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TITLE: Potential Side Effect of Inadvertent Intravascular Administration of Liposomal Bupivacaine

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N/A

14. ABSTRACT

The project examines the safety aspects of the use of EXPAREL for peripheral nerve blocks. EXPAREL is a novel form of the commonly used bupivacaine, which if injected into the close proximity of nerves, can block the conduction of pain signals, thereby acting as a local anesthetic. Potential adverse events might arise during these procedures if the drug is accidentally injected into the vasculature.

These adverse events may arise for at least two distinct reasons:

1. The bupivacaine component of EXPAREL can provoke local anesthetic systemic toxicity (LAST), which in severe cases might cause convulsions and even heart failure. For this reason, it is important to determine the tolerable and toxic doses of EXPAREL, and to study the effectiveness of currently recommended rescue protocols for accidental intravascular injection of local anesthetics in animal studies before human clinical trials can be started.
2. The liposomal component of EXPAREL might also have a potential side effect: complement activation related pseudo-anaphylaxis (CARPA), a hypersensitivity reaction that is triggered by some liposomal drugs, and can occur at the first administration, without prior sensitization, and can have a severe outcome. To study the possibility of these reactions we analyze the cardiovascular and immunological reactions following intravenous administration of liposomal bupivacaine in swine, the most sensitive model currently available.

During the first year of the study we administered Exparel and bupivacaine to rats intravenously as a continuous infusion. Asystole was observed at a dose of 43 mg/kg with Exparel and at a dose of 13.5 mg/kg with bupivacaine. During the period covered by this report we used an up-down method to identify the minimum lethal bolus dose to induce asystole, which was 40 mg/kg for Exparel and 20 mg/kg for bupivacaine.

During the first year of the project we identified that intravenously administered Exparel in swine caused severe hemodynamic alterations at doses as little as 25ul. Further experiments have been performed during the year covered by this report to verify the results. In these experiments we confirmed that Exparel causes severe hemodynamic changes at doses of 50ul or more, which can be prevented by pretreatment with indomethacin, suggesting that cyclooxygenase and thromboxane may have a central role in the etiology of the reaction.

15. SUBJECT TERMS

animals, Exparel, liposomal bupivacaine, intravascular, local anesthetic systemic toxicity, complement activation, rats rodents, swine

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The text of the report must include all sections addressed in the table of contents to include the following. **DO** include the bolded section headings, but **DO NOT** include the *italicized* descriptions of section contents in your submitted reports.

1. **INTRODUCTION:** The project examines the safety aspects of the use of EXPAREL for peripheral nerve blocks. EXPAREL is a novel form of the commonly used bupivacaine, which if injected into the close proximity of nerves, can block the conduction of pain signals, thereby acting as a local anesthetic. If proven to be safe and effective, it could be a viable alternative to continuous infusion of local anesthetics via catheters that can be difficult to place, require expensive pumps, close monitoring, and may be a site for infection. However, potential adverse events might arise during these procedures if the drug is accidentally injected into the vasculature. The bupivacaine component of EXPAREL can provoke local anesthetic systemic toxicity (LAST), which in severe cases might cause convulsions and even heart failure. It is also necessary to study the effectiveness of currently recommended rescue protocols for accidental intravascular injection of local anesthetics because certain properties of EXPAREL differ from the conventional solution of bupivacaine. Intravenous lipid emulsion (ILE) has been shown to be effective in bupivacaine toxicity, and the American Heart Association has recommended its use in the Advanced Cardiac Life Support (ACLS) guidelines. However, in EXPAREL the bupivacaine is encapsulated in liposomes, which might decrease the ability of the intravenously administered lipid emulsion to neutralize the systemic toxic effects. Therefore, we conduct experiments to compare the effectiveness of various resuscitative measures using chest compressions alone, and supplemented with lipid emulsion, epinephrine, vasopressin, and their combinations in rats to find the optimal treatment for EXPAREL overdose. The liposomal component of EXPAREL might also have a potential side effect: complement activation related pseudo-anaphylaxis (CARPA), a hypersensitivity reaction that is triggered by some liposomal drugs, and can occur at the first administration, without prior sensitization, and can have a severe outcome. To study the possibility of these reactions we analyze the cardiovascular and immunological reactions following intravenous administration of liposomal bupivacaine in swine, the most sensitive model currently available.

2. **KEYWORDS:** Exparel, liposomal bupivacaine, intravascular, local anesthetic systemic toxicity, complement activation, rats, rodents, swine
3. **ACCOMPLISHMENTS:**
    - **What were the major goals of the project?**
        - Major Task 1 - Protocol preparation and approval process (6 months) – 100% complete
        - Major Task 2 - Rat studies to determine MTD (4 months) – 100% complete
        - Major Task 3 - Rat studies to determine LD50 (4 months) – 100% complete
        - Major Task 4 - Rat studies to compare effectiveness of ACLS methods for toxicity by EXPAREL (7 months) – not yet started
        - Major Task 5 - Swine experiments to study hypersensitivity to EXPAREL (4 months) – 100% complete
        - Major Task 6 - Publication and final report (5 months) – poster abstract accepted for IASP 2018.
    - **What was accomplished under these goals?**
        - *1) major activities during the period of June 2017 – June 2018: Performance of rat experiments and swine experiments.*
        - *2) specific objectives: Determine Maximum tolerable dose and LD50 of Exparel and Bupivacaine in rats. Determine anaphylactic potential of Exparel in swine*

- *3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative): In swine, intravenously administered Exparel had severe hemodynamic effects at doses as little as 25ul. Indomethacin pretreatment prevented the development of symptoms. In rats, asystole is caused by intravenous infusion of Exparel at a dose of 43 ml/kg and by bupivacaine at a dose of 15 mg/kg. Bolus doses of 40 mg/kg and 20 mg/kg will be used for the comparison of resuscitative methods. The details of the experiments are outlined below.*

A) Rat experiments

Background

The planned research addresses the focus areas of alternatives to current opioid analgesics for severe pain management on the battlefield, remote locations, and in clinical, non-deployed settings. Special emphasis is placed on the safety of an alternative non-opioid analgesic approach utilizing liposomal bupivacaine for peripheral nerve block.

Local anesthetic agents can be used for analgesia by blocking nerve conduction from the site of injury or surgery. Regional anesthesia has played an important role in the care of wounded soldiers in the current conflicts and has become a very important anesthetic technique for managing battlefield casualties. The use of continuous peripheral nerve blocks has become a standard of civilian and military trauma analgesic care. Bupivacaine solutions, a local anesthetic/analgesic widely used in the perioperative and postsurgical settings, have been used for many years by multiple administration routes for the relief of postoperative pain, e.g. via continuous peripheral nerve blocks and direct injection. Continuous infusion of local anesthetics via catheters may extend the duration of the effect, but they can be difficult to place, require expensive pumps, close monitoring, and may be a site for infection.

A recent innovation in the application of local anesthetics is the design of novel drug delivery systems that enable slower, gradual release of the active ingredient, allowing a longer duration of action after a single administration, without the need of continuous infusion. This also leads to a slower uptake into the systemic circulation, eliminating the undesired excessively high peak plasma concentrations and reducing the risk of local and systemic reactions. This would simplify pain management in remote settings and also in the hospital during the postoperative period.

The first FDA approved liposomal local anesthetic formulation, EXPAREL (bupivacaine liposome injectable suspension), is a sterile suspension of multivesicular liposomes created using proprietary DepoFoam formulation technology to release bupivacaine over several days. EXPAREL was designed to provide prolonged analgesia for 72 hours after wound infiltration in patients. A recent study found no local signs of toxicity, including no histological evidence for any increase in local reactions or general exacerbations of bupivacaine toxicity after peripheral nerve block in rabbits and dogs. A single administration of EXPAREL was demonstrated to be safe when tested in comparison with bupivacaine HCl and saline. EXPAREL did not cause overt irritation or local tissue damage even when injected at high dose or concentration around the brachial plexus nerve bundle in these animals.

EXPAREL has recently gained Food and Drug Administration approval exclusively for wound infiltration, however if it proves to be safe and effective, it might become a valuable option for single injection, extended duration peripheral nerve blocks as well. If liposomal bupivacaine proves to be suitable for peripheral nerve block as well, it would provide a valuable alternative to current opioid analgesics for severe pain management by the medic/corpsman on the battlefield and remote locations as well as for management of acute pain under the care of a clinician in non- deployed settings.

However, before studying the feasibility and effectiveness of the use of liposome encapsulated bupivacaine in human clinical trials the safety of this novel formulation must be comprehensively investigated in animal models. The increased use of local anesthetics drew attention to toxic side effects of these drugs including local tissue toxicity. Inadvertent intravascular injections and the related local anesthetic systemic toxicity (LAST) is one of the most feared complications associated with the use of local anesthetics. Although its incidence is less than 0.2%, LAST is difficult to treat and is potentially fatal.

LAST can impair function of the central nervous system and cause cardiovascular collapse, with potentially lethal consequences. A single study in healthy volunteers with plain bupivacaine has defined the toxic plasma concentration of free bupivacaine to have a range between 0.13 and 0.51 mg/L with a mean value of 0.3 mg/L, but there is no similar published data for EXPAREL. The new formulation probably has different pharmacokinetic properties, and the effects of inadvertent intravascular injection are unknown.

LAST and rescue interventions for its reversal are areas of great interest. Several reports in the recent literature have demonstrated the effectiveness of intravenous lipid emulsion (ILE) in the reversal of cardiovascular and central nervous system symptoms of local anesthetic and other lipophilic drug overdoses. ILE is gaining acceptance and has been included in practice advisories of the American Society of Regional Anesthesia, the Association of Anesthetists of Great Britain, and is also recommended in the Advanced Cardiac Life Support (ACLS) guidelines by the American Heart Association for cardiac arrest secondary to lipophilic beta and calcium channel blockers when conventional resuscitative therapies have failed.

However, ILE might not be effective in the case of systemic toxicity due to the accidental injection of liposomal bupivacaine into the circulation. The most commonly proposed mechanism of action of ILE is the lipid sink theory. This is based on the lipophilic characteristics of local anesthetics and the partition between the blood plasma and the intravenously injected ILE. According to this theory the lipid sequestrates the local anesthetic from the plasma space and prevents its binding to the sites of toxic action in the central nervous system and the heart. However, liposomal formulations of local anesthetics (EXPAREL in particular) are already encapsulated in liposomes and the applicability of lipid rescue in the case of their inadvertent intravascular injection is questionable.

Methods

In the first phase of the project a dose response study was performed with continuous infusions of (a) EXPAREL and (b) plain bupivacaine correlating them with cardiovascular symptoms. Our hypothesis is that the maximum tolerated dose (MTD) of EXPAREL is higher than the MTD of plain bupivacaine. Maximum tolerated dose is defined as the highest dose level at which ≤ 33% of subjects experience

dose-limiting toxicities. We are going to define both MTDA and MTDX. For MTDA the dose-limiting toxicity will be signs of arrhythmia and for MTDX the dose-limiting toxicity will be asystole.

Rats were anesthetized in an induction chamber with isoflurane to allow tracheal intubation. All animals were then placed on a heated stand under a warming lamp and mechanically ventilated with 1-2% isoflurane in 100% oxygen, using a rodent ventilator (RoVent Jr., Kent Scientific, Torrington, CT) with parameters determined by the machines algorithm based on the animal's weight. Catheters were inserted into the left or right femoral vein (22GA angicath, BD, Franklin Lakes, NJ) for drug administration, and the left or right femoral artery (22GA angiocath, BD, Franklin Lakes, NJ) for hemodynamic monitoring and blood sampling. Arterial blood pressure and ECG was continuously monitored and recorded by a PowerLab data acquisition system and Chart 5 software (AdInstruments, Colorado Springs, CO)

Phase 1: After a 10 minutes stabilization period a continuous intravenous infusion of the test substances was administered at 10 mg/kg/min. The primary endpoints were total dose and time to arrhythmia (MTDA), total dose and time to 50% of baseline of mean arterial pressure, and total dose and time to asystole (MTDX). Blood samples of 2 ml were collected at the time of asystole for plasma drug concentration analysis in the future.

Phase 2: As preparation for the experiments evaluating the effectiveness of the various rescue methods, the 30-minute LD50 of EXPAREL and plain bupivacaine was determined and compared. Based on the results from our previous series of experiments, we used Dixon's up and down method to estimate the 30-minute LD50 for each drug. This method uses an iterative dose-selection algorithm. Starting with an initial dose of 10 mg/kg for bupivacaine and 20 mg/kg for EXPAREL, each subsequent dosage was raised or lowered based on the survival of the preceding animal. The drugs were administered undiluted, in volumes of approximately 0.5-1.5 ml, as a bolus over a few seconds.

Results

During the period covered by the report the methodology has been refined and experiments to determined MTDA, MTDX and LD50 has been completed. Data analysis is ongoing.

During the period covered by the previous annual report the experiments with rats to determine maximum tolerable dose have been started. After the first 4 experiments, it was determined that the respiration of the animals needs to be controlled with a rodent ventilator. The equipment has been selected, acquired and set up. After finalizing the methodology for the experiments, 5 additional experiments have been completed with controlled ventilation and the project is in progress.

The experiments to determine MTDA, MTDX and LD50 were continued during the period covered by this report. A total of 16 experiments has been completed to determine the maximum tolerable dose by slow infusion of the test substances while the animals' hemodynamic parameters were monitored and recorded constantly. The first few experiments were done to refine the methodology. After finalizing the dosing and infusion parameters the MTDX was found to be 43.2 ± 4.5 mg/kg for Exparel and 15 mg/kg for bupivacaine, and MTDA was 19.3 ± 9.9 mg/kg for Exparel and 0.5 mg/kg for bupivacaine. The Exparel infusion experiments are shown in Table 1.

ID	Weight	Time to arrhythmia (min)	Dose to arrhythmia (mg/kg)	Time to asystole (s)	Dose to asystole (mg/kg)
1	680		25.00		40.00
3	960	1.07	10.70	4.00	40.00
4	771	0.67	6.70	4.08	41.00
8	750	2.80	28.00	5.17	51.70
9	880			4.42	44.20
10	710	2.63	26.30	4.22	42.20
AVG	791.83	1.79	19.34	4.38	43.18
SD	107.18	1.08	9.87	0.47	4.46

Table 1. Exparel infusion at 10 mg/kg/min.

An additional 19 experiments have been performed to determine the appropriate bolus dose to be used in the next phase for the comparison of effectiveness of resuscitative methods. The up-down dose finding experiment are shown in sequence in Table 2.

Bupivacaine dose (mg/kg)	Outcome	Exparel dose (mg/kg)	Outcome
10	Survived	20	Survived
15	Died	30	Survived
10	Survived	40	Died
15	Survived	30	Died
20	Died	25	Survived
15	Survived	30	Died
20	Died	25	Died
15	Died	25	Died
12	Survived	20	Survived
15	Died	25	Survived
12	Died	30	Survived
10	Survived		
12	Survived		

Table 2. Dose finding for bolus administration

Based on the survival of animals, we determined that we are going to use a dose of 20 mg/kg for bupivacaine and 40 mg/kg for Exparel in the resuscitation experiments. Interestingly, the cause of death from Exparel intoxication seemed to be a decrease in systemic blood pressure, rather than asystole or cardiac conduction block. This implies a different mechanism from that seen with bupivacaine and warrants further studies.

B) Swine experiments

Background

An additional safety concern during inadvertent intravascular injection of liposome-encapsulated bupivacaine arises from the liposome component of the formulation. A large variety of chemical substances as well as medicinal products have been suspected or proven to provoke adverse immunological reactions. One of the most common side effects of drugs is hypersensitivity reaction that often prevents or limits their use. In the past decade several drugs and chemicals were shown to have a potential to trigger complement activation related pseudo-anaphylaxis (CARPA). (15) These also include but are not limited to liposomal formulations such as Doxil and Ambisome. (16)

The monitoring of CARPA became an important aspect in the development of these pharmaceuticals. Underlying the importance of this new type of hypersensitivity, in vitro and in vivo testing of complement activation became a recommended toxicology test by the US Food and Drug Administration. (17)

Unlike IgE-mediated allergy, these reactions arise without prior sensitization and are mediated by the complement system. The outcomes include activation of mast cells, polymorphonuclear cells and platelets, the release of vasoactive mediators, such as thromboxane and histamine, with severe cardiovascular and other effects, with potentially lethal consequences. (18) To study the possibility of these reactions we intend to analyze the hemodynamic and immunological reactions following intravenous administration of liposomal bupivacaine in swine.

Methods

Instrumentation: Five Yorkshire swine (20 - 25 kg) were sedated with ketamine (15-25 mg/kg IM, 18-19 gauge needle, dorsolateral neck muscles), and anesthesia was induced with cone-mask inhalation of 3-4% isoflurane. After tracheal intubation (6.5-7.0 mm endotracheal tube), ventilation was controlled (100 ml/kg/min, Narkomed 2B; North American Drager, Telford, PA), and anesthesia was maintained with 1-4% inhaled isoflurane as needed. Waste gas from the anesthesia machine was scavenged via carbon filter. A catheter (18 gauge) was placed in the right ear vein for IV maintenance fluids (0.9% NaCl at 1-2 ml/kg/hr) and injection of liposomal bupivacaine (Exparel, Pacira Pharmaceuticals, Parsippany, NJ). An 18 gauge catheter was inserted percutaneously into the superficial femoral artery to provide access for serial blood sampling and systemic arterial blood pressure (SAP) and heart rate (HR) monitoring. A 9 Fr Cordis percutaneous introducer was placed into the right external jugular vein, and a Schwan-Ganz catheter was floated through the right atrium and right ventricle to the pulmonary artery for pulmonary arterial pressure (PAP) measurements. Continual respiratory rate (RR), end-tidal carbon dioxide (ETCO2), EKG, and rectal temperature was monitored (M1026A Gas Analyzer and Model 68 clinical monitor; Hewlett-Packard, Andover, MD). Normal body temperature (37-38 degree C) was maintained by an external warming device.

Upon completion of instrumentation and a 15- minute stabilization period, baseline blood samples were taken for biochemical analyses. All blood samples drawn during the experiment were 10 ml into tubes containing EDTA, centrifuged, plasma separated and frozen for later immunologic and complement assays.

After the baseline blood draw, bolus doses of Exparel were injected via the femoral arterial catheter according to the injection schedule described below. Hemodynamic parameters were recorded continuously. Blood samples of 10 ml were collected at 3, 6, 9, and 12 minutes after each injection. There was at least 20 minutes of stabilization period between boluses to allow the return of hemodynamic parameters to baseline.

At the end of the experiments the animals were euthanized with Euthasol provided by LAM. The maximum time that any pig was maintained from initiation of anesthesia until euthanasia was 3 hours.

Results

Changes in the hemodynamic parameters are summarized in Table 1.

animal ID	treatment	PAP before (mmHg)	PAP after (mmHg)	SAP before (mmHg)	SAP after (mmHg)	ETCO2 before (mmHg)	ETCO2 after (mmHg)	comments
6	25 ul Exparel	12	13	80	80	50	51	
	50 ul Exparel	13	14	80	81	50	51	
	100 ul Exparel	12	19	81	82	49	49	
	200 ul Exparel	13	24	81	86	49	49	
	500 ul Exparel	14	33	83	20	49	27	
	1 ml Exparel	16	30	74	14	47	18	
	2 ml Exparel	14	30	48	17	45	8	apnea, circulatory collapse
7	25 ul Exparel	14	16	77	77	50	47	
	50 ul Exparel	16	24	74	79	50	49	
	100 ul Exparel	16	37	71	54	50	45	
	200 ul Exparel	18	45	76	22	47	25	dyspnea
	500 ul Exparel	16	35	76	23	46	35	
	1 ml Exparel	17	33	68	12	49	5	apnea, circulatory collapse, rash
	2 ml Exparel	19	31	58	10	44	9	apnea, circulatory collapse
8	200 ul Exparel	12	20	73	74	44	48	
	1 ml Exparel	14	40	73	27	46	43/53	
	100 mg indomethacin	15	19	69	129	45	30	
	1 ml Exparel	12	14	71	65	34	36	
	5 ml Exparel	18	44	72	45/84	36	0	apnea
9	1 ml Exparel	13	43	62	83/45	47	33	
	2 ml ETOH slow	17	29/20	54	84	49	50	
	1 ml Exparel	18	21	71	68	46	47	

	2 ml Exparel	21	28 (slowly)	67	62	47	50	
	1 ml ETOH bolus	29	35	62	26	50	54	
10	1 ml Exparel	17	40	62	18	49	12	apnea, circulatory collapse, rash
	2 ml ETOH	20	37	67	40/87	48	53	
	1 ml Exparel	19	40	63	18	46	10	apnea, circulatory collapse, rash
	2 ml indomethacin	23	33	66	96	44	37	
	1 ml Exparel	25	31	88	93	43	46	
	1 ml Exparel	31	37	87	94	44	42	
	1 ml Exparel	36	42	91	81	45	41	
	3 mg Zymosan	39	40	91	91	45	45	
	12 mg Zymosan	36	41	93	92	45	45	
	5 ml Exparel	38	48	94	16	45	4	apnea, circulatory collapse

Table 1. Hemodynamic changes following injection of study drugs. PAP: pulmonary arterial pressure, SAP: systemic arterial pressure, ETCO2: end-tidal CO2.

Conclusions

These experiments have confirmed what we found in the first five animals during the period covered by the previous annual report. Intravascular injection of Exparel in doses of at least 50-100ul provokes hemodynamic changes, characterized by significant dose dependent increase in pulmonary arterial pressure, increase or decrease in systemic arterial pressure, increase in end tidal CO2, respiratory distress. Inhibition of the cyclooxygenase cascade by injections of 5 mg/kg indomethacin prevented the hemodynamic reactions to intraarterial injection of 1 ml Exparel, but subsequent injection of 5 ml Exparel caused an increase in pulmonary arterial pressure, apnea and circulatory collapse.

-
    - *4) other achievements: nothing to report*
- **What opportunities for training and professional development has the project provided?**
    - *Nothing to report*
- **How were the results disseminated to communities of interest?**
    - *Nothing to report*
- **What do you plan to do during the next reporting period to accomplish the goals?**
    - *Complete the rat experiments to determine LD50. Complete rat experiment comparing resuscitative methods.*

4. **IMPACT**
    - **What was the impact on the development of the principal discipline(s) of the project?**
        - *Our findings from the swine experiments raise a significant and novel characteristic of Exparel, which might have important implications for clinical use and guidelines. The hemodynamic reactions observed after intravenous administration of Exparel in swine may also occur in humans, in which case preventive measures must be taken every time Exparel is used. The results from the swine experiments might have an impact on the FDA approval status of Exparel and its use in clinical practice.*
        - Our finding from the rat experiments also show a novel hemodynamic effect of Exparel, as opposed to bupivacaine, the dose-limiting toxicity was not primarily asystole or cardiac block, but rather decrease of systemic blood pressure, hinting at a mechanism that is independent from the sodium channel blocking properties of the bupivacaine component.
    - **What was the impact on other disciplines?**
        - *Nothing to report*
    - **What was the impact on technology transfer?**
        - *Nothing to report.*
    - **What was the impact on society beyond science and technology?**
        - *Nothing to report*
5. **CHANGES/PROBLEMS:**
    - **Changes in approach and reasons for change**
        - *Nothing to report*
    - **Actual or anticipated problems or delays and actions or plans to resolve them**
        - There has been a delay with the availability of funds. Due to this complication, we began the project in Spring of 2015 and all projected milestones will be delayed accordingly. We also need to prepare a new IACUC protocol and submit a triennial renewal and seek a new approval from IACUC and ACURO.
    - **Changes that had a significant impact on expenditures**
        - *Nothing to report*
    - **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
        - *Nothing to report*
    - **Significant changes in use or care of human subjects**
        - *Nothing to report*

- **Significant changes in use or care of vertebrate animals.**
  - *Nothing to report*
- **Significant changes in use of biohazards and/or select agents**
  - *Nothing to report*

6. **PRODUCTS:** *Nothing to report*
7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**
   - **What individuals have worked on the project?**

Name:	Chester Buckenmaier
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Dr. Buckenmaier provided scientific and administrative oversight
Funding Support:	USUHS
Name:	Peter Bedocs
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Dr. Bedocs designed the protocol, coordinated submission and review correspondence, trained in methodology, designed and performed experiments and performed laboratory setup
Funding Support:	W81XWH-15-1-0130
Name:	Kelly Kiser
Project Role:	Program Manager
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Ms. Kiser provided administrative support
Funding Support:	W81XWH-15-1-0130

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  - *Nothing to report*
- **What other organizations were involved as partners?**
  - *Nothing to report*

8. **SPECIAL REPORTING REQUIREMENTS**
   - *Nothing to report*
9. **APPENDICES:** *Nothing to report*