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A clinical update of using albumin as a drug vehicle — A commentary

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ABSTRACT Q4

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Albumin is the most abundant protein in blood plasma and in addition probably the most extensively researched plasma protein to date. In 1985, Theodore Peters, Jr. published his seminal review article *Serum albumin* [1] which was followed in 1996 by the first comprehensive book by the same author [2].

Medical applications were restricted to intravenous administration of human serum albumin (HSA) as a blood substitute for treating patients with severe burns or cachexia. In the mid 1990s a handful of research groups began to investigate the potential of albumin as a carrier protein, either for targeting drugs to inflamed or malignant tissue or extending their half-life. These efforts have resulted in marketed drugs or drugs in a clinically advanced stage.

In 2008 [3] and 2010 [4] we reviewed the state-of-art of albumin-based drug delivery systems in this journal which emerged as highly cited articles in this field of drug delivery and drug design. In this õcommentary, I present a current update of the clinical progress of albumin-binding peptides, prodrugs and drugs in the two major indications — diabetes and oncology.

The two principle albumin-based technologies which have been developed in the past 15–20 years are illustrated in Fig. 1. In the approach shown on the left hand side, lipophilic drugs and HSA are passed under high pressure through a jet to form albumin-drug nanoparticles, in a second approach albumin-binding peptides or prodrugs are administered intravenously and bind *in situ* to circulating albumin — either physically or covalently. HSA with a molecular weight of 66.5 kDa is the chief carrier protein in the blood circulation per se: It acts as the solubilizing agent for long chain fatty acids and is therefore essential for the metabolism of lipids; it acts as a detoxifying protein binding for bilirubin, the breakdown product of heme, and heavy metal ions such as lead(II), platinum(II) and gold(III); it binds copper(II) and nickel(II) in a specific manner and calcium(II) and zinc(II) in a relatively nonspecific manner and acts as the transport vehicle for these metal ions in the blood; and finally it binds a great number of therapeutic drugs such as antibiotics, anticoagulants, anti-inflammatory drugs, anesthetics, and benzodiazepines to name just a few. Q5

The first three-dimensional structure of HSA was elucidated by X-ray structure analysis in 1989 after the crystals had been grown in space, and towards the end of the 1990s the first structure with and without 5 myristic acid molecules bound to HSA (see Fig. 2A and B) was in public domain.

HSA is one of the smallest proteins present in blood plasma. Both size and abundance explain the fact that so many metabolic compounds and therapeutic drugs are transported by this protein. The binding sites for metabolic substrates and diagnostic as well as therapeutic drugs have been extensively studied and reviewed.

1. Improving the pharmacokinetic profile of insulin or of insulin-producing peptides

The Danish pharmaceutical company Novo Nordisk was the first to exploit the long half-life of HSA of ~19 days in order to improve the

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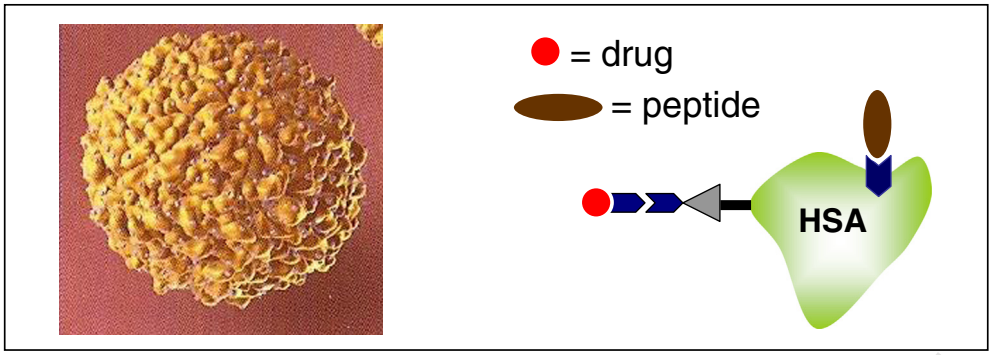

Q2 **Fig. 1.** Albumin as a drug vehicle: (left) drugs are bound physically to HSA and form a drug nanoparticle [3,4]; (right) an albumin-binding peptide is bound physically or an albumin-binding prodrug is bound covalently to HSA after subcutaneous or intravenous administration.

pharmacokinetic profile and compliance of insulin for treating diabetes. Globally, estimated 350 million people have diabetes type 1 or 2, non-juvenile diabetes 2 accounting for around 90% of cases. Type 1 diabetes is characterized by a lack of insulin production whereas the body's cells no longer respond adequately to the insulin that is produced as is the case in type 2 diabetes. Both types 1 and 2 diabetes are major causes of premature illness and death in most countries, especially in low- and middle-income countries, due to an increased risk of blindness, amputation, cardiovascular disease, and kidney failure.

The hallmark of diabetes treatment is therefore to decrease the raised glucose blood levels by adapting to a diet low in sugar and saturated fats as well as avoiding obesity and medically by taking oral antidiabetic drugs, by substituting insulin or enhancing the body's insulin production.

The therapeutic method of choice for treating juvenile diabetes or advanced type 2 diabetes is to compensate the lack of insulin production. Ideally, a long-acting form of insulin is preferred to decrease and normalize the blood glucose level over 24 h. The principle of attaching a fatty acid to insulin which subsequently binds to the 5–7 fatty acid binding sites present in the HSA molecule is indeed so apparent that it is surprising that this idea was not realized earlier, but strangely enough facts and circumstances not far to seek are often the heart of an invention.

Novo Nordisk developed a novel insulin analog for treating diabetes in which myristic acid is bound to the lysine amino acid at position B29. Levemir® (insulin detemir) was approved 2004 for treatment of diabetes mellitus 1 and 2 and is administered subcutaneously as a water-soluble solution with a predictable and prolonged pharmacokinetic profile that makes Levemir® suitable as a basal component in a basal-bolus treatment regimen with a duration of action of approximately 26 h. In 2013 sales for Levemir® were over US$ 1.8 billion [5].

The other option of controlling glucose levels in diabetes is to stimulate insulin secretion. The peptide hormone GLP-1-(7-37) results from selective cleavage of the proglucagon molecule and increases insulin secretion in pancreatic cells but only has a half-life of 1.5–2 min due to degradation by ubiquitous enzymes. In analogy to Levemir®, GLP-1-(7-37) is derivatized with a fatty acid, in this case with palmitic acid, at the ε-amino position of lysine introduced at the N-terminal position of glutamic acid in the GLP-1 peptide sequence. The resulting new drug liraglutide (Victoza®) is an albumin-binding derivative of GLP-1 stable against metabolic degradation due to albumin-binding and has a plasma half-life of 11–15 h after subcutaneous administration. Victoza® was approved 2009 in Europe and 2010 in the USA and is marketed by Novo Nordisk with sales meanwhile reaching over US$ 1.7 billion in 2013, primarily for treating type 2 diabetes [5].

The most recent development by Novo Nordisk is insulin degludec (Tresiba®), a follow-up product to Levemir®, the difference being that palmitic acid is conjugated through a gamma-L-glutamyl spacer to the amino acid lysine at position B29 of the insulin molecule. Insulin degludec is an ultra-long-acting basal insulin analog exceeding the duration of action that lasts up to 40 h. It was approved in Japan towards the end of 2012 and in Europe at the beginning of 2013. In the United States, the U.S. Food and Drug Administration (FDA) has requested additional cardiac safety studies prior to market approval.

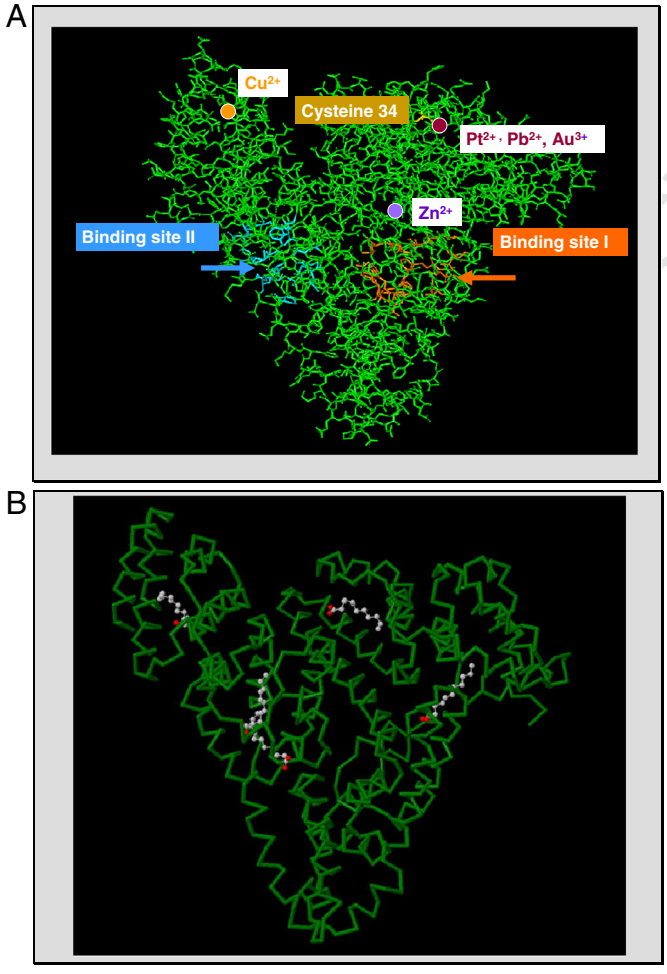

Fig. 2. (A) X-ray structures of HSA of the defatted protein structure (pdb-entry 1ao6); (B) the albumin structure in which five molecules of myristic acid are bound (pdb-entry 1bj5). The binding sites for metal ions, fatty acids as well as the binding sites I and II (the so-called Sudlow's binding sites) where numerous drugs are physically bound are highlighted.

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