The potential of cell-assembled extracellular matrix for biological sutures: A promising innovation

Fabien Kawecki

Biotechnology — Commentary

SCIENCE PROGRESS

The potential of cell-assembled extracellular matrix for biological sutures: A promising innovation

Science Progress
2023, Vol. 106(4) 1–7

DOI: 10.1177/00368504231219180
journals.sagepub.com/home/sci
Sage

Fabien Kawecki
University of Bordeaux, INSERM, BioTis, Bordeaux, France

Abstract

Most surgical procedures require using suture materials that are mechanically efficient and accepted by the patient's body. These sutures are essentially composed of synthetic polymers. However, once implanted in patients, they are recognized as foreign bodies and generate chronic inflammation. Thereafter, the patient's immune system will degrade, encapsulate, or even expel the materials. Our innovation, the Cell-Assembled extracellular Matrix (CAM), synthesized from mesenchymal cells, replicates native tissue environments and promotes integration, reducing complications. In a recent study, we introduced CAM-based biological sutures, demonstrating favorable mechanical properties and vascular surgery compatibility. Controlled culture duration tailors CAM for specific applications. Diverse CAM-based suture models were *ex vivo* tested in animal aorta anastomoses, confirming compatibility. *In vivo* carotid anastomoses in sheep validated the clinical significance of these innovative sutures. CAM sutures, derived from immunologically favorable allogeneic fibroblast cells, offer high biocompatibility and exhibit superior mechanical properties compared to synthetics by reducing permeability and increasing burst resistance. *In vivo* testing in sheep underscores clinical applicability, achieving hemostasis and immediate complication prevention. Importantly, CAM-based sutures are compatible with existing vascular surgery techniques, facilitating adoption by surgeons. In conclusion, our findings underscore the effectiveness and clinical significance of these innovative biological sutures.

Keywords

Suture materials, biological suture, cell-assembled extracellular matrix, biocompatible material

Comment on: Borchiellini P, Rames A, Roubertie F, et al. Development and characterization of biological sutures made of cell-assembled extracellular matrix. *Biofabrication*. 2023 Aug; 31;15(4).

Corresponding author:
Fabien Kawecki, BioTis – Laboratory for the Bioengineering of Tissues, INSERM U1026, University of Bordeaux, Campus Carreire, 146 Rue Léo Saignat, case 45, Bordeaux Cedex, 33077, France.
Email: fabien.kawecki@inserm.fr.

Introduction

Sutures are among the most widely used medical devices worldwide and have been a fundamental component of surgical practice for centuries.[1] They serve as a crucial tool in closing and repairing wounds, surgical incisions, and various tissues. With the aging population, the number of surgeries will considerably increase, and consequently, the need for suture materials will rise. In 2021, the global surgical suture market was evaluated at US $4 billion and should reach US $7 billion by 2030 with a compound annual growth rate of 6.2%.[2]

The market encompassed a wide range of suture types that can be made of natural or synthetic polymers, such as Prolene™ (polypropylene), Vicryl™ (polyglactin), Maxon™ (polyglycolic acid and trimethylene carbonate) or Nylon™ (polyamide). They can be absorbable or non-absorbable and take the form of monofilament or multifilament materials with different thread diameters. The intrinsic mechanical properties of the suture material and its behavior within the biological environment are critical for the successful outcome of the surgery. The ideal suture material should be strong enough to provide favorable handling, display high flexibility and, depending on the application, it should have resorption capacity.[3,4] However, in all cases, it should be accepted by the patient without generating foreign body reactions or chronic inflammation. In addition, it should resist infection and be able to integrate and be remodeled by the patient's body.

Synthetic polymer-based sutures remain the gold standard for surgeries because of their mechanical strength. However, these materials are recognized as foreign bodies and generate inflammatory reactions.[5] Intense efforts have been realized to maximize the biocompatibility of these plastic-based suture materials by modifying their composition and/or surface. However, these new materials (polyvinylidene fluoride, ultrafine polyethylene terephthalate, or thermoplastic polyurethane) are still recognized as foreign bodies and can generate intrafilamentous granulomas.[6] Other plastic-based sutures, such as Maxon™, have shown calcification at the suture material after 12 weeks of implantation in a preclinical pediatric cardiovascular context.[7] Nylon™ can also cause a foreign body reaction resulting in uncontrolled expelling of the material out of the body's patient.[8] Furthermore, these plastic materials are favorable to bacterial biofilm formation and can consequently be a source of infection.[9,10] Surgeons typically consider these limitations when selecting the most appropriate suture material for a particular procedure, considering factors such as the patient's medical history, the type of tissue being sutured and the anticipated healing process.

Biological sutures are a category made from natural materials derived from biological sources. It can be made of purified collagen, catgut, or silk. These sutures are designed to be biocompatible and biodegradable, offering several advantages in medical and surgical applications. Catgut sutures are a type of biological sutures made from the submucosal layer of the small intestines of sheep or goats that have been used in surgery for centuries and have led the market of biological sutures. However, catgut suture has been banned for human use in Europe and Japan due to potential transmission risks of bovine spongiform encephalopathy (mad-cow disease).[11] The restriction of catgut sutures in these markets created an opportunity for alternative biological sutures that do not pose similar risks. These biological suture alternatives, such as purified collagen, silk, and other biocompatible proteins, have gained acceptance in these markets. These sutures are considered

safe and biocompatible and have been developed to provide consistent quality, absorption rates, and tensile strength. The transition away from catgut sutures has led to developing and adopting alternative biological sutures in Europe, Japan and other regions with similar regulatory concerns. Furthermore, market dynamics can change, and new materials and products continue to emerge.

The cell-assembled extracellular matrix (CAM): An alternative material for biological sutures

Suture material research is an active area of medical innovation, and new materials are continually being explored and developed. Our research group has developed biological materials synthesized in the laboratory by mesenchymal cells.[12–14] This material, the so-called Cell-Assembled extracellular Matrix (CAM), is produced in culture flasks as a strong sheet that can be cut into ribbons. We selected adult dermal fibroblast cells for CAM production for several reasons. Indeed, they are readily available in the skin, making them easily accessible for isolation and culture. This abundance simplifies the process of obtaining the necessary cells for CAM production. In addition, the dermal fibroblast cells are well-known for their role in producing extracellular matrix (ECM) components in the body. When cultured in the laboratory, these cells produce and assemble ECM proteins, creating a tissue-like environment. They also tend to be less immunogenic than other cell types, and they can be obtained from the patient's own skin (autologous source) or donors (allogeneic source), providing flexibility in choosing the cell source based on individual patient needs. Other mesenchymal cells, such as adipose-derived stem/stromal cells (ADSCs), bone marrow stem cells (BMSCs), or induced pluripotent stem cells (iPSCs), can synthesize an ECM when exposed to favorable conditions and could be used for CAM production. However, the accessibility of ADSCs and BMSCs is more limited than dermal fibroblast cells, and their extraction can result in heterogeneous cell populations for culture. Using iPSCs involves a complex and labor-intensive culture process, and ensuring their long-term stability in storage and culture remains challenging. Moreover, depending on the sources or individuals, iPSCs may have varied proliferative and ECM production capacities. Despite these limitations, each cell source has advantages and can be chosen based on the specific requirements and goals of CAM production. Overall, the choice of dermal fibroblast cells for CAM production aligns with the goal of recreating the native tissue environment by allowing cells to deposit ECM components in a way that closely mimics the structure and composition of healthy tissue. This can promote the integration of the newly regenerated tissue with the surrounding host tissue, which can improve functional outcomes and reduce the risk of complications. The CAM material generated by the patient's own or donor cells is less likely to trigger an immune response or tissue rejection. In addition, our approach eliminates the need for synthetic or exogenous scaffolds in some cases, simplifying the tissue engineering process. This can reduce the risk of foreign body reactions and complications associated with synthetic materials. The CAM material can be applied to a wide range of applications, and it is not limited to a specific tissue or organ system, making it versatile for various regenerative medicine applications.

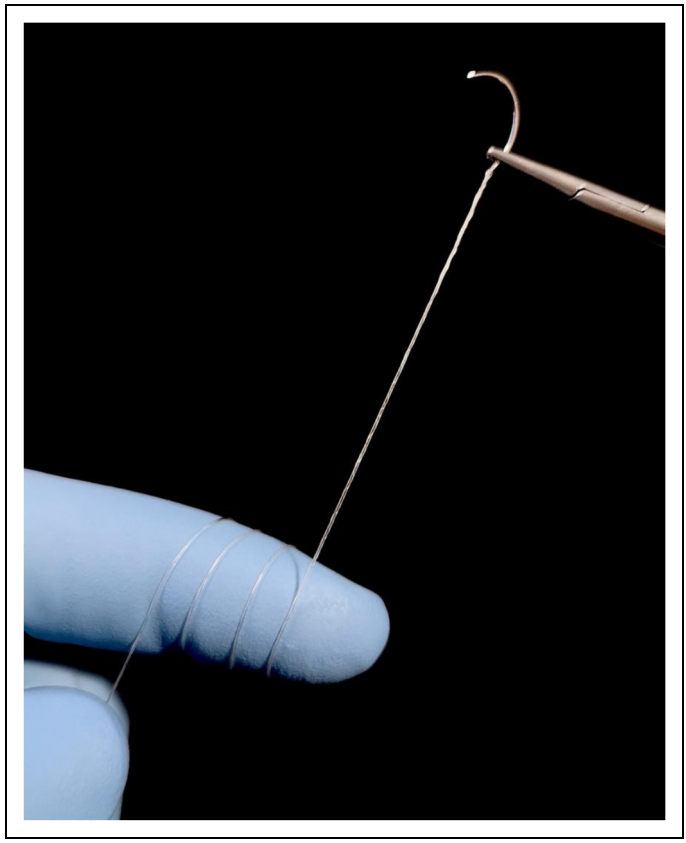

Figure 1. Biological suture made of CAM.

In a recent study, we introduced the first biological suture made of an allogeneic CAM material (Figure 1) that exhibits favorable mechanical properties and compatibility with vascular surgery.[15] Indeed, we demonstrated that we can adapt the CAM material properties (strength, hydroxyproline content and thickness) by controlling the time of culture. This allowed us to produce material with properties adapted to the application. Then, we designed and tested different models of biological sutures made of CAM by crimping eyeless surgical needles with CAM-based ribbons. Briefly, the first step of the CAM-based biological suture production process consists of cutting the CAM sheet following a double-spiral pattern to obtain two long ribbons (Figure 2). We selected a double spiral pattern to create the longest ribbons with the smoothest curves, minimizing the risk of stress concentration points. Then, hydrated ribbons are twisted and dried to obtain a thin thread that can be easily inserted within the hole of a surgical needle. Finally, the ribbon is crimped within the needle using a standard pneumatic attaching machine, which is used to produce commercialized sutures (Figure 2). We mechanically characterized these models by realizing *ex vivo* anastomoses of animal aortas, and we finally performed *in vivo* carotid anastomoses in sheep to demonstrate that our biological

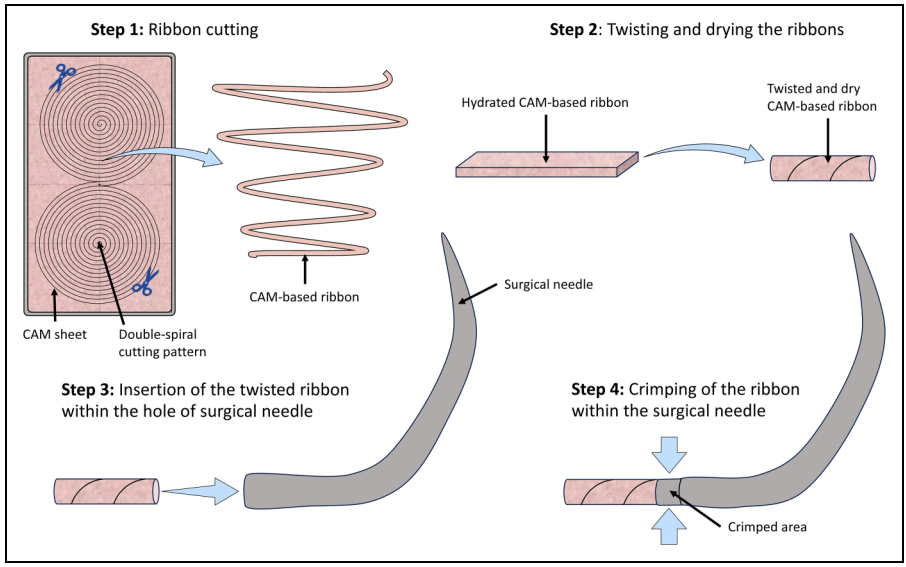

Figure 2. Schematic of the production process of the CAM-based biological suture.

sutures are compatible with standard vascular surgery techniques. Our findings emphasize the clinical relevance of these innovative biological sutures. The fact that they are compatible with regular surgical procedures and that there were no observed complications during anastomosis, such as thrombus formation or blood leakage, is significant. These findings imply the potential for a new and more biocompatible suture material that could improve outcomes in cardiovascular surgical procedures, but not exclusively.

Clinical relevance of the CAM-based biological suture

Based on our first results, the clinical relevance of a biological suture made of CAM is potentially significant and promising. Indeed, CAM-based biological sutures are derived from natural ECM produced by poorly immunogenic and allogeneic devitalized fibroblast cells, making them highly biocompatible. This reduces the risk of adverse tissue reactions, inflammation, and foreign body responses associated with synthetic sutures. Biocompatibility is a crucial factor in surgical materials, as it can contribute to better healing and patient outcomes. In addition, CAM-based sutures displayed favorable mechanical properties, including lower permeability and higher burst resistance compared to standard synthetic sutures like Prolene™. These mechanical characteristics are important for the reliability and durability of the sutures in surgical procedures.

The fact that in vivo testing was conducted in sheep for carotid anastomoses is noteworthy. No thrombus formation or blood leakage was observed within the first 10 minutes after closing the anastomosis. This suggests that the CAM-based sutures were effective in achieving hemostasis and preventing immediate complications. These successful outcomes in live large animal models offer the potential clinical applicability of these sutures in humans. Furthermore, these biological sutures are compatible with standard vascular

surgery techniques. This is crucial because it means that surgeons can adopt these sutures without requiring major procedural changes or adaptations. However, it is important to note that further research and clinical trials are needed to confirm the safety and efficacy of this new medical device before it can be widely adopted in clinical practice.

Finally, CAM-based biological sutures can offer improved biocompatibility, mechanical strength, and reduced complications compared to existing synthetic options, and they could address a clinical need and potentially enhance patient outcomes in cardiovascular surgery, but not exclusively. The CAM-based biological sutures offer several advantages but also have limitations and potential shortcomings. Indeed, producing these biological sutures can be a complex process, particularly when using patient-specific adult or stem cells. This complexity may increase production costs and timelines. Furthermore, ensuring the consistency and quality of CAM-based biological sutures, especially when CAM is derived from different cell sources, can be challenging. In addition, these sutures may need to undergo regulatory approval processes, which can be time-consuming and costly, before they can be used in clinical practice. The cost of production is higher compared to conventional synthetic sutures. This could also be a limiting factor for their widespread adoption. In summary, while CAM offers some advantages for regenerative medicine applications, including potential use in the production of biological sutures, further research and development are necessary to explore the feasibility of CAM-based sutures and to optimize their characteristics to meet the specific requirements of surgical sutures. Collaborations between researchers and industrials in the fields of tissue engineering, regenerative medicine, and surgical materials would be essential in pushing this innovative product through the market.

Acknowledgements

The author thanks his mentor, Dr. Nicolas L'Heureux, and his clinician collaborator, Dr. François Roubertie, for participating in developing this innovative biological suture. The author wants to specifically acknowledge Paul Borchiellini and Adeline Rames for their intensive work in the development and characterization of the CAM-based biological sutures.

Declaration of conflicting interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The author received financial supports from the French "*Agence Nationale de la Recherche (ANR)*" (Grant Number: ANR-21-CE17-0001-01), the French Federation of Cardiology (FFC), and the "*Fondation pour la Recherche Médicale (FRM)*" (Grant Number: SPF202004011810) for the development of the CAM-based biological sutures presented in this commentary. However, he did not received financial support for the publication of this article.

ORCID iD

Fabien Kawecki https://orcid.org/0000-0002-1409-623X

References

1. Dennis C, Sethu S, Nayak S, et al. Suture materials – current and emerging trends. *J Biomed Mater Res A* 2016; 104: 1544–1559.
2. Strategic Market Research. Surgical sutures market by type (automated suturing devices and sutures), material (Hospitals, Ambulatory Surgical Centers (ASCs), Clinics & Physician Offices), Application (Cardiovascular Surgeries, General Surgeries, Gynecological Surgeries, Orthopedic. Published 2022. Accessed March 8, 2023. https://www.strategicmarketresearch.com/market-report/surgical-sutures-market.
3. Hochberg J, Meyer KM and Marion MD. Suture choice and other methods of skin closure. *Surg Clin North Am* 2009; 89: 627–641.
4. Debus ES, Geiger D, Sailer M, et al. Physical, biological and handling characteristics of surgical suture material: a comparison of four different multifilament absorbable sutures. *Eur Surg Res* 1997; 29: 52–61.
5. Lock AM, Gao R, Naot D, et al. Induction of immune gene expression and inflammatory mediator release by commonly used surgical suture materials: An experimental in vitro study. *Patient Saf Surg* 2017; 11: 1–8.
6. Eickhoff RM, Bolle T, Kossel K, et al. Improved biocompatibility of profiled sutures through lower macrophages adhesion. *J Biomed Mater Res B Appl Biomater* 2019; 107: 1772–1778.
7. Reimer J, Syedain Z, Haynie B, et al. Implantation of a tissue-engineered tubular heart valve in growing lambs. *Ann Biomed Eng* 2017; 45: 439–451.
8. Ryu KJ, Ahn KH and Hong SC. Spontaneous complete migration of suture material after subcuticular continuous suture in cesarean section: A case report. *BMC Surg* 2014; 14: –6.
9. Mahesh L, Kumar VR, Jain A, et al. Bacterial adherence around sutures of different material at grafted site: A microbiological analysis. *Materials (Basel)* 2019; 12: –8.
10. Masini BD, Stinner DJ, Waterman SM, et al. Bacterial adherence to suture materials. *J Surg Educ* 2011; 68: 101–104.
11. Langley-Hobbs SJ. Sutures and general surgical implants. In: Langley-Hobbs SJ, Demetriou JL and Ladlow JF (eds) *Feline soft tissue and general surgery*. Amsterdam, The Netherlands: Elsevier, 2014, pp.105–116. doi:10.1016/B978-0-7020-4336-9.00010-X.
12. Magnan L, Labrunie G, Fénelon M, et al. Human textiles: a cell-synthesized yarn as a truly "bio" material for tissue engineering applications. *Acta Biomater* 2020; 105: 111–120.
13. Torres Y, Gluais M, Da Silva N, et al. Cell-assembled extracellular matrix (CAM) sheet production: translation from using human to large animal cells. *J Tissue Eng* 2021; 12: 204173142097832.
14. Kawecki F, Gluais M, Claverol S, et al. Inter-Donor variability of extracellular matrix production in long-term cultures of human fibroblasts. *Biomater Sci* 2022; 10: 3935–3950.
15. Borchiellini P, Rames A, Roubertie F, et al. Development and characterization of biological sutures made of cell-assembled extracellular matrix. *Biofabrication* 2023; 15: 45018.

Author biography

Fabien Kawecki is a young investigator at the laboratory for the Bioengineering of Tissue (BioTis, INSERM, U1026) of the University of Bordeaux, France. His researches focuse on using Cell-Assembled extracellular Matrix (CAM) material in pediatric cardiovascular applications to improve patient treatments. His expertise encompasses tissue engineering of various connective tissues, including vessels, cardiac valves, bone, and skin.