"Sensate" Cartilage Covered Scaffolds Can Detect Subtle Load Changes In Vivo Following ACL Disruption

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Statement of Purpose: Anterior cruciate ligament (ACL) disruption, if untreated, leads to osteoarthritis (OA) which affects nearly 10% of Americans. This costs the US over $60 billion/yr and leads to joint replacement surgery. However, surgeries can require radical tissue resection causing reduced proprioception and an increased risk of falls. Also, wear and loosening of implants can require a second surgery. Our research goal is the development of a "sensate" scaffold with a tissue engineered cartilage layer to allow joint resurfacing and load monitoring of patients' joints during healing. This approach is critical to, developing functional engineered tissues that integrate into native tissues, and to better understand the effect of loading on arthritis development.

In this study "sensate" scaffolds were used to collect *in vivo* load measurements following ACL disruption. This allowed characterization of loads in the joint to demonstrate that this approach can be used to understand changes and develop repair techniques or pharmaceutical treatments to preventing progression of OA.

Methods: 1000-ohm strain gauges were attached to polybutylene terephthalate trabeculated scaffolds which were waterproofed and hydroxyapatite coated using published procedures. An MTS test machine was used to establish load-strain calibration curves for scaffolds. Scaffolds with transmitters were sterilized for surgery.

The NIH animal care guide was followed in this study. Five male hounds (27 to 35 kg) were treadmill trained and divided into groups. The first group received a scaffold only and a second a scaffold with cells. Adipose tissue was isolated during a minor surgery 24 hrs. prior to scaffold placement, when cells were used. Adipose derived stem cells (ADSCs) were isolated and converted to chondrocytes using 10ng/mL TGF-beta3. Cells were suspended in agarose and grown for 24 hr then placed on the scaffold and implanted. In all dogs, the medial femoral condyle was exposed and concentric holes were drilled to pass wires and place the scaffold. Scaffolds were recessed to within 1 mm of the native articular cartilage surface. A transmitter, connected to the sensors, was placed subcutaneously. During post-op treadmill running, loads were acquired via telemetry. Load analysis was based on detection of specific peaks and minimums. Peak load rate and impulse distribution were determined.

A second procedure was performed to disrupt the ACL 4 months following cell covered scaffold placement. An anterior medial approach was used, followed by capsule incision to expose the joint. A type II avulsion injury was created by scoring the ACL insertion. The avulsed end of the ACL was removed and the incision closed. Treadmill running resumed 1 week post-op and loads were collected. Pre- and post-Rimadyl treatment measurements were also collected. Histology and histomorphometry were carried out on both intact and implanted joints.

Results: Measurements with the ACL intact indicated that as walking speed increased, total impulse decreased and paw strike loading rate increased. Increased speed also resulted in an increase in paw strike and mid-stance impulse as well as a decrease in toe off impulse. Maximum load did not change as a function of speed (p=07) but did as a function of time post-op (21 to 88 N i.e. 8 to 33% body weight) to 4 months.

Examination of scaffold surfaces placed without cells revealed a tenuous fibrous tissue layer(Fig. 1a) in contrast to the hyaline-like cartilage seen on the seeded scaffold (Fig. 1b). Histology confirmed the presence of hyaline-like cartilage (Fig. 2) and no damage was noted on tibial surfaces of either group. Measurements 1 week after ACL disruption, showed a 55% peak load drop, but a 24% increase in paw strike loading rate. A 65% decrease in unloading rate relative to pre-surgical values was noted. Administration of Rimadyl increased peak loads 29%.

Figure 1a: Left-gross image of a condyle with unseeded scaffold 1b: Right two gross images of cartilage on the surface of scaffold seeded prior to placement.

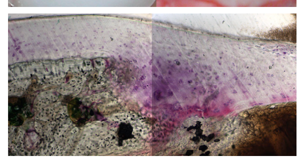

Figure 2: Collage shows hyaline-like engineered cartilage and junction between native cartilage and tissue engineered cartilage.

Conclusions: Normal joint peak loads did not vary with changes in gait speed but load rate did in agreement with published evidence. Measurements demonstrated that load changes over time can be used to monitor healing and potentially to develop better post surgical rehabilitation.

Extensive hyaline-like cartilage was only observed when ADSC's (converted to chondrocytes) had been placed on the scaffold surface prior to implantation.

The size of the decrease in peak load following ACL transection is in agreement with published force plate data. Our measurements also confirmed impact load rate changes predicted by published knee specific kinematic analysis. The 24% increase is likely the result of increased knee extension velocity during paw-strike, while a 65% decrease in unloading rate is likely be due to decreased flexion velocity. This indicates that published force plate and motion analysis data previously thought to be inconsistent or contradictory are in agreement when evaluated in light of our *in vivo* measurements.

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