Evaluation of small-intestinal submucosa implants for repair of meniscal defects in dogs

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Objective—To assess the effects of porcine small intestinal submucosa (SIS) implants on the healing of meniscal lesions in dogs.

Animals—16 adult Greyhounds of both sexes.

Procedure—Unilateral osteotomy was performed at time 0 to disrupt the medial collateral ligament attachment, and two (1 cranial and 1 caudal) 4-mm circular defects were created in the avascular portion of the medial meniscus. One defect was filled with an SIS graft, and the other defect remained empty (control). Three months later, the identical procedure was performed on the contralateral limb. Three months after the second surgery, dogs were euthanatized, and meniscal tissue specimens from both stifle joints were collected for gross, histologic, biomechanical, and biochemical evaluations.

Results—Regenerative tissue was evident in 4 (2 SIS-implanted and 2 control) of 16 defects examined histologically. In 3 defects, this thin bridge of tissue was composed of immature haphazardly arranged fibrous connective tissue with a relatively uniform distribution of fibroblasts. Aggregate modulus, Poisson ratio, permeability, and shear modulus were not significantly different between control and SIS-implanted defects either 3 or 6 months after surgery. Hydroxyproline content also did not differ between SIS-implanted and control defects at 3 or 6 months.

Conclusions and Clinical Relevance—Implantation of porcine SIS into experimentally induced meniscal lesions in dogs did not promote tissue regeneration. (*Am J Vet Res* 2002;63:427–431)

Meniscal injury is a common secondary lesion in dogs with ruptured cruciate or collateral ligaments and is the most frequent injury in the knee joint of people.[1] Partial meniscectomy is usually performed to treat affected dogs and humans, and although less injurious than total meniscectomy, this procedure does induce degenerative changes in the articular surfaces of the femur and tibia.[2-4] The primary limiting factor to healing of meniscal lesions is an insufficient blood supply. The blood supply to the menisci arises from branches of the medial and lateral genicular arteries. Branches from these vessels supply the joint capsule, which in turn provides vessels to the peripheral aspect of the meniscus.[2,5] Arnoczky et al[5] has shown that these vessels only penetrate the peripheral 15 to 25% of the width of the menisci; the remaining inner aspects of the menisci are devoid of a blood supply. Unfortunately, meniscal injuries often involve the inner portion of the meniscus.[2]

Clinical alternatives to partial meniscectomy include the use of allografts and biological scaffolds.[1] Fresh-frozen and gamma-sterilized meniscal allografts have been used in humans, but their use carries the risk of immune-mediated inflammation.[1,6] An example of a biological scaffold is porcine **small-intestinal submucosa (SIS)**.[a] Small-intestinal submucosa is an acellular extracellular matrix material. When implanted as a biomaterial for tissue replacement, SIS induces site-specific tissue remodeling.[7] Porcine SIS has been used as graft material in cardiovascular, urologic, orthopedic, neurologic, dermatologic, reconstructive, and ophthalmologic applications.[8-28,b] In a previous study[23] of dogs with experimentally induced cranial cruciate ligament damage, implanted SIS grafts were replaced with large bundles of organized connective tissue covered by a synovial membrane. The tissue resembled the native cranial cruciate ligament, and there was no histologic evidence of an immune-mediated reaction to the graft material. Given the success of SIS as an intra-articular graft in that study, the objective of the study reported here was to determine the effects of porcine SIS implants on the healing of meniscal lesions in dogs.

Materials and Methods

Animals—All procedures were approved by the Auburn University Institutional Animal Care and Use Committee. Sixteen adult (2 to 3 years old) conditioned Greyhounds of both sexes were used for this study. Dogs were found to be healthy and free from orthopedic disease on the basis of results of CBC, serum biochemical analysis, urinalysis, occult *Dirofilaria immitis* tests, fecal analyses for parasites, serologic titers against *Ehrlichia* spp, complete physical and orthopedic examinations, and radiography of the stifle joints. Dogs were housed individually in runs and fed a commercially available maintenance diet.

Experimental design—Dogs were assigned a number (1 through 16). Surgery to create lesions in the medial meniscus of 1 stifle joint was performed at time 0. The operated side was chosen randomly. Three months later, the identical procedure was performed on the contralateral limb. Dogs were euthanatized with an overdose of pentobarbital 3 months after the second surgery (ie, 6 months after the first surgery). Thus, 6-month specimens were collected from the stifle joint that was operated at time 0, and 3-month specimens were collected from the joint operated at 3 months. Three surgeons (RDM, JAW, WRS) performed the procedures, and 32 stifle joints were evaluated. Joints from 6 dogs (dogs 3, 6, 7, 9, 11, and 13) were used for biomechanical testing, joints from another 6 dogs (dogs 2, 4, 12, 14, 15, and 16) were used for biochemical testing, and joints from the remaining 4 dogs (dogs 1, 5, 8, and 10) were used for histologic evaluation.

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Surgical procedure—On the day of each surgery, dogs were premedicated with buprenorphine (0.02 mg/kg, IM) and acepromazine (0.03 mg/kg, IM). Anesthesia was induced with thiopental (10 to 20 mg/kg, IV) and maintained with isoflurane delivered in oxygen. Prior to surgery, each dog received an epidural injection of preservative-free morphine (0.1 mg/kg) at the lumbosacral space. Using aseptic technique, a medial parapatellar approach was used to perform unilateral osteotomy of the medial collateral ligament attachment. Two 4-mm circular defects were created in the medial meniscus, 1 cranially and 1 caudally, using a dermal biopsy instrument.[c] The defects occupied the inner two thirds of the meniscus. One defect was filled with an SIS graft,[a] and the other defect remained void to serve as a control. The position of the SIS graft (cranial or caudal lesion) was chosen randomly.

Preparation of SIS implants—Sterilized SIS was provided as a multilaminate sheet of approximately 30 layers. A 4-mm biopsy punch was used to excise circular implants of SIS with dimensions identical to the meniscal defect. A single horizontal mattress suture of 5-0 prolene[d] was placed in the center of each SIS implant to stabilize its layers and to serve as a postmortem marker for the position of the implant. The SIS implants were placed within the defects and sutured to the periphery of the meniscus, using a single suture of 5-0 prolene in a mattress pattern.

Postoperative management—After each surgery, a soft padded bandage was applied to the affected stifle joint and changed daily. Dogs were treated with buprenorphine (0.02 mg/kg, IV or SQ, q 6 h) and acepromazine (0.03 mg/kg, IV or SQ, q 6 h) for 24 hours and carprofen (2.2 mg/kg, PO, q 12 h) for 7 days. In addition, dogs were observed daily, and rectal temperature, pulse rate, respiratory rate, appetite, attitude, activity level, and degree of lameness were recorded.

Gross evaluation and specimen preparation—After dogs were euthanatized, stifle joints were visually inspected, dissected free of muscular attachments, and excised by osteotomy of the mid-diaphysis of the femur and tibia. The femur was removed by sharp transection of the cruciate ligaments, collateral ligaments, and adjoining joint capsule. The menisci were left attached to the tibial plateau and submitted for histologic, biomechanical, or biochemical analysis.

Histologic evaluation—For histologic evaluation, menisci were immersion-fixed in neutral-buffered 10% formalin for 72 to 96 hours and decalcified in 5% EDTA. After complete decalcification, 6-mm transverse sections were cut from each meniscus. Each section included either a control site or a site repaired with an SIS implant and the underlying articular cartilage and subchondral bone. Specimens were processed for paraffin embedding. Twelve serial sections, each 5 mm thick, were cut from each specimen. Respective serial sections were stained with the following stains: H&E, Masson trichrome, Alcian blue-periodic acid Schiff, and safronin 0. Sections were microscopically evaluated for evidence of inflammation around and within the SIS implant, vascular ingrowth into the SIS implant and surrounding meniscus, organization of the collagen fibers in the SIS implant and surrounding meniscus, degeneration of collagen fibers within the SIS implant and surrounding meniscus, and the relative amount and type of ground substance within the SIS implant and surrounding meniscus.

Biomechanical evaluation—Menisci were transported on dry ice to the Musculoskeletal Bioengineering Center[e] for biomechanical evaluation. On arrival, frozen specimens were immediately stored at –80 C. Tests were conducted on specimens of control and SIS-implanted meniscal defects, original SIS specimens, meniscal tissue specimens adjacent to control sites, and meniscal tissue specimens adjacent to SIS-implanted sites. In situ creep and recovery deformation behavior of each specimen were quantified by use of an automated **creep indentation apparatus (CIA)**.[29,30,f] Specimens were thawed for 30 minutes in normal saline (0.9% NaCl) solution containing protease inhibitors prior to the test and then attached with cyanoacrylate cement to a sample holder. Meniscal specimens were loaded, using a 0.5-mm diameter flat-ended porous indenter tip with a step force of 0.015 N. Data were collected and plotted every 2.5 μm or 50 seconds, whichever came first. The CIA computes 3 intrinsic properties of soft tissues: the aggregate modulus (measure of compressive stiffness), Poisson ratio (apparent compressibility, a dimensionless quantity), and permeability (the ease or difficulty with which interstitial fluid flows past the solid matrix). The shear modulus was also calculated from the aggregate modulus and Poisson ratio. Results were reported using a semianalytical-seminumeric technique.

Biochemical testing—The 4-mm defects in each meniscus were evaluated for hydroxyproline (collagen) content. Only defects partially or completely filled with tissue were included in these analyses. Meniscal tissue specimens were quick frozen, pulverized under liquid nitrogen, and lyophilized. Samples were then hydrolyzed in 6 N hydrochloric acid at 100 C for 18 hours. Hydrochloric acid was removed by evaporation under vacuum, and the residue was redissolved in water and assayed for hydroxyproline content according to the method of Stegemann et al.[22,31]

Statistical analyses—Material properties of meniscal specimens were compared between control and SIS-implanted groups at 3 and 6 months by use of ANOVA. When the F-test was significant, means were compared by use of a Fisher least significant difference multiple comparisons test. Hydroxyproline content was compared between groups by use of a Student *t*-test. The number of filled cranial defects was compared with the number of filled caudal defects by use of χ^2 analysis. Significance was set at $P < 0.05$ for all tests.

Results

Surgery—All dogs recovered from each anesthetic episode without complications. A weight-bearing lameness was detected on the operated limb for approximately 1 week after surgery. Dogs returned to normal weight-bearing patterns over the next 2 weeks. Five dogs developed acute signs of pain and lameness 3 to 4 weeks after at least 1 of the 2 surgeries (first surgery, dogs 3, 8, and 10; second surgery, dogs 8, 11, and 16). Orthopedic examination revealed lateral luxation of the affected patella in these dogs because sutures in the medial retinacular tissues had dehisced. The retinacular tissues and medial parapatellar fibrocartilage was resutured and the lameness resolved in all cases.

Gross postmortem evaluation—Both stifle joints from all 16 dogs were grossly evaluated. Thus, 64 meniscal defects were evaluated, 2 (control and SIS-implanted) in each of the sixteen 3-month specimens (created during the second surgery) and 2 (control and SIS-implanted) in each of the 6-month specimens (created during the first surgery). There was either an absence of, or incomplete filling with, tissue in 39 of these 64 defects. Twenty-five of 39 (64%) unfilled sites were located in the caudal portion of the meniscus, and 14 (36%) were located cranially. The difference in number of unfilled defects was significant ($P = 0.004$) between cranial and caudal defects. Seventeen of the 39 (43.6%) unfilled sites had been implanted with SIS, and 22 (56.4%) were controls.

Histologic evaluation—Meniscal specimens from 4 dogs were submitted for histologic evaluation. Thus, 16 defects (4 control and 4 SIS-implanted from 3-month specimens, and 4 control and 4 SIS-implanted from 6-month specimens) were evaluated. Four of these 16 (25%) defects were filled with tissue. Two had been implanted with SIS, and 2 were control defects. Of the 4 filled defects, 1 (control) was obtained from a dog that developed bilateral lateral patella luxation after the second surgery. If this dog were excluded from analysis, the number of filled defects would decrease to 3 of 16 (18.8%; 2 SIS-implanted and 1 control).

In 1 of the filled SIS-implanted defects, the tissue filling the original defect consisted of a thin layer of fibrovascular granulation. In the other 3 filled defects, this thin bridge of tissue was composed of immature haphazardly arranged fibrous connective tissue with a relatively uniform distribution of fibroblasts. Inflammation or neovascularization of these bridges was not observed. The remaining 12 SIS-implanted and control defects were not filled with tissue. Specimens of these defects consisted of only the body of the meniscus, which had an irregular blunted-free edge covered by either fibrous connective tissue or pannus. Identifiable residual SIS was not observed in any (filled or unfilled) SIS-implanted defect.

Biomechanical evaluation—Menisci from 6 dogs were submitted for biomechanical evaluation. Twenty-four defects (6 control and 6 SIS-implanted from 3-month specimens and 6 control and 6 SIS-implanted from 6-month specimens) were originally submitted. However, because unfilled defects were excluded from evaluation, biomechanical testing was performed on 11 (8 SIS-implanted [3 month, n = 5; 6 month, 3] and 3 control [3 month, 2; 6 month, 5]) defects. None of the filled defects were obtained from dogs that developed postoperative patellar luxation. Aggregate modulus, Poisson ratio, permeability, and shear modulus were not significantly different between control and SIS-implanted defects at 3 or 6 months. The only significant differences were found between defects and adjacent tissue; aggregate modulus and shear modulus were lower in SIS-implanted and control defects at 3 and 6 months, compared with adjacent tissue (**Table 1**).

Biochemical analysis—Menisci from 6 dogs were submitted for biochemical analysis. Twenty-four defects (6 control and 6 SIS-implanted from 3-month specimens, and 6 control and 6 SIS-implanted from 6-month specimens) were originally submitted. However, analysis was possible on 7 (3 month, n = 4; 6 month, 3) of the 12 control defects and 11 (3 month, 6; 6 month, 1) of the 12 SIS-implanted defects. The remaining defects were unfilled and therefore not testable. Hydroxyproline content was not significantly different between SIS-implanted and control defects at 3 or 6 months (3 months: control, 22.16 ± 7.10 µg/mg wet weight of tissue; SIS-implanted, 19.63 ± 3.10 µg/mg wet weight of tissue; 6 months: control, 25.58 ± 2.92 µg/mg wet weight of tissue; SIS-implanted, 23.23 ± 4.86 µg/mg wet weight of tissue). One dog in this group developed unilateral patellar luxation after the second surgery. Both the SIS-implanted and control defects from the affected stifle joint of this dog were filled and included in the biochemical analysis. However, excluding data from this dog from statistical analyses did not change results.

Table 1—Biomechanical characteristics of experimentally induced meniscal defects in dogs that were left void (control) or implanted with porcine small-intestinal submucosa (SIS)

Specimen (time)*	H_A (Mpa)	ν_S	K ($10^{15}m^4/N''s$)	μ_s (Mpa)
SIS (3 mo)				
Defect (n = 5)	0.11 ± 0.02†	0.14 ± 0.05	0.93 ± 0.75	0.05 ± 0.01†
Adjacent (n = 4)	0.21 ± 0.04	0.21 ± 0.03	0.90 ± 0.73	0.08 ± 0.02
Control (3 mo)				
Defect (n = 2)	0.06 ± 0.01†	0.14 ± 0.02	1.58 ± 1.15	0.03 ± 0.00†
Adjacent (n = 5)	0.29 ± 0.11	0.21 ± 0.03	0.47 ± 0.22	0.11 ± 0.03
SIS (6 mo)				
Defect (n = 3)	0.11 ± 0.05†	0.13 ± 0.11	1.78 ± 2.10	0.04 ± 0.02†
Adjacent (n = 4)	0.25 ± 0.11	0.06 ± 0.07	0.81 ± 0.23	0.09 ± 0.03
Control (6 mo)				
Defect (n = 1)	0.10†	0	1.00	0.04†
Adjacent (n = 4)	0.29 ± 0.09	0.11 ± 0.11	1.14 ± 0.36	0.12 ± 0.05
Original SIS	0.08 ± 0.01	0.01 ± 0.01	3.81 ± 1.033	0.04 ± 0.00

Data reported as mean ± SD.

*Specimens were obtained from the site of the original defect or from tissue adjacent to the defect. Defects were induced 3 or 6 months prior to euthanasia and collection of specimens. †Significantly ($P \leq 0.05$) less than value for the adjacent tissue determined at the same time.

H_A = Aggregate modulus, a measure of compressive stiffness. n_S = Poisson ratio, the apparent compressibility. K = Permeability; the ease or difficulty with which interstitial fluid moves past the solid matrix. μ_s = Shear modulus.

Discussion

The results of the present investigation indicate that implantation of porcine SIS was not effective in promoting regeneration of meniscal defects in dogs. No significant differences were found in any of the variables assessed between SIS-implanted and control defects. Only 4 of 16 defects examined histologically were filled with tissue (ie, had evidence of healing). The morphology of the fibrous connective tissue bridge was the same in SIS-implanted and control defects, indicating that formation of the tissue filling meniscal defects was the result of the normal host response to meniscal injury.

Twenty-four defects were submitted for biomechanical evaluation, and 11 were testable. Although there were no significant differences in aggregate modulus, permeability, or shear modulus between SIS-implanted and control defects, the aggregate modulus and shear modulus were significantly greater in tissue adjacent to either type of defect. This indicates that the regenerative tissue (ie, tissue filling meniscal defects) did not regain the material stiffness of the adjacent tissue.

Twenty-four defects were submitted for biochemical evaluation, and 18 were testable. Amino acids frequently contained in collagen include glycine, proline, alanine, hydroxyproline, and hydroxylysine. Hydroxyproline content closely parallels collagen content, because this amino acid is unique to collagen in meniscal tissue. There was no significant difference in hydroxyproline content between SIS-implanted and control defects, indicating that the tissue response was no more evolved in defects implanted with SIS.

Our findings are in contrast to those of Cook et al,[21] who used a different model to demonstrate the efficacy of SIS in meniscal healing in dogs. In that model, subtotal

medial meniscectomy was performed. Approximately 50% of the medial meniscus was incised from the caudal margin of the collateral ligament to the caudal meniscal attachment. In treated dogs, a SIS graft was trimmed to match the size and shape of the resected tissue and sutured to the cranial, caudal, and peripheral attachment sites. Operated limbs were placed in a splint for 3 weeks after surgery. Twelve weeks after surgery, replacement tissue was grossly indistinguishable from normal meniscal tissue in 4 of 5 treated dogs. Replacement tissue also closely resembled normal meniscal tissue with respect to chondroid differentiation, collagen content, and zonal architecture.[21]

There are biological and mechanical differences between our study and the study by Cook et al.[21] With subtotal meniscectomy, SIS grafts were sutured to peripheral attachments, which have a vascular supply. King[32] showed that meniscal lesions that lacked communication with the synovial membrane and the vascular supply were not healed at follow-up examinations 3 weeks to 2 months after surgery. If the lesion communicated with the synovium, however, there was evidence of tissue ingrowth and healing. The 4-mm circular defects created in the present study occupied the medial two thirds of the meniscus, which is an avascular zone. Because the vascular supply is limited to the outer 10 to 25% of the meniscus, the meniscus has been divided into a red or vascular zone (approx the outer third) and a white or avascular zone (the inner two thirds). The border between these 2 is termed the red-white zone.[1] The defects created in the present study were positioned in the region of the white and red-white zones. The outer 10 to 25% of the meniscus was excluded; thus, healing may have been inhibited.

The size of the circular defects created in the present study could have imposed excessive biomechanical stress by removing too much meniscal tissue. The number of unfilled biopsy sites was greater in the caudal region of the meniscus (25/39 [64%]) compared with the cranial region (14/39 [36%]). A destabilized meniscus would be more vulnerable to injury by normal weight-bearing forces. In a flexed standing position, a greater share of weight-bearing forces is imposed on the caudal portion of the meniscus than the cranial portion.[2] This concentration of forces could compromise tissue regeneration in an unstable meniscus. The greater number of unfilled lesions in the caudal portion of the meniscus can be more readily explained as a biomechanical problem rather than a biological problem.

Collier et al[33] stated that circular defects in the meniscus have an inherent degree of stability. In that study, the healing of untreated 1.0-mm circular defects in the anterior third of the medial meniscus of rabbits was compared with the healing of untreated longitudinal defects. By 8 weeks after surgery, most of the circular lesions had healed via filling with hyaline-like cartilage. In contrast, the longitudinal defects had not healed by 12 weeks after surgery. The authors speculated that forces on the meniscus would tend to shear apart the opposing surfaces of a longitudinal lesion, whereas a circular defect would merely deform and recover.[33] Despite this evidence, the maximum size of a circular defect that can safely be created in the meniscus is not known. It is possible that the removal of 4 mm of tissue could make the remaining meniscus vulnerable to injury.

The development of postoperative lateral patellar luxation in 5 dogs was an unexpected complication of medial stifle arthrotomy. Secure suturing of the medial parapatellar fibrocartilages and overlying femoral fascia can avoid this complication. In this study, 5 of the 6 lateral patellar luxations were associated with the surgeon having the most experience operating on human knees and could thus represent a difference in anatomy or postoperative activity between dogs and humans. There is a concern that postoperative patellar luxation could alter the biomechanical stresses on the stifle joint. The function of the patella is to increase the mechanical advantage of the extensor apparatus. The cranial cruciate ligament is responsible for limiting craniocaudal motion, internal rotation, and hyperextension. The collateral ligaments are primarily responsible for limiting varus and valgus motion of the tibia. Although patellar luxation results in discomfort and lameness, it would not be expected to destabilize the stifle joint. However, patellar luxation would create inflammation within the joint, and the effect of this on healing of the meniscal defects is unknown. Exclusion of data from the 6 affected joints did not change the conclusions of this study.

Arnoczky et al[34] demonstrated that 2-mm defects in the menisci of dogs that were repaired by implantation of an autogenous fibrin clot healed via proliferation of fibrous connective tissue that eventually modulated into fibrocartilaginous tissue. These findings support the hypothesis that it is not the absence of a blood supply per se that limits healing of the avascular portions of the meniscus but rather the absence of growth factors that are normally present in a wound hematoma.[34] As in the normal sequence of wound repair, the clot acts as a scaffold for migration of cells and provides a chemotactic and mitogenic stimulus for cellular recruitment, proliferation, and matrix production. The fibrin clot contains fibronectin and **platelet-derived growth factor (PDGF)**, 2 growth factors essential to regeneration of meniscal tissue.[34]

Porcine SIS contains fibronectin.[35] Preliminary results of cell culture studies suggest that collagen I and fibronectin in SIS promote the attachment of human dermal microvascular endothelial cells to porcine extracellular matrix. Specifically, integrin-dependent adhesive sequences present within tissue fibronectin induce cellular attachment to the extracellular matrix in porcine SIS.[35] Platelet-derived growth factor is a large glycoprotein that promotes initiation of the cell cycle and cell division. It is chemotactic for monocytes, neutrophils, and fibroblasts; mitogenic for mesenchymal cells; and it stimulates collagen production by fibroblasts.[36] Spindler et al[1,37] showed that 200 ng of PDGF/ml added to culture media stimulated a 2.5-fold increase in proliferation of ovine menisci. Attempts to isolate PDGF from porcine SIS indicate that, if present, PDGF exists in quantities lower than those in serum.[8] When used as a graft in the avascular portion of the meniscus, SIS may not contain all of the growth factors necessary for induction of cellular regeneration.

Splints were not applied after surgery to the dogs in this study. Increased motion of the stifle joint could

theoretically disrupt meniscal healing. Dowdy et al[38] evaluated the effect of postoperative exercise on meniscal healing in dogs. Longitudinal lesions were made in the vascularized portion of the medial meniscus, and affected limbs were either placed in a cast or mobilized immediately. The percentage of collagen in the healing meniscal lesion 10 weeks later was significantly greater in limbs that were not casted, compared with limbs that were cast immobilized. This evidence suggests that splints are not required for healing of meniscal lesions. The effect of joint movement on healing of circular meniscal lesions is not known.

[a]SIS, Depuy Inc, Warsaw, Ind.

[b]Winker JT, Swaim SF, Sartin EA, et al. The effect of Vet Bio Sis T on wounds with exposed boneabstract (abstr), in *Proceedings*. 3rd SIS Symp 1998;15.

[c]Key's biopsy punch, Acuderm Inc, Ft Lauderdale, Fla.

[d]Prolene, Ethicon, Somerville, NJ.

[e]Musculoskeletal Bioengineering Center, San Antonio, Tex.

[f]Shin D, Athanasiou KA. Stress relaxation indentation of articular cartilage: biphasic finite element/optimization and experimental validation (abstr). *ASME Adv Bioeng* 1994;28:209–210.

[g]Liang HA. Determination of platelet-derived growth factor in small intestinal submucosa (abstr), in *Proceedings*. 2nd SIS Symp 1998;93.

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