Final Report, Emtech Bio Program. PeopleSoft Project Number: 2506C81, PeopleSoft Fund Number: RA308, Document Id: 110678.

Design and Manufacture of Helical Tissue Support for Surgical Correction of Age-Related Macular Degeneration

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Abstract: *Age-Related Macular Degeneration (AMD) is a disease that causes severe loss of vision in the elderly. It can be corrected by a surgical procedure involving a tissue graft. Success of this procedure is heavily dependent on translocation of the delicate tissue within the eye with minimal damage and wrinkling. This report describes the design of a device that performs this task. The device can be inserted through a 1 mm incision in the eye and is used to translocate a 3-5 mm patch of tissue. Prototypes of multiple device designs were tested. Two designs that use the shape memory effect of nitinol show promising results in animal studies.*

1. Introduction

Age-related macular degeneration (AMD) is a disease that causes loss of vision due to deterioration of delicate photo-receptors in a specialized region of the retina known as the macula (refer to Fig. 1). The macula is a 1.5 mm diameter region of the retina that has the highest density of cone photo-receptors in the eye. It is responsible for sharp central (15-20 deg of visual angle) vision and color. A section of the tissue in the macular region is shown in Fig. 2. Dry AMD is caused by extracellular deposition (drusen) underneath the Retinal Pigment Empithelium (RPE). Wet AMD is caused by a leaking blood vessel below the RPE. The National Eye Institute has identified AMD as a significant cause of vision loss in Americans 60 years and above [1].

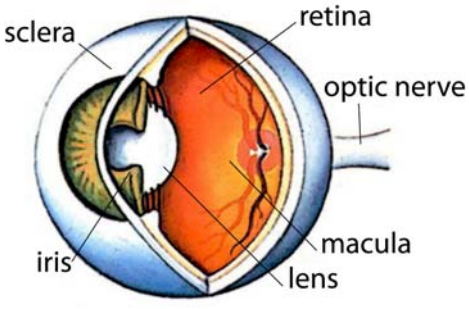

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Figure 1: Anatomy of human eye

AMD can be treated by medication but is extremely expensive [2]. Surgical correction of AMD offers a possibility of a more cost effective cure to the disease. The procedure usually involves reconnecting the macula with the healthy choroid by means of a standard 3-port par plana vitrectomy. The damaged

tissue under the macula is replaced with a healthy graft of RPE, Bruch's membrane and partial or full thickness choroid. This graft could be from another portion of the eye, from animal source, a donor eye or a synthetically grown tissue.

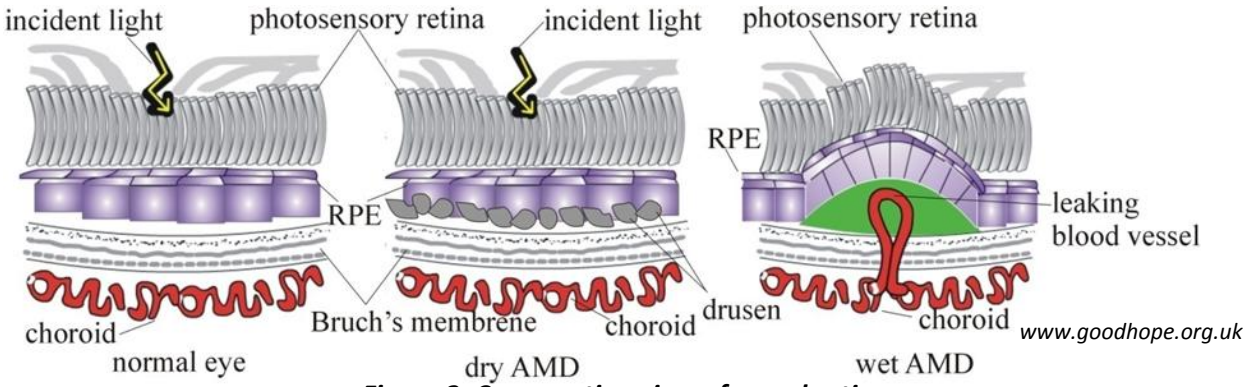

Figure 2: Cross section view of macular tissue

The surgical correction procedure suffers from the limitation that the tissue gets damaged during translocation. Furthermore, in some cases, the graft is not successful because of wrinkling or inadequate positioning of the tissue [3]. The success of the procedure can be increased by using a support structure or device that holds the tissue stretched during translocation. The device can also be used to orient the tissue correctly under the retina. This report summarizes the design, manufacture, and evaluation of such a device. Various design approaches are considered in the next few sections and are analyzed for suitability for use during surgery.

2. Preliminary Design Iterations

Prior research in this area at the University of Minnesota resulted in a device consisting of two rings made from the biocompatible alloy, Nitinol (55% Ni, 45% Ti). These rings were used to sandwich the tissue and translocate it [4]. The limitation of this method was that the rings would slip relative to the tissue and damage the graft. Hence, it was decided to connect the two rings together forming a monolithic structure that would prevent unwanted relative motion. The requirements of the device are summarized below:

- Biocompatible
- Prevent tissue folding
- Insertable through a 1 mm cannula in to the eye
- Prevent rubbing of device against tissue
- Should not have protruding parts
- Structure should have a total thickness less than 500 µm
- Flat contact surface with tissue

Based on these design requirements, a variety of design and fabrication approaches were considered (refer to Fig. 3). The first approach was to build the structure from a biocompatible polymer using micro-SLA or micromolding. While this approach has the advantage of being extremely convenient for mass

production, the biocompatible polymers used in this method are too brittle to be able to withstand the stresses induced during the surgery. Another approach to connecting the two rings together was to weld them using a laser. However, the welded region was found to be more brittle than the parent material. Next, various monolithic wire-based structures were considered with a hinge to connect the two rings. However, the protruding hinges used in this design would obstruct insertion under the tissue and could also tear the tissue. Based on prototypes of these preliminary designs, the monolithic wire based structures were judged to perform the best. To address the issue of the protrusion, the design was modified to use the special shape memory effect of Nitinol.

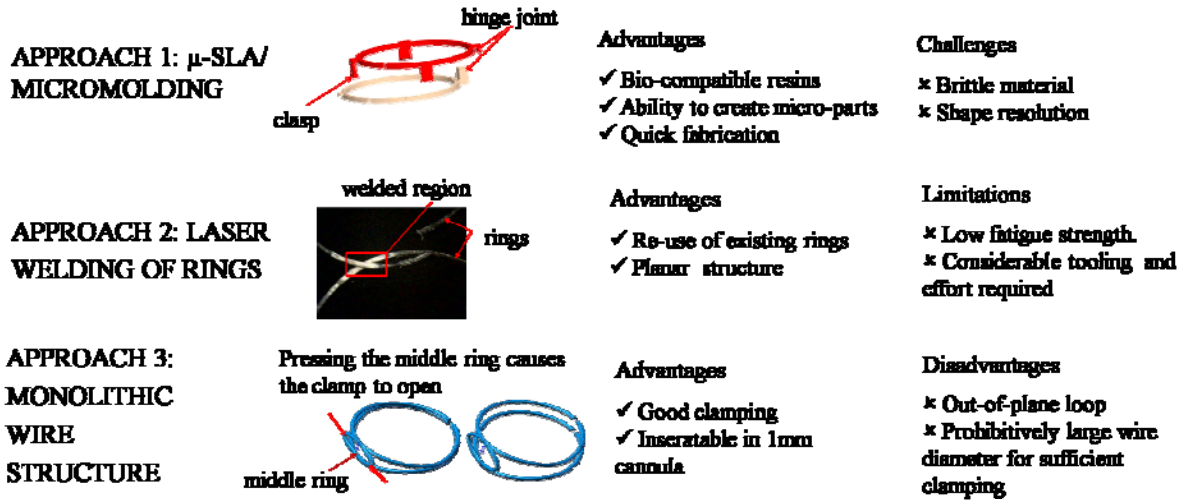

Figure 3: Design approaches for support structure

3. Shape Memory Wire Based Design

The shape memory wire based design is illustrated in Fig. 4. The structure uses the shape memory effect (SME) of Nitinol. This property enables the material to be trained to a particular shape. It can then be deformed to any shape, but regains the trained shape when heated to a temperature beyond its transition temperature (70 °C in this case).

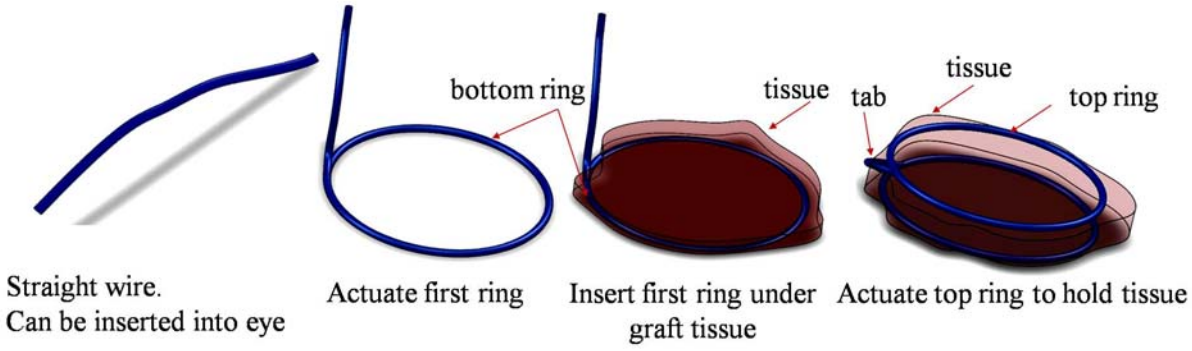

Figure 4: Shape memory alloy wire based design

The SME property was applied to this device as shown in Fig. 4. The trained configuration of the device is the final configuration in the figure. The device is first straightened to insert it into the eye through a 1mm canula (tube). This is easily achieved since the diameter of the wire is about 0.1 mm (100µm). The wire is then heated with a laser to form the bottom ring. The ring is inserted under the tissue graft. The top ring is now heated and it clamps down on the tissue. The device is then heated further to cause the tissue to adhere to the ring. The tissue is then cut from the surrounding tissue and translocated as intended. The tab is used to grasp the device during this procedure.

3. 1. Manufacturing Procedure

The SMA device is manufactured by the steps illustrated in Fig. 5. The SM wire (Flexinol, Dynalloy Inc.) is wound around a stainless steel mandrel to give it the required shape. The mandrel allows multiple rings to be trained in a batch by heating them in a furnace to 450°C. Individual support structures are then cut from the coil of wire giving it the final form of the device. However, in the process of cutting, the ends of the wire are damaged and tend to protrude out of the plane of the device. This could damage the tissue during surgery. Hence, the structures are placed under a weight on a hot plate and retrained. Multiple devices were manufactured from 100 µm, 150 µm, 250 µm and 500 µm wire stock. In the fourth step material is removed from the top of the wire by micromilling to make it thinner. The process also roughens the surface which improves its adhesion with the tissue.

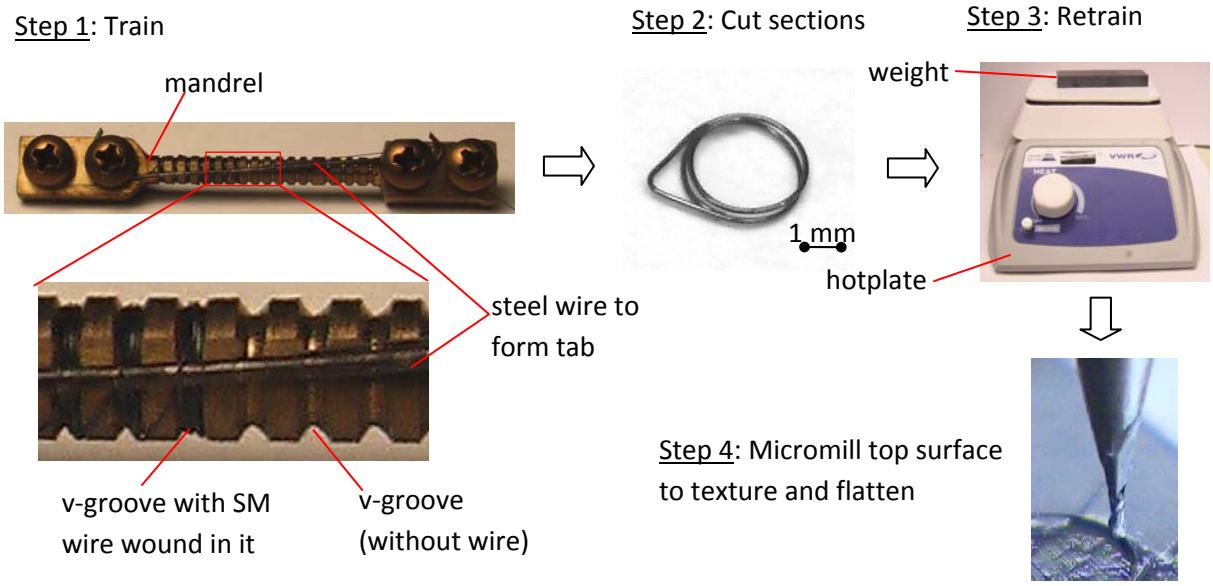

Figure 5: Steps involved in the manufacture of SM wire based design

3.2. Testing and Refinement

The manufactured devices were first tested with cadaver pig eyes (ex-vivo). A 250 µm wire based design was tested by heating it with a surgical laser in air. A patch of tissue was adhered to the structure and translocated as shown in Fig. 6. The wire diameter was further reduced to 150 µm and tested again in live pig eyes (in-vivo). In this case, however, the structure did not close fully and therefore did not adhere to the tissue. This is attributed to the presence of the tissue between the two rings causing the support to remain wedged open. Furthermore, the presence of fluid inside the eye results in higher heat

loss from the support structure, which would call for higher laser power during actuation of the structure. However, operating the laser at this higher power can damage the graft tissue.

The first step to solve these problems was to explore if the clamping force of the structure could be increased. One method to increase the clamping force is to cross the rings after training, thus forcing the rings together due to the elastic stresses in the wire. This behavior is similar to elastic stresses in a paperclip. This modification was tested in-vivo and was found to close much better than the structures that had not been crossed over. However, when the laser was removed, the structure tended to open up again. It was therefore decided that experiments be conducted to investigate what increase in wire diameter would result in sufficient closing force due to the SM effect.

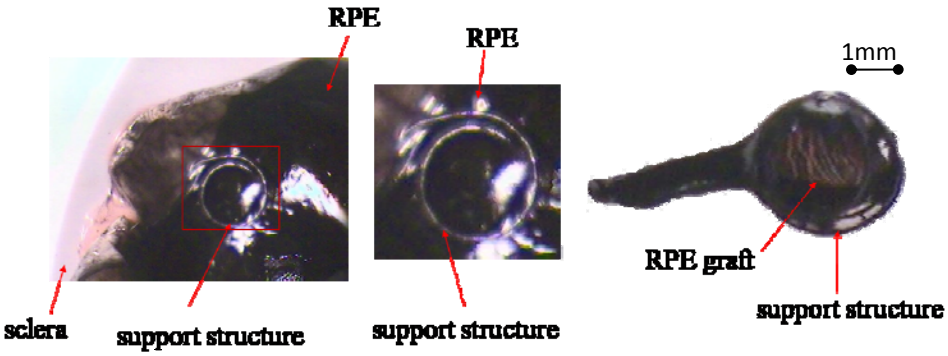

Figure 6: Results of ex-vivo test with wire based tissue support structure

Experiments were conducted to measure the clamping force exerted by the structure during actuation (Fig. 7a). Tests were also conducted to measure how much force it would take to pull a thin piece of collagen out of the support structure after it had closed (Fig. 7b). The results of the test are shown in Table 1. It can be seen that the clamping force is negligible for diameters below 500 µm. A similar conclusion is drawn for the pulling force. A wire diameter of over 150 µm cannot be used in the eye since it would increase the risk of autoimmune rejection. Hence, it is concluded that the wire-based design cannot generate the required force to clamp the tissue.

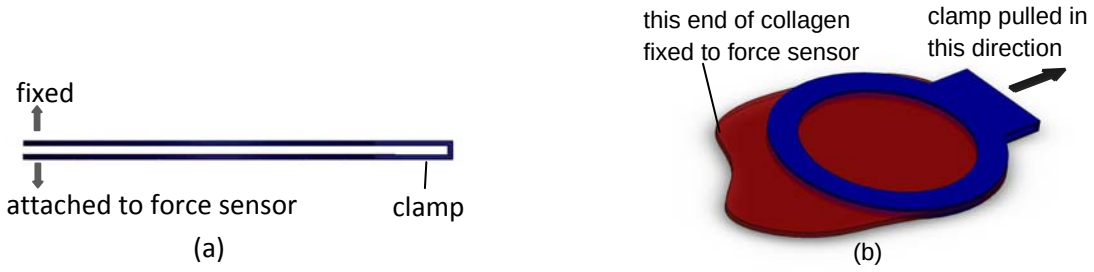

Figure 7: Schematic of force measurement set-up and directions of (a) closing force (b) pulling force

In spite of the low clamping force, the structure can still be used to translocate tissue if it can be adhered to the tissue using heat. The structure can be brought in contact with the tissue using forceps and then heated using the laser to adhere to the tissue. However, if the laser is operated at a power

high enough to adhere the structure to the tissue, it damages the graft. This is because the laser energy is not localized to the metal surface of the support structure.

Table 1: Clamping force measurements

Wire diemeter (μm)	100	150	250	500
Clamping force (N)	0.005	0.05	0.1	0.5

Based on the experiments with the wire based design, the following conclusions are drawn:

- Adhesive forces should be used to hold the tissue and keep it stretched
- Heating should be localized to the device and should not damage the surrounding tissue

Adhesive forces can be increased by increasing the area of contact between the tissue and the support structure. Hence, a structure that has a larger annular region while still maintaining a small thickness normal to the tissue surface would be advantageous. This led to the development of the foil based design discussed in Section 5. Localized heating can be achieved using electrical heating and is discussed next.

4. Localized heating

Electrical Radio frequency (RF) heating is commonly used in surgery to cauterize tissue. This method was applied to heating the rings by modifying two 23 gage forceps (Alcon/Grieshaber) to be energized electrically as shown on Fig. 8. A notable feature of this design is that it allows the disposable tip to be easily replaced even after the modification. These forceps are connected to the RF source in the surgical suite (Accurus System, Alcon Inc.) and can be used to heat the length of the support structure held between them. Heating is expected to be limited to the area of contact between the structure and the tissue and a fairly negligible area around it [5].

Figure 8: Modified pair of forceps for electrical actuation of support structure

5. Foil based design

The area of contact between the tissue and the structure can be increased if the structure is created from a Nitinol foil instead of a wire. This approach also makes possible more elaborate geometries of the support structure while retaining the advantages of the SM effect. Some of these designs are

illustrated in Fig. 9. The locking mechanisms in Fig. 9b and Fig. 9c can be used to lock the two rings together.

The designs shown in Fig. 9 were micromilled from a 50 µm foil as shown in Fig. 10. As shown in Fig. 10b, the micromilled structure in Fig. 10a is folded over to form the tissue support structure. The tissue is to be held between the two annular sections. Figures 10c and 10d illustrate the more detailed features that can be created by this process. The foil is rolled up as shown in Fig. 11 to form a compact cylindrical structure that can be inserted in to the eye. It is then heated using the forceps and opens up to form the support structure. The structure is opened up and one ring is inserted under the tissue. The structure is then heated again using the forceps so that the top ring closes down on to the tissue. The structure is then heated further to adhere it to the tissue.

Figure 9: Shape memory foil-based support structures

Figure 10: Micromilled foil support structures

Testing

The support structures were tested along with the electrical actuation system ex-vivo with cadaver pig eyes and in-vivo with live pigs. Results of the ex-vivo tests are shown in Fig. 12. It can be seen that the structure can be used to translocate tissue. It is to be noted that the tests were carried out in saline solution. No significant damage due to electrical heating can be visually observed in the tissue patch. In-vivo tests with the foil based designs were not as successful partly due to severe bleeding inside the eye during surgery. Also, it is possible that the structure was being cooled a lot quicker due to the continuous flow of saline solution compared to the ex-vivo tests where still saline solution was used. The locking mechanisms proved to be too stiff to be opened inside the eye using the delicate surgical instruments.

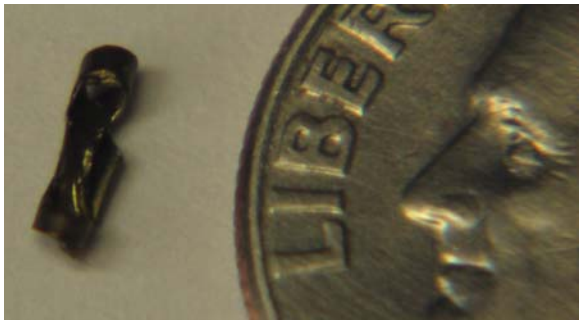

Figure 11: Rolled configuration of foil

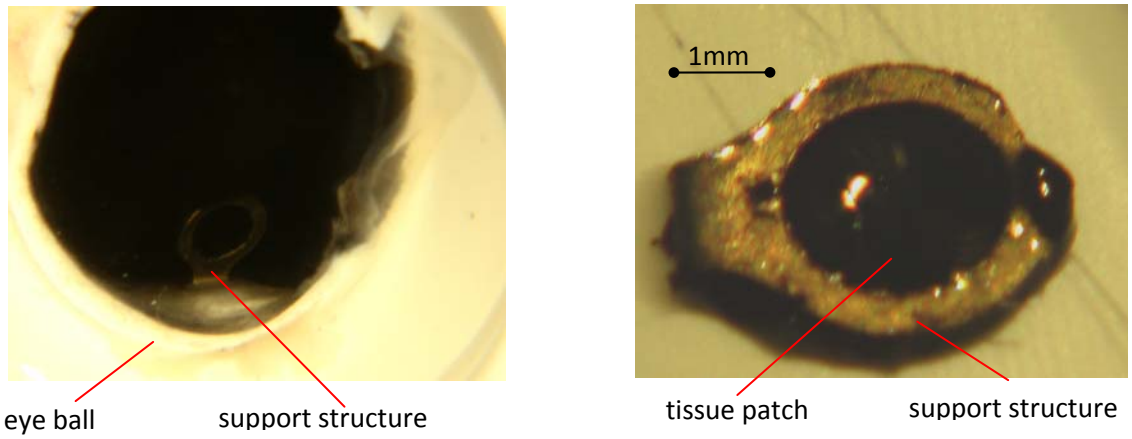

Figure 12: Ex-vivo tests of foil based structure

6. Conclusions

This report summarizes the design and manufacture of a support structure that can be used inside the eye to translocate a tissue graft. From the preceding discussion it can be concluded that the SM based structure holds promise to perform this task. Both the wire based and foil based structures were manufactured and tested. Low clamping force is an issue with the small dimensions required for this device. However, this limitation can be overcome by relying on adhesive forces instead. The foil based structure has the advantage of a higher contact area with the tissue which could provide higher adhesive forces. Also more detailed structures can be made using this approach. Electrical heating of the structure causes less damage to the tissue than heating using laser.

7. Future work

While ex-vivo tests have been quite successful, further study of the electrical power, heating duration and heating location would be required to replicate the same results in-vivo. Also, the adhesive forces achieved in the device need to be quantified to ensure that they are high enough to hold the tissue during translocation. Furthermore, the roughening or texturing of the surface of the foil may be used to achieve better bonding with the tissue. For example, the contact surface of the foil design shown in Fig.

13 has been modified with a series of holes that would provide areas for penetration of the denatured, heated tissue. Also, the structures will be machined from a 25 µm foil to make it even more compact and easy to insert in to the eye.

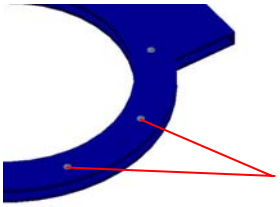

Figure 13: Modified design of support structure

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Appendix

List of Experiments

Test date	Type	Number of eyes	Results
7-Aug-10	Ex-Vivo	2 eyes	Force measurements. Force required to pull adhered and translocated tissue out of the foil structure was measured using Kistler dynamometer. Data not usable due to sensor drift.
4-Aug-10	Ex-Vivo	2 eyes	Tests from July 28 repeated. (Dr. Olsen present)
28-Jul-10	Ex-vivo	1 eyes	Foil and wire based structures were tested ex-vivo. More peripheral heating was used to attach the tissue. Tissue successfully translocated. (Dr. Olsen absent)
17-Jul-10	In-vivo	2 pigs, 4 eyes	100 µm, 150 µm (crossed-over) wire based and 50 µm foil based structures were tested. Foil designs were made by micromilling. Electrically activated forceps used. Insertion of foil in to the eye was possible. Foil structure closed without gap. However it did not adhere fully to the tissue. Hence, the tissue came out of the structure during manipulation. Locking tabs were too stiff to be opened by 23 and 20 gage forceps.
24-Apr-10	In-vivo	2 pigs, 4 eyes	100 µm and 150 µm wire based designs, both crossed-over and non-crossed-over were tested. A few 50 µm foil based structure with and without lock were tested. Foil designs were made by punching and shearing. Laser was used to activate the structures. Insertion of foil in to the eye was possible. Foil structure closed without gap. However it did not adhere to the tissue. The foil designs had too many sharp corners, but were easy to handle.
12-Feb-10	In-vivo	2 pigs, 4 eyes	100 µm and 150 µm wire based non-crossed-over designs were tested. Tissue did not adhere. Rings were not fully aligned.
13-Nov-09	Ex-vivo	2 eyes	100 µm and 150 µm wire based non-crossed-over designs were tested. Some of the rings were flattened in a vice increasing contact area with tissue. Tissue did not adhere. Rings did not fully close.