Appendix 2 – One Year Rabbit Implantation Study of a Zirconium Based Beryllium Bearing Metallic Glass

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$Zr_{35}Ti_{30}Be_{35}$ and $Zr_{35}Ti_{30}Be_{29}Co_6$ were chosen for further biocompatibility testing. $Zr_{35}Ti_{30}Be_{35}$ exhibited one of the best corrosion resistances in HCl, had moderate GFA = 6mm, had a moderate $\Delta T = 120$ °C and good strength to weight ratio. $Zr_{35}Ti_{30}Be_{29}Co_6$ had good corrosion resistance, but much better GFA = 15mm, $\Delta T = 155$ °C, and showed good potential for TPF. Samples were sent to a testing company, NAMSA, and short term *in vitro* and *in vivo* studies were done to assess biocompatibility. Both alloys performed as well as the control specimen and were considered biocompatible in these short term trials. A cell culture class at PCC provided me with the opportunity to test the cytotoxicity of the 10x PBS solutions in which the metals were tested for corrosion resistance over a period of three months. The solution was diluted to 1x strength and no visible damage to the cells resulted after they were exposed to the media and allowed to grow to 90% confluence. We became aware of extensive biocompatibility testing performed for Liquidmetal Technologies on samples of Vitreloy 1 and a glassy composite material called LM2 as part of Liquidmetal's effort to obtain FDA approval. Liquidmetal Technologies kindly agreed to let me summarize and publish the results of the tests. The summary was submitted to the Journal of Materials Science: Materials in Medicine under the title “One Year Rabbit Implantation Study of a Zirconium Based Beryllium Bearing

Metallic Glass," but was not accepted. The reviewer stated that the paper seemed more appropriate for a technological review and was likely correct. It is included here because it presents important findings about the biocompatibility of ZrTiNiCuBe alloys.

A2.1 Abstract

A one year implantation study in specific pathogen free New Zealand White Rabbits was performed to test the local response of bone and muscle tissue to a zirconium based beryllium bearing bulk metallic glass, LM1, and a toughened glassy composite material, LM2. Short term *in vitro* and *in vivo* studies conducted prior to the implantation study are summarized and show that both LM1 and LM2 elicit responses similar to the negative control material in each study. The implantation study shows LM1 elicits a mild but worsening response with time while LM2 is statistically similar to 316L stainless steel used as control. LM1 and LM2 have highly desirable mechanical properties including low Young's modulus, yield strengths double those of titanium alloys, and elastic limits 5-10 times greater than crystalline metals.

A2.2 Introduction

Bulk metallic glasses, BMG, are relatively new highly elastic materials with high hardness, high strength, and low modulus [1-3]. BMG are alloys composed of mixtures of elements that frustrate crystallization pathways sufficiently that samples greater than 1mm in all dimensions can be cast completely amorphous. Unlike crystalline materials which have periodic arrangements of atoms or molecules, the atoms of glasses solidify into a random structure. Crystalline materials have much higher theoretical strengths than are ever observed in nature. This is because all crystals have defects, and the defects dramatically weaken the material. Glasses, on the other hand, have near theoretical

properties because the structure is random and atom-size defects are nonexistent. A commercially available BMG called Vitreloy1 or LM1 with composition $Zr_{62.6}Ti_{11.0}Cu_{13.2}Ni_{9.8}Be_{3.4}$ (weight percent) is of particular interest to the BMG community because of its exceptional glass forming ability (parts with sections >1 inch thickness can be cast) and good mechanical properties [4]. LM1 has a tensile yield stress of ~ 1.9 GPa and a Vicker's hardness of ~ 600 Kg/mm^2 (double that of 316L stainless steel). It has an elastic limit of 2% (10 times greater than most crystalline metals) and a Young's modulus of ~ 90GPa (less than half the value of 316L stainless steel and 20% lower than titanium alloys) [5]. The disadvantage of LM1 is that it fails catastrophically if the yield strength is exceeded. Such stresses would never be observed in biological environments, but efforts have been made to avoid the catastrophic failure mode. Another commercially available alloy, LM2 ($Zr_{71.9}Ti_{9.2}Cu_{6.2}Ni_{4.6}Be_{1.6}Nb_{6.5}$), is a composite material with a glassy matrix and soft crystalline inclusions that absorb energy when failure initiates, allowing for graceful failure and plastic elongation of up to 5% in tension [6]. This material yields at 1.4 GPa. Both LM1 and LM2 have been studied in fatigue loading conditions and values ranging from 60 MPa - 700 MPa at 10^7 cycles have been reported, so no conclusive statements can be made about the fatigue endurance limit [7-9]. This, along with corrosion fatigue characterization, is an area where more research is needed.

In the simplest approximation, cytotoxicity can be thought of as a corrosion problem [10]. Given the high cytotoxicity of metallic salt forms of nickel, copper and beryllium [11], it may seem surprising that a material containing all three would be tested for biocompatibility. However, due to the high corrosion resistance of these alloys, both

LM1 and LM2 performed as well as the negative control in a wide range of *in vitro* and *in vivo* tests. Zr based BMG exhibit excellent corrosion resistance in saline environments. In a study conducted by Morrison et al., a Zr based BMG was shown to have corrosion resistance higher than 316L stainless steel and comparable to CoCrMo and Ti-6Al-4V in a saline environment [12].

A2.3 Experimental Method

Biological testing was performed by AppTec Laboratory Services or Louisiana State University Health Sciences Center Department of Orthopaedics. Studies were conducted in compliance with U.S. Good Laboratory Practice (GLP) regulations set forth in 40 CFR Part 160, 40 CFR Part 792, or 21 CFR Part 58. Samples obtained from Liquidmetal Technologies were either chemically sterilized or sterilized with steam. All extractions to obtain leachable materials from LM1 and LM2 were performed while maintaining the ratio of $60cm^2$ to 20mL.

Samples for *in vitro* and *in vivo* tests were produced by Liquidmetal Technologies. >99% pure elements were melted under an inert argon atmosphere in a water cooled crucible and cast into plates or rods. The amorphous nature of the material was verified using X-ray spectroscopy. The material was cut and polished into specimens with the dimensions and surface finish specified by AppTec Laboratory Services or Louisiana State University Health Sciences Center Department of Orthopaedics.

A2.4 Preliminary Tests and Results

The cytotoxicity of both materials was assessed using two different methods set forth in ISO10993-5. In one study, LM1 and LM2 were extracted in Eagle's Minimal

Essential Medium (E-MEM), supplemented with 5% (v/v) Fetal Bovine Serum (FBS) and one or more of the following: L-glutamine, HEPES, gentamicin, penicillin, vancomycin, and Fungizone at 37 ± 1 °C and 5 ± 1% CO_2 for 24 hours. A ratio equivalent of 60.0cm^2 test article and 20mL E-MEM + 5% FBS was maintained in the extraction process. L929 mouse fibroblast cells obtained from ViroMed Laboratories, Inc., Minnetonka, MN, were grown and used as monolayers in disposable tissue culture labware at 37 ± 1 °C and 5 ± 1% CO_2. After the extraction period, the maintenance culture media was removed from the test culture wells and replaced with test media/extract and control media. Positive and intermediate controls were media spiked with $CdCl_2$ and negative control was normal media. All samples were tested in triplicate and cultures were evaluated for cytotoxic effects by microscopic observation after 24, 48, and 72 hour incubation periods at 37 ± 1 °C and 5 ± 1% CO_2. Positive control showed nearly complete destruction of the cell layer. Intermediate control showed no extensive cell lysis or empty areas between cells, but 20 - 50% of cells were round and devoid of intracytoplasmic granules. Negative control, LM1 and LM2 showed no reactivity. In the other study, leachable extracts were allowed to diffuse through an agarose barrier and contact cultured cells. The agar was composed of 1% agarose, 1X E-MEM, and 5% FBS + supplements listed in the first study. The maintenance media was removed from the L929 cells cultured as in the first study and it was replaced with the agar mixture. The cultures were held at room temperature until the agarose solidified, and the test material was placed directly onto the agar surface for 1 hour and incubated as in the first study. At the completion of the incubation period the perimeter of the test articles was outlined in indelible ink and then removed. All cultures were flooded with 0.01% neutral red stain, incubated for 1 hour

and then observed microscopically. LM1, LM2 and the negative control, dram vial cap, showed no detectible zone under or around specimen, and the positive control, Davol Penrose Drain Tubing, showed definitive cytotoxic effects in a zone greater than 1cm beyond the edge of the specimen.

The propensity of the materials to cause mutation was determined by three methods outlined in ISO 10993-3. The first test was conducted on five strains of Salmonella typhimurium. The positive and negative controls behaved as expected and saline extracts of LM1 and LM2 showed no statistically significant tendency to induce histidine (his) reversion in S. typhimurium (his- to his+) caused by base changes or frameshift mutations in the genome of tester organisms.

The second test, conducted on L5178Y mouse lymphoma cells, determines the ability of a test article to induce forward mutation at the thymidine kinase (TK) locus in the presence of trifluorothymidine (TFT). TK is an enzyme that allows cells to salvage thymidine from the surrounding medium for DNA synthesis. If the thymidine analog TFT is included in the growth medium, the analog will be phosphorylated via the TK pathway and will cause cellular death by inhibiting DNA synthesis. Cells which are heterozygotes at the TK locus (TK+/-) may undergo a single-step forward mutation to the TK-/- genotype in which little or no TK activity remains. These mutants are as viable as the heterozygotes in normal medium because DNA synthesis proceeds by *de novo* synthesis pathways that do not involve thymidine as an intermediate. TK-/- mutants cannot utilize toxic analogs of thymidine. Cells which may grow to form colonies in the presence of TFT are therefore assumed to have mutated, either spontaneously or as a result of exposure to the test article, at the TK+/- locus. Neither test article extract (either

with or without metabolic activation) induced appreciable differences in cell density throughout the expression and recovery period as compared to the concurrent negative control.

The third test was an *in vivo* mouse micronucleus assay. The Mouse Micronucleus Assay evaluated the potential of 0.9% sodium chloride for injection (saline) and cottonseed oil (CSO) extracts of the test article to induce *in vivo* clastogenic events or damage to the mitotic spindle in polychromatic erythrocytes obtained from mouse bone marrow of CD-1 mice.

Male and female CD-1 mice were treated with one of the test article extracts, or negative or positive controls. Twenty-four and forty-eight hours after treatment, the animals were sacrificed and the bone marrow harvested. All negative control treated preparations demonstrated normal levels of spontaneously occurring aberrations while positive control treated cultures demonstrated dramatic, dose-dependant increases in aberrant cells. None of the mice treated with the test article preparations exhibited overt signs of toxicity either immediately post-treatment or during the induction period. The levels of micronucleated cells were within normal negative ranges. Based on the criteria and conditions outlined in the study protocol, the results indicate that the test article is non-mutagenic in this test system.

Hemolytic activity of LM1 and LM2 was investigated by placing the metals in direct contact with New Zealand White Rabbit blood for 1 hour, removing the test article, centrifuging, and analyzing the absorbance of the supernatant at 545nm using a standard laboratory spectrophotometer. LM1 and LM2 showed the same hemolytic activity as

isotonic saline and are therefore considered non-hemolytic under the test conditions employed.

In a test where isotonic saline extracts were injected intravenously into Specific Pathogen Free New Zealand White Rabbits, body temperature was measured at 30 minute intervals for 3 hours and no evidence of pyrogenicity was found.

Allergic reactions and evidence of edema or erythema induced by direct contact with the metal or injection/contact with extracts were tested according to three methods detailed in ISO 10993-10. In one study adult Hartley strain guinea pigs had topical applications of isotonic saline extracts and direct contact with the material on shaved regions of their back for 24 hours as well as intradermal injections in the back of extracts of LM1, LM2, and positive chlorodinitrobenzene and negative 316L stainless steel controls. Edema and erythema were evaluated at 24, 48, and 72 hours after treatment. LM1, LM2, and 316L stainless steel elicited no visible skin edema or erythema while the positive control showed deep lesions at the same stages validating the methodology. LM1 and LM2 showed no allergic potential in either bulk or extracted form. In the second and third tests specific Pathogen Free New Zealand White Rabbits were tested. In the second test, rabbits were treated with isotonic saline extracts of LM1 and LM2 applied via gauze patches to the flank for four hours and no local irritation or sensitization was observed. In the third test, isotonic saline and cottonseed oil extracts of LM1 and LM2 were injected intradermally into the backs of the rabbits. No local irritation in the dermal tissues of the rabbits was observed at 24, 48, or 72 hours.

An ISO10993-11 Test for Systemic Toxicity was also performed. In this test Specific Pathogen Free Albino Swiss Mice were injected intravenously with saline

extracts of LM1, LM2, or were injected intraperitoneally with cottonseed oil extracts of the materials. Control injections were saline and cottonseed oil with no extract. Extraction was performed at 37 °C for 72 hours and dosage was 0.05mL/g. Body weight and general health were evaluated at 4, 24, 48, and 74 hours. Based on the observations it was concluded that LM1 and LM2 do not contain leachable materials that cause toxic effects as a result of a single-dose injection in mice.

Given the promising results of these *in vitro* and *in vivo* short term trials, a one year implantation study in 21 Specific Pathogen Free New Zealand White Rabbits was done to test for local effects after implantation.

A2.5 Long Term Implantation Study

The tissue response to polished and bead blasted samples of LM1 and LM2 was compared to the control material, 316L stainless steel (SST) by implanting specimens into specific pathogen free New Zealand White Rabbits.

Twenty-one specific pathogen free New Zealand White Rabbits were purchased from Harlan World Headquarters, Indianapolis, IN. Animals of both sexes were used. This test method and species have historically been used to assess systemic safety in determining the biocompatibility of materials used in medical devices. The animal species, number and route of test article administration were as recommended in ISO 10993-6:1995.

Each animal was anesthetized with a 50+5 mg/kg Ketamine/Xylazine cocktail, according to SOP-0001. At the initial injection, a 0.1 mg/kg of acepromazine was added. Subsequently a surgical plane of anesthesia was maintained by injections of 50 mg/kg of Ketamine. Sterilized cylindrical implants of the two test materials and stainless steel

controls were implanted into the paraspinal musculature and distal femora of 21 New Zealand White Rabbits using sterile surgical technique according to SOP-0012. Each animal received two types of implants – one test material on the left side and a different one on the right side. The total number of implants per animal was 12: four in the right and four in the left paravertebral musculature, and two unicortal implants placed into each femur. Paravertebral implants were cylindrical in shape, 3mm diameter x 10mm length. Bone implants were also cylindrical in shape, 2mm diameter x 7mm length.

All animals survived the implantation procedures and through to their planned sacrifice time with no major complications. Animals were followed postoperatively daily for two weeks and then at a minimum of bi-weekly until their sacrifice date. Animals were sacrificed at 3, 6 and 12 month intervals. At the time of sacrifice, blood was withdrawn for complete blood counts and chemical analysis. Part of the liver and one kidney were retrieved for histological examination and were observed for gross evidence of abnormalities. Implants in both muscle and bone were retrieved for histological examination with some surrounding tissue. Tissues were observed for gross evidence of rejection such as necrosis, cysts or extended granulation tissues. Histologically, muscle and bone implants were evaluated and graded according to the criteria listed in Table A2.1. Transcribed results from the histological evaluations and blood chemistry and CBC are included in the supplementary materials section.

Gross examination of the implants and surrounding tissues revealed no overt signs of rejection such as cysts or necrosis and no gross evidence of local inflammation. The only significant findings were three muscle implants that had migrated to the fatty tissues. One of these was surrounded by hemorrhage without overt inflammation or necrosis.

Additionally, one bony implant was placed on the proximal tibia rather than the distal femur due to technical error. All retrieved kidneys and livers appeared grossly normal.

The histological data regarding bone implants show no fibrosis, degeneration or inflammatory reaction with direct apposition of bone on all three materials, and remodeling to partially or completely surround the implant. As is shown in the statistical analyses in Tables A2.2 - A2.7, these responses had no association with the implanted material. Thus for all materials, excellent compatibility with bone is in evidence.

Statistical analysis of the implant local reaction data were performed using non-parametric methods (Kruskal-Wallis); statistically significant post-hoc Student Neuman Keuls comparisons are reported where appropriate (i.e., where there is significant main effect and a post-hoc result with statistical significance). All evaluations are performed at a 0.05 significance.

The histological data regarding muscle implants show what appears to be evolving tissue responses. Histological examination showed stable encapsulation of muscle implants with minimal to mild intracapsular inflammation for all materials, but adverse response to the LM1 test material was greater than the control material at 6 and 12 months. Statistical analyses were performed on the results of the histologic analysis of the slides. The first stage of the analyses shown in Tables A2.2 - A2.7 examines the effect of materials at each time interval.

Because there were significant effects on muscle implants of fibrosis thickness, intracapsular inflammation, degeneration, extracapsular inflammation grade and distance at the 12 month time period, interaction analyses (multi-way analysis of variance) were performed to assess combined effects on the materials (SST, LM1, LM2), finish

(polished, bead blasted), and time post-implantation (3, 6, 12 months). Statistically significant post-hoc Student Neuman Keuls comparisons are reported where appropriate (i.e., when there is a significant main effect and a post-hoc result with statistical significance). Similarly, interaction trends are described where significant in Tables A2.8 – A2.12.

The results of this study suggest that LM2 creates a local tissue response that is essentially similar to that of the control material. LM1 creates a local tissue response that is substantially greater than that of the control material. Although local tissue responses of LM1 were within the mild category, trends indicated that local degeneration would continue to evolve through the one year endpoint for this material.

A2.6 Conclusion

High strength Zr based Be bearing BMG and composite materials show good evidence of biocompatibility despite the presence of Cu, Ni, and Be. This is attributed to the high corrosion resistance of Zr based BMG. In short term *in vitro* and *in vivo* trials, LM1 and LM2 elicited biological responses similar to control materials. Only in the long term implantation study were statistically significant differences apparent. It was found that, independent of surface finish, LM2 creates a local tissue response similar to 316L stainless steel. LM1, however, creates a mild response worse than either SST or LM2 that appears to be increasing with time. When the compositions of LM1 and LM2 are compared, one will note that LM2 contains about half the Cu, Ni, and Be as is found in LM1 and additionally LM2 contains Nb. The data collected in these studies does not indicate which elements caused the most adverse effects, but the decrease of Cu, Ni, Be, and/or the addition of Nb improved the local tissue response to the material LM2. Given

the excellent mechanical properties of these materials and the good biocompatibility in evidence here, LM1 and LM2 may find utility as biomaterials in the future.

Appendix 2 References

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Table A2.1: Muscle and bone implant histological grading criteria.

Parameter	Grade	Description
Fibrosis	0	None
	1	< 1/3 circumference
	2	1/3 < 1/2 circumference
	3	1/2 < 3/4 circumference
	4	> 3/4 circumference
		Thickness (μm)
Intracapsular Inflammation	0	None
	1	1-5 cells/high powered field
	2	6-10 cells/high powered field
	3	11-25 cells/high powered field
	4	26-50 cells/high powered field
	5	> 50 cells/high powered field
Degeneration	None	None
	Mild	Minimal changes - nuclear pyknosis and/or minimal loss of striation
	Moderate	Nuclear karryorhexix/karyolysis and/or extensive loss of striation
	Severe	Coagulation necrosis
Fatty Infiltration	None	None
	Mild	Focal, interfascicular and/or intermyocyte
	Moderate	Multifocal, interfascicular and/or intermyocye
	Severe	> 3/4 Circumferential, interfascicular and/or intermyocyte
Extracapsular Inflammation	0	None
	1	1-5 cells/high powered field
	2	6-10 cells/high powered field
	3	11-25 cells/high powered field
	4	26-50 cells/high powered field
	5	> 50 cells/high powered field
		Distance (μm) inclusive from implant interface
Granulomatous Inflammation	None	None
	Mild	Focal, unicellular histiocytes or < 5 cell aggregates
	Moderate	Multifocal, unicellular histiocytes or > 5 cell aggregates
	Severe	Shees of histiocytes and/or foreign body giant cells
Bone Remodeling	None	None - cortical hole present with or without periosteal lining
	Minimal	Focal osteoblastic/osteoclastic activity with < 1/3 encasement of the implant and/or cortex resorption
	Moderate	1/3 - 1/2 encasement of the implant and/or cortex resorption
	Extensive	> 1/2 encasement of the implant and/pr cortex resorption
Necrosis	No	No evidence of necrosis
	Yes	Nuclear debris and/or capillary wall breakdown

Table A2.2: 3 Month Muscle Implants: Significance of Material Type vs Parameter.

Parameter		**P-value**	**Significant Post Hocs (if applicable)**
Fibrosis	Grade	0.368	N/A
	Thickness	0.093	N/A
Intracapsular Inflammation		0.075	N/A
Degeneration		0.155	N/A
Fatty Infiltration		0.553	N/A
Extracapsular Inflammation	Grade	0.227	N/A
	Distance	0.146	N/A
Granulomatous Inflammation		0.138	N/A
Necrosis		(none observed)	N/A

Table A2.3: 3 Month Bone Implants: Significance of Material Type vs Parameter.

Parameter		**P-value**	**Significant Post Hocs (if applicable)**
Fibrosis	Grade	(none observed)	N/A
	Thickness	(none observed)	N/A
Inflammation		(none observed)	N/A
Degeneration		(none observed)	N/A
Granulomatous Inflammation		(none observed)	N/A
Bone Remodeling		0.955	N/A
Necrosis		(none observed)	N/A

Table A2.4: 6 Month Muscle Implants: Significance of Material Type vs Parameter.

Parameter		**P-value**	**Significant Post Hocs (if applicable)**
Fibrosis	Grade	0.360	N/A
	Thickness	0.108	N/A
Intracapsular Inflammation		0.010	LM1>SST
Degeneration		0.560	N/A
Fatty Infiltration		0.331	N/A
Extracapsular Inflammation	Grade	0.136	N/A
	Distance	0.242	N/A
Granulomatous Inflammation		(none observed)	N/A
Necrosis		0.643	N/A

Table A2.5: 6 Month Bone Implants: Significance of Material Type vs Parameter.

Parameter		**P-value**	**Significant Post Hocs (if applicable)**
Fibrosis	Grade	(none observed)	N/A
	Thickness	(none observed)	N/A
Inflammation		(none observed)	N/A
Degeneration		(none observed)	N/A
Granulomatous Inflammation		(none observed)	N/A
Bone Remodeling		0.153	N/A
Necrosis		(none observed)	N/A

Table A2.6: 12 Month Muscle Implants: Significance of Material Type vs Parameter.

Parameter		**P-value**	**Significant Post Hocs (if applicable)**
Fibrosis	Grade	0.091	N/A
	Thickness	0.0485	LM1>LM2
Intracapsular Inflammation		0.003	LM1>SST; LM1>LM2
Degeneration		0.018	LM1>SST; LM1>LM2
Fatty Infiltration		0.061	N/A
Extracapsular Inflammation	Grade	0.003	LM1>SST; LM1>LM2
	Distance	0.0002	LM1>SST; LM1>LM2
Granulomatous Inflammation		(none observed)	N/A
Necrosis		0.145	N/A

Table A2.7: 12 Month Bone Implants: Significance of Material Type vs Parameter.

Parameter		**P-value**	**Significant Post Hocs (if applicable)**
Fibrosis	Grade	(none observed)	N/A
	Thickness	(none observed)	N/A
Inflammation		(none observed)	N/A
Degeneration		(none observed)	N/A
Granulomatous Inflammation		(none observed)	N/A
Bone Remodeling		0.460	N/A
Necrosis		(none observed)	N/A

Table A2.8: Fibrosis Thickness Interaction Analysis: Muscle Implants by Time, Finish, and Material.

Factor	P-value	Post Hoc (Or Interaction Tendencies)
Material	0.336	N/A
Finish	0.137	N/A
Time	0.886	N/A
Material * Finish	0.471	N/A
Material * Time	0.129	N/A
Finish * Time	0.764	N/A
Material * Finish * Time	0.428	N/A

Table A2.9: Intracapsular Inflammation Interaction Analysis: Muscle Implants by Time, Finish, and Material.

Factor	P-value	Post Hoc (Or Interaction Tendencies)
Material	0.0001	LM1>SST; LM1>LM2
Finish	0.041	Bead Blasted > Polished
Time	0.046	12 months > 3 months
Material * Finish	0.167	N/A
Material * Time	0.001	LM1 increases with time
Finish * Time	0.386	N/A
Material * Finish * Time	0.797	N/A

Table A2.10: Degeneration Interaction Analysis: Muscle Implants by Time, Finish, and Material.

Factor	P-value	Post Hoc (Or Interaction Tendencies)
Material	0.885	N/A
Finish	0.026	Bead Blasted > Polished
Time	0.866	N/A
Material * Finish	0.894	N/A
Material * Time	0.006	LM1 increases; SST decreases
Finish * Time	0.644	N/A
Material * Finish * Time	0.039	Material and finish affect time response

Table A2.11: Extracapsular Inflammation Grade Interaction Analysis: Muscle Implants by Time, Finish, and Material.

Factor	P-value	Post Hoc (Or Interaction Tendencies)
Material	0.0003	LM1>SST; LM1>LM2
Finish	0.0027	Bead Blasted > Polished
Time	0.404	N/A
Material * Finish	0.063	N/A
Material * Time	0.088	N/A
Finish * Time	0.356	N/A
Material * Finish * Time	0.878	N/A

Table A2.12: Extracapsular Inflammation Distance Interaction Analysis: Muscle Implants by Time, Finish, and Material.

Factor	P-value	Post Hoc (Or Interaction Tendencies)
Material	0.340	N/A
Finish	0.048	Bead Blasted > Polished
Time	0.209	N/A
Material * Finish	0.429	N/A
Material * Time	0.359	N/A
Finish * Time	0.204	N/A
Material * Finish * Time	0.445	N/A