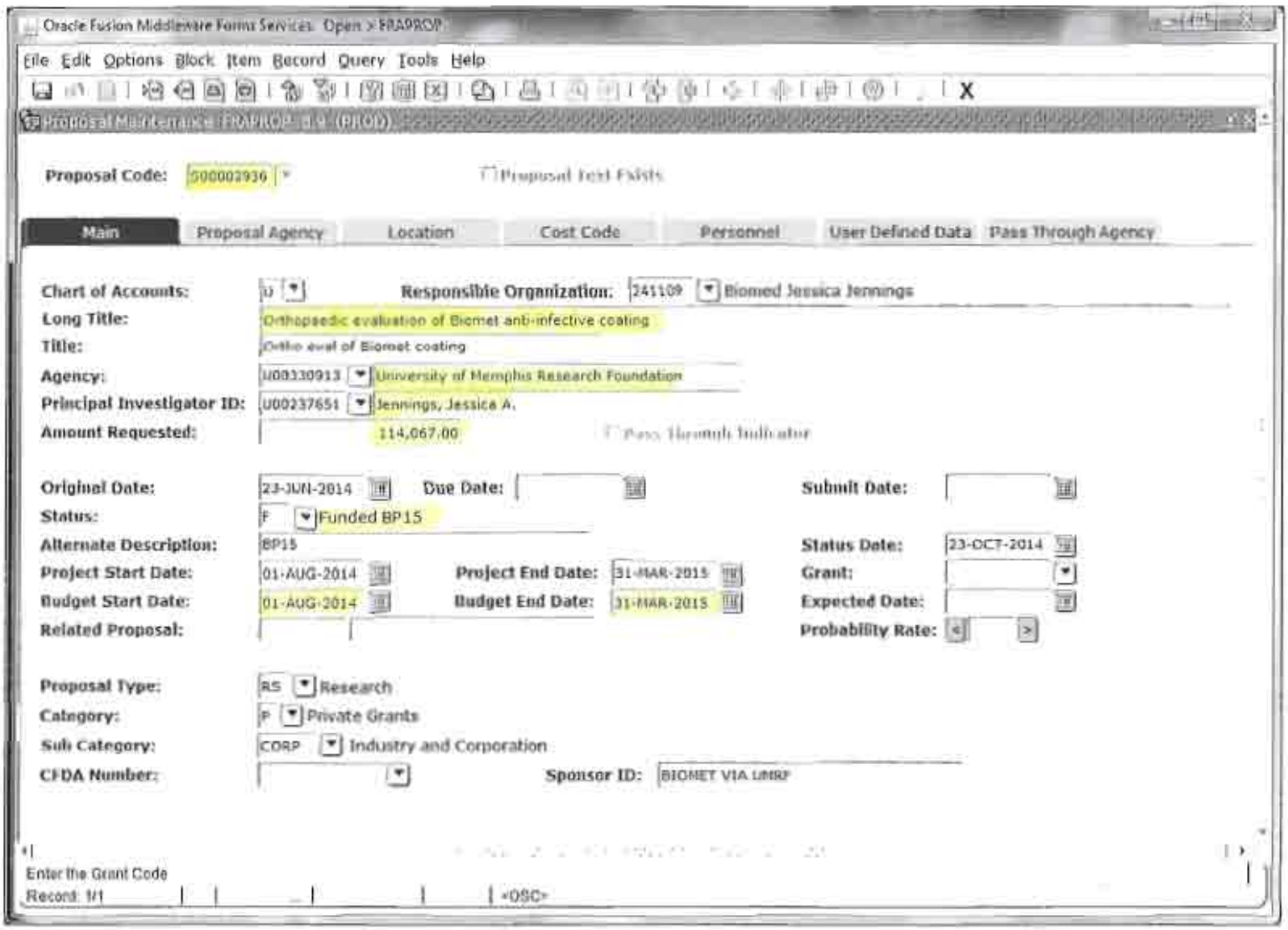
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Proposal Maintenance FRAPROP 11.1 (PROD)
Proposal Code: 500003936
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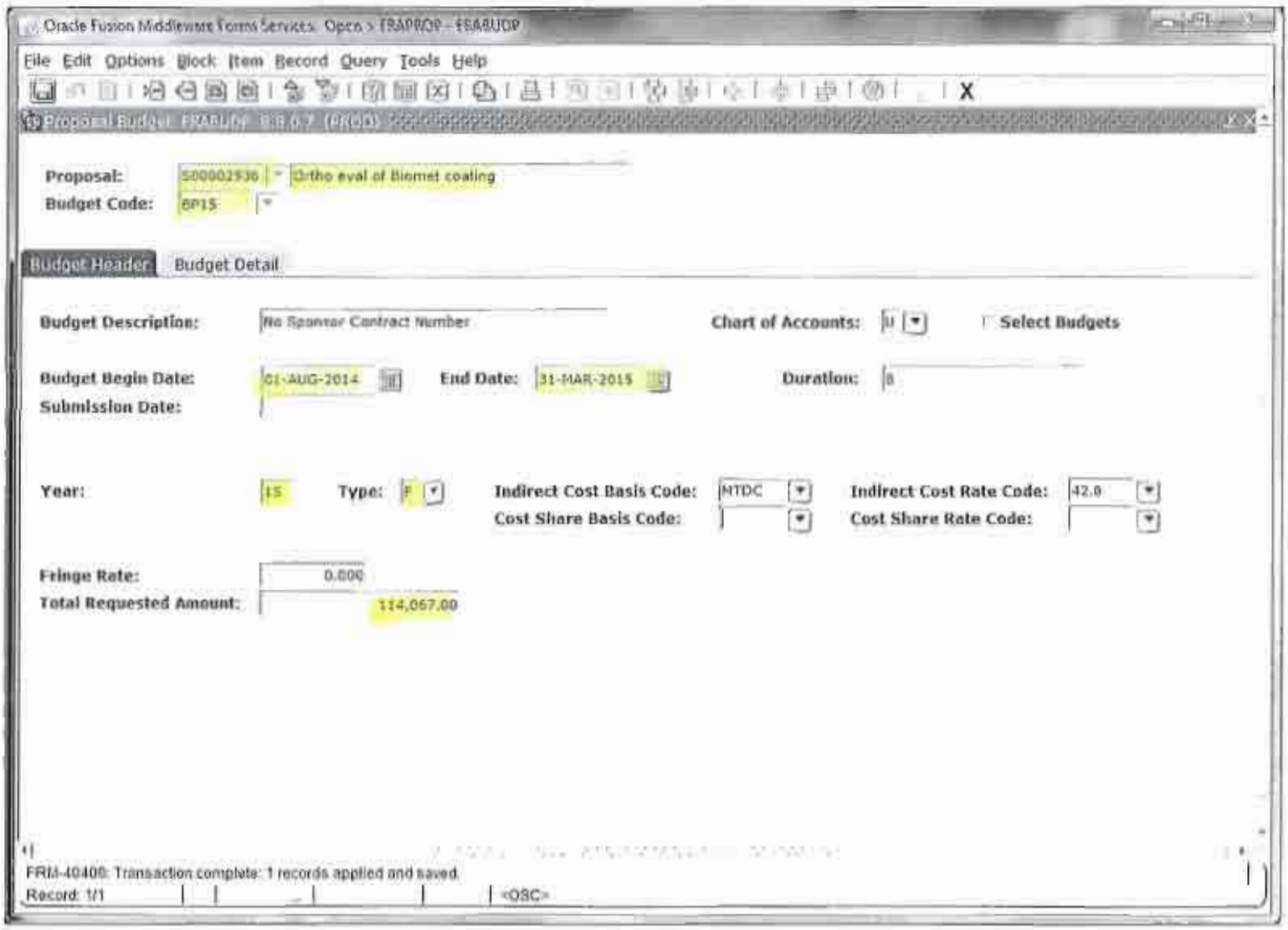
Main
Proposal Agency
Location
Cost Code
Personnel
User Defined Data
Pass Through Agency
Chart of Accounts: U
Responsible Organization: 241109 Biomed Jessica Jennings
Long Title: Orthopaedic evaluation of Biomet anti-infective coating
Title: Ortho eval of Biomet coating
Agency: U00330913 University of Memphis Research Foundation
Principal Investigator ID: U00237651 Jennings, Jessica A.
Amount Requested: 114,067.00
Pass Through Indicator
Original Date: 23-JUN-2014
Due Date:
Submit Date:
Status: F Funded BP15
Alternate Description: BP15
Status Date: 23-OCT-2014
Project Start Date: 01-AUG-2014
Project End Date: 31-MAR-2015
Grant:
Budget Start Date: 01-AUG-2014
Budget End Date: 31-MAR-2015
Expected Date:
Related Proposal:
Probability Rate:
Proposal Type: RS Research
Category: P Private Grants
Sub Category: CORP Industry and Corporation
CFDA Number:
Sponsor ID: BIOMET VIA UMRF
Enter the Grant Code
Record: 1/1
<OSC>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Proposal: S00002936 Ortho eval of Biomet coating
Budget Code: BP15
Budget Header
Budget Detail
Budget Description: No Sponsor Contract Number
Chart of Accounts: U
Select Budgets
Budget Begin Date: 01-AUG-2014
End Date: 31-MAR-2015
Duration: 8
Submission Date:
Year: 15
Type: P
Indirect Cost Basis Code: MTDC
Indirect Cost Rate Code: 42.0
Cost Share Basis Code:
Cost Share Rate Code:
Fringe Rate: 0.000
Total Requested Amount: 114,067.00
FRM-40400: Transaction complete: 1 records applied and saved.
Record: 1/1
<OSC>

Total Project Costs 241,064
Proposed Budget for PI: A Jennings
Sponsor: Biomet
Project Title: Orthopaedic evaluation of anti-infective coating
Project Number: S-
Budget prepared by: J A Jennings FOR INTERNAL USE ONLY
jw 5/28, 6/6 Please complete all cells that apply Totals are calculated automatically.
6/19/14
aj 08/04/14 awf 09/04/14

Project Period Start 08/01/14
Project Period End 03/31/15
Budget Period Start 08/01/14
Budget Period End 03/31/15

Banner Code	awf 08/06/14 - (adjusted UAMS sub budget to match their justification)		Base Salary	% Effort	phase I Year 1 Months 1-5 Sponsor	UM	Phase II Year 2 Months 5-12 Sponsor	UM	Year 3 Sponsor	UM	Total Sponsor	UM
I Salaries and Wages												
Salaried (monthly) Employees												
A Co-Investigator		Warren Haggard										
Please indicate all effort on the project regardless of funding source.												
61266 1 Acad yr			$ 187,527	5%		5,860	-		-		-	-
61254 2 Summer (9 month appointments only)			46,881	10%							-	-
B Principal Investigator		Amber Jennings										
61266 1. Acad yr		Phase I	$ 66,438	37%	10,243				-		10,243	-
61266 1. Acad yr		Phase II	$ 66,438	20%			7,751				7,751	
61254 2 Summer (9 month appointments only)			22,146	0%	-		-				-	-
C Co-Investigator												
61266 1. Acad yr			$ -	0%	-		-				-	-
61254 2 Summer (9 month appointments only)			-	0%	-		-		-		-	-
D Co-Investigator												
61266 1. Acad yr			$ -	0%	-		-		-		-	-
61254 2. Summer (9 month appointments only)			-	0%	-		-		-		-	-
E Other (monthly)Personnel		specify	$ -	0%	-		-		-		-	-
F. Hourly (bi-weekly) Employees		specify	$ -	0%	-		-				-	-
G. Temporary Employees											-	-
							-				-	-
											-	-
H. Student Employees			# std	Rate/mo							-	-
61257 Graduate Assistants (include tuition amount below)							-				-	-
1. Acad yr (9 mos)			0	$1,917	-		-				-	-
2 Summer (3 mos)			0	$1,917	-		-		-		-	-
61410 Student Workers - hourly		(TBD)	2	800	8,000		11,200		-		19,200	-
Total Salaries & Wages					18,243	5,860	18,951	-	-		37,194	5,860
											-	-
II. Fringe Benefits											-	-
35.8%		salaried employees (monthly)			3,647	2,086	2,759	-	-		6,406	2,086
57.1%		hourly employees (bi-weekly)			-	-	-	-			-	-
7.8%		temporary employees			-	-	-	-			-	-
62000		Subtotal II			3,647	2,086	2,759	-	-		6,406	2,086
											-	-
III Travel - Domestic or International (select)					1,600		1,600		-		3,600	-
73000		Subtotal III			1,600	-	1,800	-	-		3,600	-
											-	-
IV. Supplies < $5000											-	-
74500 Supplies					4,000		2,000		-		6,000	-
74504 Non-capitalized equipment < $5,000					-		-		-		-	-
		Subtotal IV			4,000	-	2,000	-	-		6,000	-
											-	-
V. Equipment >$5000					-		-		-		-	-
		Subtotal V			-	-	-	-	-		-	-
											-	-
VI. Tuition/fees for graduate assistant(s) @			10,310		-		-		-		-	-
79713 est for 2011-12		Subtotal VI			-	-	-	-	-		-	-
											-	-
VII. Consultant		Harry Courtney			700		800		-		1,500	-
Consultant		Robert Skinner			2,000				-		2,000	-
		Subtotal VII			2,700	-	800	-	-		3,500	-
VIII.												
Subawards												
77830 Subcontracts < $25,000									-		-	
77840 Subcontracts greater than $25,000							-				-	
77830 Subcontracts < $25,000		UAMS-Smeltzer			25,000		-		-		25,000	
77840 Subcontracts greater than $25,000					35,413		89,637				125,050	
77830 Subcontracts < $25,000					-						-	
77840 Subcontracts greater than $25,000					-		-		-		-	
					-		-		-		-	
		Subtotal VIII			60,413		89,637		-		150,050	-
VIV												
Other (list all applicable expenses)											-	-
74160 Publication							-		-		-	-
74220 Long distance											-	
		Subtotal VIII			-	-	-	-	-		-	-
											-	-
		Total Direct Costs			90,803	7,946	115,947	-	-		206,750	7,946
IX For Research Support Services completion											-	-
Facilities and Administration Costs*											-	-
Choose MTDC or TDC. Enter rate in one box and 0 in other box												
MTDC 42.0% Full rate charged to sponsor					23,264		11,050		-		34,314	-
MTDC 0.0% University contribution						3,337					-	3,337
TDC 0.0% Reduced rate charged to sponsor					-		-				-	-
MTDC 41.0% University contribution - waived F&A											-	-
79800		Subtotal IX			23,264	3,337	11,050	-	-		34,314	3,337
											-	-
		Total Project Costs			114,067	11,283	126,997	-	-	-	241,064	11,283

* F&A: Exception to the full federal indirect cost rate is requested for the following reason:
_____ State of TN agency @ 15% TDC
X Prime sponsor allows a maximum of 42% as verified by
_____ sponsor guidelines (provide reference)

Please provide an index number for all direct costs borne by the University at the time the budget is submitted. Multiple index numbers should be provided if portions of the budget will be charged to different accounts.

Sponsored Research Agreement

THIS SPONSORED RESEARCH AGREEMENT (hereinafter, "Agreement"), effective 08/01/2014 (hereinafter the "Effective Date"), is entered into by and between The University of Memphis Research Foundation (hereinafter "UMRF"), with offices located at 308 Administration Building, Memphis, TN 38152, and Biomet Manufacturing LLC, with offices located at 56 East Bell Drive, Warsaw, IN 46581 (hereinafter "Sponsor").

WITNESSETH

WHEREAS, Sponsor is interested in scientific research related to "***Orthopaedic Evaluation of Biomet Anti-Infective Coating – Phase I***" and Sponsor is willing to fund such research.

WHEREAS, UMRF and the University of Memphis (hereinafter referred to as "University") have entered into an agreement wherein University performs research and service projects under agreements executed by UMRF with outside sponsors, and UMRF manages and controls University's interest in intellectual property rights created under said agreements with outside sponsors; and

WHEREAS, research contemplated by this Agreement may be of mutual interest and benefit to UMRF and Sponsor, will further the instructional, research and public service missions of University in a manner consistent with its status as a nonprofit, tax-exempt, educational institution, and may derive benefits for both University and Sponsor through the advancement of knowledge;

WHEREAS, UMRF is interested in proceeding with such research if Sponsor is willing to fund such research;

WHEREAS, UMRF expects that $ 114,067.00 in outside funding for the research will come from Sponsor.

NOW, THEREFORE, in consideration of the premises and the mutual covenants and conditions hereinafter recited, the parties do hereby agree as follows:

1. Definitions

For purposes of this Agreement, the following definitions apply:

1.1 "Contract Period" shall mean the period commencing on the Effective Date of this Agreement and terminating on March 31, 2015. The term of this Agreement may be extended by the mutual written consent of the duly authorized representatives of UMRF and Sponsor.

1.2 "Principal Investigator" shall mean Dr. J Amber Jennings, appointed by UMRF to conduct the Project Research hereunder.

1.3 "Project Research" shall mean research pertaining to "Orthopaedic Evaluation of Biomet Anti-Infective Coating Phase I" as described more fully in Exhibit A, which is attached hereto and incorporated herein by reference.

1.4 "Project Funds" shall mean those funds paid by Sponsor to UMRF for the Project Research in accordance with this Agreement.

1.5 "Project Team" shall mean the Principal Investigator and the research technicians under the Principal Investigator's direction and control who are supported in whole or in part by the Project Funds.

2. Research

During the Contract Period, the Project Team shall conduct Project Research on behalf of Sponsor. UMRF agrees to commence the performance of the Project Research within a reasonable time after the effective date of this Agreement, and further agrees to complete such Project Research substantially in accordance with the terms and conditions of this Agreement. UMRF agrees to advise Sponsor of the results of the Project Research. Status reports on a regular basis and in response to inquiries from Sponsor shall be provided either orally or in writing. A final written report setting forth the results achieved under and pursuant to the Project Research shall be submitted by UMRF to Sponsor within ninety (90) days of termination of the research which is the subject of this Agreement.

UMRF may elect and shall promptly advise Sponsor in respect to any changes in the personnel comprising the Project Team, including changes to the Principal Investigator. If, for any reason, the Principal Investigator ceases to be associated with the UMRF or University, or otherwise becomes unavailable to work on the Project Research, a qualified replacement at the UMRF or University shall be mutually appointed by UMRF and Sponsor to be the Principal Investigator, or, at Sponsor's sole option, this Agreement shall be terminated on thirty (30) days written notice provided that Sponsor agrees to reimburse UMRF for all costs/fees accrued by UMRF as of the effective date of termination.

3. Payments

3.1 Sponsor shall pay UMRF the Project Funds in the following manner:

(a) Amount: $114,067.00

(b) Method of Payment: Fixed Fee, payable in Three (3) payments

(c) Payments: Three (3) payments as follows:
[1] $ 57,033.00 – Phase One: First payment due upon contract execution.
[2] $ 47,034.00 – Phase One: Second payment due upon completion of surgeries.
[3] $ 10,000.00 - Phase One: Third and final payment due upon submission and receipt of the final report.

3.2 Payments under the terms of this Agreement shall be made by check payable to:

Name on check: The University of Memphis Research Foundation
Administration Building, Room 308
Memphis, Tennessee 38152
Reference: PI: Jennings S-2555

UMRF Tax ID #: 20-5400381

3.3 Anything herein to the contrary notwithstanding, should this Agreement be subject to early termination pursuant to Articles 2 and 6 herein, Sponsor shall pay all costs covered under this Agreement accrued by UMRF as of the effective date of termination, but in no event shall such costs exceed the amount of Project Funds set forth in Section 3.2(a).

4. Non-Disclosure Agreement and Publications

4.1 Subject to that certain Confidentiality and Non-Disclosure Agreement between Sponsor and University, dated June 3, 2013, nothing in this Agreement shall be construed to limit the freedom of the Principal Investigator, physicians, research scientists, or other individuals conducting the Project Research, whether paid under this Agreement or otherwise, to engage in similar research performed independently under other grants, contracts, or agreements with parties other than Sponsor.

4.2 In the exercise of the rights of academic freedom of an educational institution or research foundation and its faculty, UMRF, University, the Principal Investigator, and the Project Team shall have the right to present at symposia, national or regional professional meetings and to publish in scientific or other journals, the

results of the Project Research conducted under this Agreement. In order to permit Sponsor the opportunity to properly protect any of Sponsor's patent and/or proprietary rights relating to the Project Research, and to preserve its trade secrets, a copy of each proposed publication shall be provided to Sponsor forty-five (45) days in advance of submission for publication to permit Sponsor time in which to prepare application(s) for letters of patent regarding the subject matter of such publication, or to require deletion of proprietary information covered by trade secrets. Any final proposed publication provided to Sponsor shall be considered as acceptable for submission for publication unless Sponsor notifies UMRF and the Principal Investigator in writing within thirty (30) days of receipt of the proposed publication that it requires additional time to secure protection for Sponsor's patent and/or proprietary rights, in which case Sponsor shall have an additional forty-five (45) days to undertake such action before publication; or that there are trade secrets disclosed in the proposed publication and Sponsor will have an additional 45 days to attempt to reach an agreement with UMRF and the Principal Investigator as to the deletions or changes required in the proposed publication. In the event that Sponsor and UMRF and Principal Investigator are unable to reach such agreement, then Sponsor shall advise which portions of the proposed publication must be deleted to avoid disclosure of the trade secret information. Sponsor shall also receive final drafts of any proposed publication and Sponsor shall be named in the publication as Sponsor of the Project Research or, if applicable, the licensor or licensee of such technology. The right to review publications as set forth herein shall extend only to the work product of the Principal Investigator and the Project Team pursuant to the Project Research and not to the work product of other research conducted in the laboratories of the Principal Investigator, or member of the Project Team, or in the laboratories of other researchers at the UMRF or University.

5. Ownership of Intellectual Properties

Sponsor shall retain sole ownership of anti-infective lipid paste and all intellectual property rights associated therewith; provided, however, that Sponsor hereby grants to UMRF and University non-exclusive rights to use anti-infective lipid paste during the contract period solely in connection with the Project Research as stated in Exhibit A. Any UMRF or University intellectual properties, including methods, procedures and survey instruments, utilized in performance of the Project Research shall remain the property of the UMRF or University.

6. Termination

This Agreement shall remain in effect for the Contract Period unless extended in accordance with the terms of this Agreement, as set forth in Section 1.1. In the event that either party shall be in default of any of its obligations under this Agreement and shall fail to remedy such default within thirty (30) days after receipt of written notice thereof, the party not in default shall have the option of canceling this Agreement by giving ten (10) days written notice of termination to the other party.

Either party may terminate this Agreement without cause upon thirty (30) days prior written notice. If Sponsor shall be the terminating party, Sponsor shall be responsible for any required payments under this Agreement through the date of the termination notice. If UMRF shall be the terminating party under this paragraph, then Sponsor's obligation to make any further payments from the date of the notice of termination shall be eliminated and UMRF shall refund to Sponsor the amount of Sponsor's last payment to UMRF under Section 3.1 remaining after deduction of all costs and expenditures incurred as of the date of the notice of termination.

The Project Research requires approval by the University Institutional Review Board (IRB). In the event IRB approval is not granted this Agreement shall be terminated; such termination shall not be considered breach of agreement.

Termination of this Agreement shall not affect the rights and obligations of the parties which shall have accrued prior to termination. No termination of this Agreement, however effectuated, shall release the parties from their rights and obligations under Articles 3, 4, 5, 6, 7, 11 and 18 herein.

7. Indemnification

Sponsor agrees to defend, indemnify and hold harmless the UMRF, University, the Tennessee Board of Regents, and the State of Tennessee and their officer and employees (all such parties are hereinafter referred to collectively as the "Indemnified Parties") from and against any and all liability, claims, lawsuits, losses, demands, damages, costs, and expenses (including reasonable attorney's fees and court costs), arising directly or indirectly out of the Project Research or the design, manufacture, sale or use of any embodiment or manifestation of the Project Research relating to Sponsor's gross negligence or intentional misconduct. Notwithstanding the foregoing, Sponsor will not be responsible for indemnification of UMRF or University pursuant to this Article 7 for any liability, claims, lawsuits, losses, demands, damages, costs, and expenses (including attorney's fees and court costs) which arise solely from:

(a) the gross negligence or intentional misconduct of UMRF, University or the Principal Investigator, and
(b) actions by UMRF, University or the Principal Investigator in violation of applicable laws or regulations.

Sponsor agrees to provide a diligent defense against any and all liability, claims, lawsuits, losses, demands, damages, costs, and expenses (including attorney's fees and court costs), brought against the Indemnified Parties with respect to the subject of the indemnity contained in this Article 7, whether such claims or actions are rightfully or wrongfully brought or filed. UMRF and/or University shall be indemnified by Sponsor after UMRF and/or University have completed the following:

(a) within a reasonable time after its receipt of notice of any and all liability, claims, lawsuits, losses, demands, damages, costs, and expenses, or after the commencement of any action, suit, or proceeding giving rise to the right of indemnification, notify Sponsor, in writing, of said liability, claims, lawsuits, losses, demands, damages, costs, and expenses and send to Sponsor a copy of all papers served on the Indemnified Party; and

(b) allow Sponsor to retain control of any such liability, claims, lawsuits, losses, demands, damages, costs, and expenses, including the right to make any settlement; provided that the Attorney General for the State of Tennessee reserves the right to participate in the defense of any such action on behalf of the University and the parties further acknowledge that no settlement or compromise shall be binding upon University and the State of Tennessee unless approved by the Attorney General and/or binding upon UMRF without prior written approval by UMRF.

8. Insurance

During the term of this Agreement, Sponsor shall maintain in full force and effect a policy or policies of:

general liability insurance (with broad form liability endorsements) with limits of not less than $5,000,000 per occurrence and $5,000,000 in the aggregate; and products liability insurance with limits of not less than $5,000,000.

9. Conflict of Interest

Sponsor warrants that no part of the total contract amount provided herein shall be paid directly or indirectly to any officer or employee of the UMRF, University or State of Tennessee as wages, compensation, or gifts in exchange for acting as officer, agent, employee, sub-contractor, or consultant to Sponsor in connection with any work contemplated or performed relative to this Agreement.

10. Independent Contractors

Sponsor and UMRF shall act as independent parties and nothing contained in this Agreement shall be construed or implied to create an agency or partnership. Neither party shall have the authority to contract or incur expenses on behalf of the other except as may be expressly authorized by collateral written agreements. No member of the Project Team shall be deemed to be an employee of Sponsor.

11. Use of Institution Name

The use by Sponsor of UMRF's name, University's name, Principal Investigator's name, or any other names, insignia, symbol(s), or logotypes associated with the UMRF or University or any variant or variants thereof in advertising, publicity, publications or promotional activities or media is expressly prohibited unless required by law or written consent is provided by UMRF. Sponsor shall submit requests for use of name, insignia, symbol or logotypes to the Principal Investigator with copy to Dr. Andrew Meyers, at the addresses in Article 15. The request for use of name shall include a copy of the actual graphic, print document or other media which incorporates the name, symbol, insignia or logotype. Project Team members, including the Principal Investigator, are not authorized to grant consent.

12. Choice of Law

This Agreement shall be governed, construed and enforced in accordance with the laws of the State of Tennessee as the site for performance of this Agreement without regard to its conflict of laws.

13. Severability

If any one or more of the provisions of this Agreement shall be held to be invalid, illegal or unenforceable, the validity, legality or enforceability of the remaining provisions of this Agreement shall not in any way be affected or impaired thereby.

14. Waiver

The failure of any party hereto to insist upon strict performance of any provision of this Agreement or to exercise any right hereunder will not constitute a waiver of that provision or right. This Agreement shall not be effective until approved by UMRF's Executive Director or his designee.

15. Notices

Any notice or communication required or permitted to be given or made under this Agreement by one of the parties hereto to the other shall be in writing and shall be deemed to have been sufficiently given or made for all purposes if mailed by certified mail or overnight express courier, postage prepaid, return receipt requested, addressed to such other party at its respective address as follows:

If to Sponsor:

Dr. Karen Troxel
Director, Biomaterials Research
56 East Bell Drive
Warsaw, IN 46582
Phone: (574) 372-1604
Fax: (574) 268-2742

If to UMRF:

Dr. Andrew Meyers, Executive Director
University of Memphis Research Foundation
308 Administration Building
Memphis, Tennessee 38152
Phone: (901)678-2590
Fax: (901) 678-2199

If to Principal Investigator:

Dr. J. Amber Jennings

University of Memphis
Department of Biomedical Engineering
330 Engineering Technology Building
Memphis, TN 38152
Phone (901) 678- 3733
Phone (901) 678-5281

16. Assignment

Neither party shall assign their rights or obligations under this Agreement without the prior written consent of the other party, except to an affiliate of a party in connection with any reorganization or restructuring. However, by execution of this Agreement, Sponsor agrees that the work can be performed by the University of Memphis on behalf of the UMRF.

17. Entirety

This Agreement represents the entire agreement of the parties and it expressly supersedes all previous written and oral communications between the parties. Neither party was induced to enter into this Agreement by any statements or representations not contained in this Agreement. This Agreement may be modified only by written amendment executed by all parties hereto.

18. Warranties

Sponsor and UMRF make no warranties, express or implied, concerning the results of the Project Research or of the merchantability or fitness for a particular purpose of such Project Research or results.

19. Civil Rights

Neither party shall discriminate against any individual including, but not limited to, employees or applicants for employment and/or students because of race, religion, creed, color, sex, sexual orientation, age, disability, national origin, or status as a disabled or Vietnam era veteran. Further, the parties agree to take affirmative action to ensure that applicants are employed and that employees are treated during their employment without regard to their race, religion, creed, color, sex, age, disability, national origin, or status as a disabled or Vietnam Era veteran.

20. Headings

The headings of sections and subsections, if any, to the extent used herein are for convenience and reference only, in no way define, limit, or describe the scope or intent of any provision hereof, and therefore shall not be used in construing or interpreting the provisions hereof.

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be executed in duplicate counterpart original by their duly authorized representatives to be effective as of the Effective Date.

BIOMET MANUFACTURING LLC

By: _____

10/17/2014
Date

THE UNIVERSITY OF MEMPHIS RESEARCH FOUNDATION

By: _____
Andrew Meyers
Executive Director

10/17/14
Date

(Proprietary)

Orthopaedic evaluation of Biomet anti-infective coating
Research Proposal
Pls: Jessica Amber Jennings; Warren O. Haggard
University of Memphis

Overview

The growing clinical need for inventive and effective therapeutic approaches to treat musculoskeletal infections following fractured bone, musculoskeletal implants, and bone grafts is evidenced by the incidence rate of infection reported at between 3.6–8.1% for closed fractures and as high as 17.5%–21.2% in open factures [1]. The imperative for revised approaches is underscored by the facts that infection is the listed cause for 25.2% of knee implant revision surgeries, the estimated cost per case is between $50,000 and $60,000, and the number of knee implant revisions is estimated to have grown from 22,000 in 2000 to 58,000 in 2010 [2-4]. In treating musculoskeletal infections, local delivery of antibiotics offers an advantage over standard systemic antibiotic administration, improving antimicrobial efficacy while reducing toxic side effects. The most commonly used antibiotic delivery systems have limitations in biodegradability, antibiotic concentration and coverage levels, compatibility with selected drug, and/or inflexible drug elution kinetics. Thus, there is an urgent clinical need for more effective therapeutic approaches, including novel antimicrobial delivery mechanisms, as well as preventive procedures for musculoskeletal infections that will improve outcomes and lower health care costs. Customizable, naturally degradable local delivery systems that can be applied directly to an implant for used for fixation, stabilization, or joint replacement are needed to eliminate infection and thus promote bone repair.

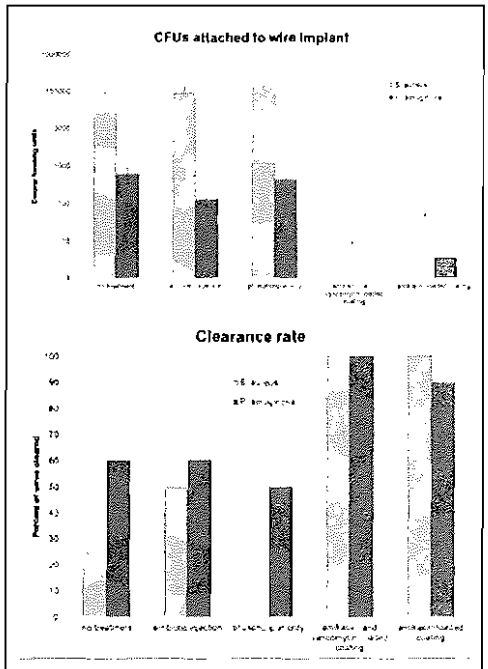

Figure 1. A) Graph of CFU count from wire implants retrieved from in vivo study (n=10). B) Rate of clearance of implants from bacterial attachment. Data represented is mean ± standard deviation. Asterisks represent significant reduction in CFUs compared to uncoated control.

In a recent proof of principle study, an anti-infective coating composed of antibiotic-loaded phospholipon demonstrated efficacy in vitro and in vivo in prevention of bacterial biofilm formation. The coatings were found to 1) elute active antibiotics, 2) inhibit or prevent biofilm formation on metal surfaces, and 3) prevent colonization of bacteria on coated wires in a polymicrobial preclinical in vivo model (Figure 1). The advantage of this mouse catheter model was that it

provides a relatively high-throughput method to screen for efficacy of treatments in the clinically relevant context of the intrinsic resistance of biofilm-associated infections. In this model, catheters are implanted subcutaneously to provide an easily accessible substrate for biofilm formation and for delivery of alternative therapeutic reagents [5].

In order to fully characterize performance of the implant coating in the context of orthopaedic implants, further studies are required. Efficacy in preventing bacterial contamination in bone fractures and/or medical implants, tissue response, and issues of implant handling should be evaluated in relevant preclinical models.

Hypothesis/ Objective

Our hypothesis for the proposed study is that coating a representative orthopaedic implant with antibiotic-loaded crayon coating will prevent bacterial contamination of the implanted device and surrounding tissue, reduce the degree of osteomyelitis, and promote normal bone healing and tissue responses. To test this hypothesis, the objective of this study will be to evaluate the efficacy of the antibiotic-loaded crayon in the context of a preclinical orthopaedic infection model in the rabbit radius.

Specific Aims

- **Specific Aim 1.** Efficacy in reducing bacterial attachment to implant materials and in reducing progression of osteomyelitis in a rabbit radial model will be characterized through bacterial and histologieal methods.
- **Specific Aim 2.** Soft tissue and bone response, as well as implant apposition, in the osteomyelitic model will be investigated through radiographic and histological techniques.

Approach

The involvement of a large bone segment makes infection treatment extremely critical because of the poor vascular supply, mineral and peptide content favoring bacterial adherence, and complex porous structure sequestering bacteria. Due to the high rate of occurrence of bacteria attaching to the surface of these implanted biomaterials, prevention and treatment of contaminating bacteria and adherent biofilm formation within an orthopaedic defect with metal fixation implants presents a much more challenging problem. Therefore, we will evaluate the effectiveness of local delivery of antibiotics through the point-of-care antibiotic crayon using a rabbit model of postsurgical bone- and implant-associated bacterial contamination and infection (or "rabbit radial model") with fixation using an intramedullary (IM) nail [6]. This established complex infected rabbit model for prevention and treatment has additional anatomical space and both bone and soft tissue involvement for more effective evaluation of implant performance and tissue response of the coating over smaller models [7].

Experimental Design

The procedures for these studies will provide an assessment of the utility of the antibiotic crayon for prevention of bacterial growth and biofilm formation leading to potential orthopaedic infection following surgery with emphasis on the role of orthopaedic devices often required for fixation. To these ends, we will employ an established rabbit model of postsurgical bone infection to establish proof-of-principle and evaluate dosing of antibiotics and coating (Figure 2). The rabbit model has been adapted for the use of various types of implants, but in these

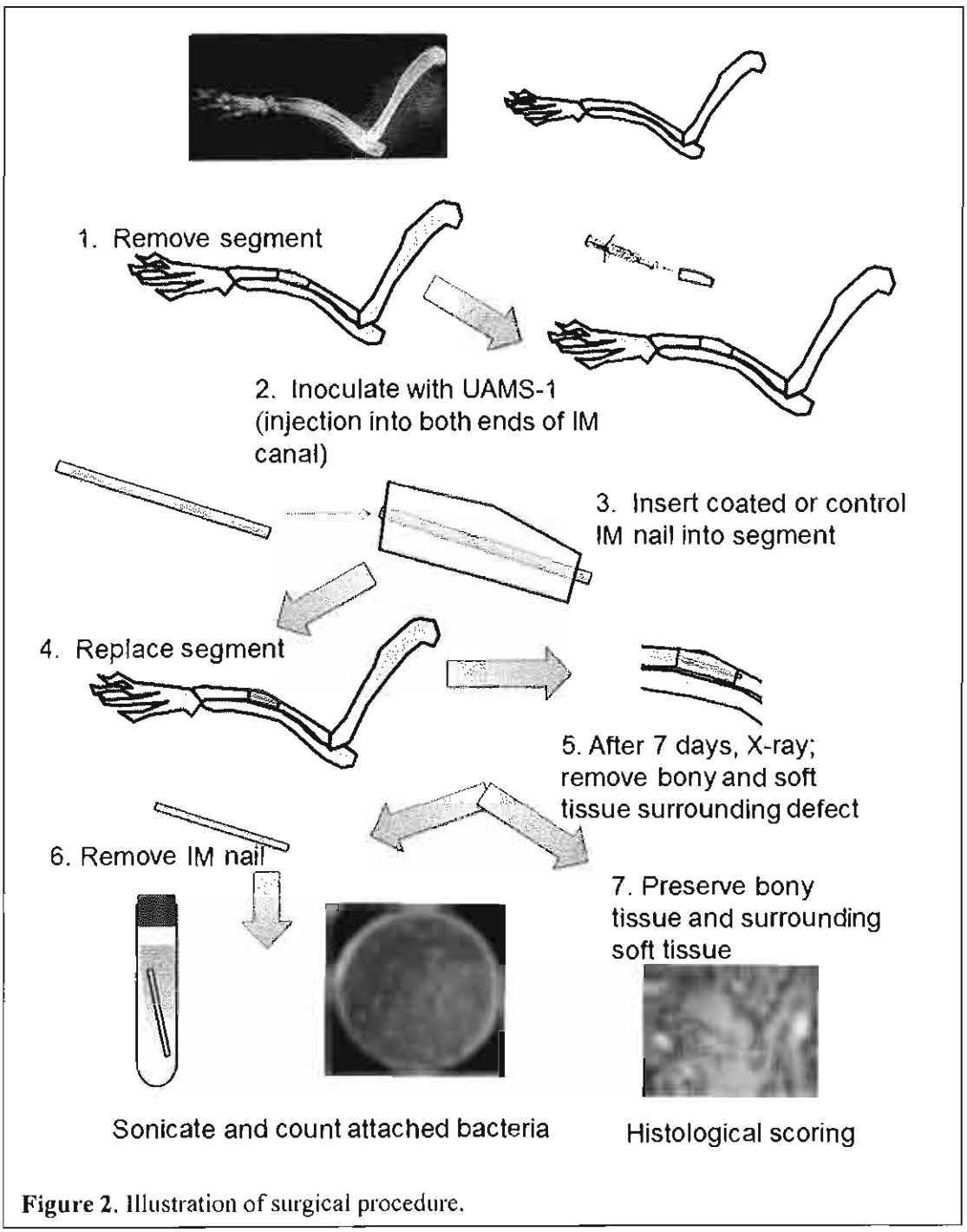

Figure 2. Illustration of surgical procedure.

Table 1. Projected animal use

Pilot study

No treatment	Coated pin 25% vancomycin crayon	**Total**
6	6	**12**
	Grand total	**12**

experiments we will employ an IM nail based on its relative simplicity and accurate reflection of a clinically relevant use (Figure 3). The IM nail will be modified to increase surface roughness to retain more coating and increase the available antibiotic for release.

Phase I studies

The rabbit radial model uses male New Zealand White rabbits weighing 2–3 kg (slightly larger rabbits will be used to facilitate the surgical procedures). Initially a pilot study with 6 animals in each group will be conducted with the current antibiotic dosage level identified to inhibit biofilm in the catheter wire model (Table 1) compared to implanted pin with no coating. This pilot study will confirm the appropriateness of the model as well as identify any potential dose, formulation, or implantation issues that may need to be revised prior to the definitive expanded study. Revisions to the model after analysis of results may include revising coating procedures, implant surfaces, or the use of a different model such as the murine model of osteomyelitis [7]

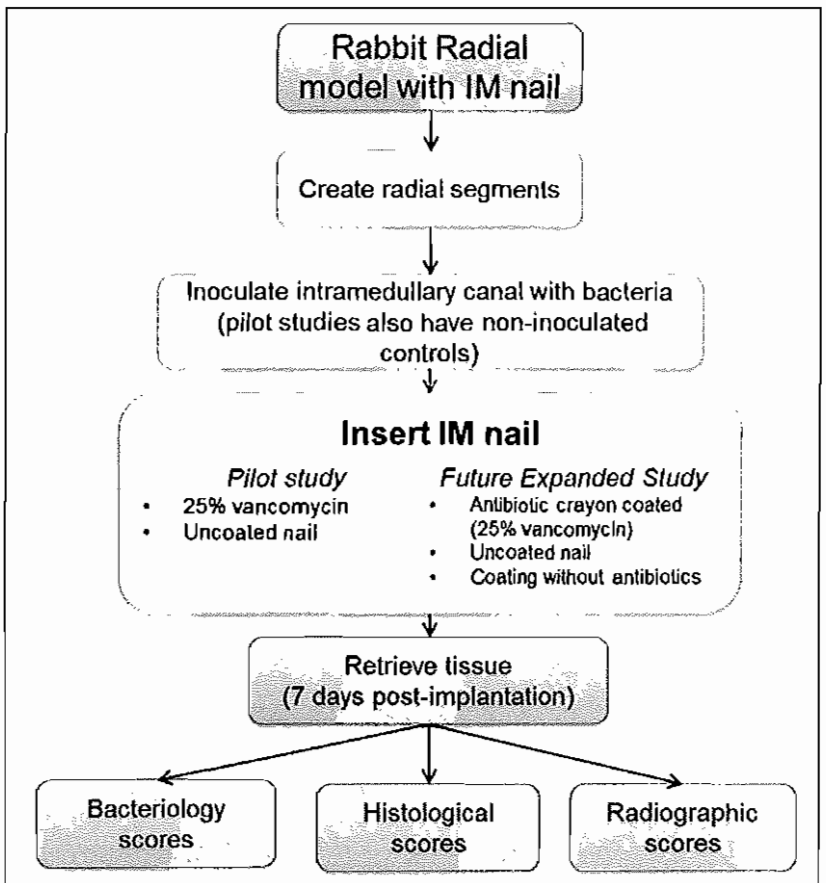

Figure 3. Flow chart of in vivo experiments.

Future studies will expand on groups for meaningful control groups for thorough evaluation of tissue response and

antimicrobial efficacy. Groups for expanded studies will include antibiotic-coated pins, pins coated with phospholipon only, and uncoated pins. Further, baseline non-infected tissue response will be confirmed. The expanded study will also increase animal numbers in groups with antibiotic-coated pins to uncoated pins improve the power to detect statistical differences in responses. In the expanded, definitive study, each experimental group will consist of 6 rabbits based on the statistical analysis of our preliminary experiments including the power analysis [6, 8].

Under sedation and anesthetic, a one-cm midradial segment will be excised from the right forelimb. The remaining bone tissue will be subsequently infected by inoculation of bacteria directly into the intramedullary canal of the segment. A titanium nail (Biomet), coated with antibiotic crayon or uncoated control will be inserted into the intramedullary canal after inoculation with bacteria. After surgery, rabbits will be removed from the anesthetic and observed until awake and mobile. Postoperative analgesics (0.05 mg Buprenex per kg) will be administered to all animals immediately after surgery and will be continued with any animals that exhibit a reluctance to use the affected limb. Rabbits will be examined daily and monitored for any signs of systemic disease (e.g., fever). Rabbits infected as we describe typically exhibit a normal appetite within several hours after surgery and, because the ulna is left intact, return to full mobility within 1–2 days. Nevertheless, any animal that develops systemic signs of disease will be treated and excluded from the experiment. Rabbits will be euthanized after 7 days and imaged by X-ray, and limbs and surrounding tissue will be retrieved for subsequent histological and bacteriological analysis [6, 9] The IM pin will be removed, vortexed and sonicated to remove bacteria, and analyzed to determine the degree of bacterial attachment to the orthopaedic hardware.

At the completion of the overall experiment (7 days post initial surgery), the infection status of each rabbit will be confirmed by multiple assessments. Specifically, we will note signs and symptoms of osteomyelitis including swelling, redness, warmth, abscess, and draining sinus tract from the infected site. At the end of each experiment, rabbits will be sedated as described above and then euthanized by administration of 0.25 ml pentobarbitone per kg delivered by intra-cardiac puncture. The entire right forelimb will then be removed for analysis. The disarticulated limb will be X-rayed using an AXR closed-system small animal radiograph. Both anterior-posterior (AP) and lateral views will be taken. Any extraneous skin and musculature will then be removed. A sample of the bone will be obtained for bacteriological analysis using a sterile Rongeurs. The remainder of the specimen will be processed for histology. Stains will include both H&E and a Gram-stain to detect the presence of intraosseous Gram-positive cocci.

This study will be used to assess the coating as a preventative measure. Future evaluations may include treatment of established infection as in recent publications with collaborators [8, 10]. In these studies modeling chronic infection or infected revision procedures, infection is allowed to develop for 3 weeks prior to implant placement, after which it is

minimally debrided and implants and local delivery devices are placed. Procedures for analysis are similar to those previously described [10].

Statistical Analyses. Based on previous studies, which to date have used almost 1000 rabbits, we have established that differences in bacteriological, radiographic, and histological scores range between 1.5 to 2.5 standard deviation (SD) when comparing treated and control groups. These studies will employ 6 rabbits/group and will have at least 0.80 power to detect differences of at least 1.8 SD with .05-level tests.

Expected Results. Investigators and collaborators have extensive experience with this model, including the surgeries themselves, debridement, installation of hardware, and comprehensive and quantitative analysis of results. We are confident that the antibiotic crayon will provide prophylactic inhibition of bacterial attachment to implants and reduce the development of bone infection. Results of this project will set the stage for further improvement and development of the delivery matrix itself and provide a platform for testing these coatings with different antibiotics and/or different formulations for efficacy in the specific context of the growing problem of biofilm-associated bone and implant-associated infections.

Potential Problems and Alternative Solutions. The tested drug delivery system or positive control may not completely eliminate contaminating bacteria in this rabbit radial model. In that case, the IM nail design will be examined and revised as needed. Alternative antibiotics or combinations of antibiotics also may be investigated. Coating procedures and studies of coating retention may also be pursued. A murine model of osteomyelitis is also available to model bone healing in a small animal with implanted orthopaedic pin [7].

Animal Model Justification

We believe the use of this model is justified because it is not possible to accurately evaluate diagnostic and treatment modalities relying solely on *in vitro* protocols. Importantly, the rabbit model allows us to address issues that cannot be addressed with other models including surgical debridement, localized antibiotic delivery, and the impact of metallic implants on biofilm formation and treatment response. More specifically, the choice of animal is based on 1) the ease with which the surgical procedure can be performed, 2) the fact that, because the ulna is left intact, removal and reinsertion of the midradial bone segment does not disable the animal and 3) we have carefully established the appropriate time and dose parameters required for the successful completion of the experiments we propose. This model involves both bone and soft tissue as found in infected orthopaedic sites and can be conducted with and without fixation hardware [10].

EXHIBIT A

Budget

Tasks and Projected Timeline

Months	1	2	3	4	5
Protocol writeup-Phase I					
Protocol approval- Phase I					
Coating fabrication					
Surgical procedures-Phase I					
Retrievals					
Analysis					
Final report-Phase I					
Protocol writeup-Phase II					
Manuscript/Abstract preparation					

[illegible]	[illegible]
Phase I	
Supplies	$5,000
Travel-UAMS/conference presentation	$2,556
Animal study (UAMS)	$30,913
Professional services	$34,918
Total	$114,087

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