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# Harnessing albumin as a carrier for cancer therapies☆

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ABSTRACT

Serum albumin, a natural ligand carrier that is highly concentrated and long-circulating in the blood, has shown remarkable promise as a carrier for anti-cancer agents. Albumin is able to prolong the circulation half-life of otherwise rapidly cleared drugs and, importantly, promote their accumulation within tumors. The applications for using albumin as a cancer drug carrier are broad and include both traditional cancer chemotherapeutics and new classes of biologics. Strategies for leveraging albumin for drug delivery can be classified broadly into exogenous and *in situ* binding formulations that utilize covalent attachment, non-covalent association, or encapsulation in albumin-based nanoparticles. These methods have shown remarkable preclinical and clinical successes that are examined in this review.



**Contents**



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## 1. Introduction

Albumin, a long-circulating and highly abundant protein in the blood, has unique promise as a carrier for cancer therapeutics based on several key characteristics: (1) it is a natural carrier of native ligands and other hydrophobic cargo (2) it is rescued from systemic clearance and degradation by natural mechanisms (3) it accumulates at sites of vascular leakiness and (4) it is more highly taken up and metabolized by rapidly growing, nutrient-starved cancer cells. Investigators have sought to leverage these characteristics for the delivery of several classes of approved and investigational anticancer agents, which will be reviewed herein.

### 1.1. Properties of albumin

Albumin is the most abundant protein in human blood with a concentration of about 40 mg/mL and a molecular weight of ~67 kDa [1]. Notably, it exhibits an extraordinarily long half-life of 19 days [2,3]. Albumin is synthesized in the liver with approximately 13–14 g of albumin entering the circulation every day [2]. When albumin extravasates into tissue, it is returned to the vascular space *via* the lymphatic system through a natural recycling mechanism. The same approximate mass of 13–14 g of albumin entering the intravascular space is also catabolized from it every day. Importantly, albumin is known to be a carrier of a wide variety of both endogenous and exogenous compounds [4]. This facilitates the colloidal solubilization and transport of hydrophobic molecules such as long chain fatty acids as well as a variety of other ligands such as bilirubin, metal ions such as zinc and copper, and drugs such as warfarin and ibuprofen [5]. Fig. 1 shows the crystal structure of albumin and the sites where these ligands can bind [6]. Of interest to the design of albumin-binding drugs is the distinct affinity and nature of each of these binding sites. For instance, Sudlow's site I is known to bind dicarboxylic acids and bulky heterocyclic molecules with a negative charge (e.g., warfarin) whereas Sudlow's site II is characterized by binding to aromatic carboxylic acids with a single negatively charged acid group separated by a hydrophobic center (e.g., diazepam, ibuprofen) [7].

Albumin naturally transcytoses across the vascular endothelium, a process which can ordinarily pose a significant barrier for drugs to reach cells inside the tissue [8]. This process is attributed to the receptor GP 60, also known as albondin. GP 60 is present in continuous vascular endothelium and alveolar epithelium. Albumin binds to GP 60, which

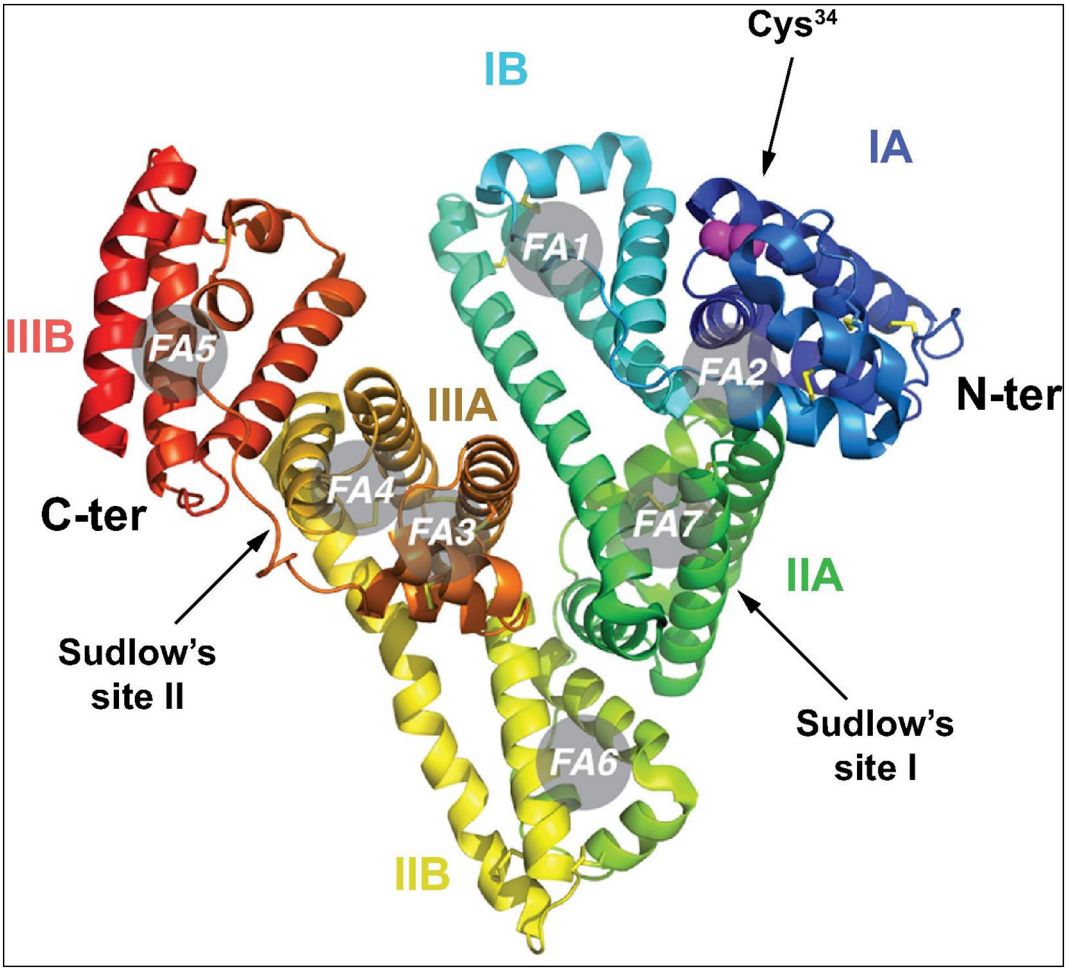


**Fig. 1.** Crystal structure of human serum albumin. Albumin contains three alpha helical domains each comprised of two subdomains. Its seven fatty acid binding sites are distributed asymmetrically across the protein. Additional sites of importance in binding include the free thiol located at the cysteine-34 amino acid residue and Sudlow's sites I and II, which bind a variety of hydrophobic drugs. Figure reproduced from Arroyo et al. [6] with permission of the Journal of Hepatology.

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