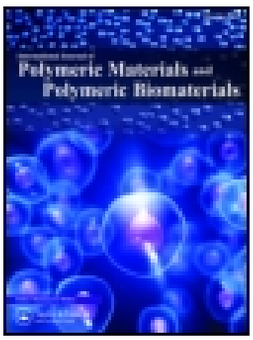

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Albumin-Based Biomaterial for Lungs Tissue Engineering Applications

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Abstract

The role of albumin-based biomaterials in Tissue engineering (TE) cannot be over-emphasized. In this paper, we reviewd the role of albumin in lungs scaffold grafting which promotes cell seeding. Albumin grafted on decellularized lungs scaffold is presented as a great support material for cell-tissue interaction, for ease in attachment, growth and differentiation when seeded with different types of cells. Albumin scaffold fabrication from different sources is a promising approach that may facilitate medical treatments from bench-to-bed, although, the role of this scaffold in lungs surfactant proteins regeneration and binding need to be fully elucidated.

Keyword; Albumin, Scaffold, Tissue Engineering, Regenerative Medicine, Lungs and Biomaterial.

LIST OF ABBREVIATION

3D	Three Dimension
Ad-MSc	Adipose tissue-derived mesenchymal stem cells
ADSCs	Adipose derived stem cells

ASA Autologous serum-derived albumin

BALF Bronchoalveolar lavage fluid

BSA Bovine Serum Albumin

CC Clara cells

CPG Calcium phosphate glass

CRD Carbohydrate recognition domain

DNA Deoxy ribonucleic acid

ECM Extracellular matrix

ECs Endothelial Cells

EPS Exogenous pulmonary surfactant

HA Hydroxyapatite

HSA Human Serum Albumin

MSCs Messenchymal stem cell

OECs Olfactory ensheathing cells

PCL Polycaprolactone

PLGA Poly (lactic-coglycolic acid)

PLLA Poly (L-lactide)

PSA Porcine serum albumin

SCI Spinal Cord Injury

SP Surfactant protein

SPARC Secreted proteins acid and rich in cysteine

TE Tissue engineering

UV Ultra violet

VSCs Smooth vascular muscle cells

1.0 INTRODUCTION

Langer & Vacanti [1] introduced biomaterial-based TE. It was defined as an interdisciplinary field employing engineering and life sciences principles to support biological substitutes which restore, maintain, or improve the function of a tissue or a whole organ [1], [2]. Most researchers have outlined six components for TE, namely, cells, cell-cell interaction, scaffolds, growth factors, bioreactors and stimulation (mechanical etc.).

Cellularizing decellularized organs like lungs, represents another method of obtaining a whole transplantable, and functional organs [3]–[6]. An intersection between biotechnology and biomedical engineering named TE, was established to support and promote *denovo* synthesis of scaffolds, so also as to repair defective damaged tissues according to the patient's regeneration potential. In recent therapy, it is necessary to provide cells with a surrounding that will regulates and improve their proliferation and differentiation for regeneration of tissue i.e. monitoring cellular growth and differentiation in TE constructs. Biomaterial scaffold is capable of providing in addition to physical support, the chemical and biological clues needed in forming functional tissue [7]–[9]. Biomaterial technology is essential in the creation of this local cell environment, and various synthetic and natural materials such as polymers, ceramics, conjugated metals, or their composites, have been studied and utilized in different manners [8], [10]. Protein derived biomaterials like albumin, vitronectin, fibronectin, laminin, collagen, elastin, casein, zein, also provides suitable enviroment for the growth of cells [7], [8].

Transplantation and biomaterial engineering were recently utilized for disease healing, with the aftermath of the former, being cancer and graft rejection [8]. The unique characteristics like mechanical properties, high availability, low cost, easy design and synthesis of polymeric materials have made them a good substrates [9], [12] for organ scaffold synthesis and support. However, only a few polymers provide the biocompatibility [13] and affinity with other matrix proteins and growth factor *in vitro* and *in vivo* [3], [13], [14].

In other to initiate lungs regeneration process and to simultaneously solve the problem of graft rejection, biomaterial polymers research has been focused on, as biopolymers are biodegradable, biocompatible and could be replaced by human tissue produced by the cells surrounding the material [15].

In addition to being biodegradable, proteins scaffolds are cheap and can be produced in large scale [16], [17]. For these reasons, great effort has been made in the utilization of proteins as a biomaterial scaffold for TE application [18]–[21]. However, the lack of mechanical strength, high rate of biodegradation, risk of auto-immune rejection, some properties, like wettability, adhesion, and surface composition are insufficient for many applications [22]–[24].

Fabrication is also important when synthesizing a protein scaffold, the protein chains functional groups, for instance, must be cross-linked either within themselves or with the

help of chemically cross-linking agents like glutaraldehyde, formaldehyde [25] or grafting them on decellularized lungs tissue, and simultaneously maintaining their structure, which in-turn reserve their functionality. Self-crosslinking have been said to be better since there won't be an incorporation of toxic chemicals into the scaffold by the use of the reagents, which in-turn may interfere with the process of lungs tissue regeneration.

Albumin; the most abundant human serum protein, have been said to influence the attachment of cells to various scaffold material in a similar and better fashion as collagen and fibronectin after some treatments. They can serve as an interface between cells and scaffold, thereby mediating the integration of these two components. In this review, milestone of albumin based TE biomaterials was addressed, and ways they have assisted in cellular adhesion to scaffold in bone, cardiac, and neural TE. Their potential role in grafting decellularized lungs tissue before recellularization with various kinds of cells was discussed, and possible challenges in Lungs TE was pointed.

2.0 ALBUMIN-BASED BIOMATERIALS

Found in blood serum (human, horse, pig, sheep etc), egg white, milk, and many other plants and animal tissues, with a slight variation in amino acid composition. Previous data have supported the notion that different sources of albumin are relevant substrate for TE application (Table 1). The most common albumin types used in TE scaffold include, Human serum albumin (HSA), Bovine Serum Albumin (BSA), Ovalbumin, and Porcine Serum Albumin (PSA).

2.1 Types

2.1.1 Hsa

Structure And Properties Of HSA

HSA protein was observed as a component of human blood and to be the most abundant blood protein (35 - 50 g/L) as early as the 20th century. From then on, it has been extensively studied and applied in several aspects of biomedical science. Its structural information was obtained based on low angle X-ray scattering, hydrodynamics as well as *in silico* prediction studies. The structures of HSA purified from blood and that obtained by recombinant DNA technology are basically identical. However, despite its well-characterized molecular structure (Fig. 1), it has been slow to find its use as scaffolding material in TE.

According to Carter and Ho [26], X-ray crystallographic studies , HSA is a heart-shaped molecule (globular), coded for by a gene located on chromosome 4 and has a high alpha-helical content (~67%), with a molecular mass of 66.5 kDa, rich in disulphide bridges (17 in total) and has one free cysteine residue at position 34 [26]. It is made of 585 amino acid residues that make up three repeating helical peptide domains (labeled I–III) and each of these domains is divided into two sub-domains (Fig. 1). Hydrodynamic studies have revealed that HSA has a high affinity to a very wide range of materials, including metals such as copper and zinc, fatty acids, amino acids as well as a vast number of metabolites. Of late, a number of structures of HSA have been published which helped shed light on the structural features of the HSA and how the protein binds a number of ligands in some biomedical applications.

Considering normal physiological conditions, about 10-15 grams of HSA are produced in the hepatocytes daily, with none or very low intracellular storage. HSA can be polymerized by cross-linking [22] and other fabrication methods, its synthesis is stimulated by hormones, such as insulin, cortisol and growth hormone, and inhibited by pro-inflammatory substances, including interleukin-6 and tumor necrosis factor-α [27], [28]. Albumin scaffold have been said to display a very similar result when compared with collagen based tissue scaffold, both of them have high water binding characteristics and excellent resilience capacity, exhibiting approximately the same tensile strengths and possessing extremely high porosities (97%). In addition, they have good cell binding properties because they are peptide based biomaterial and this has been helpful for cellular growth, thus, in this regard, they have been examined [29].

Function

HSA binds and carries lots of hydrophobic molecules like endogenous molecules (i.e., cholesterol, bilirubin, fatty acids, thyroxina) or exogenous substances (i.e., toxins and drugs), gas like NO with consequent solubilization, transport, metabolism and detoxification [30], [31], maintaining the reducing power, osmotic pressure and pH of the mammalian blood [32], [33]. The HSA molecule also contribute to the stabilization of the endothelial layer and for the maintenance of the normal capillary permeability probably by reducing oxidative damage and modulating inflammation [34].

HSA has been established for hepatitis B virus and hepatocyte binding which in turn partake in hepatitis pathology [35]. It is capable of binding proteins like membrane associated gp60 (albondin), drugs, as well as secreted proteins acid and rich in cysteine (SPARC). The receptors of albondin localized on tumor vessels endothelial cells allows for transcytosis of albumin via continuous endothelium whereas overexpressed SPARC leads to the buildup of interstitium tumor albumin. HSA has been a suitable gene therapy agent since it prevent undesired reaction with serum that often follow intravenous injection of transfection complexes. Recombinant HSA (Recombumin) in addition has been synthesized and their tolerability, safety, pharmacodynamics and pharmacokinetics to the native HSA have been presented [36], [37].

2.1.2 Bsa

Obtained from cows blood, BSA is one of the component in tissue culture medium, albumin-based scaffold will remain a good substrate since it plays a structural support part in cell and TE [29], [30]. BSA is a globular protein (66kDa), containing 583 amino acid residues linked together on a single chain with a known sequence [38]. The 3D (three- dimensional) conformation of BSA comprises of 3 homologous domains (I, II, III) which is specific for fatty acids and metals. Each domain represent the product of 2 subdomains, which are chiefly helical and extensively cross linked by sulfide bridges [38].

2.1.3 Ovalbumin

Ovalbumin is one of the first isolated proteins, which is the major protein in avian egg-white (60-65% of total egg-white protein) [39]. The structure and function of ovalbumin reveal that this protein belongs to the seprin superfamily [40]. It is basically a glycoprotein comprising of 386 amino acids [41] and a carbohydrate side chain linked covalently to amide N of Asn293. Ovalbumin does not show any protease inhibitory activity despite sequence identity of 30% with antitrypsin and other inhibitor proteins of serpin family [39].

2.2 Albumin Scaffold

A scaffold is a support, matrix or delivery vehicle for promoting the binding and migration of cells or bioactive molecules used for restoring, repairing or regenerating tissues [42]. Scaffold provides 3D cell culture template upon which activation of seeded cells is initiated for full tissue regeneration and controlled degradation of the scaffold, after the tissue has been fully grown. Tissue engineered scaffold plays a role in mimicking functions of native ECM partially.

Pore structure and size should also be considered when synthesizing a scaffold for TE, wider and well linked pores gives rise to a good mass transfer and in-turn increase cell viability. Pore size between the range of 100 to 150mm is always essential for tissue growth [43], this size also shows a longitudinal larger pore size when compared to cross sectional size of a novel scaffold.

However, when synthesizing an albumin scaffold (Fig. 2), the type of method employed should be taken into account as well. A number of process have been established for the fabrication of different types of albumin scaffold which have been employed in bone, cardiac and neural tissue engineering, these include but not limited to chemical/enzymatic cross-linking method, freeze-drying method, templating and leaching method, solution evaporation method and 3-D printing method [54]–[59]. Albumin scaffold synthesized by cross-linking (Table 1) has a good wettability [44], [45], aids craniofacial regeneration [46]–[49], when combine with collagenI promotes osteogenesis differentiation [50], possesses a very porous structure, resilience, moderate mechanical strength, good compatibility and support long period of osteogenic differentiation of MSCs [29].

On the other hand, albumin scaffold synthesized through heat aggregation (Table 1) has been said to possess mechanical strength at pH8.5, and those at isoelectric albumin pH4.8 showed lowest biodegradation rate and those at pH12 gives the highest biodegradation rate [51]. Using another method; electrospinning (Table 1) albumin to form a scaffold was reported to produce a scaffold that is nontoxic, biodegradable, and supported endothelial and muscle cell adhesion [52] *in vivo*, the functional group present on the electron fiber encourage facile protein conjugation, and this can contribute to the growth of tissue [53] like lungs by enhancing physiological processes. Generally for proteins and specifically albumin, cross-linking, freeze-drying, heat aggregation and electrospinning methods, have proved to be efficient in the fabrication of their scaffold.

2.3 Albumin Scaffold Protein Degradation

The principle behind an ideal scaffold and how it works involve, the migration of cells throughout the entire part of the scaffold, after which the scaffold is being degraded by specific enzyme, this must be a long time process to maintain the shape of the scaffold after which the tissue has been fully developed. Increasing protein instability and solubility with time *in vivo* and *in vitro*, due to enzymatic action are important in characterization of proteins. Long-term scaffold integrity and mechanical stability are crucial for cells for enough period of time and stiffness to create their tissue-specific matrix. Therefore, adjusting factors like physical properties of scaffold, protein type, and other factors (inhibitors or promoters to proteases, the cross-linking between molecules of protein, processing conditions, and the biocompatibility of scaffolds) could control protein scaffold degradation [60].

It is difficult to sterilize collagen without altering its structure [61], rapid degradation of collagen based matrices remain an issue, since they are degraded and dissolved by cellular activities leading to an unstable architecture when they are being seeded with cell in vivo [29]. Cross-linked albumin may follow a different degradation pattern when compared to other polymers like collagen and fibrin. Collagenase degrade collagen, plasmin degrade fibrin, but specific protease responsible for serum albumin or polymerized albumin degradation is rear [29] and this has made it a better scaffold than its counterpart. Moreover, biodegradation of albumin to its building blocks, that is, amino acids, may provide nutrition to cells in the microenvironment [53].

3.0 SURFACE CHEMISTRY OF LUNGS

Heterogeneous epithelium links the lungs with its external environment. The proximal conducting airways are lined with a pseudostratified epithelium which is continuously replaced by distal airways cuboidal cells and by a very thin epithelial lining covering the aveoli lungs surface. Goblet, Clara cells, ciliated, and basal cells, are all present along the airways [62]–[64]. The lungs epithelium and alveolar primary function is to provide thin surface for the exchange of gases. The pulmonary epithelium also preserve the gaseous exchange capacity, providing a barrier that shield the host from the environment by separating inhaled foreign agents, and it controls the movement of solutes and water, contributing to the maintenance of lung fluid balance. The lung epithelium also plays an active role in the metabolism of endogenous mediators and xenobiotic agents, and is capable of regeneration, allowing normal cell turnover and restoration of airway and alveolar functions after lung injury. Beyond this, the lung epithelium produces complex secretions, among which is the mucus blanket, a surface-active agent (surfactant), as well as several proteins important for host defense [65]–[68]. Among these proteins are the 16-kD Clara cell secretory protein (CC16, CC10), three surfactant-associated proteins (surfactant protein [SP]-A, SP-B, and SP-D) and mucin associated antigens, as recognized by monoclonal antibodies (KL-6, 17-B1, 17-Q2).

Pulmonary surfactant is a complex material shielding the alveolar surface of the lung. It comprises chiefly of structurally heterogeneous phospholipids. Pulmonary surfactant reduces the surface tension at the air–liquid interface of the alveolus, thereby inhibiting alveolar disintegration on expiration. Four surfactant-specific proteins, possessing different functional and structural properties, have been studied. They were named SP-A

[69]–[71], SP-B [72], [73], SP-C [74], [75], and SP-D [76]–[78] according to how they are discover. Organic solvents extraction of the lipid-rich pellet recovered after ultracentrifugation of bronchoalveolar lavage fluid (BALF) helps in the separation of this protein into two groups: lower molecular-weight hydrophobic SP-B and SP-C, and higher molecular-weight hydrophilic SP-A and SP-D [79], [80].

The interaction between a collagenous tail with a globular head possessing a carbohydrate recognition domain (CRD) is a functional and structural properties of an ancient family of proteins present in prokaryotes: the collectins or lectins (collagenous lectins) [81]–[85]. CC16, or CC10 is a homodimer having 70 aminoacid subunits in antiparallel orientation linked by two disulfide bonds [86]. Molecular mass of clara protein determined by mass spectrometry is 15,840, justifying CC16 abbreviation to designate the protein. However, because of an irregular electrophoretic movement, the protein molecular size of both 10 kD and 7.8 kD on gel electrophoresis, under reducing and non-reducing state, abbreviated as CC10 [87].

Albumin has been reported to cause disaggregation in EPS (exogenous pulmonary surfactant) on interaction, without a loss in its surface activity, serum protein also caused inactivation and disaggregation of EPS, although, it has been argued that serum component different from albumin has been responsive for this inactivation [88].

4.0 APPLICATION OF ALBUMIN IN TISSUE ENGINEERING

4.1 Bone Tissue Engineering

Bone defects arising from disease or trauma often lead to loss of function, and their successful repair is challenging in reconstructive surgery [89]. Bone TE using appropriate scaffold with MSCs provides an alternative means [50]. Appropriate scaffold is important for osteogenic differentiation and cell growth in bone TE. A highly porous material is essential for an ideal scaffold, it must also have a good osteointegrative and biocompatible properties. Various porous scaffolds like protein, hydroxyapatite, tricalcium phosphate, and polymethylmethacrylate have been developed [90], [91]. Albumin scaffold has been successfully verified and applied in bone tissue engineering [44], [45], [47], [48], [50], [92], [93], using various fabrication method as depicted in (Table 1), they have high seeding efficiency, biocompatible, non-immunogenic, cheap and possesses controlled degradation.

4.2 Cardiac Tissue Engineering

Albumin fiber scaffolds with mechanical properties related to cardiac tissue has been successfully fabricated. This fibers serves as scaffolds for engineering functional cardiac tissues [53], and proves to be superior in function when compared to PCL fibers. The ability of this cardiac scaffold to bind serum proteins promotes cell adherence, the functional groups on albumin scaffold promotes facile protein conjugation, enhancing physiological processes and improving tissue growth. However, serum protein binding, the release of therapeutic biomolecules that will improve tissue function, and ability of the engineered patches to improve heart functions after infarction is yet to be explored fully [53].

4.3 Neural Tissue Engineering

Spinal cord injury (SCI) is an overwhelming situation that usually produces partial or complete motor and sensory loss below the injury level [94]. Biodegradable polymer scaffolds provides structural support to connect the injury site, and also guide axon regeneration [95], [96].

Progress in SCI research, biomaterials and cell culture techniques foresee future treatments of patients with SCI or some other nerve injuries [94]. Human serum-derived spongy scaffold is capable of improving motor function reconstruction in SCI rats, and provide future therapy for studies devised to examine the potential and safety of this novel albumin scaffold [94].

4.4 Prospective Role Of Albumin In Lungs Tissue Regeneration

The challenges in cultivating complex 3D functional lung tissues *ex vivo* will be in reiterating the normal dynamic integrated network of fundamental cells, function and orientation of its ECM, perfusion-ventilation relationships, and immune response, which are all required for perfect lungs function [97].

Inoculation of different cell lines through the airway or vascular routes into small, cut out segments of the decellularized lungs showed lung scaffolds to fully support initial engraftment and proliferation of each cell type for just a month. On the other hand, even though cells bind, they couldn't survive for more than a week in emphysematous lungs. However, cell engraftment and growth on solubilized ECM homogenates of decellularized normal, and emphysematous lungs tissue coated onto the tissue culture

plates was similar but not defective, this suggested that the 3-D decellularized emphysematous scaffolds is probably deficient in fundamental ECM architecture to assist cell growth [98].

There have been several reports about the use of albumin as surface grafting material (Table 1), grafting it on the surface of HA/CPG for periodontal intrabony defects, causes a resorption and regeneration of cementum [92]. Seeding bone graft with cells, or grafting them with collagen or fibronectin is not sufficient enough for regeneration, whereas albumin-coated bone chips is capable of the mediation of tissue regeneration [93], the active functional group present in the albumin might have been responsible for this rapid regeneration process [99], [100]. In a similar way, isolated albumin can be grafted on lungs before seeding with a stem cell of interest, since the lungs surface marker will cooperate with the albumin scaffold.

5.0 CONCLUSION AND FUTURE DIRECTION

Since there is a shortage of donor organ world-wide, the regeneration of human-scale lung scaffolds brings the goal of organ regeneration one step closer to clinical application. The field must now tackle the larger challenges of recellularization and restoring organ function to ultimately create transplantable organs for clinical use [101]. Albumin scaffold is an autogenic biomaterial which is at ones disposal in an unlimited quantities, since they are easily synthesize, biodegradable, biocompatible with different cells and scaffold materials, and non-immunogenic. Albumin-based biomaterial application has been established in Bone, Cardiac and Neural TE, this biomaterial can as

well be grafted on decellularized lungs before recellularization process. Thus we propose the supportive role of this biomaterial for a robust cell engraftment, proliferation and differentiation on the lungs. This will be possible considering their interaction with lungs surface protein. Further research will be needed to clarify the serum content other than albumin responsible for ESP inactivation.

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Table 1; Summary of albumin biomaterials as applied to Tissue Engineering and Regenerative Medicine

AUTHOR	ARTICLE	YEAR	TYPE	SCAFFOLD FABRICATION	SEEDED WITH	AIM/RESULT
WOO ET AL. [102]	NANO-FIBERS AND PROTEINS	2002	HSA and BSA	BSA grafted on PLLA nano fibrous polymer Scaffolds.	Osteoblastic cell	Pre-wetting PLLA scaffold with HSA and BSA creates a more accommodating environment for attachment of cells.
YAMAZOE AND TANABE [44]	WILEY INTERSCIENCE	2008	BSA	BSA crosslinked with ethylene glycol diglycidyl ether,	Mouse fibroblast L929 cells	Prepared a water-insoluble albumin film that possessed suitable flexibility and native albumin

				polyethylene glycol diglycidyl ether and genipin with varying concentration at 4.3,43 and 215mM.		properties, like cell adhesion resistance and drug binding ability. Cell fails to adhere.
YAMAZOE ET AL. [45]	LANGMUIR	2008	BSA	BSA cross-linked with ethylene glycol diglycidyl ether and	Mouse fibroblast L929 cells	Described a novel facile fabrication procedure for a micro-patterned surface cell patterning, using UV-induced

				subsequently casted on the cell culture dish.		conversion of the cell adhesive features of albumin.
KIM ET AL. [92]	BIOMEDICAL MATERIALS	2008	BSA	Coating HA/CPG with 2% BSA.	Osteoblastic cell	Evaluated the effect of BSA treatment on HA/CPG scaffolds to confirm if it promote osteoblastic cell adhesion during bone formation.
ROHANIZADEH AND KOKABI [51]	JOURNAL OF MATERIAL SCIENCE	2009	HSA	Heat aggregated albumin		Determined the effects of fabricating parameters such as the concentration of

						albumin, pH, and denaturation/aggregation temperature on the mechanical characteristics and biodegradability of albumin-based biomaterial.
GALLEGO ET AL.[48][47][46]	TISSUE ENGINEERING: Part A	2010.	HSA	HAS crosslinked with 25% glutaraldehyde + lyophilization	Human alveolar osteoblasts	Albumin Scaffold implanted into experimental rat mandibular defects for bone regeneration.
WESZL ET AL.[93]	ORTHOPAEDIC RESEARCH	2011	HSA	Freeze-dried bone	Human MSCs from either dental	Examined bone structure proteins effect

				graft	pulp/bone marrow.	or serum components on bone graft and freeze dried allograft colonization by MSCs.
FERRERO-GUTIERREZ ET AL. [94]	HISTOLOGY AND HISTOPATHOLOGY	2013	Serum-derived albumin	Crosslinked with 25% glutaraldehyde + lyophilization	Adipose derived stem cells (ADSCs) and olfactory ensheathing cells (OECs)	Verified the regeneration of axon, and recovery of locomotor in rats induced with spinal cord injury and treated with a novel serum-derived albumin scaffold seeded with (ADSCs) and (OECs). Their findings

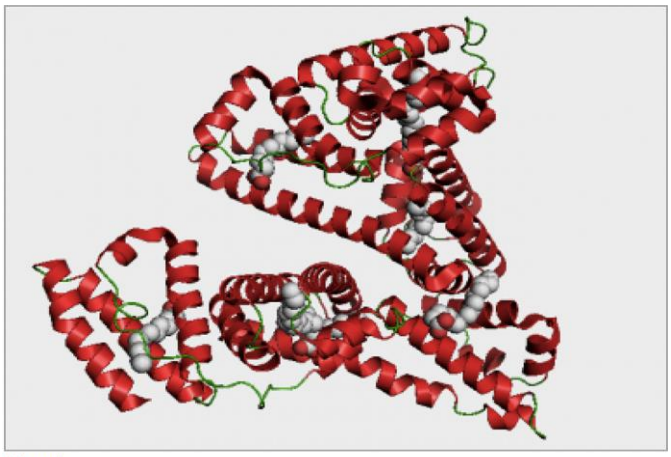
						pointed to the feasibility of albumin scaffold as a being potent for use in the studies of spinal cord injury repair.
KANG ET AL. [50]	JOURNAL OF BIOMATERIALS SCIENCE	2013	Serum-derived albumin	Cross-linking and freeze-drying procedures	Adipose tissue-derived mesenchymal stem cells (Ad-MSCs)	Evaluated *in vitro* osteogenesis of canine adipose tissue-derived mesenchymal stem cells (Ad-MSCs) seeded on a scaffold made of the combination of porous serum-derived albumin and collagen 1

						gel.
NSEIR ET AL. [52]	TISSUE ENGINEERING: Part C	2013	Serum Albumin	Electrospinning and salt-leached technique	fibroblasts, muscle cells, and endothelial cells (ECs) in vitro	Explored the mechanical and biological features of electrospun scaffolds that solely consist of albumin fibers, and compared them with those of scaffolds made of polycaprolactone (PCL) and poly (L-lactide) /poly(lactic-coglycolic acid) (PLLA/PLGA).
FLEISCHER ET	BIOTECHN	2014	BSA	Addition	Rat neonatal	Fabricated

AL. [53]	OLOGY AND BIOENGINE ERING			of mercapt oethanol + electros pinning + evaporat ion	cardiac cells	electrospun albumin fibers and seeded it with cardiac cell. Induced the assembly of aligned cardiac tissues with high aspect ratio cardiomyocytes and massive actinin striation.
LI ET AL [29]	NATURE	2014	HSA, BSA and PSA	Added microbia l transglut aminase +freeze-drying-based molding	Human MSCs	Presented a new procedure for synthesizing a tissue engineered scaffold from different animal blood albumin.
KASÁLKOVÁ	NANOSCAL	2014	BSA	Grafted	Smooth	Determined the

ET AL. [99]	E RESEARCH LETTERS			on the surface of plasma-treated poly-L-lactic acid and polyethylene.	vascular muscle cells (VSMCs) derived from rat aorta.	interaction of the vascular smooth muscle cells with BSA modified polymer surface.
YOON ET AL. [49]	JOURNAL OF VETERINARY SCIENCE	2015	Serum Derived Albumin	Freezing drying and Chemical cross-linking.	Canine adipose tissue-derived mesenchymal stem cells (Ad-MSCs)	Evaluated osteogenesis of autologous serum-derived albumin (ASA) scaffolds seeded with (Ad-MSCs)

Figure 1. Schematic representation of HSA Molecular structure. The picture was generated from PDB.



Albumin.

Figure 2. Step-wise process of scaffold fabrication of HSA. (A) Obtaining the Serum of human that needs the transplantation. (B) Isolating HSA from Serum. (C) Fabrication of HSA using various polymerization techniques to form a microporous scaffold. (D) Seeding scaffold with cells and transplanting to the patient.