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REVIEW ARTICLE

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# The role of adjunct nanofibrillar collagen scaffold implantation in the surgical management of secondary lymphedema: Review of the literature and summary of initial pilot studies

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## Abstract

Secondary lymphedema is a worldwide affliction that exacts a significant public health burden. This review examines the etiology, presentation, and management of secondary lymphedema. In addition, emerging adjunctive strategies are explored, specifically evidence from animal and pilot human studies regarding implantation of a collagen nanofibrillar scaffold (BioBridge™; Fibralign Corporation, Union City, CA) in promoting lymphangiogenesis, preventing and treating lymphedema, and enhancing outcomes with lymphaticovenous anastomosis and vascularized lymph node transfer.

**KEYWORDS**
collagen scaffold, lymphaticovenous anastomosis, secondary lymphedema, vascularized lymph node transfer

## 1 | ETIOLOGY AND PRESENTATION OF SECONDARY LYMPHEDEMA

Secondary (acquired) lymphedema is a chronic debilitating and progressive disease that develops when the lymphatic system is physically compromised and unable to sufficiently transport interstitial fluid and macromolecules from affected region(s) of the body to the central circulation. Lymph node extirpation and the associated structural damage to the lymphatic vasculature leads to the inexorable accumulation of interstitial fluid, accompanied by regional compromise of immune function and, ultimately, irreversible structural changes of the affected tissues of the limb(s).[1]

Secondary lymphedema remains a significant problem globally and in the United States. The most common cause of secondary lymphedema worldwide is infection with *Wuchereria bancrofti*, affecting more than 90 million people.[2] In Western countries, lymphedema most commonly occurs as a delayed complication of cancer treatment in survivors of breast, or gynecological cancers, or melanomas. According to a recent meta-analysis, the overall incidence of lymphedema among cancer survivors is 15.5%, with increased risk among patients who undergo pelvic dissections (22%) or radiation therapy (31%).[3] In the United States alone, there are an estimated 2 to 3 million people affected by lymphedema, most of which are secondary cases.[3] Breast cancer treatments are the most common cause of secondary lymphedema in an average of 1 in 5 women (20%),[4,5] but with a number of studies reporting an increased incidence of up to 60%.[6-8] As such, lymphedema is one of the most pressing survivorship issues among women who have been treated for breast cancer.[3]

The disease has profound functional and psychosocial implications. Lymphedema mainly occurs in upper or lower limbs, but occasionally develops in the genital area, neck, face, abdomen, or thorax. The presentation of the disease is associated with edema of the affected area, pain, feeling of heaviness, and multiple recurrent infection episodes such as erysipelas, lymphangitis, and cellulitis. Patients affected with multiple infections require oral or intravenous antibiotics and the therapy duration could span several months or even years.[9,10] If lymphedema remains untreated, it gradually may progress to elephantiasis. Often patients with lymphedema experience greater levels of functional impairment, poorer psychological adjustment, anxiety, and depression than the general population.[11]

  

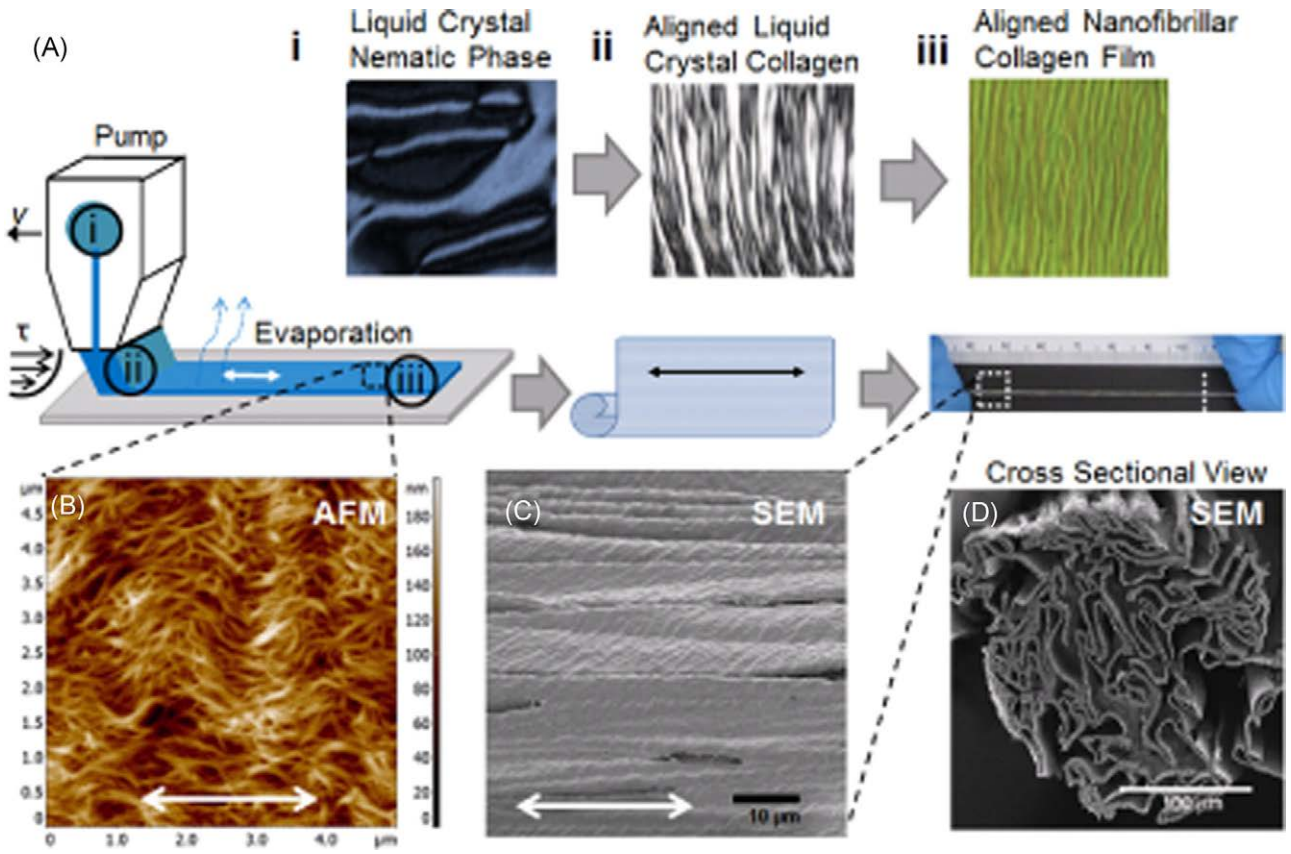


**FIGURE 1** Schematics of BioBridge™ manufacturing. A, Fabrication of the aligned nanofibrillar collagen membrane. Polarized microscope images of: i. liquid crystal collagen in nematic phase; ii. aligned collagen under shear with the control speed V and shear rate τ produced by the deposition head; and iii. crimped nanofibrillar collagen membrane. B, Atomic force microscopy image (AFM) of aligned collagen membrane. C, Scanning electron microscopy (SEM) image of BioBridge™ surface. (D) SEM image of BioBridge™ cross-section. From[38] [Color figure can be viewed at wileyonlinelibrary.com]

## 2 | CURRENT PREVENTION AND TREATMENT OF SECONDARY LYMPHEDEMA

Symptomatic secondary lymphedema patients were traditionally managed conservatively, but in last two decades microsurgical techniques such as free vascularized lymph node transfer (VLNT) and lymphaticovenous anastomosis (LVA) have been increasingly used to treat such cases. The effectiveness of new microsurgical procedures in volume reduction, decrease of erysipelas or cellulitis, and functional improvement of the affected limb, has been described in many studies, but the results widely vary.[12-14] Reported rates of volume reduction following VLNT or LVA typically are less than 60%.[12]

Consequently, a focus on limiting progression of disease with early physical therapy has emerged in the form of lymphedema surveillance programs.[15-20] In these programs, patients with newly diagnosed breast cancers are evaluated preoperatively to obtain critical baseline objective measures of the at-risk extremity followed by close postoperative surveillance. Early diagnosis of lymphedema and implementation of therapy has been correlated with improved long-term outcomes in randomized controlled trials.[19] In parallel, a novel approach to surgically prevent lymphedema in high-risk patients, such as those undergoing axillary lymph node dissection (ALND), has been developed which includes lymphovenous bypasses to an axillary vein tributary that is performed at the time of ALND.[21-28] The published data indicate a variable reduction in lymphedema rates, for example, offering Lymphatic Microsurgical Preventive Healing Approach with ALND decreased an institutional rate of lymphedema from 40% to 12.5%.[28] Long-term follow-up and randomized controlled trials are necessary to further elucidate the effects of this surgical technique. An additional evaluation of viability of the created lymphovenous interface and its metastatic potential is also required.

## 3 | COLLAGEN SCAFFOLDS IN ANIMAL MODELS

Nanofibrillar collagen scaffolds have been shown to promote angiogenesis, arteriogenesis, and lymphangiogenesis in animal models. Several studies have evaluated the safety and efficacy of BioBridge™ (Fibralign Corporation, Union City, CA), an implantable surgical mesh ribbon that contains multiple folds of a thin membrane with aligned fibrils of purified type 1 porcine collagen with removed telopeptides.[29] This construct measures 0.3 to 0.4 mm wide and 150 mm in length, and is designed to reinforce areas of weakness and deficiency in soft tissues.

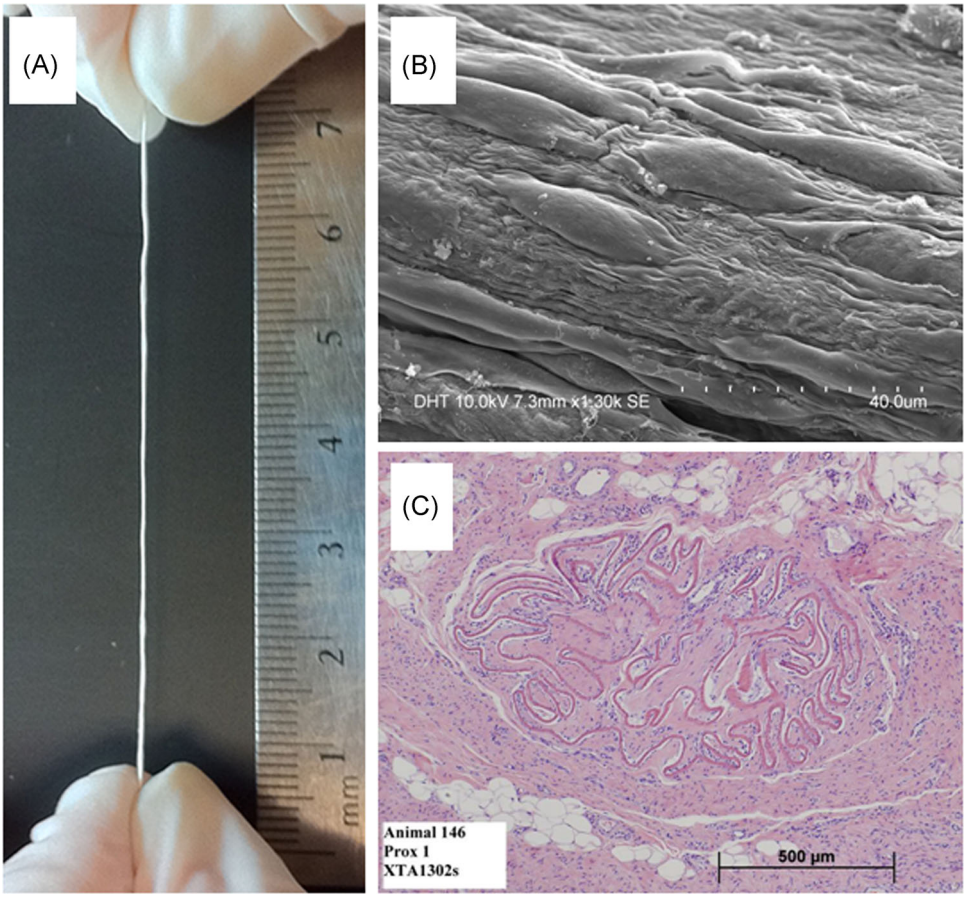


**FIGURE 2** Nanofibrillar collagen scaffold. A, supports elongated morphology of lymphatic endothelial cells in vitro and B, integrates into irradiated tissue, as shown in scanning electron microscopy image. C, H&E staining of scaffold cross-section 3 months after implantation. Images provided by Fibralign Corp., Union City, CA [Color figure can be viewed at wileyonlinelibrary.com]

These scaffolds are produced from medical grade monomeric collagen in a specific liquid crystal phase under flow conditions[30-35] (Figure 1A), such that they are biomimetic (ie approximating the native tissue structure at nano- through micro-scale), possess high mechanical strength, maintain the structure pattern over a full length, and are biodegradable with a rate defined by the level of crosslinking. Atomic force microscopy and scanning electron microscope analysis of the nanofibrillar collagen scaffold show a structure with highly aligned collagen fibrils and an additional translational order formed by the peaks of helices of the helical-like fibrils ("crimp") (Figure 1B,C). The crimps are perpendicular to the direction of fibril alignment, and collectively, they form the crimp pattern.[36] The crimped configurations of collagen fibrils are typical for collagen-based fibrous tissue when external load is reduced. They mimic the woven spiral structure of collagen bundles in relaxed blood vessels.[37] BioBridge™ devices are produced as ultrathin (1-2 μm) membranes from liquid crystal collagen in nematic phase (Figure 1A, B) and are further fabricated into thin ribbon, or threadlike, nanopatterned scaffolds with large surface area and interconnected cavities (Figure 1A and C,D) that enable cell infiltration as well as local interstitial flow. Thus, this material offers an advantage over commercially available biodegradable scaffolds that have sufficient tensile strength and provide good cell adhesion[36,38] but lack the aligned fibrillar structure, have limited surface area, and do not promote cell alignment.

### 3.1 | Functional properties

It has previously been demonstrated that human microvascular endothelial cells (ECs) respond to parallel-aligned nanopatterned scaffolds by morphologically reorganizing the cytoskeleton along the direction of the nanofibrils.[39] In addition to inducing morphological changes, aligned nanofibrillar scaffolds also modulated EC function by enhancing cell survival and by inhibiting inflammation.[36] The BioBridge™ thread-like dimensions (Figure 2A) allow it to be implanted and positioned to bypass the obstruction caused by the scar tissue. Its aligned collagen fibrils allow endothelial cells to attach throughout the scaffold, proliferate, and migrate along the fibrils (Figure 2B) to eventually develop functional vessels inside and in the vicinity of the scaffold integrated into the tissue (Figure 2C).

### 3.2 | Promotion of angiogenesis and arteriogenesis

Huang et al[36] described the development of aligned nanofibrillar collagen scaffolds that mimic the structure of collagen bundles in vascular structures (the BioBridge™ matrix) and examined the effects of these materials on EC alignment, function, and in vivo survival. After EC transplantation into both subcutaneous tissue and the ischemic hindlimb, EC viability was enhanced when ECs were

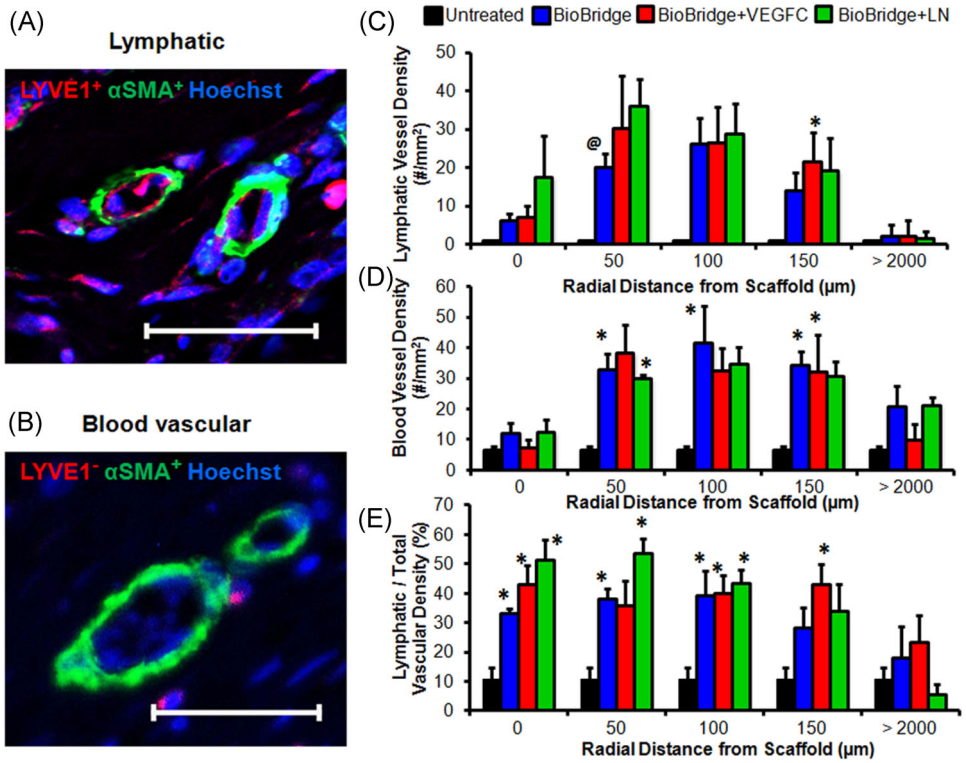


**FIGURE 3** Immunohistochemistry analysis of lymphatic and blood vascular regeneration. Immunofluorescent staining demonstrates A, lymphatic collectors (LYVE1+, α-SMA+) and B, blood-vascular arterioles (LYVE1-, α-SMA+) on confocal microscopy images in the lymphedematous limb[47] (scale bar, 50 μm). Quantitative analysis shows the density of C, lymphatic collectors and D, blood-vascular arterioles, and the lymphatic fraction of total (blood+lymphatic) vascular density (n ≥ 3). *$P < .05$ vs untreated irradiated tissue (control group), #$P < .05$ vs surrounding irradiated tissue at >2000 μm for the same animal. From[1] [Color figure can be viewed at wileyonlinelibrary.com]

cultured and implanted on aligned nanofibrillar scaffolds, in contrast to nonpattern scaffolds. ECs derived from human induced pluripotent stem cells and cultured on aligned scaffolds also persisted for over 28 days, as assessed by bioluminescence imaging, when implanted in ischemic tissue. Thus, this study demonstrates that the nanofibrillar collagen scaffolds guide cellular organization, modulate endothelial inflammatory response, and enhance cell survival after implantation in normal and ischemic tissues.

Nakayama et al[38] further examined the capability of collagen scaffolds to augment arteriogenesis. In this study, thread-like nanofibrillar scaffolds with porous structure (the BioBridge™ matrix) were fabricated from aligned-braided membranes generated under shear from liquid crystal collagen solution. Human ECs showed greater outgrowth from aligned scaffolds than from nonpattern scaffolds. The data in this study suggest that treatment with EC-seeded aligned nanofibrillar scaffolds improved blood perfusion and arteriogenesis, when compared to treatment with cells alone or scaffold alone.

## 3.3 | Promotion of lymphangiogenesis

Initial studies by Huang et al[36] and Nakayama et al[38] indirectly supported the hypothesis that the use of collagen scaffolds as an adjunct to autologous lymph node transfer would provide the necessary support to augment both microlymphatic vascular engraftment through its favorable effect on lymphatic endothelial biology in the repair response, and microlymphatic vascular repair in analogy to its effect on arteriogenesis, respectively. In addition, chronic scarring is a known pathologic component of later stages of lymphedema. A study by Muthusubramaniam et al[40] demonstrated that fibril alignment decreases excessive fibroblast proliferation and therefore reduces scar formation, again suggesting a potential clinically relevant application to lymphedema models.

Hadamitzky et al[1] showed that in a porcine model of acquired lymphedema, implantation of BioBridge™ scaffolds facilitated reestablishment of lymphatic drainage. The porcine model used is regarded as the best animal context in which to model the human disease. The study results demonstrate that, after BioBridge™ device implantation, the lymphatic tissue was repaired during the period of observation, with formation of new functional lymphatic vessels to restore functional integrity of the lymphatic system and reduce the fluid buildup associated with the disease. Furthermore, during the course of the study, a total of 120 BioBridge™ devices were implanted with no identified complications after implantation or through histological analysis.

Postmortem macroscopic analysis in animal subjects with lymphedema improvement or resolution showed that new lymphatic collectors were observed in the zone of antecedent surgery and radiation. CT imaging confirmed the correspondence between the lymphatic neovasculature and direction of the implanted collagen threads. Macroscopically, the newly formed collectors had no abnormal architecture. Standard histological analysis demonstrated

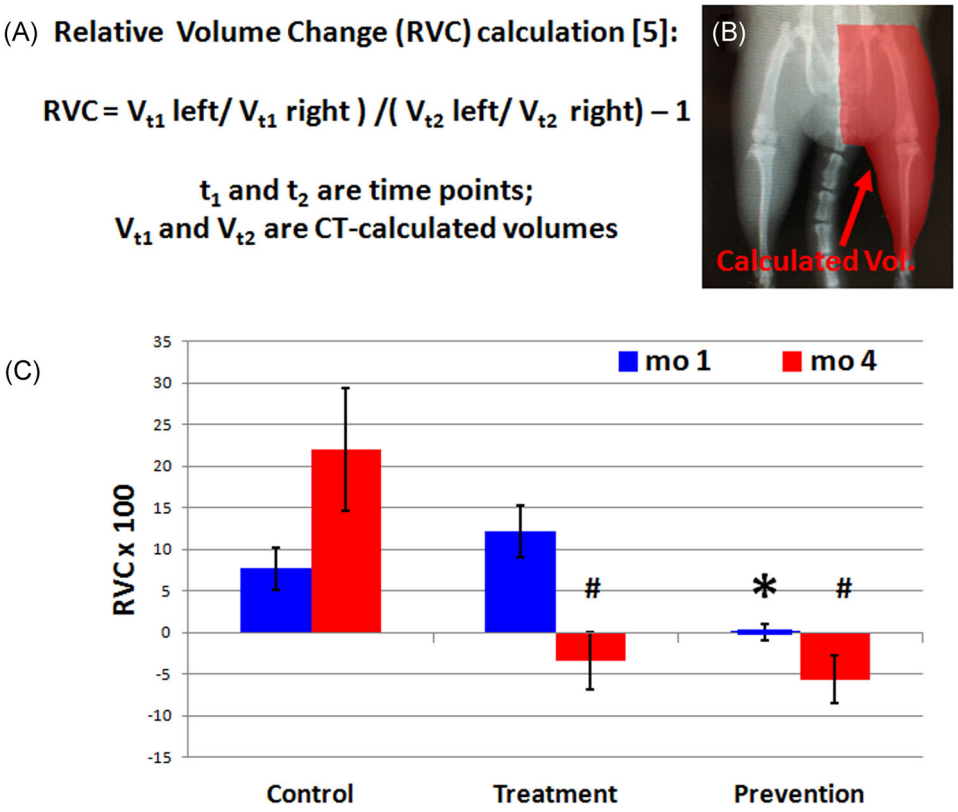


**FIGURE 4** Micro CT-based volumetric analysis of the change in affected limb volume. Relative volume change (RVC) was calculated by the formula (A) from the CT-based calculated volume for the selected area (B). The data shown as RVC × 100 demonstrate the changes in RVC for two time points (C). From[41] [Color figure can be viewed at wileyonlinelibrary.com]

integration of the nanofibrillar collagen scaffold into the irradiated tissues (Figure 2C).

Microscopical analysis of immunohistochemistry (Figure 3A,B) revealed a higher number of lymphatic collectors in the proximity of the implanted collagen scaffold in all treatment groups, when compared to the surrounding irradiated tissue or to untreated irradiated tissue (Figure 3C). The number of blood vessels was also increased in this area (Figure 3D); however, the balance between the lymphatic and blood vessels in the vicinity of the scaffold was shifted toward lymphatics, as shown by the increase in the lymphatic fraction of the total microvascular density (lymphatic+blood) when compared to untreated irradiated tissue (Figure 3E).

### 3.4 | Prevention and treatment of lymphedema

Nguyen et al[41] investigated the implantation of BioBridge™ at the time of lymphadenectomy, and into lymphedema-affected limbs, to evaluate the role of this construct in both prevention and treatment of lymphedema, respectively. The study used a standard rat lymphedema model, involving inguinal and popliteal lymphadenectomy followed by 20 Gy radiotherapy (RT).[42] Subjects in the prevention group received implantation of BioBridge™ immediately after lymph node resection and before RT. Subjects that developed lymphedema 1 month after lymphadenectomy/RT either received implantation of BioBridge™ seeded with allogenic adipose-derived stem cells (ADSC; treatment group) or remained untreated (control group). At 4 months, micro CT-based volumetric analysis (Figure 4) and near infrared lymphography (Figure 5) demonstrated that implantation of BioBridge™ at the time of lymphadenectomy prevented development of lymphedema (Relative Volume Change [RVC][43] at month 1 was 0.1 ± 0.9, and at month 4 was − 5.7 ± 2.9) and led to development of new lymphatic vasculature with collaterals crossing the midline toward the contralateral inguinal area. An additional finding was that

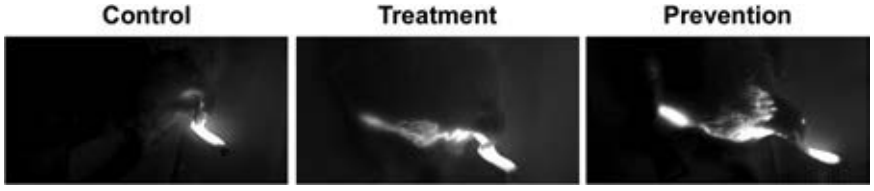


**FIGURE 5** Near-infrared lymphography of the lymphatic collector growth. The panel shows representative images for each group at 4 months after lymphadenectomy, showing regenerated lymphatics growing toward contralateral groin. From[41] [Color figure can be viewed at wileyonlinelibrary.com]

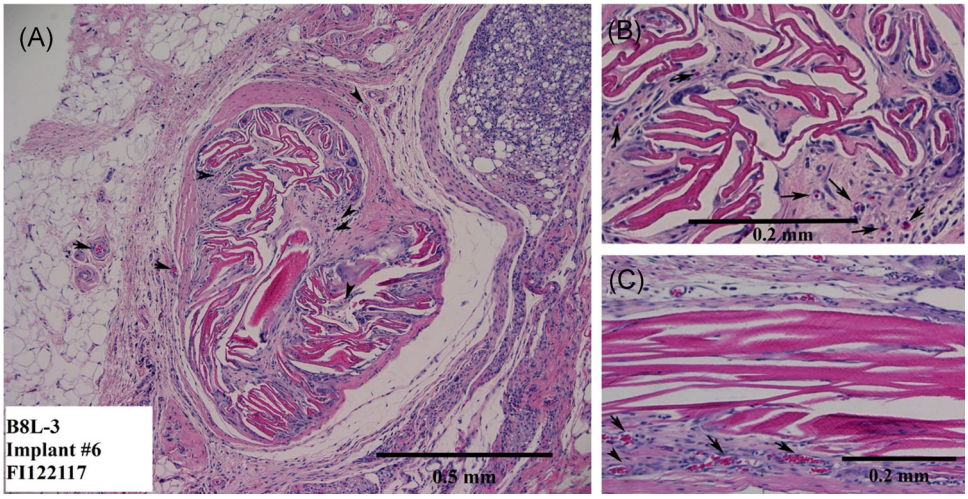


**FIGURE 6** Vascular regeneration in the vicinity of the BioBridge™. H&E stained transverse (A, B) and longitudinal (C) sections of BioBridge™ show neovessels formed close to BioBridge™ (black arrows and or yellow circles). From[41] [Color figure can be viewed at wileyonlinelibrary.com]

implantation of BioBridge™ seeded with adipose derived stromal cells (ADSCs) into lymphedema-affected limbs significantly reduced the volume of the limb (RVC at month 1 was 12.2 ± 3.1, and at month 4 was − 3.4 ± 2.9), with a prevalent regeneration pattern of collector growth across the midline toward the contralateral inguinal area (Figure 5). Routine H&E histology analysis showed formation of blood capillaries in the vicinity of the BioBridge™ (Figure 6).

## 4 | PILOT STUDIES OF COLLAGEN SCAFFOLDS AS ADJUNCT LYMPHEDEMA TREATMENT IN HUMAN SUBJECTS

The concept of guiding lymphangiogenesis with collagen scaffolds suggests that such scaffolds may also improve the efficiency of well-established lymph node procedures in human subjects. Two pilot studies have examined the effect of BioBridge™ implantation on lymph node fragment transfer (LNFT) and vascularized lymph node procedures, respectively.

### 4.1 | Collagen scaffolds as adjunct to lymph node fragment transfer

A pilot clinical study in Dominican Republic using BioBridge™ collagen scaffolds in lymphedema patients was first to demonstrate its safety in humans.[44] To address the limitations of current treatments for secondary lymphedema, the study group developed an experimental surgical procedure with transfer of nonvascularized autologous lymph node fragment supplemented by nanofibrillar collagen scaffold with and without autologous ADSCs out from the stromal vascular fraction. ADSCs were seeded on the scaffolds, which supported the cell survival, maintenance, and function at the targeted site. The pilot study had 12 patients enrolled. A nonvascularized autologous LNFT as a basic treatment was used for all patients. It was supplemented by implantation of: BioBridge™ scaffolds (n = 5); BioBridge™ scaffolds with ADSCs (n = 2); BioBridge™ scaffolds with injected ADSCs (n = 1); and injected ADSCs only (n = 4; control group). In the therapy groups, no complications were reported after 1 year. For all patients in the BioBridge™ treatment group, the L-Dex bioimpedance index was reduced after the surgery at 3, 6, 9, and 12

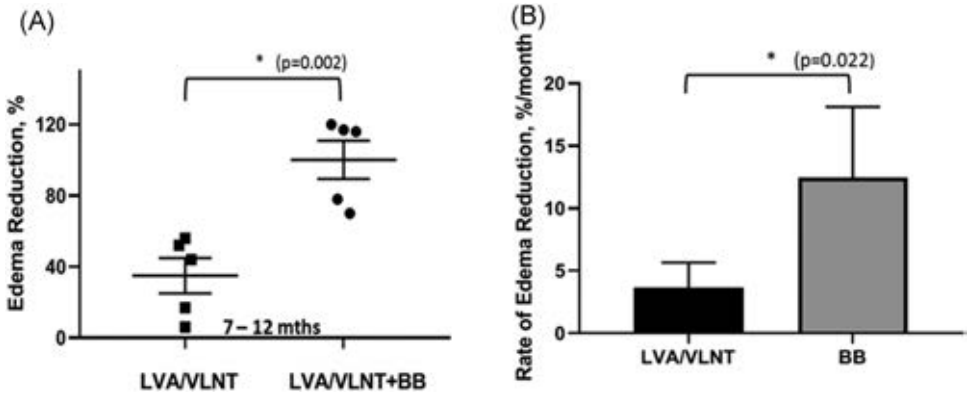


**FIGURE 7** Edema reduction in patients treated with VLNT/LVA with or without BioBridge™ (A), and rate of edema reduction (B) for the same patients. T-test has been used for statistical analysis (n = 5). From[45]

months. The mean L-Dex reduction (12 L-Dex units) for all 8 patients at 12 months was clinically meaningful. Six of the 8 patients using BioBridge™ responded to the treatment after 6 months with an average volume reduction of approximately 20%. Two of these patients attained a normal limb volume ratio (≤ 1.1) at 3 months after surgery. The average edema reduction in the control group (n = 4) was 1.1% at 4 months after surgery.

### 4.2 | Collagen scaffolds as adjunct to lymphaticovenous anastomosis or vascularized lymph node transfer

On the basis of promising results from animal studies, investigators performed a retrospective study of patients who underwent lymphaticovenous anastomosis (LVA) or vascularized lymph node transfer (VLNT) followed by BioBridge™ implantation.[45] In this Institutional Review Board-approved study, BioBridge™ was examined in accordance with its FDA-approved indication of providing soft tissue reinforcement. Volumetric analysis[46] demonstrated that compared to pre-procedure baseline, LVA/VLNT yielded a mean of 35% ± 22.2% edema reduction over an average of 9.2 months (range 7-12 months). Compared to LVA/VLNT alone, collagen scaffold implantation led to a statistically significant increase in mean edema reduction (100.2% ± 24.1% vs 35.0% ± 22.2%, $P = .002$) over the total study period (average 18.0 months) (Figure 7A). The addition of BioBridge™ enhanced the average rate of edema reduction to 7.4%/month vs 3.6%/month ($P = .022$) (Figure 7B). Overall, the authors concluded that nanofibrillar collagen scaffold implantation enhances lymphatic regeneration and augments edema reduction compared to LVA/VLNT alone. An additional publication fully detailing this study is forthcoming.

## 5 | CONCLUSIONS

Secondary lymphedema remains an inadequately addressed problem that primarily affects cancer survivors in Western countries. Nanofibrillar collagen scaffold implantation has the potential to enhance lymphatic regeneration and augment edema reduction compared to standalone existing treatments. Future large randomized controlled studies are needed to prospectively evaluate the impact of this promising adjunct treatment.

### DISCLOSURES

Funding support for preliminary animal studies comes from unrestricted grants for lymphedema research from donors, including Fibralign Corporation. There are no other disclosures.

### DATA AVAILABILITY

Data will be made available upon reasonable request.

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