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Engineering dextran-based scaffolds for drug delivery and tissue repair

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Abstract

Owing to its chemically reactive hydroxyl groups, dextran can be modified with different functional groups to form spherical, tubular and 3D network structures. The development of novel functional scaffolds for efficient controlled release and tissue regeneration has been a major research interest, and offers promising therapeutics for many diseases. Dextran-based scaffolds are naturally biodegradable and can serve as bioactive carriers for many protein biomolecules. The reconstruction of the *in vitro* microenvironment with proper signaling cues for large-scale tissue regenerative scaffolds has yet to be fully developed, and remains a significant challenge in regenerative medicine. This paper will describe recent advances in dextran-based polymers and scaffolds for controlled release and tissue engineering. Special attention is given to the development of dextran-based hydrogels that are precisely manipulated with desired structural properties and encapsulated with defined angiogenic growth factors for therapeutic neovascularization, as well as their potential for wound repair.

Keywords

dextran; hydrogel; stem cell; vascularization; wound healing

The discovery of dextran can be dated back to 1874 [1]. Dextran is a nontoxic, hydrophilic homopolysaccharide, mainly composed of linear α -1,6-linked β -glucopyranose residues with a low percentage of α -1,2-, α -1,3- and α -1,4-linked side chains. As a bacterially derived biopolymer [2], dextran can be synthesized from sucrose with dextransucrase or from malto dextrins with dextrinase [1]. In the meantime, dextran is subject to enzymatic degradation by dextranase, which exists in mammalian (including human) tissues.

The biocompatibility of dextran has been well documented; thus, dextran has been extensively explored in biomedical and pharmaceutical applications [3–5]. Dextrans are commonly used to decrease vascular thrombosis [6,7], reduce inflammatory response [8] and prevent ischemia–reperfusion injury in organ transplantation [9–11], in which dextran

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acts as a mild reactive oxygen species scavenger and reduces excess platelet activation [12]. Dextran has volume expansive properties and therefore its inclusion can improve blood flow [13]. Occasionally, soluble dextran complexes can also be used to replace lost blood in emergency situations when replacement blood is not available [14]. In addition, dextran has been largely used as coating material to protect and improve biocompatibility [15] and for many other applications [16–18]. Consequently, dextran is an excellent candidate for biomedical exploration.

The active hydroxyl groups of dextran can be chemically modified to incorporate various functional groups and as a result it can be developed with specific characteristics. Heretofore, dextran has been chemically engineered to form various scaffolds, including spheres [19–21], tubules [22] and hydrogels [3,23,24]. These nano- and microstructured biological scaffolds are highly efficient drug delivery systems, tissue regeneration devices and cell therapy vectors [25]. However, the potential of dextran may still be underestimated.

Constructing novel and functional scaffolds for controlled release and tissue regeneration offers promising therapeutics for many diseases. Understanding the details of their mechanisms can improve targeted delivery efficiency and tissue regeneration therapy. Controlled release is an independent research area, but it is also an indispensable part of tissue engineering and regenerative medicine. Tissue engineering encompasses the integration of stem cells with scaffolds as regenerative templates that require the presence of various growth factors to regulate cell activities. A precise release of growth factors thus plays an important role in tissue regeneration [26].

The aims of this article are to describe the recent development of dextran-based nano- and micro-structured materials for controlled release; vascularization on the basis of dextran scaffolds; and tissue repair with dextran-based hydrogels. This article will discuss the primary requirements in designing dextran scaffolds for structure manipulation, degradation and functionalities to achieve efficient drug release and tissue regeneration. Perspectives will also be provided on the potential applications of unexplored dextran scaffolds.

The rationale of dextran modification

Unlike other polysaccharides, such as chitosan, alginate and hyaluronic acid, which have various functional groups (e.g., amine and amide), dextran only has hydroxyl groups, which do not support cell attachment. Incorporation of functional affinity binding sites via chemical modification is thus very desirable. Although dextran lacks functional groups, these can be created with precise control of desired functionalities. Some biopolymers, such as chitosan, possess functionality owing to their amine groups; chemical modification could convert some amine groups into other groups and thus change the molecule's initial functional characteristics. For dextran, new novel dextran derivatives can be built by incorporating different functionalities without compromising its primary properties. In each repeat unit, dextran has three hydroxyl groups (Figure 1), and the reactivity of the individual hydroxyl groups decreases in the order $C2 > C4 > C3$ [3]. The degree of substitution of dextran derivatives refers to the number of replaced hydroxyl groups per unit and usually influences the properties of its derivatives. The degree of substitution value can be estimated

from the ^1H NMR spectrum [3]. Consequently, dextran could be precisely engineered via chemical modification for various purposes.

Fabrication of dextran-based spherical scaffolds

The development of intravenously administered carriers that can continuously deliver drugs, imaging agents or other entities to specific target sites has been a major challenge [27]. Micron- and submicron-scale carriers can be tuned to achieve site-specific controlled delivery. Because of their tiny sizes, nanospheres that can penetrate deep into targeting tissues through fine capillaries can be easily taken up by tumor cells [28]. Additionally, nanospheres can be transported to distant target sites by localized delivery [29]. Furthermore, nanospheres can be conjugated with site-specific targeting groups that direct them to target sites [28,30]. It is interesting to note that their administration efficiency is organ specific [31]. Ideally, nanospheres could concurrently serve as vehicles for drug carriers, cell imaging indicators and photothermal therapy [32], if multifunctional targeting groups could be coupled onto them, thus improving both therapeutic and diagnostic capabilities. As a result of their distinct advantages, biodegradable polymeric nanospheres have been extensively investigated in biomedical and pharmaceutical fields [33–36].

Molecular self-assembly is an important bottom-up approach to fabricate nanostructures. Self-assemblies are regulated by noncovalent or weak covalent interactions [37], among which electrostatic forces dominate the interactions of charged molecules and can drive them into spherical nanostructures. Generally, nanospheres are self-assembled from amphiphilic molecules [38]. Recently, the present authors reported that hollow nanospheres could self-assemble from oppositely charged dextran-based hydrophilic macromers (Figure 2) [39]. Two oppositely charged complementary dextran macromers were synthesized from 2-bromoethylamine (Dex-BH) and chloroacetic acid (Dex-CA). In a pH 5.0 buffer solution, Dex-BH and Dex-CA became protonated and deprotonated, respectively, and the electrostatic interaction propelled them to self-assemble into well-defined hollow nanospheres. These nanospheres have a uniform diameter of approximately 160 nm. However, their size and distribution are largely dependent on the molecular weight of dextran and the pH value of the buffer solution. An *in vitro* albumin release study further elucidated the nanosphere architecture, which was affirmed by the release profile. Collectively, the present authors' data suggested that the hollow structure is attributed to the hydrophilic characteristics of dextran macromers. As only a fraction of hydroxyl groups were substituted, more functional groups may be introduced onto the dextran backbone without altering its characteristics, and the nanospheres retain great potential as intelligent drug delivery systems (DDSs).

Self-assembly of dextran tubules

Although spherical structures can deliver drugs into cells, they suffer short circulation times and thus are cleared quickly from the body [40]. Therefore, nonspherical modes of delivery, such as tubular structures, are also widely studied as efficient drug carriers [41,42]. Because of their unique structural features, tubules have become increasingly interesting both in basic and applied research [43,44]. Tubular structures are mostly self-assembled from amphiphilic

molecules such as lipids [43], copolymers [45,46], and peptides [47,48]. Tubule self-assemblies are mainly driven by hydrophobic interactions, in which the non-polar region of each molecule forces the water molecules away so to array themselves towards one another [49]. Although many tubule self-assemblies have been explored, the details of their mechanisms remain poorly understood, especially tubular structures self-assembled from hydrophilic polymers.

Recently, the present authors reported for the first time a tubular structure self-assembled solely from hydrophilic dextrans via electrostatic interaction [22]. In brief, the tubular structures were fabricated from Dex-BH and Dex-CA in a solution of pH 4.0 at a concentration of 2.5 mg/ml, which is significantly higher than those of nanosphere self-assemblies. The self-assembly of nano- and micro-sized tubular structures was dependent on both pH and salt concentrations. Scanning electron microscopy and light microscopy substantiated our hypothesis that the tubules have hollow structures up to 100 μm long with a diameter between 600 nm and 2 μm . The x-ray study confirmed that only non-ordered molecular structure was present in the tubules. As evidenced by scanning electron microscopy data, the present authors suggested that the dextran macromers first interact with one another to form tiny bead-like aggregates, followed by ring formation through electrostatic interactions. After such ring structures form, they simultaneously grow in both transverse and longitudinal directions until tubules form (Figure 3). It is interesting to note that, without initial ring formation, it is unlikely for dextran macromers to self-assemble into tubular structures. This tubule model provided a complementary assembly mechanism to what had been proposed, although it may still need further exploration to confirm its validity. Insights gained from this tubule self-assembly study may offer significant directions for fabricating novel materials.

Engineering functional dextran hydrogels

Hydrogels are 3D hydrophilic networks that are structurally similar to natural extracellular matrix (ECM). Other than their appealing biomimetic structures, hydrogels also have unique biocompatibility, flexible methods of synthesis, a wide range of constituents and desirable physical characteristics. They have thus been the material of choice for many applications in regenerative medicine [50,51]. Hydrogels can be engineered to incorporate different functionalities and protect biologically active molecules from being altered, thus they are used as intelligent DDSs [52,53]. Many biochemical and physical cues can be incorporated to mimic the *in vivo* microenvironment, enabling the hydrogel to act as a definitive tissue regeneration template to provide an instructive environment for 3D cell assembly into functional tissues or organs.

Tissue engineering requires cell signaling protein molecules (e.g., growth factors and cytokines) to direct cell activities and self-assemble cells into functional tissues. The encapsulation and controlled release of these biomolecules thus play a critical role in tissue regeneration. As a result, controlled release and tissue engineering are becoming inseparable, and the development of polymeric scaffolds is vital for controlled delivery with implications in tissue engineering and regenerative medicine. Moreover, the scaffold should provide a cell environment similar to the native tissue to maintain cell phenotype and

organization to promote tissue repair. In tissue engineering, cells act as the engineers in tissue reconstruction, but they cannot survive without aqueous media. Consequently, one of the primary requirements for scaffolds is to protect cells from dry environments. Thanks to their hydrophilicity, hydrogels can swell dramatically and retain the absorbed liquid [3], thus making them an ideal scaffold for cell therapy.

Hydrogels are synthesized by either chemical or physical crosslinking methods. However, chemical modification of the dextran backbone allows the development of dextran hydrogels with desired characteristics [25]. To understand how to enhance dextran functionality for controlled release and tissue-engineered scaffolds, a series of dextran-based derivatives were synthesized by incorporating various functional groups, including allyl isocyanate (Dex-AI), followed by further integration of ethylamine (Dex-AE), chloroacetic acid (Dex-AC) and maleic anhydride (Dex-AM) into Dex-AI [23]. To tune the properties of dextran hydrogels, polyethylene glycol diacrylate was introduced as a crosslinker. These hydrogels were found to have different physical and biological properties, including swelling, degradation rate, mechanics, crosslinking density, biocompatibility (*in vitro* and *in vivo*) and release profiles, and each of these properties was also influenced by many factors [3,23,24]. The results also suggested that the integration of amine groups with dextran resulted in hydrogels with better biocompatibility and release properties. In brief, the incorporation of different functional groups affects the fundamental properties of a dextran-based hydrogel network and amine groups are preferred to generate hydrogels for biomedical use.

Embedding dextran tubules within hydrogels

In a prior study, self-assembled tubules inevitably congregated during either the growth or the drying process, making it impossible for them to be separated from each other once they were dried [22]. Such congregation made it difficult for the subsequent release test. As previously discussed, the incorporation of amine groups into dextran hydrogels creates effective interactions and enhances sustained protein release [3,24]. The present authors speculate that these amine groups could influence self-assembled tubules if they are grown in the dextran hydrogel. Once the amine groups become protonated and charged, the electrostatic interactions could change the tubule self-assembly [22], thus they can separate themselves from one another and disperse in a relatively undisturbed environment.

To investigate the aforementioned interactions and to improve protein release, the present authors self-assembled Dex-BH and Dex-CA into tubular structures and impregnated them into Dex-AE/polyethylene glycol diacrylate hydrogel [54]. It was first found that the self-assembled tubules aggregated in the pure polyethylene glycol diacrylate hydrogel, while the amine-incorporating hydrogel dispersed the tubules within the hydrogel network. This result confirms earlier speculation that the amine groups of Dex-AE provide tubule binding sites. An increase in the amine content of Dex-AE resulted in more evenly distributed structures and further study indicated that self-assembly tends to occupy the binding sites within the hydrogel before they can grow. Moreover, we found that the implantation of the self-assembled tubules had no distinct effect on the swelling capacity of the hybrid self-assembly embedded hydrogels. The *in vitro* drug release test revealed that the implantation of tubular self-assembly reduced the burst release and slowed down the release (Figure 4). The drug

loading efficiency study indicated that more than half ovalbumin could be encapsulated into the self-assembled entities. These results may suggest that separate encapsulations within both tubule self-assembly and hydrogel could allow this self-assembly-impregnated hydrogel to function as a dual polymeric DDS. Dual DDSs can deliver multiple biomolecules and have been proved to be effective in both drug delivery and tissue engineering [55–57]. The present authors' findings demonstrate that the impregnation of tubular self-assembly into hydrogels makes the hybrid hydrogel an excellent protein delivery agent.

Hydrogel scaffolds for therapeutic vascularization & tissue regeneration

Therapeutic vascularization is a promising avenue but remains a significant challenge in regenerative medicine [58]. Successful regeneration of ischemic and wound tissues requires timely and functional vascularization [59,60]. The newly formed vasculature will bring blood rich in various cells and nutrients to repair the injured tissues, or help integrate tissue-engineered scaffolds with host tissues to restore their functions [61]. Thus far, there are three general strategies to enhance vascularization of tissue-engineered scaffolds [50]. The first is the incorporation of regulatory factors (e.g., RGD, VEGF and mechanical stimulus) that induce the growth of vasculature from surrounding tissues or recruit endothelial progenitor cells (EPCs) [55]; the second is *in vitro* vascularization via cell engineering [62,63]; the third strategy is prevascularization *in vivo* before transplantation to the injured tissues [50,55,61,64,65]. Levenberg *et al.* demonstrated that prevascularization improved blood perfusion and survival of tissue-engineered constructs after transplantation [66].

However, the above vascular strategies cannot be achieved without an efficient hydrogel scaffold. Accordingly, a biomimetic scaffold is critical for vascular development and tissue repair. Although a number of hydrogels have been developed for drug delivery [67], the design of functional hydrogel scaffolds remains a huge challenge for tissue repair, owing to insufficient vascularization. The creation of 3D synthetic scaffolds with regulatory signals (molecular and physical) requires a full understanding of how each factor contributes to neovascularization and tissue or organ regeneration. Therapeutic vascularization has thus become a major research focus but remains a critical challenge in regenerative medicine [68]. In recent years, much effort has been devoted to developing bioactive scaffolds for functional vascularization [69], but the design of a practical and feasible scaffold for implantation has yet to be fully realized. In addition to basic prerequisites, such as non cytotoxicity, biocompatibility and biodegradation, other physical properties, including porosity, pore size, mechanics, topography and shapeability, are also critical for developing a vascularized scaffold. A porous scaffold should have interconnected channels to transport chemicals, nutrients and metabolic wastes. Kloxin *et al.* demonstrated that a hydrogel without porous structure did not support cell migration [70], while Phelps *et al.* further showed that a matrix metalloproteinase-degradable hydrogel promoted vascularization [68]. An ideal scaffold is capable of loading and releasing signal-directing biomolecules to support vascularization [71–74]. Furthermore, the scaffold should have enough mechanical strength to support and promote appropriate cell growth and differentiation. Encapsulating endothelial cells within hydrogels offers many attractive features in vascular engineering [75]. Hydrogels provide structural support for cells to enable them to differentiate and form

different vascular structures. Therefore, the hydrogel scaffold should support the presence of several vascular cell types (e.g., endothelial cells, smooth muscle cells and fibroblasts) and organ-specific cell types (e.g., hepatocytes and cardiomyocytes) [69]. Once implanted, bio degradable hydrogels will integrate with host tissue via microvascular structures and degrade quickly while new tissues infiltrate.

Engineering dextran hydrogel for neovascularization

Vascularization is a complex process including mobilization, chemotaxis, adhesion, proliferation and differentiation of progenitor cells [76]. Vascular engineering encompasses the construction of delicate scaffolds, incorporating and releasing signaling molecules, encapsulating stem cells, and transplanting functional vascular structures to the injured tissues [69]. Clinical applications of engineered tissues have been limited due to poorly vascularized tissues [77]. Engineering complex and highly vascularized tissues presents many challenges. A major concern is how to incorporate biochemical and physical cues to mimic the *in vivo* microenvironment, thus enabling us to maintain large masses of viable and functional constructs and transfer them from *in vitro* conditions into the patient. Appropriate scaffolds are crucial for advancing vascular engineering theory from the bench to practical application.

Recently, the present authors' study found that angiogenic growth factors have a synergistic effect under certain conditions. It was further demonstrated that manipulating and tailoring the physical properties of dextran hydrogels could induce a rapid and functional neovascularization into the scaffolds under optimal growth factor conditions [59]. Macroporous interconnected hydrogel scaffolds facilitate nutrient transport and cell infiltration [78]. Towards this end, the present authors redesigned the hydrogel structure by reducing the degree of substitution of cross-linking groups, thus attaining more porous but mechanically stable hydrogels with optimized crosslinking density. Such modification led to improved properties including reduced rigidity, increased swelling and prolonged VEGF release capability. VEGF immobilized in the dextran hydrogels promoted cell infiltration and tissue ingrowth, leading to rapid biodegradation. The co-encapsulation of VEGF plus Ang-1, and VEGF plus IGF-1 plus SDF-1, induced more and larger blood vessels than any individual growth factor, while the combination of all growth factors had a synergistic effect and dramatically increased the size and number of neovascular vessels. It is worth noting that no synergistic effect was established without the presence of VEGF, which is consistent with other studies [79]. Both the hematoxylin and eosin and α -smooth muscle actin staining of histological sections revealed that red blood cells were preserved in the vessel, indicating the blood vessels were functional (Figure 5). Dvir *et al.* demonstrated that the combined growth factors VEGF plus SDF-1 plus IGF-1 promoted prevascularization [61], which was in good agreement with the results of the present authors. However, the present authors' study further demonstrated that incorporating Ang-1 into the combination of these three growth factors significantly increased both the number and size of functional blood vessels. Altogether, the present authors demonstrated that functional neovascularization could be achieved by precisely tuning the dextran hydrogels under the favorable angiogenic growth factor condition. These data give an insight into how to design an efficient hydrogel scaffold

for vascular engineering. The present authors believe that this dextran hydrogel has great potential as a device for therapeutic regenerative medicine.

Dextran hydrogel promotes wound healing & complete skin regeneration

Skin is the largest organ in the human body and is difficult to repair after being injured [80]. Wound healing of adult skin is one of the most complex biological processes, requiring the collaborative efforts of various tissues and cell lineages, and matrix synthesis, as well as extracellular and intracellular signals [81–83]. Although research has elucidated many details of the basic wound healing process [84], the regeneration of perfect skin remains a challenge in tissue engineering [85]. In human adults, the wound repair process commonly leads to nonfunctioning scar tissue formation and wound induration [83]. Perfect skin regeneration has recently become a major aim in wound healing [83,85].

Angiogenesis and neovascularization are critical components of wound healing outcomes [86,87]. Functional vascularization facilitates oxygen and nutrient transport as well as waste removal [84]; thus it is critical for tissue growth and governs deep wound healing outcomes. The present authors demonstrated in a deep burn wound model that dextran hydrogel promoted dermal regeneration with complete skin appendages (Figure 6) [88]. The hydrogel scaffold facilitated early inflammatory cell infiltration, which led to a rapid degradation of the hydrogel scaffolds, promoting the infiltration of angiogenic cells into the healing wounds. Endothelial cells homed into the hydrogel scaffolds to enable neovascularization by day 7, resulting in an increased blood flow significantly greater than treated and untreated controls. By day 21, burn wounds treated with the hydrogel developed distinct mature epithelial and collagen layers with significantly increased presence of hair follicles. After 5 weeks of treatment, the hydrogel scaffolds promoted new hair growth and mature skin structure similar to a normal mouse. Other dextran-based hydrogels were also reported to promote wound healing [89,90], but, unlike the present authors' study, those dextran hydrogels did not show any potential to regenerate complete skin structures, thus making the present authors' hydrogel a unique candidate for wound repair.

Skin regeneration therapy is the ideal treatment for many wound injuries. With the proper design of tissue engineering frameworks, along with stem cells and the release of growth factors, normal skin structures can be restored for all kinds of wound injuries. For complete skin regeneration, other than the fact that the dextran hydrogels promote neovascularization, the dextran hydrogel can be customized in terms of wound shape and patient situation (e.g., age and general health). Meanwhile, depending on the skin disease type, a hydrogel can also deliver genes and cytokines, and even manipulate mechanical force or other stimuli to induce wound healing and perfect skin regeneration.

Temperature-responsive dextran as a cell-detaching substrate

Stem cell therapy has greater potential than traditional treatment in facilitating tissue repair [91,92]. In order for stem cells to be translated into clinical use they must be treated with substances that will not harm their bioactivity and be cultured on biocompatible substrates that will not pose a threat to the patient once the cells are implanted. In cell cultures, proteases are traditionally used to detach cells from the culture substrate to enable their

expansion. Cells attach to hydrophobic culture surfaces via cell membrane proteins and ECM components. To detach cells, proteases digest both membrane and ECM proteins [93], which results in delayed cell proliferation and differentiation. Moreover, proteases also degrade growth factors [94] and, if they remain in cell solution, they also lead to a delay in tissue regeneration.

In recent years, temperature-sensitive polymers (TSPs) have been developed as a suitable and advantageous substrate for cell detachment. At temperatures below its lower critical solution temperature (LCST), a TSP is water soluble; however, at its LCST or higher, the hydrogen bond interactions between the TSP and water become weak, and the TSP becomes more hydrophobic [95]. Typically, a TSP is coated on a cell culture flask prior to cell seeding. When cells are cultured on temperature-responsive surfaces, the interconnection between the ECM and the hydrophilic culture surface is released only by reducing the temperature below the LCST. Then, the cells detach together with proteins intact. Unlike using proteases to detach cells, this mild technique of cell detachment preserves cell-to-cell and cell-to-ECM interactions [96].

Most current TSPs are not completely biodegradable [95–97] or they exhibit cytotoxic characteristics [98,99]. A completely biodegradable and biocompatible TSP is desirable for the *in vitro* expansion of human stem cells in regenerative medicine applications. The present authors developed and examined a biodegradable, temperature-sensitive dextran-allyl isocyanate-ethylamine (TSDAIE) as a non enzymatic cell detachment polymeric substrate for human EPCs (Figure 7) [100]. TSDAIE has a LCST, and its phase transition occurred at from 18°C to 22°C. For EPC culture, cell culture flasks were coated with TSDAIE and type I collagen. The TSDAIE coating enabled EPC detachment when the culture was cooled to 4°C. EPC detachment was found to be concentration-dependent. At the determined optimal concentration, TSDAIE was found to be compatible for use in EPC culture, as revealed by cell attachment, spreading, proliferation and phenotype. Because of its complete biodegradability, TSDAIE can be used directly in the culture of stem cells without requiring the additional step of removing nondegradable polymer. This advantage can expedite stem cell scale-up for clinical use.

Conclusion & future perspective

A functional, efficient and instructive scaffold plays a critical role in both controlled release and tissue engineering. Controlled release can be an independent research area, such as drug release, as well as part of tissue engineering that directs the distribution of growth factors. A well-designed scaffold provides cells with both physical and biochemical cues to support cell adhesion and migration as well as, ultimately, vascular structure formation accompanied by tissue repair and regeneration. The scaffold will eventually degrade and be replaced by the host tissues.

These studies have demonstrated that, with proper modification and formulation, dextran can be modified to incorporate different functionalities and form nano- to macro-structured scaffolds, and these scaffolds have found various applications in drug delivery and tissue engineering [25].

With an unlimited modification capacity, the incorporation of targeting molecules by either chemical or physical bonding may bring about new possibilities. For wound healing with dextran hydrogels, further studies may reveal how the dextran hydrogel promotes complete wound healing, and how hair follicles are formed. The present authors may further extend its application for hair growth treatment. With the ultimate goal of translational research, some of the scaffolds discussed in this paper will be further exploited for preclinical and clinical studies; it will be possible to translate more dextran-based biomaterials into clinic. However, realizing laboratory advances requires the multidisciplinary collaboration of scientists, engineers, biologists and surgeons.

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Executive summary

Chemically engineered dextrans can form various scaffolds

- Dextran is a nontoxic hydrophilic homopolysaccharide with many hydroxyl groups that can be modified to incorporate various functional groups, thus allowing the development of dextran-based materials with specific characteristics.
- Dextran can be formulated into spherical, tubular and 3D network structures for either drug release or tissue engineering.

Dextran-based hydrogels are efficient drug delivery & tissue regeneration templates

- Dextran-based hydrogels are efficient drug delivery agents for therapeutic proteins.
- Precise tuning of dextran hydrogels with the delivery of angiogenic signaling biomolecules synergistically induces functional neovascularization.

Dextran hydrogels promote dermal regeneration with complete skin appendage

- Customized dextran-based hydrogel alone, with no additional growth factors, cytokines or cells, promoted remarkable neovascularization and skin regeneration and may lead to novel clinical treatments of full-thickness dermal wounds.
- With proper delivery of regulatory signals (molecular and physical), skin regeneration therapy offers the ideal treatment for many wound injuries.

Dextran as a cell-detachment substrate

- Dextran can be chemically engineered into a temperature-responsive polymer that acts as a cell-detaching substrate.

Figure 1. The reactivity of dextran

Each repeat unit has three hydroxyl groups and the reactivity of the individual hydroxyl groups decreases in the order C2 > C4 > C3. A wide range of functional groups can be incorporated into dextran via these hydroxyl groups.

Figure 2. Nanosphere self-assembly from hydrophilic dextran macromers

Oppositely charged Dex-BH and Dex-CA attract each other in aqueous solution through electrostatic interactions to form spherical structures.

Dex-BH: Dextran-bromoethylamine; Dex-CA: Dextran-chloroacetic acid.

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Figure 3. Tubule self-assembly

Dex-BH and Dex-CA first form polyvalent tiny bead-like aggregates, which line up to form circles due to the alternating positive and negative charges. These ring structures simultaneously direct the growth of the tubule self-assembly in both longitudinal and transverse directions.

Dex-BH: Dextran-bromoethylamine; Dex-CA: Dextran-chloroacetic acid.

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Figure 4. Self-assembly implantation into dextran hydrogels

(A) Tubule implantation. (B) Cumulative release of ovalbumin from tubule-embedded hydrogels reduced with the increased amount of tubule embedment.

DBC-0: Pure hydrogel; DBC-5, -10, -15: Increasing amount of tubule embedment; Dex-AE: Dextran-allyl isocyanate-ethylamine; Dex-BH: Dextran-bromoethylamine; Dex-CA: Dextran-chloroacetic acid; PEGDA: Polyethylene glycol diacrylate. Reproduced with permission from American Chemical Society [54].

Figure 5. Robust scaffold neovascularization with delivery of angiogenic growth factors
 (A) Manipulation of dextran hydrogels with reduced DSs. Varying DSs of Dex-AE are represented by the C=C double bonds in the chemical structure, and the crosslinked dots in the resulting hydrogel structures. (B–E) Representative images of H&E and α -SMA staining of histological sections of Dex-AE/PEGDA after (B & D) 5 weeks with VEGF and (C & E) 3 weeks with VEGF, SDF-1, IGF-1 and Ang-1. Scale bars: 100 μ m.
 α -SMA: α -smooth muscle actin; Dex-AE: Dextran-allyl isocyanate-ethylamine; DS: Degree of substitution; H&E: Hematoxylin and eosin; PEGDA: Polyethylene glycol diacrylate.
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Figure 6. Dextran hydrogel as a therapeutic modality promotes complete skin regeneration (A) Representative images of histological sections at time intervals show that dextran hydrogel promoted wound healing with complete skin appendage regeneration. Masson's trichrome staining indicates distinct collagen structures formed in dermal layer by day 21. Normal hair grows on the wound treated with hydrogel by day 35. (B) Doppler images of angiogenic response to wound injuries on day 7. (C) Representative α -smooth muscle actin staining of wound area treated with hydrogel on day 7. (D) Hematoxylin and eosin staining of newly regenerated skin treated with hydrogel after 35 days. (E) Quantification of skin thickness after 3- and 5-week long hydrogel treatment compared with normal mouse skin. Scale bars: 100 μ m.

***Significance level was set at $p < 0.001$.

C: Control scaffold; E: Eschar; F: Follicle; H: Hydrogel scaffold; W: Wound area
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Figure 7. Dextran-based temperature-sensitive substrate detaches cells nonenzymatically

Dextran-based temperature-sensitive dextran-allyl isocyanate-ethylamine (TSDAIE) is a biodegradable, temperature-sensitive polymer developed for cell detachment. At temperatures higher than its LCST, TSDAIE is hydrophobic and facilitates cell attachment; at temperatures lower than its LCST, TSDAIE is hydrophilic and promotes cell detachment. LCST: Lower critical solution temperature; T: Temperature; TSP: Temperature-sensitive polymer.

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