

## Albumin as a Delivery Carrier for Rheumatoid Arthritis

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### Abstract

Rheumatoid Arthritis (RA) is a chronic autoimmune disease and considered to be one of the major public health problems worldwide. In the past decade numerous drug delivery systems have been developed to improve the treatment outcome of RA. A stable endogenous protein, albumin has been employed as a non-immunogenic delivery carrier and extensively researched in various disease therapies. To provide the prospective for future research, this review summarizes the application of albumin as drug or imaging agent carriers for RA and proposes potential future directions. There are three major types of albumin-based carrier systems for RA, including albumin drug conjugates, albumin particles and genetic infusion albumin. Their imaging or therapeutic effects have been proved in clinic or pre-clinical studies.

**Keywords:** Albumin; Rheumatoid arthritis; Inflammation; Delivery carrier

### Introduction

Albumin is the most abundant protein in plasma, accounting for more than half of human plasma protein [1]. It is important for various physiological processes such as providing colloidal osmotic pressure, solubilizing long chain fatty acids, delivery of nutrients to cells, and balancing plasma pH. Albumin has been widely studied as a protein carrier for drug delivery. Currently, there are around seven albumin-based drugs or imaging agents on market (Table 1) and more than ten products under clinical trials [1,2]. They have various applications including oncology, diabetes, hepatitis C and rheumatoid arthritis. There are several advantages of using albumin as drug carrier: 1) as an endogenous protein, Human Serum Albumin (HSA) is native to the body. It is biodegradable in nature, nontoxic and non-immunogenic; 2) Albumin is a robust protein. It is stable over a wide pH range (4-9), could be heated at 60°C for up to 10 h without deleterious effect, is unaltered by denaturing agents and solvents at moderate concentrations [3,4]. Therefore, albumin could remain stable under typical processing conditions; 3) as the most abundant protein in plasma, albumin is readily available. It has been used in clinical setting for more than 30 years; 4) the half life of albumin is 19 days in blood circulation. It may play an important role as a carrier in improving the pharmacokinetic property of small drug molecules, peptides or protein based drugs.

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects a large number of people throughout the world. Uncontrolled active rheumatoid arthritis causes joint damage, disability, and decreased quality of life along with other co-morbidities. The metabolism of synovial cells is highly up-regulated in RA patients [5,6]. The uptake of albumin is probably a relevant source of covering their high demand for nitrogen and energy. Therefore, patients with active rheumatoid arthritis frequently have high albumin consumption at sites of inflammation and therefore develop hypoalbuminemia [7,8].

Meanwhile, there is increased permeability of the blood vessels in the inflamed joints [9,10]. The fenestration allows for the extravasation of macromolecules at the inflammation site. It has been shown that fluorescein or <sup>111</sup>In labeled albumin preferentially accumulate at paws affected by RA in a mouse model [11]. Therefore, albumin is an attractive carrier targeting inflamed joints. There are three major types of albumin-based delivery systems for RA.

### Albumin-Drug Conjugate

Methotrexate (MTX) is a common used drug for treating RA and cancer. To overcome the lack of specificity with regard to the inflamed tissue as well as increasing the half life, methotrexate-albumin conjugate (MTX-HSA) was developed by directly coupling MTX to lysine residues of HSA. Compared with equivalent dosage of MTX, MTX-HSA was more effective in a collagen-induced arthritis mouse model [11]. Meanwhile, MTX-HSA has shown to significantly reduce synovial fibroblast invasion and cartilage degradation in a humanized rheumatoid arthritis model using severe combined immunodeficient mice [12].

Besides MTX-HSA, an albumin-binding prodrug of MTX was also developed. After intravenous application, EMC-d-Ala-Phe-Lys-Lys-MTX (EMC= 6-maleimidocaproic acid, AWO54) could rapidly and selectively bind to the cysteine-34 position of endogenous albumin to form a stable conjugate in human plasma. The conjugate is cleaved by cathepsin B and plasmin, two proteases that are over expressed at arthritic sites, and release a MTX lysine derivative [13]. The conjugate had a significantly better anti-arthritic effect than MTX in a murine collagen-induced arthritis model, especially for late stage RA [14].

Currently, HSA-MTX is the only drug candidate conjugated with albumin for RA treatments. There are many albumin drug conjugates developed for other diseases, such exendin-4 albumin conjugate for diabetes (in clinical trial). Coupling other anti-inflammatory drugs with albumin for RA treatment is a research area worth exploring.

### Albumin Particles

Albumin microcapsules were developed for delivering anti-

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Product	Drug	indication	Current status
ABI-007 (Abraxane®)	Albumin-paclitaxel nanoparticle	Oncology	Marketed
<sup>99m</sup> Tc-Albures	<sup>99m</sup> Tc –aggregated albumin	Oncology	Marketed
<sup>99m</sup> Tc-Nanocoll	<sup>99m</sup> Tc –aggregated albumin	Oncology	Marketed
Vasovist®	Albumin-binding Gadolinium (III) complex	Oncology	Marketed
B-22956/1	Albumin-binding Gadolinium (III) complex	Oncology	Marketed
Levenir®	Albumin-binding fatty acid derivative of insulin	Diabetes	Marketed
Liraglutide (Victoza®)	Albumin-binding fatty acid derivative of GLP-1	Diabetes	Marketed
Albuferon®	Albumin-fusion protein of interferon-α-2b	Hepatitis C	Phase III
AT-103 (Ozoralizumab)	Albumin-binding nanobody directed against human TNF-α	Rheumatology	Phase II
INNO-206	Albumin binding prodrug of doxorubicin	Oncology	Phase II
ABI-008	Albumin-docetaxel nanoparticle	Oncology	Phase II
MTX-HSA	Methotrexate albumin conjugate	Oncology	Phase I/II
MM-111	Albumin fusion protein directed against ErbB2 and ErbB3	Oncology	Phase I/II
AFL-HSA	Albumin conjugate of aminofluorescein	Oncology	Phase I/II
CjC-1134-PC	Albumin conjugate of exendin-4	Diabetes	Phase I/II
ABI-009	Albumin-rapamycin nanoparticle	Oncology	Phase I
ABI-010	Albumin nanoparticle with a HSP90 inhibitor	Oncology	Phase I

**Table 1:** Albumin-based drugs or imaging agents on market and under clinical trials.

inflammatory drugs [15]. Generally, the microspheres were produced by chemically linking albumin using glutaraldehyde or by addition of an organic solvent and stabilization at high temperatures. The size of the microspheres was usually in a range of 1-100 μm. The drug was dispersed through the albumin matrix and released continuously as the microcapsules were degraded by intracellular proteolytic enzymes [16,17]. After encapsulating an antisense NF-kappaB oligonucleotide, the albumin microsphere could effectively reduce the paw swelling in a rat RA model. Meanwhile, long-term use of these microspheres was non-toxic and there were no observable allergic reactions in the rats [18,19].

Albumin nanoparticles have been extensively researched for cancer treatment. Albumin-paclitaxel nanoparticle (Abraxane™) is commercially available, whereas albumin-docetaxel nanoparticle and albumin-rapamycin nanoparticles are in clinical trials [1]. The albumin matrix effectively incorporates drugs or electrostatically adsorbs charged molecules (including gene) because of the high content of charged amino acids (eg. lysine) in albumin. In addition, the presence of functional groups (amino and carboxylic groups) on the nanoparticle surface makes it possible to conjugate targeting ligands.

Aspirin loaded albumin nanoparticles were prepared by coacervation method. The particle size ranged from 47-191 nm with an aspirin/albumin ratio of 0.06-1.0 [20]. Aspirin was released from the nanoparticle at a sustained rate for prolonged duration with 50% total cumulative release at the end of 20 hours [20]. However, there is no *in vivo* data evaluating the therapeutic effects. Another albumin-based nanoparticle based on active targeting mechanism was also developed. Folate receptor beta (FRβ) is specifically expressed on activated macrophages in inflamed joints, and therefore is used as a target for drug delivery in RA [21,22]. Both therapeutics and imaging agents based on folate modified nanoparticles have been developed and their efficacies have been proved *in vivo* in RA model [23,24]. Rollett A et al. [25] developed folic acid-functionalized HSA nanocapsules with size around 440 nm and a narrow distribution. *In vitro* cell culture study showed specific binding and internalization of the HSA nanoparticles by FRβ-positive macrophages. Future investigations loading different anti-inflammatory drugs and further therapeutic evaluation for the treatment of RA are needed.

Besides therapeutic drugs, albumin-based diagnostic nanoparticles

have also been developed. Technetium-99m (<sup>99m</sup>Tc) is a metastable nuclear isomer widely used for medical diagnostics. <sup>99m</sup>Tc-labeled human serum albumin is used in nuclear medicine for diagnosing various conditions including cancer and infectious diseases [26,27]. Many preparation kits for this formulations are available on market from a number of manufacturers, such as <sup>99m</sup>Tc-Nanocoll®, <sup>99m</sup>Tc-Albures® and <sup>99m</sup>Tc-Human Serum Albumin®. In these formulations, the human serum albumin aggregated particles has a wide range of size from a few nm to up to 1000 nm depending on the application. The precise structures of the aggregated albumin complexes are currently unknown. There are many reports using <sup>99m</sup>Tc-albumin nanocolloid in diagnosing arthritis in both animals [28] and patients [29-31].

### Albumin Fusion Protein

The pro-inflammatory cytokines play a vital role in the development of rheumatoid arthritis. TNF-α is one of the key inflammatory cytokines. Modulation of TNF-α has been proved to be an effective treatment for rheumatoid arthritis. There are four anti-TNF-α antibodies on market, including Enebre® (etanercept), Remicade® (infliximab), Humira® (adalimumab) and Cimzia® (Certolizumabpegol). A novel type of anti-TNF-α antibody based on albumin was developed. The camelid anti-TNF-α-anti-HSA trivalent nanobody is composed of two anti-TNF-α domains and one anti-HSA domain. This novel trivalent bispecific antibody showed significant therapeutic effect in RA animal models. The using of albumin as carrier significantly prolonged the serum half-life and promoted the targeting to inflamed joints [11,32]. Currently, this novel antibody (Ozralizumab) is under phase II clinical trial for treating RA.

Another important proinflammatory cytokine for RA is interleukin-1 (IL-1) [33]. IL-1 receptor antagonist (IL-1ra) is a naturally occurring cytokine that blocks biological activity of IL-1 via binding to IL-1 type I receptor with the same affinity as that of IL-1β. Recombinant human IL-1ra (rhIL-1ra), Anakinra, has been approved for the treatment of patients with moderate-severe RA. However, Anakinra exhibits rapid clearance from the circulatory system and poor retention in the inflamed joint. To solve these problems, genetic fusion protein composed of IL-1ra and HSA was developed. The plasma half life of IL-1ra was extended to more than 30-fold and selectively accumulated in the inflamed joints of a collagen-induced mouse RA model [34].

## Conclusion and Future Directions

The above mentioned studies have demonstrated inspiring effects of using albumin as carriers for RA. There are many common pathophysiological features among inflammatory diseases, including vasculature restructuring, inflammatory cell recruitment and elevated inflammatory cytokines [10]. The enhanced vascular fenestration allows albumin-based delivery systems to extravasate at the inflammation site. The albumin systems developed for RA might be applicable to other inflammatory diseases because of this passive-targeting mechanism. Meanwhile, as there are lots of albumin-based delivery systems developed for other diseases, these systems might also be applied to RA. For example, the albumin-binding gadolinium complexes based MRI contrast agents Vasovist® for cancer may also be used for RA diagnose. The albumin microencapsulated dexamethasone which has been developed for infection disease might be potent in treating RA since the therapeutic effect of dexamethasone in treating arthritis has been widely proved [35]. More anti-inflammatory drugs may also be conjugate with albumin or incorporated into albumin particles to increase their therapeutic efficacies and decrease side effects. In addition to folate, other inflammation targeting moieties may also be employed to increase the therapeutic efficacy to RA. As a versatile carrier, there are many exciting avenues for the application of albumin in treating RA and other inflammatory diseases that have not been fully explored.

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