, treatment, and prevention to address the escalating global burden of the disease. Conventional therapeutic strategies which include surgery, radiotherapy, and chemotherapy have improved cancer patient survival rates; however, their efficacy in achieving complete eradication is limited. (6) The surgery effectiveness is often hindered by the varying reactions of early-stage malignant tissues, causing significant disruptions in nearby organs or tissues. (7) Radiation therapy side effects include early symptoms, predominantly skin reactions like erythema and desquamation, delayed effects including atrophy, fibrosis, and damage to blood vessels and neurons. (8) When administered through traditional delivery systems, chemotherapeutic agents lack specificity toward cancer cells, leading to severe adverse effects, such as dose-dependent hematotoxicity, acute cardiotoxicity, and the emergence of multi-drug resistance following prolonged drug exposure. (9), (10), (11) The lack of specificity is further aggravated by disease-related challenges since tumours become extremely heterogeneous as cancer progresses, resulting in a mixed population of cells with varying molecular characteristics and therapeutic response profiles. (12) Additionally, the traditional delivery of anticancer agents suffers from other drawbacks like poor drug solubility, limited bioavailability, and pre- or post-absorption inactivation.

To address these challenges, there is a pressing need for unconventional targeted delivery methods. Nanoparticle-based drug delivery systems offer the potential to selectively target cancer cells while minimizing damage to healthy tissues, thereby

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improving treatment efficacy and reducing side effects. (13) Besides, due to their versatility and customizable nature, nanoparticles (NPs) improve treatment effectiveness by enhancing drug stability and bioavailability, thus expediting drug development. (14) To date, several classes of NPs have been developed and investigated for targeted cancer drug delivery. Of these classes, protein nanoparticles (PNPs), namely albumin-based NPs, gained more attention, especially after nab-paclitaxel (Abraxane®) received FDA approval for metastatic breast cancer in 2005. (14)

This mini-review contextualizes the significance of protein-based NPs with a focus on albumin-based formulations, their clinical applications in cancer treatment, the challenges they encounter, and future possibilities for improving this technology.

Albumin nanoparticles properties and methods of preparation

PNPs represent a highly versatile drug delivery system for anti-cancer therapy due to their structural and functional properties. While the most used proteins in NPs formulation are gelatine and albumin, the unique characteristics of albumin have significantly contributed to its widespread adoption in various medical applications. (15) Albumin is the most abundant protein in the bloodstream, with the ability to sustain harsh conditions including heat resistance, pH changes (between 4-9), and can resist the effects of many organic solvents. (16) (17) Furthermore, albumin's abundant drug-binding sites enable efficient encapsulation of bioactive agents, reducing required drug amounts and enhancing tumour cell targeting. Albumin can be obtained from different sources. While egg albumin (a.k.a. ovalbumin) is frequently used in food industry, bovine serum albumin (BSA) and human serum albumin (HAS), known for their biodegradability and non-immunogenicity, have received significant attention in pharmaceutical field, especially to form NPs. (18)

Albumin-based NPs exhibit an extraordinary capacity at accommodating both hydrophobic and hydrophilic therapeutic agents, whether unionised or positively or negatively charged. This adaptability stems from the abundance of the various functional groups derived from amino acids, enabling the encapsulation of drugs with diverse characteristics, hence expanding the potential therapeutic applications. (18) The abundance of functional groups also facilitates modification of albumin NPs, enabling

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conjugation with targeting ligands to enhance their specificity for targeted drug delivery. (19)

Albumin NPs can be prepared by several techniques, each distinct in its approach. These are reviewed in detail by Elzoghby et al. (20) Desolvation method is commonly used whereby a dehydrating agent, such as ethanol or acetone, is added to albumin solution under contentious stirring. This exposes albumin hydrophobic region to water, reducing its solubility, thereby leading to the precipitation of albumin NPs. To stabilize obtained NPs, chemical crosslinker, often glutaraldehyde, is employed. The coacervation technique is an improved version of desolvation method, where the pH is used to adjust the albumin water solubility, enabling the desolvation agents to induce the nanoprecipitation. Albumin NPs can also be prepared via self-assembly, whereby albumin molecules self-organize spontaneously in form of NPs. Self-assembly can be induced by heat, denaturation, or by chemically reducing the internal disulfide bonds of albumin molecules. Albumin NPs can be obtained by emulsification. This technique involves the dispersion of an albumin solution in water immiscible oil, followed by solidifying the albumin droplets through chemical cross-linking (i.e., formation of NPs). Thermal gelation, inducing NPs formation via temperature changes, allows for NPs production under mild conditions. For the for large-scale production of albumin NPs, nano-spray-drying method can be used. In this technique, albumin solution is atomised through a nozzle to form a spray that dries through a gas and form albumin NBs.

Nanoparticle albumin-bound technology (Nab-technology) is an innovative method for the encapsulation of hydrophobic drug into albumin NPs. The first nanoparticle-based product approved and marketed was produced by nab-technology. During this process, hydrophobic drug is dissolved in an organic solvent and that is emulsified in albumin aqueous solution. This primary oil in water emulsion is then processed by high-pressure homogenization, leading to the albumin self-crosslinking and the formation of albumin layer around the drug core. The final step is solvent is evaporated which results in the formation of NPs. (21)

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Clinical applications in cancer treatment

Albumin-based NPs have shown significant potential in delivering anticancer drugs to tumour sites, enhancing drug accumulation, and overcoming drug resistance. (22) Four albumin-based nanomedicines, all of which are prepared by Nab-technology, have been tested in clinical trials for potential use as cancer therapeutics. Abraxane® (ABI-007), also known as nab-paclitaxel, represents a significant milestone as the first albumin-based drug approved for the treatment of metastatic breast cancer by the FDA in 2005.(14), (23) Its indications expanded to include non-small cell lung cancer and metastatic pancreatic cancer.(14) Abraxane® takes advantage of albumin's natural properties to enhance the delivery of paclitaxel, which is otherwise hindered by its poor water solubility, facilitating higher dosage administrations within shorter periods. Despite certain dose-limiting adverse effects, clinical trials highlighted Abraxane® superior performance compared to traditional paclitaxel treatments, evidenced by higher response rates, longer times to tumour progression, and increased median survival rates in breast cancer patients. (23) Abraxane® also demonstrated significant therapeutic effects in combination with other treatments, such as trastuzumab, bevacizumab, carboplatin, 5-fluorouracil, or gemcitabine. (24) Fyarro® (nab™ rapamycin) is another Nab-technology albumin nanoparticles that was approved by FDA in 2021 for Advanced malignant PEComa. (25) Other anticancer loaded Nab-technology albumin NPs that are still undergoing clinical trials include ABI-008 **(**nab-docetaxel) and ABI-011 (nab-thiocolchicine dimer). The clinical application and stage of these therapeutic agents are summarised in Table 1.

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Treatment	Type	clinical stage	Clinical application	Refs.
Abraxane® *Nab*-paclitaxel (ABI-007)	HSA-bound paclitaxel NP	Approved by FDA	Metastatic breast cancer, non-small cell lung cancer, pancreatic cancer	(26–28)
Fyarro® Nab-rapamycin (ABI-009)	Albumin bound rapamycin NP	Approved by FDA	Advanced malignant PEComa and advanced cancer with mTOR mutations	(25)
Nab-docetaxel (ABI-008)	Albumin bound docetaxel NP	Phase I/II	Prostrate & breast cancers	(27)
Nab-thiocolchicine dimer (ABI-011)	Albumin bound thiocolchicine dimer	Phase I	Advanced solid tumour malignancies and lymphomas.	(24)

Table 1: Albumin-based NP anticancer therapeutics in the clinic

Challenges

The use of Albumin NPs has attracted considerable attention especially with the approval of Abraxane®. However, several challenges need to be overcome to maximize their application and effectiveness in clinical settings. The biocompatibility and non-immunogenic nature of albumin are significant advantages, yet its combination with therapeutic agents can induce protein conformational changes, raising concerns about increased immunogenicity. (29) Moreover, the stability of albumin NPs in biological conditions, while inherently robust, often requires the use of cross-linkers to ensure sustained system stability and facilitate controlled drug release (30). The toxicity associated with traditional crosslinkers, like glutaraldehyde, along with their potential to interfere with drug efficacy and induced protein denaturation, has prompted the

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exploration of natural cross-linkers such as glucose and tannic acid. (31) (32) These alternatives offer a promising route to refining nanoparticle production processes for optimal stability, size, and minimized toxicity. The synthesis of albumin NPs presents its set of challenges, with various methods exhibiting specific drawbacks, from the risk of mechanical shear force-induced destruction in emulsification and double emulsification techniques to the necessity for toxic chemical cross-linkers in desolvation and pH coacervation methods.(20) Despite minimizing surfactant use, nab technology requires the use of toxic organic solvents like chloroform and dichloromethane, to dissolve hydrophobic drugs introducing potential risks of residual toxicity and environmental damage.(20), (21) Thermal gelation and spray drying are newer synthesis methods, but each comes with limitations regarding drug heat-sensitivity and potential protein denaturation. (21) The production of albumin-based formulations is both complex and costly, driven by the need for high-purity albumin which raises product costs and may limit accessibility. Furthermore, the inherent batch-to-batch variability in natural polymers, like albumin, requires strict control over NPs characteristics for safety and efficacy. Scaling up and regulatory compliance add further challenges, demanding process modifications or new manufacturing approaches.

Future directions for albumin nanoparticles in cancer treatment

Albumin-based nano-systems are experiencing a resurgence propelled by progress in nanomaterials and methodologies for drug delivery. Recent studies highlight promising approaches to enhance targeting ability, cellular internalization, and drug accumulation of albumin NPs. The modification of albumin NPs with long-chain fatty acids, like C18 has been shown to improve encapsulation efficiency of hydrophobic drugs such as doxorubicin, resulting in higher drug loading, controlled release, and enhanced stability, hence ultimately reducing side effects, and enhancing anticancer activity. (33) Another successful modification to albumin NPs involves incorporating 4-carboxyphenylboronic acid (CPBA), a biocompatible ligand for drug targeted delivery. CPBA interacts with overexpressed sialic acid on cancer cells, enhancing the uptake of the sorafenib and simvastatin combination within the NPs. (34) Furthermore, the adoption of innovative conjugation methods to modify albumin NPs through diverse chemical reactions has

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recently attracted considerable attention. For example, the Maillard reaction was utilized to attach maltose to bovine serum albumin. This method offered a straightforward approach, given the simplicity and well-known nature of the Maillard reaction between reducing sugars and amino groups in proteins. This approach led to reduced systemic toxicity of doxorubicin and improved stability of the resulting NPs. (35) Innovative approaches effectively integrate immunotherapy and chemotherapy by utilizing albumin NPs to enhance immune responses against cancer cells. For instance, a novel nanotherapeutic agent (PDL1-NP-FEXO), created by attaching PD-L1 aptamers to albumin nanoparticles loaded with the H1-antihistamine fexofenadine (FEXO), demonstrated higher antitumor activity, suggesting that this combination strategy may enhance the effectiveness of checkpoint blockade (ICB) therapy. (36)

Conclusion

In conclusion, albumin nanoparticles present a versatile platform for delivering anticancer agents with enhanced efficacy and reduced toxicity. The clinical success of Abraxane® has paved the way for further exploration and development of albumin-based NPs. However, the translation of additional albumin NPs into approved clinical therapies has been slow and hampered by challenges related to stability, synthesis, and production costs. Overcoming these obstacles through fine-tuning their drug targeting and release mechanisms, alongside with the adoption of innovative biorthogonal fabrication technologies, is essential for unlocking their full potential in cancer therapeutics and facilitating future approvals. Moreover, their success in cancer treatment could enable applications in other medical conditions.

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