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BST-CarGel: In Situ ChondroInduction for Cartilage Repair

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The repair of articular cartilage has posed a longstanding orthopedic challenge. The concept of marrow stimulation is basically the intentional injury of a subchondral bone below a cartilage lesion to elicit a wound repair response. However, the desire to fill the lesion with a blood clot is at odds with platelet-driven clot retraction, which results in clot shrinkage and detachment. Therefore, BST-CarGel was developed to produce a physically stabilized blood clot that is more voluminous and adherent within a debrided cartilage lesion having access to bone marrow, thus improving existing bone marrow-stimulation procedures. BST-CarGel is a soluble polymer scaffold containing the polysaccharide chitosan, which is dispersed throughout uncoagulated whole blood, and then delivered to a surgically prepared lesion. BST-CarGel allows normal clot formation, reinforces the clot, impedes retraction, increases adhesivity, and ensures prolonged residency of both the clot and critical tissue repair factors from blood. In animals, BST-CarGel was shown to increase the volume and hyaline character of repair tissue, with increased GAG and collagen content, compared with microfracture controls. A patient cohort received BST-CarGel treatment, which encompassed the spectrum of traumatic to degenerative lesions, along with other joint pathologies. Anecdotal evidence demonstrated the potential of BST-CarGel for treating focal cartilage lesions of variable etiology through both mini-open and arthroscopic approaches. Because it requires only a single minimally invasive intervention, BST-CarGel and its unique characteristics are novel in orthopedics. In addition, its use with marrow stimulation provides familiarity with well-recognized surgical techniques, bringing a simple-yet-versatile treatment modality that applies scaffold-guided regenerative medicine to a potentially wide-ranging group of indications.

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Keywords cartilage repair, implant, arthroscopy, scaffold
eral fall into 3 areas: (1) those that use cells or tissue implantation,1-4 (2) those that use cartilage and/or bone grafts,5-6 and (3) those that attempt to elicit a healing response from the underlying bone through bone marrow stimulation, including abrasion arthroplasty, Pride drilling, and microfracture.7-9 Historically, proponents of these techniques, whether they be autologous chondrocyte implantation, osteochondral grafting (either autologous or allogeneic), or bone marrow stimulation, have all claimed reasonable clinical success. Nonetheless, it is evident in the sometimes-contradictory or ambiguous nature of the clinical cartilage repair literature that there is a need for more widespread use of randomized clinical trials to help elucidate differences in efficacy. Indeed, recent reviews of the current state of cartilage repair have identified neither a method for obtaining hyaline cartilage reproducibly nor a clinically significant difference between current treatment modalities. This ambiguity is possibly the result of the low methodological quality of most published clinical studies.10,11

Besides the obvious advantages of low cost and a simple arthroscopic approach, bone marrow stimulation is a very logical act of intentionally penetrating subchondral bone below a cartilage lesion to elicit the traditional wound response and tissue repair found in most vascularized tissues of the body. A number of animal and clinical studies have clearly demonstrated that injured subchondral bone has an intrinsic ability to mount a repair response, albeit one that produces fibrocartilaginous tissue lacking hyaline articular structure and reproducibility. The use of an equine model using abrasion12 and drilled rabbit trochleas13-17 has suggested that the mechanism underlying this reparative process is initiated by bleeding in the subchondral space, followed by proliferation and migration of inflammatory and stromal cells from the cancellous marrow into a fibrin clot. This gives way to the development of a vascularized provisional and cellular granulation tissue, bone remodeling, and subsequent cartilage formation through an endochondral-like process.

However, the desire of surgeons during surgery to fill the lesion with a blood clot to promote wound repair is at odds with the well-known platelet-driven retraction of blood clots,18 which ultimately results in clot shrinkage and detachment from lesion surfaces. Consequently, these compact blood clots are poorly adherent and often are associated with the lesion only at or within the sites of bleeding, such as microfracture or drill holes, and abraded surfaces.13,17,19-21 Although bone marrow stimulation has been shown in some cases to result in a hyaline-like articular surface, the highly variable outcomes obtained in both animal and human studies strongly suggest that a critical aspect to control in bone marrow-derived cartilage repair is the quantity and quality of the initial blood clot present in the cartilage lesion. A stable blood clot that is more voluminous and adherent within a meticulously debrided cartilage lesion could thus improve existing bone marrow-stimulation procedures.

**BST-CarGel Blood Clot**

BST-CarGel was developed to stabilize the blood clot in the cartilage lesion by dispersing a soluble and adhesive polymer scaffold containing chitosan throughout uncoagulated whole blood. Chitosan, a cationic linear polysaccharide composed predominately of polyglucosamine, is derived from the deacetylation of chitin, the structural component of crustacean shells. Because of its abundance and biomaterial attributes, such as low toxicity and biocompatibility, biodegradability, and adhesivity to tissues, chitosan has been researched extensively for biomedical applications.22-24 By dissolving chitosan in an aqueous glycerol phosphate buffer,25 BST-CarGel is uniquely obtained as a liquid chitosan solution having physiological pH and osmolarity, intrinsic cytocompatibility, and biodegradability. When mixed with blood (BST-CarGel:blood ratio of 1:3), BST-CarGel allows normal clot formation while simultaneously reinforcing the clot and impeding clot retraction. This is a characteristic specific to BST-CarGel/blood mixtures and not found with other polysaccharides, including hyaluronic acid. Furthermore, the cationic nature of the chitosan increases the adhesivity of the mixture to cartilage lesions, ensuring longer clot residency. This maintenance of critical blood components above the marrow access holes allows activation of the tissue repair process.26 BST-CarGel/blood mixtures solidify in situ within approximately 10 minutes.26,27

**BST-CarGel Surgical Technique**

BST-CarGel is applied as a mixture of BST-CarGel and whole blood to a lesion that has already been debrided and treated with bone marrow stimulation (eg, microfracture). The surgical technique for BST-CarGel consists of 3 steps: (1) preparation of the lesion through careful debridement and bone marrow stimulation, (2) preparation of the BST-CarGel/blood mixture, and (3) delivery of the BST-CarGel/blood mixture to the lesion. Depending on the size and location of the lesion, as well as preference or best judgment of the surgeon, a mini-open or arthroscopic approach can be used. Strict adherence to the surgical technique described herein is critical, particularly for the lesion preparation, which has a direct impact on the success of implant residency as well as subsequent regenerative processes.

**Lesion Preparation**

Lesion preparation should be performed arthroscopically. During setup, a nonactive tourniquet should be put in place to later inhibit soft-tissue bleeding during the interval between BST-CarGel delivery and implant solidification. After determining the limits of the lesion, rough or loose articular cartilage should be removed manually using a curette (motorized burrs are not encouraged). The prepared lesion should be further debrided such that it contains sharp vertical walls that will serve to confine the BST-CarGel mixture. Limits for debridement of traumatic lesions are more obvious, but degenerative lesions typically require radical debridement of all fissured and degenerated cartilage surround-
ing the exposed bone out to healthy contained cartilage. It is therefore better to leave a minimally chondromalacic cartilage border in a degenerative lesion than to debride it so extensively that an uncontained lesion is generated that does not hold the BST-CarGel mixture adequately.

If the calcified cartilage layer is intact, it should be lightly scraped and entirely removed—a critical step considering that both noncalcified and calcified cartilage act as barriers to marrow-derived repair. Because true visualization of the calcified cartilage is normally impossible, tactile differences that are felt between the layer and the bone should guide the debridement. Care must be taken, however, to avoid excessive debridement (ie, uniform and easily observed punctuate bleeding in the base of the defect) because excessive damage to the subchondral bone plate can result in lack of bone repair, bone resorption, or subchondral cysts and, ultimately, poor clinical outcome, as in abrasion arthroplasty that was performed too aggressively. No cartilage tags or islands should remain so that the underlying subchondral bone is uniformly exposed but left structurally intact. In the case in which microfracture is used for bone marrow stimulation, holes 2- to 4-mm deep should be made evenly spaced around 3 to 4 mm apart, taking care not to break the bone between holes. Uniform distribution of holes is critical and, therefore, it is preferred to begin with microfracture holes around the periphery of the lesion, followed by evenly spaced holes that fill the center of the lesion. Peripheral holes should be close enough to the walls of the defect to promote good repair tissue integration, but not so near to the defect edge as to allow cartilage flow from the vertical walls to cover and block the hole openings. Furthermore, overall hole density (holes/cm²) should be maximized. When arthroscopic fluid pressure is reduced, bleeding and fat droplets should be seen emanating from the microfracture holes. After microfracture, a shaver should be used to remove loose bodies and bone fragments, which may block holes, and to smooth any frayed edges. The lesion should be fully readied to receive the implant before preparing the BST-CarGel/blood mixture, including preparation of the mini-arthrotomy site or draining the knee of arthroscopic fluid depending on the surgical route of application, and leg positioning as described in the section “BST-CarGel Delivery.”

**BST-CarGel Delivery**

BST-CarGel can be applied via arthroscopy or mini-open surgical techniques. However, current practice with BST-CarGel delivery requires that the knee be positioned such that the lesion is horizontal. For example, a condylar lesion will require the knee to be at a 90° angle, with the femur in the vertical plane. Typically, the leg is immobilized with the use of a leg holder or foot brace attached to the operating table (Fig. 1). Lesion preparation and leg positioning should be performed before preparing the BST-CarGel mixture. To overcome the positioning requirement, the development of a device that allows delivery to lesions at any angle is ongoing. After delivery, the BST-CarGel/blood implant solidifies during an obligatory 15-minute waiting period, after which the leg is carefully straightened. Here, minimal manipulation of the knee and leg is essential to give the BST-CarGel/blood clot the optimal conditions for residency. Once straightened and wrapped, a soft immobilizer is positioned over the knee before moving the patient.

**Miniopen Surgical Technique**

The BST-CarGel open surgical technique includes a miniarthrotomy to facilitate visualization of the lesion and delivery of BST-CarGel. The dimensions and location of the incision depend on the size and location of the lesion: a medial parapatellar incision for a medial compartment lesion and a lateral parapatellar incision for a lateral compartment lesion. Retractors are used to gain visual access and to prevent soft-tissue impingement into the lesion. Further lesion cleanup or additional bone marrow stimulation also can be performed with the open technique, if desired. The tourniquet should then be activated, the knee fully suctioned of perfusion liquid and blood, and the lesion swabbed with gauze in an attempt to create a “dry field” before applying the BST-CarGel/blood mixture. Appropriate methods to arrest bleeding and weeping of serum into the surgical site from the surrounding soft tissues should be used, such as cautering or lining exposed fascia with gauze. After receiving the syringe, the surgeon quickly applies the BST-CarGel/blood mixture in a controlled drop-wise manner over all of the bone marrow access holes and then into the entire lesion, being sure not to overfill (Fig. 2). After the 15-minute solidification period, the incisions should be closed using standard suturing techniques.

**Arthroscopic Surgical Technique**

Arthroscopic delivery to lesions is feasible when the entire lesion can be observed within the arthroscopic field of view. The aforementioned delivery device in development will address delivery to larger lesions. Once the lesion is prepared and microfractured, the joint and lesion are fully suctioned of perfusion liquid and blood to create a “dry field” in the lesion before BST-CarGel application. A metal probe can be used in

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**Figure 1** BST-CarGel treatment currently requires horizontal lesion positioning. The leg is positioned and immobilized using a leg holder or foot brace attached to the operating table. Lesion preparation and leg positioning should be performed before preparing the BST-CarGel mixture and should be maintained for 15 minutes after the delivery of the implant, without movement.
one portal to hold synovial tissue away from the lesion surface. Next, it is necessary to position the delivery needle (without yet attaching the syringe with BST-CarGel/blood mixture) directly perpendicular and central to the lesion so it is visible in the arthroscope before mixing the BST-CarGel and blood, to eliminate possible positioning delays. When the surgeon receives the syringe, it is then attached to the needle and the BST-CarGel/blood mixture is delivered in a drop-wise fashion, being sure not to overfill. After the 15-minute solidification period, the portals are closed using standard suturing techniques.

**Preparation of BST-CarGel/Blood Mixture**

When the lesion is prepared, the anesthetist draws at least 5 mL of peripheral blood from the patient’s arm (or other accessible vasculature) into a 5-mL plastic syringe. Larger syringes are not recommended as they lack necessary volume gradations. The top of the BST-CarGel mixing vial is wiped with an alcohol swab by a gloved nonsterile nurse, who then inserts a vented sterile pin (provided with BST-CarGel) by twisting through the vial’s rubber septum. Once the blood-filled syringe is received, the nonsterile nurse attaches the syringe to the pin and injects exactly 4.5 mL of blood slowly into the vial. The vial, which contains 6 small mixing beads, is immediately shaken vigorously by hand for 10 seconds. After the top of the mixing vial is again wiped with an alcohol swab, it is presented to the scrub nurse, who inserts a new sterile dispensing pin which has been preattached to a 3-mL sterile syringe, and who slowly draws 2 mL of BST-CarGel/blood mixture. For miniopen delivery, this nurse then replaces the dispensing pin on the syringe with an 18-gauge needle, and immediately gives the syringe to the surgeon. For arthroscopic delivery, the dispensing pin is removed and only the syringe is given to the surgeon, since the delivery needle has already been positioned arthroscopically. This sequence of events has been designed to optimize outcomes and must be respected and performed efficiently.

There may be additional points to consider in BST-CarGel use. Current clinical research is ongoing to understand their importance:

- Because of the nature of the BST-CarGel interactions with blood, patients must discontinue the use of aspirin and antiinflammatory medications at least 7 days before treatment. Patients should not resume use for at least 24 hours after treatment.
- The BST-CarGel/blood mixture should be delivered over individual bone marrow stimulation channels (ie, microfracture holes) first, and then over the remaining lesion.
- Overfilling of the lesion with the BST-CarGel/blood mixture may cause leakage or wicking action resulting in loss of implant material. It is recommended that the lesion be filled to ‘just under full’, to prevent loss of implant.
- After the 15-minute solidification period, minimal manipulation of the knee and leg is essential during closing, cleaning, and wrapping. The leg should be straightened in only one motion, ensuring optimal conditions for residency of the BST-CarGel/blood clot.
Rehabilitation

The rehabilitation program for BST-CarGel is currently being implemented and studied in the context of a multicenter clinical trial. BST-CarGel patients engage in nonweight-bearing activity with use of crutches for 6 weeks, followed by progressive weight-bearing activities beginning with touchdown and increasing weekly to 100% at 8 to 9 weeks after surgery. It is recommended that patients continue use of the soft immobilizer continuously for the first 24 hours after surgery, and then for the next 2 weeks during all movement with crutches and at night. This serves to protect the treated leg from sudden articulation or unexpected shocks. The BST-CarGel implant is vulnerable to sudden excessive forces, especially in the early phase when the implant is not as mechanically stable as the adjacent cartilage surfaces. Gradual loading also may protect the new repair tissue during cartilage and subchondral bone maturation and integration, especially for larger or degenerative lesions with more exposure to load. Assisted passive motion begins immediately and during the first week targeting 5° to 35° knee flexion, and increasing in following weeks. During this time, neuromuscular stimulation of quadriceps is applied and continued until active contraction is tolerated. On reaching appropriate range of motion (~110°), the patient can use a stationery bike, with assistance from his or her healthy leg. Closed chain kinetic-strengthening exercises begin at week 9. Each patient’s progress should be individualized and guided by symptoms. Return to high-impact sports or activities requiring pivoting should not be attempted for at least 12 months.

BST-CarGel Results

Animal Studies

The efficacy and underlying mechanisms of action of BST-CarGel have been examined in several animal studies and reviewed in the literature.37 Some authors used a skeletally mature (8- to 15-month old) rabbit model using drilling of surgically prepared bilateral trochlear defects elucidated BST-CarGel early reparative events and compared them with drilled controls.127 Table 1 summarizes the key findings describing how BST-CarGel mediates cartilage repair.

In another large study in adult (3- to 6-year old) sheep, the authors used microfractures in surgically prepared 1-cm² condylar and trochlear defects to investigate the quantity and quality of BST-CarGel repair tissue after 6 months compared with microfracture-only defects.20 Table 2 summarizes the efficacy of BST-CarGel treatment for cartilage repair.

As an example of the type of cartilage repair that can be achieved with BST-CarGel treatment (Fig. 4; Safranin-O/Fast Green stained section) shows a best case repair that was found in a large animal condylar lesion treated with BST-CarGel. After 6 months of repair, a relatively mature articular cartilage was observed containing superficial (SZ) transitional (TZ), and radial (RZ) zones with a reestablished tidemark (TM) above an actively remodeling bone bed. To our knowledge, such a high resemblance of repair tissue to true hyaline articular cartilage found here with BST-CarGel treat-
ment has not been previously reported with any other treatment in a skeletonally mature adult animal model.37

Interestingly, it was found that the individual mechanisms underlying BST-CarGel modulated repair were evident with both drilling and microfracture and were independent of species; they have been observed in rabbit,13,27 sheep,20 and horse (unpublished data). Given the uniqueness of these findings, we have coined this repair of cartilage as in situ chondroInduction (ICI), occurring with a technique termed scaffold-guided regenerative medicine (SGRM).

Clinical Experience
Thirty-three human subjects were treated with BST-CarGel from August 2003 to December 2004 under Health Canada’s Special Access Program for medical devices that is designed to enable compassionate use. Notably, treatment occurred on a case-by-case basis and, by law, was not considered a clinical study. In particular, the absence of a control group as well as the wide ranging characteristics of the treated patients and lesions impedes a rigorous interpretation of outcomes.

Treated patients encompassed the spectrum of both traumatic and degenerative lesions, along with other pathologies, where lesions ranged in size from 0.5 to 12 cm² with a mean area of 4.3 cm² for both men and women (Table 3). In 16 cases, opposing tibial lesions (kissing lesions) were debrided and treated with microfracture only. One case of osteochondritis dissecans and one exposed subchondral cyst were treated. Because knee stability is critical for effective cartilage repair, concomitant anterior cruciate ligament replacement with the artificial Ligament Augmentation and Reconstruction System (ie, LARS, Dijon, France) ligaments preceded treatment with BST-CarGel in 2 patients. BST-CarGel was delivered by arthroscopy for 22 patients and by miniarthrotomy for 11 patients.

All patients were directly observed for 24 hours postoperatively, and 31 of 33 patients chose to remain in a private clinic for 5 days, which facilitated observation and physiotherapy. Physiotherapy was conducted as described in the section “Rehabilitation.” Safety was assessed through general exams, knee-related medical examinations, and blood analyses. In addition, Western Ontario McMaster (WOMAC) Osteoarthritis Index38 questionnaires were administered preoperatively and again postoperatively after 3, 6, and 12 months. Incomplete patient participation led to partial data at each time point.

The safety of treatment with BST-CarGel was demonstrated because no uncharacteristic observations were made during physical examinations or blood analyses for all patients. At 12 months postoperatively, WOMAC scores for pain, stiffness, and function improved compared with preoperative baseline scores in BST-CarGel-treated patients (Fig. 5). Although recognized as anecdotal and short-term, the uniformity of the WOMAC data suggests a clinical benefit arising from BST-CarGel treatment. BST-CarGel is currently the subject of a prospective, randomized, multicenter clinical trial in Canada comparing BST-CarGel to microfracture alone in the treatment of cartilage lesions on the medial femoral condyle in 80 subjects.

Potential Indications
BST-CarGel has not been approved at this time for sale in any country. Therefore, recommendations for potential indications or contraindications described here have not been approved by regulatory agencies.

From the current understanding of BST-CarGel derived from the animal and human experience described herein, the potential indications for BST-CarGel appear to be currently limited to localized or focal damage. Determining suitability for BST-CarGel treatment in the future will be determined by lesion grade (depth), location, size as well as the status of the opposing chondral surface. Traumatic cartilage damage and focal damage resulting from degenerative processes are considered potential indications for BST-CarGel, the latter representing a large symptomatic patient population who are considered too young for total-knee replacement. Furthermore, the mechanistic evidence from animal data has shown that BST-CarGel has a reproducible and positive effect on subchondral bone remodeling,13,27 suggesting that cartilage loss emanating from subchondral bone pathologies, such as osteochondritis dissecans or cysts, may be addressed through BST-CarGel treatment. A summary of potential indications is shown in Table 4.

The presence of coexisting pathology that may adversely affect BST-CarGel-mediated repair must be addressed before or concomitantly with the application of BST-CarGel, including ligamentous instability, tibiofemoral malalignment, bone deficiency, patellofemoral malalignment, and meniscal pathology.

The future use of ICI and the SGRM approach also can be envisioned in other joints in which chondral and osteochondral lesions are extensively found. Lesions in the ankle and shoulder joints might additionally be suitable for BST-CarGel.

Table 3 BST-CarGel Clinical Experience: Characteristics and Indications of Treated Patients*

<table>
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<th>Gender</th>
<th>n</th>
<th>Average Age, Years (Mean ± SD, range)</th>
<th>Average Femoral Condyle Lesion Size, cm² (Mean ± SD, Range)</th>
<th>Tibia†</th>
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<tr>
<td>M</td>
<td>22</td>
<td>53.2 ± 9.8 (35-70)</td>
<td>4.3 ± 3.3 (0.5-12)</td>
<td>10</td>
</tr>
<tr>
<td>F</td>
<td>11</td>
<td>55.0 ± 9.1 (44-66)</td>
<td>4.3 ± 2.8 (0.5-8.75)</td>
<td>6</td>
</tr>
</tbody>
</table>

*Not a clinical study. Permission was granted by Health Canada on a case-by-case basis under the Special Access Program for medical devices.
†Number with concomitant tibial lesion that was treated with microfracture-only

<table>
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<tr>
<th>Lesion Size, cm²</th>
<th>Tibia†</th>
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<tr>
<td>M 22 53.2</td>
<td>10</td>
</tr>
<tr>
<td>F 11 55.0</td>
<td>6</td>
</tr>
<tr>
<td>F 11 55.0</td>
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therapy because of the pathological similarities and their arthroscopic accessibility.

**Conclusion**

BST-CarGel is a cartilage resurfacing treatment that initiates and amplifies intrinsic wound healing processes in subchondral bone to produce improved cartilage repair through ICI. The unique characteristics of BST-CarGel, which include chitosan, a well-studied scaffold material and wound repair facilitator, bring novelty to the cartilage repair field, whereas the use of bone marrow stimulation provides a familiarity with a well-recognized family of techniques. Requiring only a single minimally invasive intervention, BST-CarGel represents a simple-yet-potentially-versatile treatment modality that applies SGRM to a wide-ranging group of indications.

**Acknowledgments**

Excellent technical assistance was provided by Drs. Evgeny Rossomacha and Anik Chevrier.

**Table 4 Potential BST-CarGel Indications***

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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<tbody>
<tr>
<td>Acute cartilage lesion</td>
<td>Contained focal, traumatic Grades 3 and 4</td>
</tr>
<tr>
<td>Chronic cartilage lesion</td>
<td>Contained focal, degenerative Grades 3 and 4, with bordering cartilage</td>
</tr>
<tr>
<td>Associated bone changes</td>
<td>Osteochondritis Dissecans Cysts</td>
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</tbody>
</table>

*Not approved by regulatory bodies or confirmed by clinical trials.

**References**


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