A biodegradable skin regeneration scaffold system(BCAID)

Introduction

Skin tissue defects caused by various wound factors are very common clinically. Relying on the epithelium and basal tissue of their own wound margins, large wounds such as extensive burns and mechanical injuries,which are difficult to heal. Tissue engineering scaffolds have great advantages in repairing skin wounds. The excellent properties of bacterial cellulose (BC) make it to be qualified as a high-quality tissue engineering scaffold. However, the non-biodegradable cellulose in vivo is a knotty problem that restricts its application at present. Our project aims to build a biodegradable skin regeneration scaffold system (BCAID) based on bacterial cellulose. BCAID is divided into basic BC production module, auxiliary healing module, blue-light activated BC degradation module and red-light activated fibroblast suicide module. The four modules constitute the whole BCAID with complete functions and excellent characteristics. BCAID provides a solution in synthetic biology for the real application of BC tissue engineering scaffolds in human body, which is of great significance for repairing skin tissue wounds.

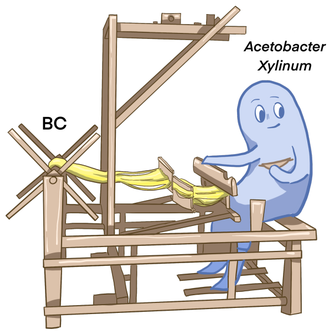
Background

Full-thickness skin tissue defects caused by various injury factors are very common in clinic. According to statistics, there are as many as 3.2 million patients who need to be treated for burns, mechanical wounds or chronic skin ulcers every year in China.

Clinical skin repair materials can be divided into two categories: one is natural skin and animal tissue, the other is tissue engineered skin (TES), which is a three-dimensional, active skin substitute formed by the interaction between tissue-engineered scaffold and functional cells. Autologous skin grafting is effective in repairing wounds, but it faces some problems, such as limited skin donor site and new wounds. Allogeneic tissue transplantation may also cause immune rejection and virus infection in addition to the above limitations. TES is expected to solve these difficulties.

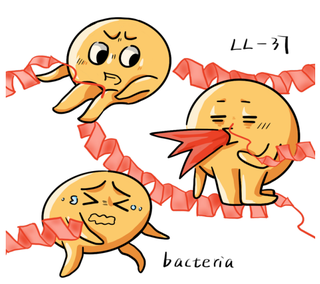
Design

Basic BC production

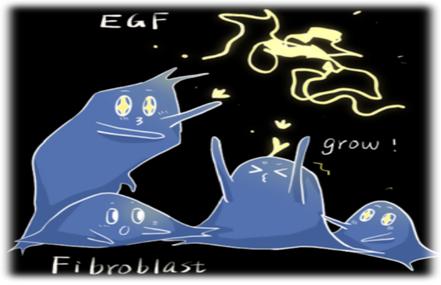


We have chosen Acetobacter xylinum to secrete BC, which has excellent performance in BC production. Then on this basis, we will further modify it, adding small molecular chitosan, hyaluronic acid, which are beneficial in the process of wound healing.We will further modify it, adding small molecular chitosan, hyaluronic acid, which are beneficial in the process of wound healing, so as to obtain scaffold materials more suitable for wound healing.

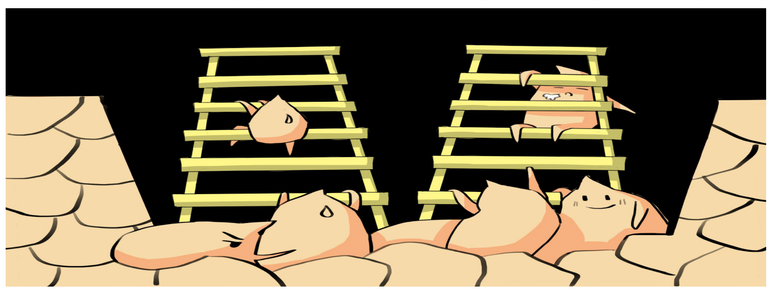
Healing promoting



LL-37： Antimicrobial peptide



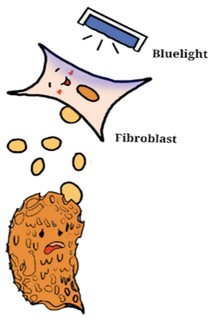
EGF: Promoting wound healing and reducing scarring



bFGF： Accelerating dermal repair and angiogenesis

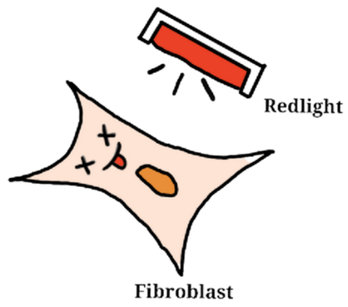
We plan to use adeno-associated virus (AAV) as the vector, and the modified AAV is expected to sprayed or injected to invade the cells in wounds, and then these cells can express functional peptides. At present, we plan to express epidermal growth factor (EGF)、basic Fibroblast Growth Factor(bFGF) and antibacterial peptide LL-37, which are small proteins with high biological activity. Both of them are human proteins, and the related research is in-depth, so there is no need to worry about security.

Blue-light activated BC degradation



Our project introduces the LightOn system initiated by blue light in fibroblasts, where transcription factors can be rapidly activated after blue light irradiation to achieve expression of cellulase. By this way ，the scaffold is endowed with in vivo biodegradability.

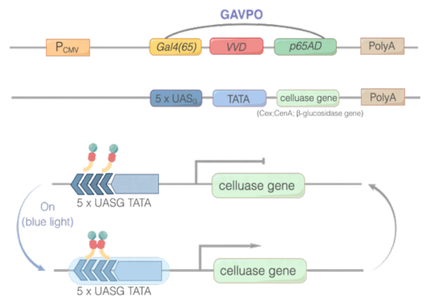
Red-light activated fibroblast suicide



In order to prevent fibroblasts from continuously secreting cellulase and causing unnecessary immune response after BC has completely degraded, the red / far red light regulation system(REDMAP) is added to control the expression of downstream toxin protein MazF. When irradiated with red light (660 nm), engineered fibroblasts will synthesize MazF toxin to interfere with the normal synthesis of their own proteins, resulting in a series of reactions and eventually leading to self apoptosis.

Modeling

The Circuit Of Cellulase Expression



Variable	Biochemical species
P	Inactive GAVPO
A	GAVPO
A_2	Dimer GAVPO
B	Cellulase
G	GAVPO Gene

Table 1 Biochemical Species In The Reactions

$$
\begin{aligned}
G &\xrightarrow{k_0} P, & \frac{d[P]}{dt} &= k_0 - k_1[A] - k_5[P] \\
P &\xrightarrow{k_1} A, & \frac{d[A]}{dt} &= k_1[P] - k_2[A]^2 - k_5[P] \\
2A &\xrightarrow{k_2} A_2, & & \\
A_2 &\rightarrow B, & & \\
B &\xrightarrow{k_3} \phi, & \frac{d[A_2]}{dt} &= k_2[A]^2 \\
A &\xrightarrow{k_4} \phi, & \frac{d[B]}{dt} &= \frac{\beta[A_2]^n}{k^n+[A_2]^n} - k_3[B] \\
P &\xrightarrow{k_5} \phi, &
\end{aligned}
$$

Ordinary Differential Equations Of The Reaction Of Cellulase Production

Description	Value	Unit	Parameter
Translation rate of [P]			k0
Translation rate of [A]			k1
Dissociation rate of dimer $[A]_2$			k2
Degradation rate of [B]			k3
Degradation rate of [A]			k4
Degradation rate of [P]			k5

Table 2 Reaction Rate

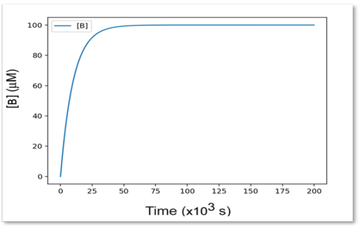
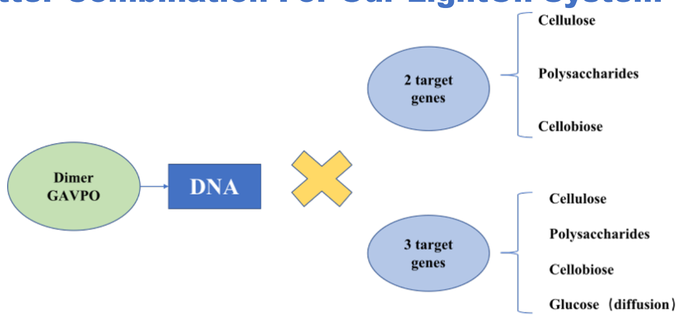


Figure 10 The Expression Of Cellulase Overtime

The Better Combination For Our LightOn System



Reference

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BNUZH CHINA

北京師範大學 珠海校区

BEIJING NORMAL UNIVERSITY AT ZHUHAI