

# Vol. 28 No.1 - 2014 Best New Investigator Award: Development Update: A Promising Surgical Procedure For Treating Secondary Lymphedema

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*Best New Investigator Award being presented at the NLN Award Luncheon. From left to right: Saskia R.J. Thiadens, Jie Deng, Michael Paukshto, Joseph Feldman.*

*Editor's note: Michael Paukshto, PhD, CTO and founder of Fibralign Corporation, was recently awarded the 2014 Best New Investigator Award at the 11th Biennial NLN International Conference, representing team members in this research from Fibralign Corporation, Stanford University, and Hannover Medical School. Earlier this year, Fibralign was also recognized for its efforts in developing a new potential therapy for treating lymphedema with the prestigious 2014 Medtech Innovator Award presented at the WSGRC Medical Device Conference, taking first out of 267 competitors.*

Despite significant research and clinical efforts, the origin of lymphedema still remains poorly understood. For instance, there isn't a clear understanding of why, after lymph node dissection procedures, lymphatic function is largely restored in most patients, but fails in almost one third of them. It is generally agreed however, that fibrotic tissue, caused in part by irradiation of the treatment

site or poor wound healing, presents a significant obstacle to the spontaneous regeneration of new vessels needed to fully restore lymphatics.

Fibralign Corporation is developing a novel treatment device that bridges across this fibrotic tissue to restore lymphatic function. This device, BioBridge™, is a thread-like collagen scaffold designed to direct and support the formation of new lymphatic vessels. With the backing of a US Department of Defense grant, BioBridge was successfully tested in an advanced large animal model that showed the formation of new functioning lymphatic vessels in animals that had lymphedema. The company is now preparing for regulatory submission with the anticipation that this treatment will be available for human patients later in 2015.

### Lymphangioplasty: A Brief History in Time

Many people don't realize that the quest for lymphedema surgical treatments actually started over 100 years ago!

In 1908, in an effort to provide fresh lymphatic pathways, W. Sampson Handley proposed using sterile silk sutures as artificial lymphatic conduits (Figure 1).<sup>1</sup> Handley showed that when these silk threads were implanted subcutaneously into the affected arms, they helped drain lymphatic fluid by means of capillary force. While this worked initially, the silk threads created foreign body reactions that resulted in the formation of a fibrous capsule around them. This reduced the lymphatic fluid drainage within a short time after implantation and created other complications.

Later, a 1976 study with a similar approach was initiated that utilized a wicking Teflon multifilament material instead of silk.<sup>2</sup> It was reported that lymphedema relief lasted for an average of 13 months before the Teflon structure succumbed to fibrotic encapsulation. Even though these results were not satisfactory to become a viable patient treatment, they confirmed that Handley's concept of creating an artificial lymphatic channel resulted in acute relief from lymphedema.

Fast forward to today, with the development of modern microsurgical tools and techniques. Current surgical procedures can be oriented towards relieving the symptoms of lymphedema (eg, resective liposuction) or trying to cure it. The latter includes the options of restoring the lymphatic function by

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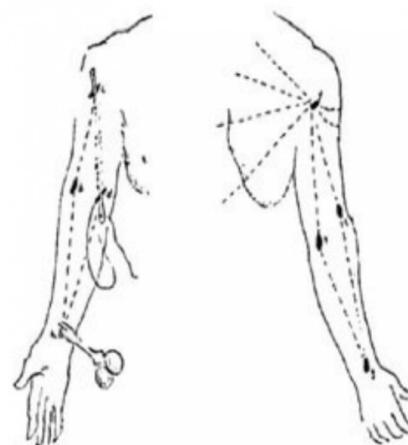


Figure 1. Early surgical treatment for lymphedema, circa 1908.

lymphatico-lymphatic anastomoses, micro or supermicro lymphatico-venous anastomoses, as well as vascularized lymph node transfer (VLNT). These approaches have provided benefits to many lymphedema patients,<sup>3</sup> but also have reported wide variation in effectiveness. It is in support of such modern procedures, initially as an adjunct to VLNT, that Fibralign tested the hypothesis that BioBridge can help in the formation of new lymphatic vessels and substantially improve patient outcomes.

## BioBridge: A New Twist on an Old Idea

Unbeknownst to Handley, providing a physical channel for lymphatic fluid flow has further benefits beyond immediate relief of swelling provided by the capillary forces. Recent studies have shown that interstitial flow is a major factor in the formation of new lymphatic capillaries.<sup>4</sup> Directional interstitial flow establishes the gradient of growth factors and steers migration of the lymphatic endothelial cells needed for vessel formation.

BioBridge's form factor takes advantage of this capillary flow along and through the thread, combining it with a precisely aligned nanofibrillar scaffold structure to guide and promote lymph- and angiogenesis (the generation of new lymph and blood vessels) along the scaffold. These scaffolds are produced from medical-grade collagen using Fibralign's proprietary advanced manufacturing process and are the result of a several year collaboration with Stanford University to optimize various essential parameters to support vessel formation. In vivo and in vitro testing demonstrated that these aligned nanofibrillar collagen scaffolds can control cell morphology and function (Figure 2), as well as guide cellular organization, modulate endothelial inflammatory response, and enhance cell survival after implantation.<sup>5</sup> A substantial improvement in comparison with the formerly described historical materials is that the device has been designed to naturally degrade and safely disappear in the body after a few months, after providing sufficient time for new lymphatic vessel to regenerate.

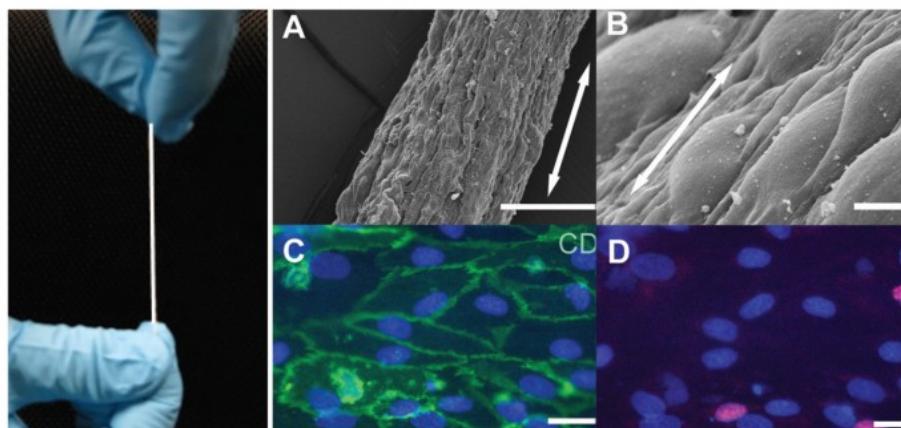


Figure 2. BioBridge structure influences cell behavior. A-B. Scanning Electron Microscopy showing alignment & directional migration of endothelial cells on BioBridge. C. Staining for CD31 (green) and nuclei (blue) of the endothelial cells along the thread. D. Staining for Ki67 (red) and nuclei (blue) of the endothelial cells along the thread. Double arrows denote direction of 30 nm collagen fibrils.

The combination of capillary properties, controllable stability, mechanical support of soft tissue, and regenerative capabilities made BioBridge a suitable candidate for using it to guide regeneration of lymphatic vessel formation under lymphedema conditions in a large animal lymphedema model.

## **Preclinical Study**

One of the challenges in developing a lymphedema treatment was finding a suitable animal model, which allows both the ability to reliably induce lymphedema and have strong correlation to humans. Fibralign adopted a proven porcine model developed at Hannover Medical School.<sup>6</sup> Lymphedema was induced in Yucatan minipigs by resection of inguinal (groin) and popliteal (back of knee) lymph nodes followed by irradiation of the groin area in order to reproduce the conditions encountered in human patients. It is believed that this six month study was the largest of its kind ever performed in North America. Yucatan minipigs were selected for the study because they have a similar physiological and anatomical functionality to humans.

Three months after lymph node resection, animals were assessed for the status of lymphedema by measuring the volume of extracellular fluid by bioimpedance, and the number of major lymphatic collectors by contrast-enhanced CT and, in selected animal subjects, by contrast-enhanced MRI to assess the presence of lymphatic dermal backflow. The number of lymphatic collectors as determined by CT strongly correlated with bioimpedance data. The CT imaging procedure developed for the study is also believed to be unique in characterization of lymphatic vessels and proved to be very useful.

The animals were then divided into four groups, three of which were subjected to different treatment surgeries that involved implantation of the BioBridge collagen scaffolds spanning the area depleted of lymphatics and subjected to irradiation. The fourth group served as a control group and did not receive any treatment. The findings of the study showed that BioBridge supported and guided the formation of new functional lymphatic vessels. Treated animals with lymphedema experienced improvement after three months, and some experienced resolution of the lymphedema during this short time period. Macroscopic analysis of collectors in the implantation area after intradermal injection of methylene blue showed a number of new lymphatic collectors aligned in the direction of the implanted threads. The study also showed that BioBridge was safe; a total of 120 devices were implanted in twelve animals without any complications. Detailed technical findings are expected to be later published after completing histology analysis.

This preclinical study has shown the promise of BioBridge scaffolds as an adjunct to surgical procedures for treating secondary lymphedema. Time will tell if this scaffolding technology could provide a platform for developing other therapies for both treating and preventing lymphedema.

#### *Acknowledgment*

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