**Rotator Cuff Repair with Purified Exosome Product (PEP) in a Canine Model.**

Ichiro Tsukamoto1, Naoya Iida1, Kai-Lan Hsu1, Margaret Brosig1, Ramona Reisdorf1, Joaquin Sanchez-Sotelo1, Scott P Steinmann1, Chunfeng Zhao1.

1Mayo Clinic Orthopedic Biomechanics Laboratory, Rochester, MN
2University of Tennessee College of Medicine in Chattanooga, Tennessee

Disclosures: The authors have no COI to disclose. This work was supported by a grant from the National Institutes of Health (NIH) (R01 AR73811).

**INTRODUCTION:**
Rotator cuff consists of four muscles with tendons, surrounding the shoulder joint capsule circumferentially and stabilize the joint biomechanically. The most common cause of shoulder pain and dysfunction in all age groups is rotator cuff tears, which affect over 35% of the population over 50. More than 4.5 million patients visit orthopedic surgeons and approximately 300,000 outpatient surgical repairs are performed at a cost of $26,000-50,000 per procedure with a return to work between 7-11 months. Surgical repair is a common treatment, but recurrent tears occur in 20 to 90% of the patients, especially in those with large or massive tears. Recently, biomaterial or mechanical augmentations has been used to accelerate tissue healing and increase mechanical strength of the repaired rotator cuff and to improve the functional outcomes following repair. Research on this topic has been energized in recent decades including cell-based therapy, tissue engineering, bioactive growth factors, etc. In our lab, a new technique to improve the repair has been developed using a biological method. Recently, Mayo Clinic Center for Regenerative Medicine developed and manufactured a GMP grade purified exosome product (PEP) for clinical translation. With the strong support of our promising preliminary data. Exosomes transfer biological signals from the donor cell to the target cell and change normal or pathological processes. Compared with other biological strategies such as plasma, PRP and stem cells, exosomes are immune-privileged and exhibit low species differences in structure and elements. A clinical translation, preclinical large animal model is needed, to show whether PEP can be effective when the repair and healing is scaled up with clinically used surgical repair techniques. The aim of this study is to define the role of the PEP on rotator cuff healing, enthesis regeneration and functional restoration using a canine rotator cuff tear model.

**METHODS:**
A total of 36 shoulders from 18 female and male canine about 1 year of age and weighing around 30kg were used. The left or right shoulder was selected randomly with the infraspinatus (ISP) tendon being exposed using a deltoteporal approach under general anesthesia. Then, the ISP tendon was detached at its insertion using a sharp knife, along with the capsule beneath, to expose the glenohumeral joint to simulate an intrasynovial tendon injury condition in a clinical scenario. A decortication of the footprint was performed using chisels and a double-row repair was performed with 4.5 mm Corkscrew FT suture anchors (Arthrex, Naples, FL) loaded with #2 FiberWire (Arthrex). The medial-row anchors were placed along the articular margin. With the lateral-row anchors placed 10 mm apart from medial-row anchors. Sutures were passed through the ISP tendon and tied with a mattress configuration. Canines were allocated to 3 groups (each, n=6): normal repair (control) group, fibrin glue added repair (TISSEEL repair) group and fibrin glue and PEP added repair (TISSEEL+PEP) group. In TISSEEL group, 4ml of commercially provided fibrin glue (TISSEEL, Baxter, Chicago, IL) was put between the detached ISP tendon and the decorticated footprint. In TISSEEL+PEP group, 4ml of TISSEEL which contained 20% PEP was put in the same way as in the TISSEEL group (Fig 1). A high radial neurctomy was performed with the radial nerve being transected above the triceps brachii to denervate the triceps muscle thus preventing elbow extension and thereby preventing weight bearing postoperatively to protect repaired ISP tendon. The canines were euthanized 6 weeks after the surgery. Immediately after the euthanization, the right shoulders were dissected as per the surgical procedures. FiberWire sutures; B, TISSEEL and #2 FiberWire sutures; A

**RESULTS:**
Average values of maximum tensile failure load (N) were 205.56±67.16(N) in time-0 control group; 446.19±12.49(N) in control group; 52.94±3.36(N/mm) in TISSEEL group and 55.24±20.58(N/mm) in TISSEEL+PEP group, respectively; the value of time-0 control group was significantly lower than those of the other groups and the value of TISSEEL+PEP was significantly higher than those of the other groups. Average values of Stiffness (N/mm) were 27.35±3.98(N/mm) in time-0 control group; 7.25±0.25(mm) in TISSEEL+PEP group; respectively; the value of time-0 control group was significantly lower than those of the other groups and the value of TISSEEL+PEP was significantly higher than those of the other groups. Average values of time-0 control group was significantly lower than those of the other groups and the value of TISSEEL+PEP was significantly higher than those of the other groups. The average tendon width was 14.5±0.5(mm) in control group, 15.5±0.5(mm) in TISSEEL group and 18.5±0.5(mm) in TISSEEL+PEP group. The average tendon thickness was 5.25±0.25(mm) in control group, 5.85±0.35(mm) in TISSEEL group and 7.25±0.25(mm) in TISSEEL+PEP group. Histological staining revealed that one specimen in the TISSEEL group raptured in the muscle and tendon junction were all specimens raptured in the tendon bone junction. Average values of stiffness were 430.66±136.67(N) in TISSEEL group and 677.55±66.13(N) in TISSEEL+PEP group, respectively; the value of time-0 control group was significantly lower than those of the other groups and the value of TISSEEL+PEP was significantly higher than those of the other groups. Weekly SWE measurements showed that TISSEEL+PEP could suppress postoperative increasing of ISP muscle stiffness.

**DISCUSSION:**
Mechanical test showed that both the maximum tensile failure load and stiffness of the TISSEEL+PEP group were significantly higher than that of the other groups and the value of TISSEEL+PEP group was significantly higher than the other groups. The average tendon width was 14.5±0.5(mm) in control group, 15.5±0.5(mm) in TISSEEL group and 18.5±0.5(mm) in TISSEEL+PEP group. The average tendon thickness was 5.25±0.25(mm) in control group, 5.85±0.35(mm) in TISSEEL group and 7.25±0.25(mm) in TISSEEL+PEP group. Histological staining revealed that one specimen in the TISSEEL group raptured in the muscle and tendon junction were all specimens raptured in the tendon bone junction. Average values of stiffness were 430.66±136.67(N) in TISSEEL group and 677.55±66.13(N) in TISSEEL+PEP group, respectively; the value of time-0 control group was significantly lower than those of the other groups and the value of TISSEEL+PEP was significantly higher than those of the other groups. Weekly SWE measurements showed that TISSEEL+PEP could suppress postoperative increasing of ISP muscle stiffness. PEP seemed to help the tendon healing after repair.

**SIGNIFICANCE/CLINICAL RELEVANCE:** TISSEEL+20% PEP improve both the maximum tensile failure load by 1.57 times and the stiffness 1.82 times against normal ISP tendon repair. PEP seems to be a good candidate for an additive to accelerate tissue healing and increase the mechanical strength of the repaired rotator cuff.