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Development of Regenerative Medical Devices Using the Artificial Protein Silk-Elastin®

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Silk-Elastin® as a Cell Scaffold Material

Cell scaffold materials create an environment that promotes the growth and differentiation of cells within the body. Consequently, they play a crucial role in inducing and promoting tissue regeneration in regenerative medicine for repairing or replacing damaged tissues.

Silk-Elastin® is an artificial protein produced by genetic recombination technology that mimics the naturally occurring proteins elastin and silk fibroin **(Figures 1 and 2)**. Due to its high content of elastin-derived sequences, it exhibits excellent cytocompatibility (the ability to integrate with cells without causing inflammation) and high elasticity (the property of restoring shape), making it suitable as a cell scaffold material. When dissolved in water, Silk-Elastin® is a liquid at low temperatures, but as temperature increases, its viscosity increases, eventually forming a gel **(Figure 3)**. Once gelled, it does not revert to a liquid state, and this gel exhibits elasticity similar to that of soft tissues, including skin. Furthermore, our proprietary interface control technology enables the processing of Silk-Elastin® into various densities and thicknesses in both sponge (Silk-Elastin® Sponge) and film (Silk-Elastin® Film) forms **(Figure 4)**. This allows for the optimization of the biological and mechanical environments necessary for effective cell scaffolding. This article introduces medical devices currently under development that utilize these properties.

Development of Wound Healing Materials

Existing medical devices for wound treatment are selected based on the depth of the wound and the risk of bacterial infection, as shown in **Figure 5**. For relatively shallow wounds, wound dressings and ointments are used to maintain a moist environment. For wounds with a low risk of bacterial infection, carboxymethyl cellulose (CMC) is used, while for wounds with a high risk of bacterial infection, hydrocolloids containing silver ions with antibacterial properties are employed. The distinctive feature of Silk-Elastin® as a wound healing

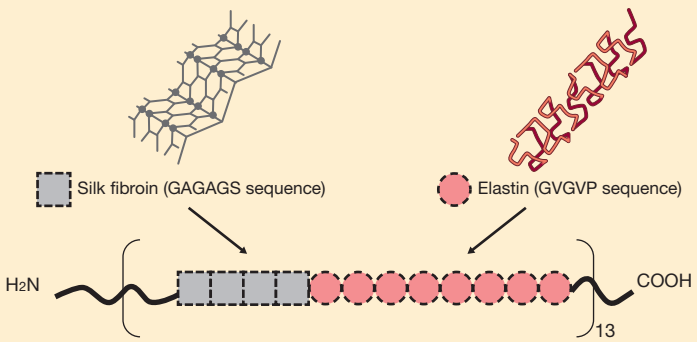


Fig. 1 Amino-acid sequence of silk-elastin

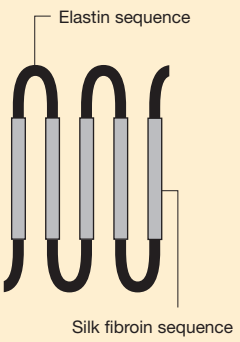
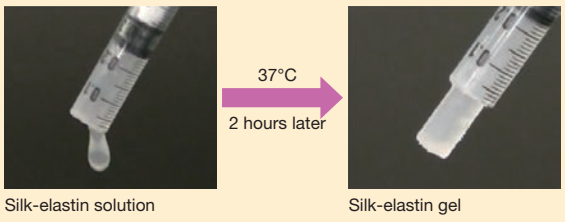


Fig. 2 Structure of silk-elastin

material is its superior adhesion and conformity to complex wounds compared to traditional wound dressings and ointments. When Silk-Elastin® in sponge form is applied to a wound, it absorbs and dissolves body fluids (exudates), spreads over the wound, and gels at body temperature. The gel formed by Silk-Elastin® on the wound surface not only maintains a moist environment but also protects the wound by keeping it stable and clean. Additionally, due to its high cell affinity, Silk-Elastin® promotes the migration and proliferation of necessary cells during the inflammation and proliferation/maturation phase (wound healing promotion). Its strong resistance to bacterial infection also makes it effective for wounds at high risk of bacterial infection. Therefore, Silk-Elastin® meets the clinical need for wound healing materials that offer both strong antibacterial properties and improved healing.

With the support of the Japan Agency for Medical Research and Development (AMED) through the Acceleration Transformative Research for Medical Innovation program (ACT-M) in 2016, the safety of Silk-Elastin® was confirmed in an investigator-initiated clinical trial at Kyoto University. Corporate clinical trials conducted in 2019, supported by AMED's Project for the Development of Medical Devices, confirmed its efficacy with favorable results. Currently, preparations for regulatory approval and market launch are underway.



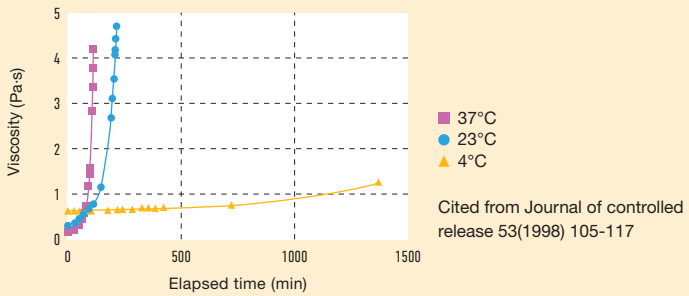


Fig. 3 Changes in viscosity in silk-elastin

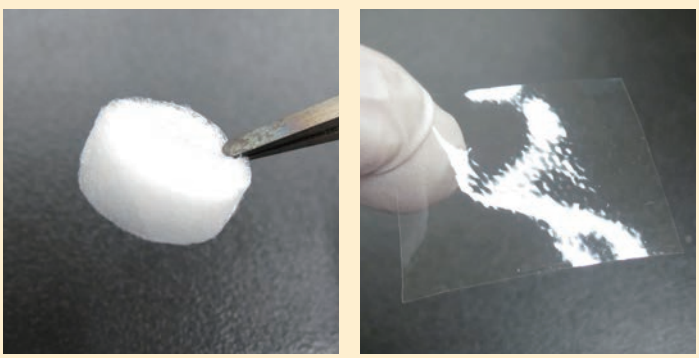


Fig. 4 Forms of silk-elastin

Development of Meniscus Regeneration Materials

In today's aging society, extending "healthy life expectancy," the period during which individuals can live healthily both physically and mentally, has become increasingly important. Musculoskeletal disorders account for 20% of the factors that shorten healthy life expectancy (necessitating nursing care), with "joint diseases" comprising a significant portion (10.9%). Among the elderly, the most common joint disease is osteoarthritis (OA). Approximately 30 million people are estimated to have OA, with around 1 million experiencing symptoms such as pain[1]. Knee osteoarthritis (knee OA) is particularly impactful, significantly reducing the quality of life (QOL) and healthy life expectancy. Therefore, there is a strong need to

prevent knee OA by restoring the knee joint as much as possible.

The knee joint is made up of ligaments, tendons, and muscles surrounding the bones, as well as articular cartilage and the meniscus. The articular carti-lage provides a smooth, elastic surface for joint smooth movement, while the meniscus acts as a shock-absorber, is crescent-shaped located on both the inside and outside of the knee **(Figure 6)**. These tissues are essential for reducing friction and absorbing shock, ensuring smooth joint movement. However, they are vulnerable to damage or deformation due to repetitive stress from aging or sports activities, leading to symptoms like pain, limited mobility (e.g. catching sensations during walking, an inability to fully bend or extend the joint), inflammation, and fluid or blood build up in the joint. Despite the body's natural healing ability, articular cartilage and the meniscus are particularly difficult to repair once damaged due to their limited blood and lymphatic flow and constant weight-bearing. While medical advances have led to techniques for regenerating articular cartilage using a patient's own cells (autologous cells), effective methods for meniscus repair are still being developed.

Traditionally, damage or deformation of the meniscus has been treated with an "arthroscopic partial meniscectomy," where the damaged portion is trimmed or removed. However, even partial removal can impair knee function and increase the risk of knee osteoarthritis (OA), leading to limited mobility and difficulty in bending, stretching, and walking. Consequently, there is a growing trend toward preserving the meniscus through arthroscopic meniscus repair, which involves suturing the meniscus **(Figure 7)**. However, in many cases, suturing is not possible due to the severity and extent of the damage. Even when successful, repairing meniscuses with compromised healing capacity often results in incomplete recovery.

Silk-Elastin® shows promise for meniscus regeneration based on its wound healing mechanisms. Supported by the FY2021 ACT-MS (Academic-Corporate Medical Innovation Creation Program-Setup Scheme) program, animal experiments on rabbits and pigs confirmed its tissue regeneration effect on the meniscus. Additionally, under the 2020 ACT-M support, an investigator-initiated clinical trial at Hiroshima University tested the safety of Silk-Elastin® in eight patients aged 17 to 52 who had complex cases where conventional suturing method were ineffective.

As a result, no significant adverse events were observed, confirming the device's safely.

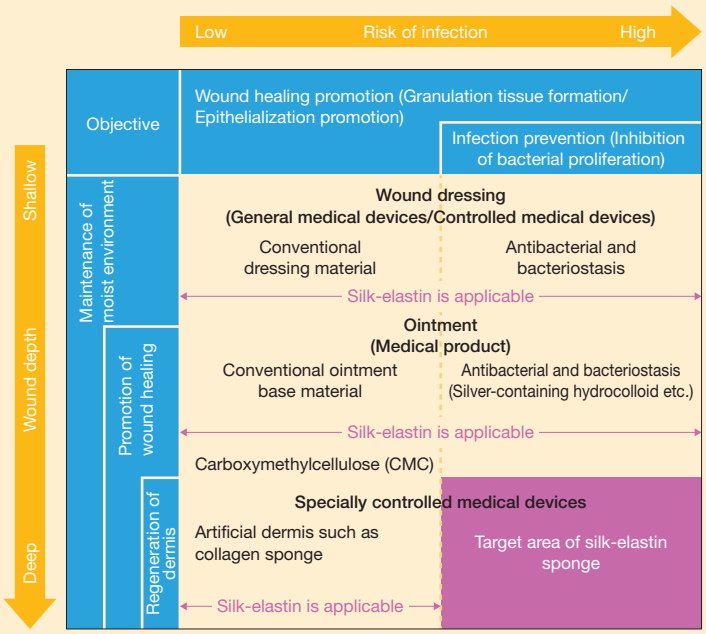
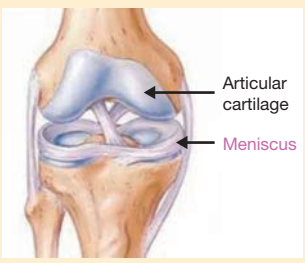


Fig. 5 Proper uses of wound healing materials



Provided by the Department of Orthopaedic Surgery, Hiroshima University

Fig. 6 Structure of the knee

Additionally, meniscus fusion was confirmed in all patients, with six achieving complete fusion three months after surgery.

The company plans to confirm the device's efficacy in a corporate clinical trial supported by the FY2024 Medical Innovation Promotion Project.

Future Development

In developing wound healing and meniscus regeneration materials, we discovered that Silk-Elastin® effectively promotes tissue repair. Building on this property, we've started developing materials for bronchial embolization and muscle regeneration, focusing on treating "hard-to-heal wounds". The bronchial embolization material is designed to prevent air leaks from bronchial tubes that can occur after lung cancer surgery. By inserting a Silk-Elastin® plug into the bronchus, it stops air leaks and encourages the bronchial tissue regeneration. This innovative approach could lead to a medical device that uses the body's own tissue to close the bronchus, offering a breakthrough solution not seen in conventional treatments.

Muscle regeneration materials are used to treat muscle damage caused by tears from sports or daily activities, where conventional treatments have often failed. In animal studies, Silk-Elastin® has been shown to attract the necessary cells for muscle repair and promote regeneration when applied to the injured area.

Silk-Elastin® holds great promise as a groundbreaking medical device for treating wounds that have been difficult to heal. After introducing Silk-Elastin® as Japan's first medical device using genetic recombination technology, we plan to explore various applications for this wound-healing material, with a focus on expanding internationally. We also aim to develop Silk-Elastin® as a material that can enhance the quality of life for a wide range of patients, including the elderly.

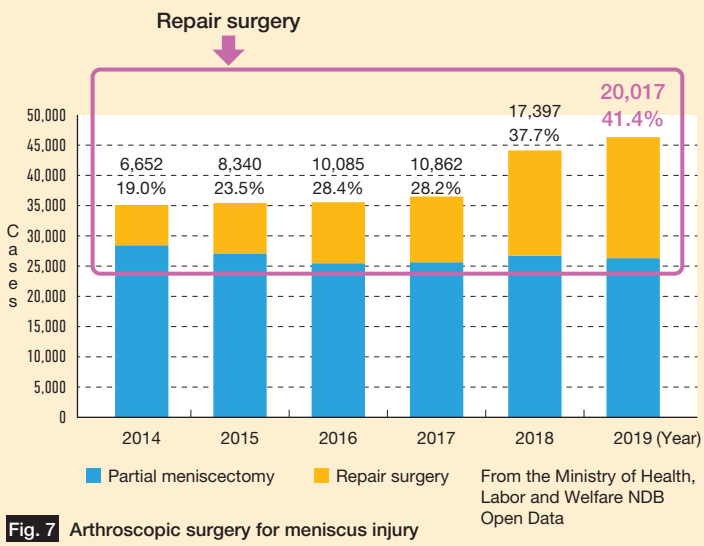


Fig. 7 Arthroscopic surgery for meniscus injury

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References

(1) Study Group on Measures against Musculoskeletal Diseases for the Promotion of Care Prevention, 2008 (Ministry of Health, Labour and Welfare)

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