

# A Pre-Clinical Test Platform for the Functional Evaluation of Scaffolds for Musculoskeletal Defects: The Meniscus

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**Abstract** In an attempt to delay the progression of osteoarthritis from an index injury, early intervention via repair of injured musculoskeletal soft tissue has been advocated. Despite the development of a number of scaffolds intended to treat soft tissue defects, information about their functional performance is lacking. The goal of this study was to consolidate a suite of in vitro and in vivo models into a pre-clinical test platform to assess the functional performance of meniscal repair scaffolds. Our objective was to assess the ability of a scaffold (Actifit™; Orteq, UK) to carry load without detrimentally abrading against articular cartilage. Three test modules were used to assess the functional performance of meniscal repair scaffolds. The first module tested the ability of the scaffold to carry load in an in vitro model designed to measure the change in normal contact stress magnitude on the tibial plateau of cadaveric knees after scaffold implantation. The second module assessed the in vitro frictional coefficient of the scaffold against cartilage to assess the likelihood that the

scaffold would destructively abrade against articular cartilage in vivo. The third module consisted of an assessment of functional performance in vivo by measuring the structure and composition of articular cartilage across the tibial plateau 12 months after scaffold implantation in an ovine model. In vitro, the scaffold improved contact mechanics relative to a partly meniscectomized knee suggesting that, in vivo, less damage would be seen in the scaffold implanted knees vs. partly meniscectomized knees. However, there was no significant difference in the condition of articular cartilage between the two groups. Moreover, in spite of the high coefficient of friction between the scaffold and articular cartilage, there was no significant damage in the articular cartilage underneath the scaffold. The discrepancy between the in vitro and in vivo models was likely influenced by the abundant tissue generated within the scaffold and the unexpected tissue that regenerated within the site of the partial meniscectomy. We are currently augmenting our suite of tests so that we can pre-clinically evaluate the functional performance at time zero and as a function of time after implantation.

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Each author certifies that his or her institution has approved the animal protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

Each author certifies that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

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## Introduction

The clinical management of young active patients with osteoarthritis presents a challenge in terms of providing long-term pain relief while allowing for a return to high-level activities. Although total joint arthroplasty is considered a safe and effective procedure [10, 11, 15], the risk of subsequent revisions in young active patients and the associated reduction in longevity with each revision [29] advocates delaying the age for a primary total joint replacement. One such paradigm is to repair injured musculoskeletal soft tissue early in the course of the problem in an attempt to prevent or delay the progression of osteoarthritis from the index injury. The meniscus, for example, functions to provide knee joint stability, load

bearing, and chondroprotection by distributing loads over a broad area of articular cartilage [19, 21, 22]. Once torn, or damaged, the chondroprotective ability of the tissue is disrupted and the cascade towards osteoarthritis initiated [26]. A goal in the surgical management of meniscal tears or defects is to recreate a mechanically functional tissue in an attempt to halt disease progression. Use of scaffolds to facilitate tissue ingrowth into meniscal defects is one such option that is under investigation.

Although not yet used clinically, cell-seeded scaffolds designed to be cultured in a laboratory setting prior to implantation have been developed for the treatment of meniscal defects [4, 18, 33]. The quest to engineer such implants has used significant funding from federal sources, venture capitalists, and private foundations, the magnitude of which is difficult to estimate, but likely exceeds hundreds of millions of dollars. Resources have thus far been largely directed to the sciences of polymer chemistry, cell biology, and cell–matrix interactions. Few resources, if any, have been used to standardize methods to assess the mechanical properties and functional performance of the candidate materials. Currently, information about the mechanical performance of materials intended for meniscal replacement such as their ability to provide knee joint stability and chondroprotection without damaging the articular cartilage is rarely reported in the scientific literature. As a result, despite 20 years of tissue engineering innovation, only one scaffold for the treatment of meniscal defects has translated into clinical use in the US—Menaflex™ (Regen Biologics, NJ, USA), yet there have been no published reports which quantify the ability of the scaffold to *mechanically function* in the knee joint. Given that the scaffold is intended to function in the highly loaded environment of the knee, which is exposed to three to five times body weight during activities of daily living [14, 27] and subjected to millions of loading cycles each year, this lack of information negatively impacts regulatory decisions as to the safety and efficacy of an implant and suggests the urgent need to standardize tests aimed at evaluating functional performance.

The closest we have come to developing pre-clinical tests that simulate functional mechanical loading is in the use of animal models; however, controversy persists as to the optimal animal model [3]. Small animal models have been used to provide an assessment of the biological response to new materials implanted into the knee joint [2, 16, 31]; however, the implants are not subjected to the high loads which would occur in the human knee. Large animal models, such as sheep [18, 25], offer the opportunity to subject the candidate materials to immediate and substantial loads, but the models are costly and time consuming to conduct. Moreover, in the event of a negative result, it is often difficult to identify the features of an implant or scaffold that caused the unfavorable result and therefore should be modified for the next design iteration. For example, every synthetic meniscal implant studied thus far in animal models has led to some degree of degeneration of articular cartilage, including fibrillation and depletion of matrix [17, 35], cartilage softening, or the formation of osteophytes [26]. None of these studies have

provided definite information about the cause of failure to feed back into the design process, leading to the abandonment rather than refinement of new technologies. A platform is needed in which the functional performance of meniscal scaffolds (whether cell-seeded or non-cell based) can be assessed prior to large-scale animal models and clinical trials. Such a platform should allow for the systematic evaluation and optimization of implant design features and screen out those constructs that are unlikely to mechanically function in vivo.

The goal of this study was to consolidate a suite of in vitro [6, 12] and in vivo test modules [24] into a pre-clinical test platform to assess the functional performance of scaffolds intended to replace a damaged meniscus. Our objective was to assess the ability of a scaffold to carry load and the degree to which the scaffold would detrimentally abrade against articular cartilage. Finally, we wished to compare these in vitro evaluations to an in vivo model which used MRI imaging to assess the structure and composition of the articular cartilage in the tibial plateau 12 months after implantation of the scaffold.

## Methods

Three test modules were developed to assess the functional performance of a porous degradable polyurethane scaffold (Actifit™; Orteq Sports Medicine Ltd., London, UK) intended as a temporary scaffold for a partial meniscal defect. The first module tested the ability of the scaffold to carry load in an in vitro model designed to measure the change in normal contact stress magnitude and contact area on the tibial plateau of cadaveric knees after scaffold implantation. This model was designed to give us confidence that the scaffold could carry load under physiological loading conditions [6]. The second module assessed the frictional coefficient of the scaffold against cartilage. This was performed in an in vitro model designed to measure the frictional characteristics of the scaffold against cartilage, immediately after implantation. This model was designed to test the likelihood that the scaffold would destructively abrade against articular cartilage in vivo [12]. The third module consisted of an assessment of functional performance in vivo. An in vivo model was designed to measure the structure and composition of articular cartilage across the tibial plateau 12 months after scaffold implantation. Our goal was to understand if the two in vitro test models predicted the in vivo response of the knee joint to the scaffold [24].

The ability of the scaffold to carry load was tested on a load controlled Instron-Stanmore KCI Knee Joint Simulator (University College London, Middlesex, UK) that was adapted to accept cadaveric ovine knees (in vivo animal model of choice). The simulator was chosen because of the ability to program and dynamically control the axial force, anterior and posterior force, and rotational moment (internal/external torque), as a function of flexion angle towards simulating activities of gait and stair climbing. By combining this technology with a Tekscan piezoelectric sensor

(4,010 N; Tekscan, South Boston, MA, USA) located underneath the meniscus and attached to the tibial plateau, a measurement of the normal contact stresses during gait was enabled. Six ovine knees were subjected to loads and flexion–extension profiles corresponding to that experienced in the ovine knee joint during gait [30]. The effect of injury (in this case a partial meniscectomy) and repair (in this case via scaffold implantation) on the joint contact stresses transmitted to the tibial plateau were assessed [6].

To study the frictional coefficient of the scaffold against cartilage, an apparatus was designed to measure the coefficient of friction of two materials which articulate against each other over a range of velocities to simulate a range of boundary conditions. In brief, the apparatus consists of a biaxial load cell to simultaneously measure frictional shear forces and compressive axial loads, while a variable-speed oscillating table is programmed to control the relative speed of the two materials. The test apparatus was used to measure the frictional coefficients of two groups of materials, which included calf cartilage discs articulated against a candidate scaffold and calf cartilage discs articulated against polished stainless steel, to simulate conditions of a hemi-arthroplasty [12]. Equine synovial fluid (ESF) from the stifle joints of three skeletally mature horses (ages 3–5 years) was used as lubricant.

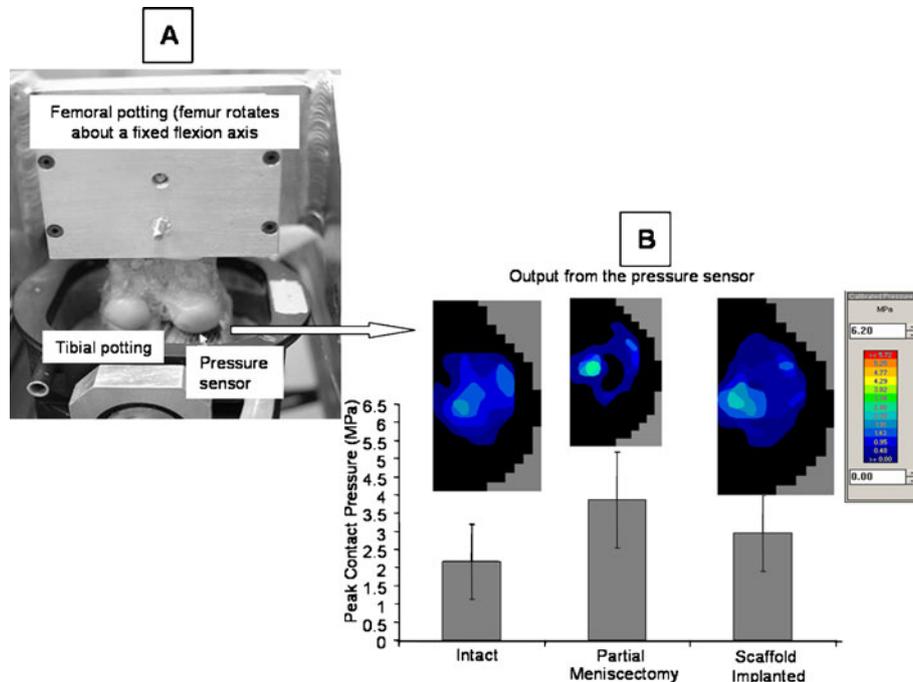
Functional performance in vivo was studied in 12 skeletally mature Columbia×Rambouillet ewes subjected to unilateral partial excision (50% the AP length of the native tissue to within 1 mm of the capsule) of the lateral meniscus. In four animals, the defect was left unfilled. A precontoured biodegradable aliphatic polyurethane scaffold with a porosity of 80% and pores ranging in size from 150 μm to 355 μm (Actifit™; Orteq) was used to fill the

defect site in the remaining eight animals and attached to the meniscus using three horizontal mattress 3-0 Ethibond sutures [24]. All animals were euthanized at 12 months, at which point the knees were assessed by magnetic resonance (MR) imaging using a previously validated cartilage-sensitive fast spin echo sequence to assess cartilage morphology [17], as well as quantitative T2 mapping to assess the collagen orientation and T1rho to assess proteoglycan distribution [34].

Joint contact stress data were analyzed using repeated measures ANOVA with post hoc contrasts; the type I error rate (alpha) was set at 0.05. Mann–Whitney tests were used to assess the coefficient of friction data, and differences in T1 and T2rho values were assessed using Student’s *t* tests, with an alpha of 0.05.

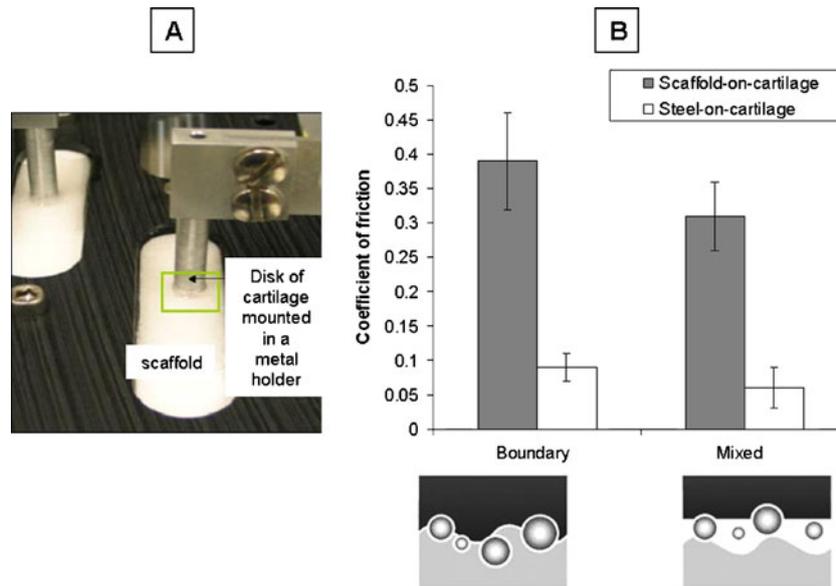
**Results**

Our in vitro tests demonstrated that a partial meniscectomy extending to 50% of the length of the native meniscus in the sheep knee led to a significant increase in joint contact stress close to the mid-line of the joint. The increase in contact stress as measured in vitro led to cartilage degeneration in vivo in the form of fibrillation, proteoglycan loss, and collagen breakdown in that zone. The relatively high coefficient of friction between the scaffold and articular cartilage as measured experimentally did not result in articular cartilage damage in vivo; this was likely influenced by the fact that abundant tissue was generated within the scaffold and unexpected tissue also regenerated within the site of the



**Fig. 1.** a The experimental apparatus used to measure the distribution of load across the tibial plateau of sheep knees is demonstrated in this photograph. b Representative images of the contact stress distribution

across the tibial plateau for each condition are illustrated. The effect of meniscal manipulation on the peak joint contact stresses across the tibial plateau is shown



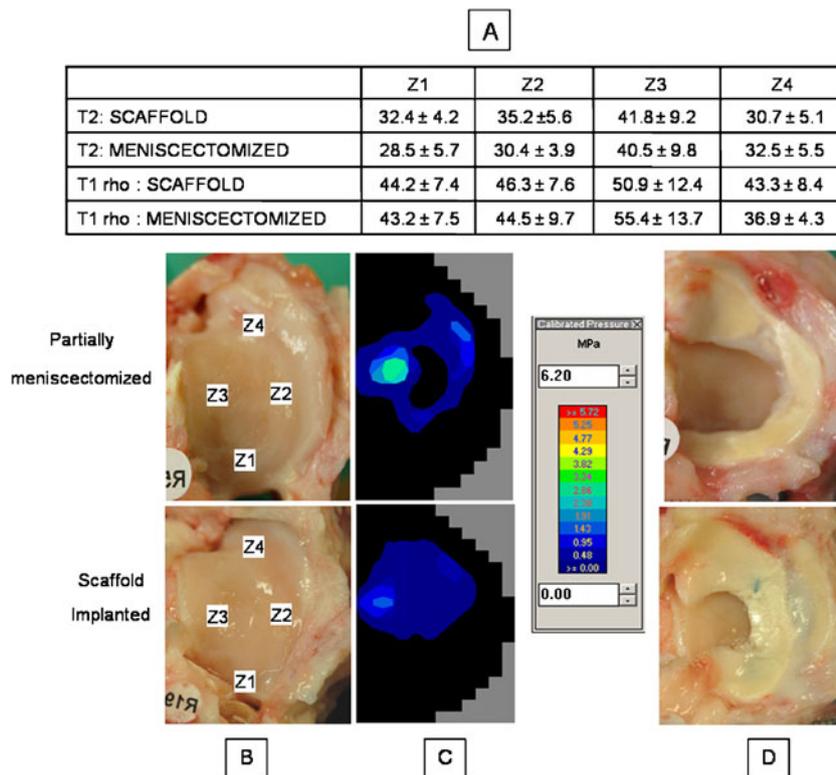
**Fig. 2.** **a** The experimental apparatus used to measure the coefficient of friction between articular cartilage and the scaffold is shown in this photograph. **b** This graph displays the coefficient of friction values as

measured for boundary and mixed mode lubrication where boundary lubrication is achieved at slow speeds and mixed mode lubrication is achieved at higher speeds

partial meniscectomy at 12 months. Our results suggest the need to include temporal effects in our in vitro models.

The tibial plateau mounted pressure sensor (Fig. 1a) indicated that while the intact knee manifested a wide area of contact across the tibial plateau, no contact was detectable

under the site of the lateral partial meniscectomy. Thus, the contact area was decreased and joint contact stress significantly increased adjacent to the defect site increase by 1.9 MPa ( $p=0.01$ ). Scaffold implantation facilitated a more even distribution of contact across the tibial plateau, with a



**Fig. 3.** Representative images of knees from both groups are shown illustrating the **a** distribution of T2 and T1rho values across the four zones for the tibial plateaus of each group. **b** Gross photographs of representative tibial plateaus are included and the zones used for MRI

analysis are labeled. **c** The representative contact stress distributions for each condition are depicted. **d** These photographs show the gross appearance of knees with the menisci intact

contact stress that was lower ( $p=0.01$ ) than that of the partially meniscectomized condition (Fig. 1b). These data suggest that even at time zero, without cell ingress or tissue ingrowth, the scaffold might function to carry and distribute loads across the tibial plateau much in the way of the native tissue.

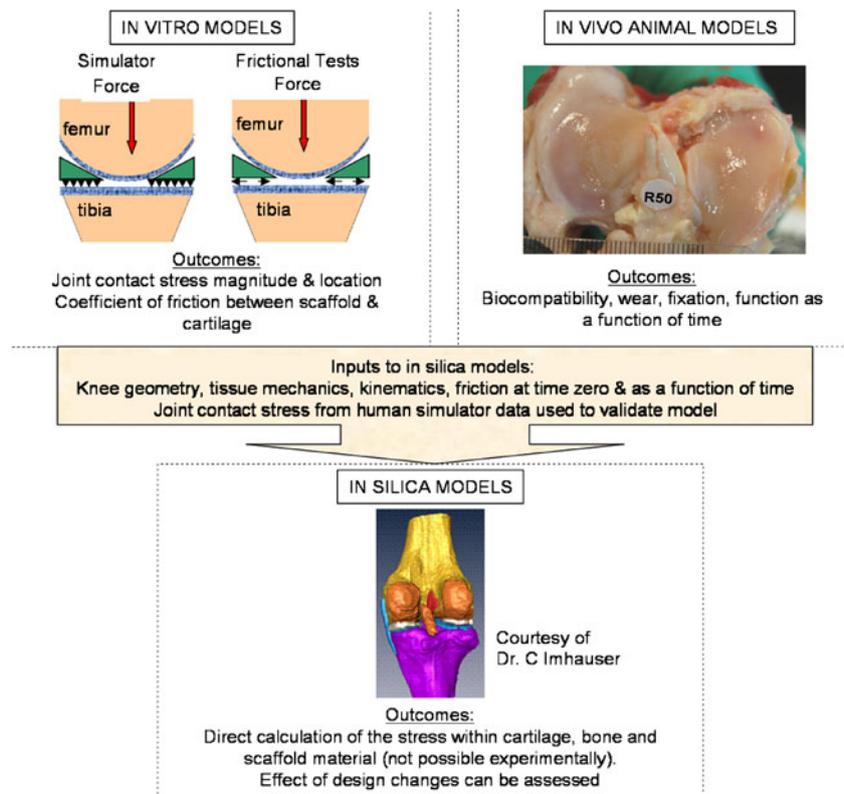
The coefficient of friction was higher (3–5-fold;  $p=0.01$ ) for the scaffold against cartilage (Fig. 2a) than for stainless steel against cartilage at all applied strains and entraining speeds (Fig. 2b). This data suggests that at time zero the scaffold might detrimentally abrade against the cartilage.

MR imaging revealed damage to the extracellular matrix of articular cartilage over the central weight-bearing area of the lateral tibial plateau in both groups. Disruption of the normally high-ordered collagen (increased T2 values) and diminished proteoglycan content (increased T1rho values) were seen (Fig. 3a). This area (zone 3) corresponded to the region close to the mid-line of the joint (Fig. 3b) in which an increase in joint contact stress was seen in the experimental model at time zero (Fig. 3c). No significant differences were found in the T2 or T1rho values for any zone between the scaffold implanted and non-scaffold implanted groups ( $p>0.1$ ).

### Discussion

The ability of the native meniscus to distribute loads across the cartilage of the knee joint is its defining functional

characteristic. A requirement of any material intended to replace or repair the meniscus is that it should restore the load-carrying ability to the damaged site and prevent damage to the cartilage with which it articulates. However, there are no pre-clinical test models with which to evaluate the functional properties of candidate materials for meniscal repair or replacement. The goal of this study was to consolidate a suite of in vitro and in vivo test modules into a pre-clinical test platform to assess the functional performance of scaffolds intended to replace a damaged meniscus. The functional parameters assessed were the ability of a scaffold to carry load without detrimentally abrading against articular cartilage. The tests were applied to evaluate a porous polyurethane degradable scaffold (Actifit™; Orteq) intended for implantation into a partial meniscal defect. Our in vitro tests demonstrated that a partial meniscectomy extending to 50% of the length of the native meniscus in the sheep knee led to a significant increase in joint contact stress close to the mid-line of the joint. The increase in contact stress as measured in vitro led to cartilage degeneration in vivo in the form of fibrillation, proteoglycan loss, and collagen breakdown in that zone. The experimental in vitro finding that implantation of the scaffold significantly decreased the contact stresses on the tibial plateau relative to the partially meniscectomized knee suggested that, in vivo, less damage would be seen in the scaffold implanted knees. This was not born out in vivo, which demonstrated no significant difference in the condition of cartilage in that zone between the two groups. Furthermore, the high coefficient of friction between the scaffold and



**Fig. 4.** This figure provides a pre-clinical test platform for the functional evaluation of meniscal scaffolds. The platform consists of in vitro experimental tests and in vivo animal models upon which validated in silica computational models are built

articular cartilage as measured experimentally did not result in articular cartilage damage. This was likely influenced by the fact that abundant tissue was generated within the scaffold and unexpected tissue also regenerated within the site of the partial meniscectomy at 12 months (Fig. 3d).

Our models had their limitations. We specifically chose the ovine model for this study, realizing that controversy surrounds the optimal animal model for the *in vivo* evaluation of meniscal scaffolds [3, 7]. The sheep model was chosen because it has been previously used to evaluate meniscal repair and regeneration technology [8, 9]. The mechanical properties of its meniscus are similar to that of the human meniscus and the contact stresses transmitted to the tibial plateau are within the range of that of human knees [6]. However, the tissue ingrowth that occurred in the empty meniscal defect group raises concern about the suitability of using a partial meniscectomy as a control in the ovine model.

Our experimental *in vitro* model to assess meniscal load carrying ability is unique in that it allows for the application of multi-directional physiological loads, a significant improvement over the static and quasi-static loads under which knee joint loading is typically assessed [1, 2, 5, 20]. The input loading profile was designed to match ovine knee gait loads thereby allowing for a direct link between the *in vitro* and *in vivo* results. By measuring the peak contact stress and contact area on the tibial plateau, our intent was to understand if implantation of a candidate material could restore the stress distribution (hence load-carrying ability) of the meniscus to that of the native tissue and thereby avoid articular cartilage degeneration. The experimental *in vitro* finding that implantation of the scaffold significantly decreased the contact stresses on the tibial plateau relative to the partially meniscectomized knee suggested that, *in vivo*, less damage would be seen in the scaffold implanted knees. This was not born out in the *in vivo* model, which demonstrated no significant difference in the condition of cartilage in that zone between the two groups. Furthermore, the *in vitro* measure of the frictional characteristics between the scaffold and cartilage suggested that cartilage damage may occur *in vivo*. Again, this was not the case. There was little or no damage in the cartilage immediately beneath the scaffold. The discrepancy between the outcome measured of the *in vitro* and *in vivo* models was caused by the robust matrix generation within the scaffold and within the site of the partial meniscectomy (which was unexpected) over time. To truly use our tests as effective pre-clinical evaluation tools, the temporal changes in the knee, scaffold degradation, cell migration, and matrix generation should ideally be included. To address this need, we have started to measure the load-carrying ability and frictional characteristics of scaffold implanted knees post-sacrifice. For example, by quantifying the frictional characteristics of the scaffold after 3 months of *in vivo* implantation, we found that the frictional characteristics of the scaffold approach that of the native tissue [12], further emphasizing the need to include temporal effects in any pre-clinical model.

Ultimately, our goal is to use this pre-clinical platform as a scaffold design tool. To this end, the knee joint simulator

has recently been further modified to allow for the effect of meniscal manipulation on knee joint contact stress distribution across *human knees*. This modification will ultimately allow for outputs from the *in vitro* and *in vivo* models to be combined and used for the creation of an *in silico* finite element model (FEM), which can more readily be used to understand the effect of scaffold implantation on the functional performance of the joint (Fig. 4). The *in silico* model of choice, a computational FEM, allows the user to define inputs—geometry, material properties, applied loads, constraints—and to understand what effect those inputs have on outputs—in the form of contact stress in the joint, and stress distribution within the cartilage and underlying bone, which cannot be measured experimentally. This concept is not new; FEMs have been used to understand the effects of native tissue structural and material properties on the functional performance of the knee joint [13, 32], but often simplify the complex mechanics of the soft tissue structures and do not mimic physiological activities, thereby limiting the clinical relevance of the data generated. Our goal is to experimentally validate a physiological model, which incorporates the viscoelastic biphasic behavior of the soft tissues and employs physiological loading conditions. Given the complexity of such models, and the wide range of possible input parameters (scaffold modulus, anisotropy, geometry, fixation, activity, and percent knee flexion), the diversity of modeling conditions needed to map the entire input–output space is computationally prohibitive. Statistically based predictors can be used to increase the computational efficiency of this process by identifying those variables that have the greatest impact on the model outputs. These statistical methods can be used to target the computational runs required to map the design space, thereby saving both resources and time, and have been used recently to understand the factors that affect the performance of hip resurfacing [23].

In summary, by combining *in vitro* measures of the load-distribution and frictional characteristics of candidate materials for meniscal repair and replacement and combining it with an *in vivo* assessment of cartilage “health”, we have demonstrated an ability to assess the functional performance of candidate materials for meniscal replacement. It is our intent to augment this suite of tests with models that can assess the temporal changes that occur in the scaffold *in vivo*, but ultimately with the help of statistically driven computational modeling we will systematically evaluate and optimize implants and scaffolds intended for meniscal replacement/repair. With our unique approach, we hope to facilitate the translation of novel technologies into clinical use to provide functional solutions for the estimated 850,000 patients for whom meniscal surgery is carried out annually [28].

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