Transplants and Grafts

Development of a Rapid, Light-activated Peripheral Nerve Repair Technology

Large gap (greater than three centimeters) peripheral nerve injury often accompanies extensive multi-trauma to injured Service members. Standard-of-care microsurgical attachment of interpositional autograft may not be available for these patients due to extensive trauma and/or amputation. Thus, there is a real need for alternative procedures that could improve functional recovery in wounded Service members. Alternatives to autologous graft, including processed allograft from cadaver tissue, are not usually indicated for nerve gaps greater than three centimeters. Nerve regeneration can be inhibited by suture attachment through needle trauma, foreign body response, inflammation, scarring and infection. Researchers at Massachusetts General Hospital (Boston, Massachusetts), and Walter Reed National Military Medical Center (Bethesda, Maryland) developed a sutureless approach, whereby light energy bonds a biocompatible nerve wrap containing a photoactive agent over the nerve/graft junction. This watertight seal prevents axonal escape and leak of growth factors important for stimulation of nerve regeneration, contributing to an optimal regenerative environment.

> Comparable functional recovery in large deficit peripheral nerve repair can now be achieved using allograft that are similar to SOC autograft, for military patients that lack donor autograft material due to concomitant trauma.

Initial studies compared various nerve wrap materials and fixation methods in a rodent model of sciatic nerve gap repair using autologous graft (*Fairbairn et al. 2015, Fairbairn, Ng-Glazier, Meppelink, Randolph, Winograd, et al. 2016*; Figure 1). Significant improvement in metrics such as histomorphometry, muscle mass retention and gait analysis were observed in the group that was repaired using the photosealing technology with a crosslinked human amniotic membrane-derived wrap. This membrane is thin, strong and has immune-privileged status due to its origin and does not provoke foreign body response or inflammation that would inhibit nerve regeneration. A further rodent study using this technology to seal processed rat allograft, rather than autograft, across the nerve gap led to outcomes that were not statistically different from standard of care (SOC) autograft attached by microsurgery and improved with respect to microsurgical attachment of allograft (*Fairbairn, Ng-Glazier, Meppelink, Randolph, Valerio, et al. 2016*).

The final phase was the investigation of nerve regeneration in a large animal (swine) bilateral forelimb model following large deficit (five centimeter) ulnar nerve injury where one forelimb was repaired by SOC microsurgical placement of autograft (greater saphenous) and the other limb was repaired using commercial Avance (AxoGen Inc.), a processed allograft, sealed in place using light-activated nerve wraps of crosslinked amnion (*Goldstein et al. 2017*). Histological studies of harvested nerve at 150 days showed axonal regeneration distal to graft in both groups. Electrophysiological measurements exhibited identical compound muscle action potential amplitude and signal latency in both cases and a

significant improvement in direct nerve conduction velocity was observed in the photosealed allograft.

Overall, this project demonstrated that allograft may be effective for repair of large nerve gap injury when attached using photoactive wraps rather than sutures. The technology was featured in the Netflix Original Series, "The White Rabbit Project" (Series 1, Episode 8), showing the light-activated repair technology as an example of a science fiction idea that has become a reality. This has considerable potential impact, particularly for wounded Service members where concomitant trauma, including amputation, limits the availability of suitable donor autograft.

This study was funded by Peer Reviewed Orthopedic Research Program, and is strategically aligned with Combat Casualty Care Research Program. The awards (W81XWH-12-1-0511, W81XWH-12-1-0512, and W81XWH-12-1-0513) were managed by Congressionally Directed Medical Research Programs.

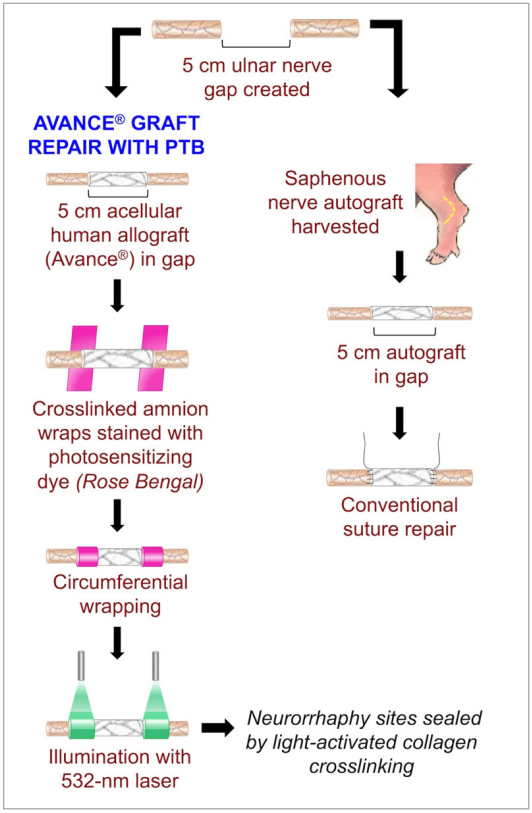

FIGURE 1: Schematic of experimental swine model of large gap ulnar nerve deficit injury in swine, comparing repair and regeneration from SOC autologous graft (right column) versus photosealed processed allograft (left column) (Figure used with permission from the authors)

REFERENCES:

Fairbairn, N. G., Ng-Glazier, J., Meppelink, A. M., Randolph, M. A., Valerio, I. L., Fleming, M. E., Kochevar, I. E., Winograd, J. M., and Redmond, R. W. 2016. "Light-Activated Sealing of Acellular Nerve Allografts Following Nerve Gap Injury." J Reconstr Microsurg 32 (6):421-30. doi: 10.1055/s-0035-1571247.

Fairbairn, N. G., Ng-Glazier, J., Meppelink, A. M., Randolph, M. A., Valerio, I. L., Fleming, M. E., Winograd, J. M., and Redmond, R. W. 2015. "Light-Activated Sealing of Nerve Graft Coaptation Sites Improves Outcome Following Large Gap Peripheral Nerve Injury." Plast Reconstr Surg 136 (4):739-50. doi: 10.1097/PRS.0000000000001617.

Fairbairn, N. G., Ng-Glazier, J., Meppelink, A. M., Randolph, M. A., Winograd, J. M., and Redmond, R. W. 2016. "Improving Outcomes in Immediate and Delayed Nerve Grafting of Peripheral Nerve Gaps Using Light-Activated Sealing of Neurorrhaphy Sites with Human Amnion Wraps." Plast Reconstr Surg 137 (3):887-95. doi: 10.1097/01.prs.0000479996.04255.60.

Goldstein, R., Randolph, M. A., Easow, J., Valerio, I. L., Winograd, J. M., and Redmond, R. W. 2017. "Photochemical Tissue Bonding Optimizes Outcomes of Large Gap Peripheral Nerve Defects Repaired with Acellular Nerve Grafts in a Porcine Model." Military Health System Research Symposium (MHSRS), Kissimmee, FL, August 27-30, 2017.