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TITLE: Topical Modulation of the Burn Wound Inflammatory Response to Improve Short and Long Term Outcomes

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14. ABSTRACT
We propose to investigate the relationship between p38MAPK signaling, wound inflammatory response, wound healing and long-term scar formation using a burn model in the female red Duroc pig. We hypothesize that topical p38MAPK inhibition will attenuate the depth of the burn by preventing hair-follicle cell apoptosis, attenuate the inflammatory phase of wound healing, and decrease the granulation layer thickness. We propose this modification in the early inflammatory response will also reduce thickness and contraction of scars formed after deep partial thickness burn injury. The knowledge gained from our proposed research will be critical to implement a potential paradigm shift in the clinical treatment of challenging dermal injuries.

15. SUBJECT TERMS
None listed

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1. INTRODUCTION

Approximately 500,000 Americans suffer burn injuries with an estimated 3,500 deaths annually. Widespread makeshift bombs contribute to burns and large wounds being one of the significant causes of warfighter causalities. The magnitude and impact of burns can be devastating as large numbers causalities occur simultaneously. Secondary organ damage and failure frequently occurs after injury. Moreover, wound complications such as hypertrophic scars may cause significant morbidity, disabling loss of function, extended difficult recovery times, dramatically affecting the patient's quality of life physically. We are investigating a topical therapy that is easy to apply and can be used by a wider range of health care providers in a mass-casualty incident.

2. KEYWORDS:

Wounds, Burn, topical, wound healing, inflammatory signaling, Mitogen activated protein kinase, hypertrophic scar, p38, combat casualty, treatment, organ failure, systemic inflammatory response syndrome, thermal injury, wound model, intervention

3. ACCOMPLISHMENTS:

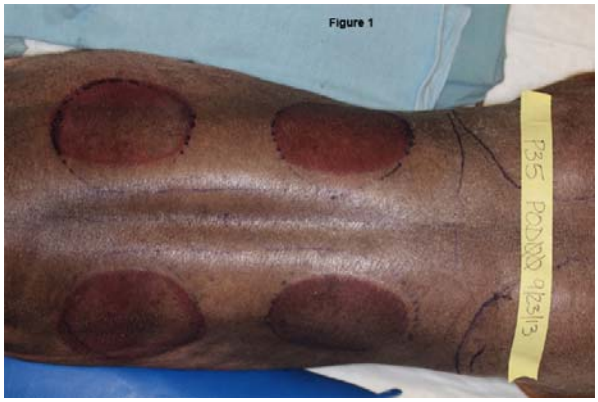
What were the major goals of the project?

1. Establish the female red Duroc pig model burn model as the appropriate wound healing model that resembles human response. At the end of the project, we will have a well-defined animal model for human wound healing. This animal model may provide a tool that other investigators can use to screen for compounds that may modify wound healing and reduce scar formation. The ability to have a standard animal model for wound healing may bring an exciting new era in the investigation and elucidating the molecular mechanisms of hypertrophic scar pathophysiology and developing therapeutic agents.
2. Define the inflammatory signaling post burn injury and elucidate the relationship between early inflammatory signaling, wound healing, and scar formation.
3. Define the role of p38MAPK in wound healing and scar formation.
4. Identify the wound healing response to topical p38MAPK inhibition. Demonstrate early wound healing and reduced scar formation with topical p38MAPK inhibition. Define the long-term wound outcome of topical p38MAPK inhibition post-burn injury.
5. Identify the optimal timing and duration of treatment for p38MAPK therapy.
6. By the end of the project, have a well-defined protocol and experimental plan to initiate human subject research to study topical p38MAPK inhibition as a therapy to decrease end-organ dysfunction, improve wound healing, and reduce scar formation in patients with burn injuries.

What was accomplished under these goals?

Goal 1. Establish the female red Duroc pig model as the appropriate wound healing model.

The first goal of the project was to establish the female red Duroc pig model burn model as the appropriate wound healing model that resembles human response. Our first 3 porcine experiments, porcine group (Pg) 001-003, were the dermatome model, demonstrating that the female red Duroc porcine model significantly correlates to human hypertrophic scarring. We started our experiments using the burn wound model with Pg004. In this model we use a 'hot water bottle' thermal injury device. Briefly, we use a 500 ml Pyrex laboratory Schott Duran bottle with the bottom glass removed, edges smoothed, bottom replaced with cling wrap, and secured with heat resistant tape. The bottles will be filled with 300 ml of water and then heated to the desired temperature of 92°C. We have improved our technique significantly over the period of the current grant. The initial wounds were not uniform. Starting with Pg 007 (Table 1), we have resolved the technical issues and burn wounds are uniform (Figure 1). We change the depth of the burn by changing the length of contact 10, 15, and 20 seconds. We have identified that all these contact times are in the range of partial thickness injury. The 20 seconds is mostly very deep partial thickness burns with central area of full-thickness injury. Goal 1 is accomplished during the year 1 period September 2014- September 2015.



Goal 2: Define Inflammatory Signaling Post Burn Injury and Elucidate Relationship…

The second goal of the grant was to define the inflammatory signaling post burn injury and elucidate the relationship between early inflammatory signaling, wound healing, and scar formation. Rather than systemic modulation of the inflammatory response, we propose a novel approach, which calls for "inflammatory source control". We define "inflammatory source control" to be all the maneuvers that can be used to control a focus of inflammation, which is thought to be the initial source of systemic immune activation. In our burn model, we control the source of inflammation by application of a topical p38 MAPK inhibitor. The p38 MAPK pathway is the key inflammatory intracellular signaling in mammalian cells. In our previous murine models, we demonstrated that topical application of p38MAPK inhibitors after burn injury attenuated wound inflammatory response and stress signaling, leading to reduced systemic inflammatory activation and end-organ dysfunction (these data already published and not part of the current investigation). In our porcine model, our goal is to demonstrate that topical p38 MAPK inhibitors will attenuate wound inflammation and reduce scarring in the red Duroc pig model of fibroproliferative scarring. We have done total of 9 pig experiments. The porcine group experiments are numbered 001-009 (Table 1).

Goals 2 (define the inflammatory signaling post burn injury and elucidate the relationship between early inflammatory signaling, wound healing, and scar formation) and 3 (define the role of p38MAPK in wound healing and scar formation) are in progress.

Table 1					
Study ID	**Wound**	**Dates**	**Treatment**	**Pigs #**	**Duration of thest udy**
Pg001	Dermatome	Feb-10	Topical p38MAPK inhibitor versus control	2	20 weeks
Pg002	Dermatome	Sep-11	Topical p38MAPK inhibitor versus control	2	20 weeks
Pg003	Dermatome	Sept 2012-Oct 2012	PGE2 agonist topical versus control	6	3 weeks
Pg004	Scald Bottle Burn	Sept 2013- Oct 2013	Topical p38MAPK inhibitor versus control	6	2 weeks
Pg005	Scald Bottle Burn	May 2014	Topical p38MAPK inhibitor versus control	6	2 weeks
Pg006	Scald Bottle Burn	Dec 2014	Topical p38MAPK inhibitor versus control	6	3 days
Pg007	Scald Bottle Burn	May 2015	Topical p38MAPK inhibitor versus control	6	3 days
Pg008	Scald Bottle Burn	Sept-Oct 2015	Topical p38MAPK inhibitor versus control	8	2 weeks
Pg009	Scald Bottle Burn	May 2016	Topical p38MAPK inhibitor versus control	8	3 days

We have analyzed these wounds using several different methods:

- Wound character: time to wound closure, color, wound infection
- Histopathology: H&E, TUNNEL assay,
- Inflammatory and wound healing gene expression
- Custom porcine RT-qPCR Array

Table 2 demonstrates all completed, in-progress, and pending analyses (N/A is not applicable; meaning that set of analysis will not be done; for instance, no wound closure analysis will be done in 3 day experiments).

We have used porcine RT-qPCR Array for wound healing, inflammatory, and apoptosis pathways. We have demonstrated a difference in pattern of pathway expression between the burn versus non-burn skin and burn treated with p38 inhibitor versus vehicle. In the burn wound healing, there is a portion of collagen arrangement that remains intact. In the dermatome model the line between “normal” collagen and “abnormal “collagen” is sharp and clear. In the burn model there is a large transition zone between the intact dermal architecture and damaged skin. This reflects the ongoing inflammation and apoptosis seen in burn injury. When we examined the gene expression differences in various depth of injury, an interesting pattern was observed. The deeper burns were associated with increasing number of over-expression of the regulatory genes. This internal consistancy in the model is very important.

Figure 2 demonstrates a heat map difference between the burn and non-burn gene expression. The figure is using Pg008 and Pg009; therefore, we can examine the gene expression after 3 days (Pg009, 72 hours) and after two weeks (Pg008, 2 weeks). The green in heat map is low activity and red is high activity. After burn injury, there is an immediate shut down of series of genes with upregulation of inflammatory and apoptotic genes. After 2 weeks the wounds have epithelialized and many of the gene expression have returned to normal.

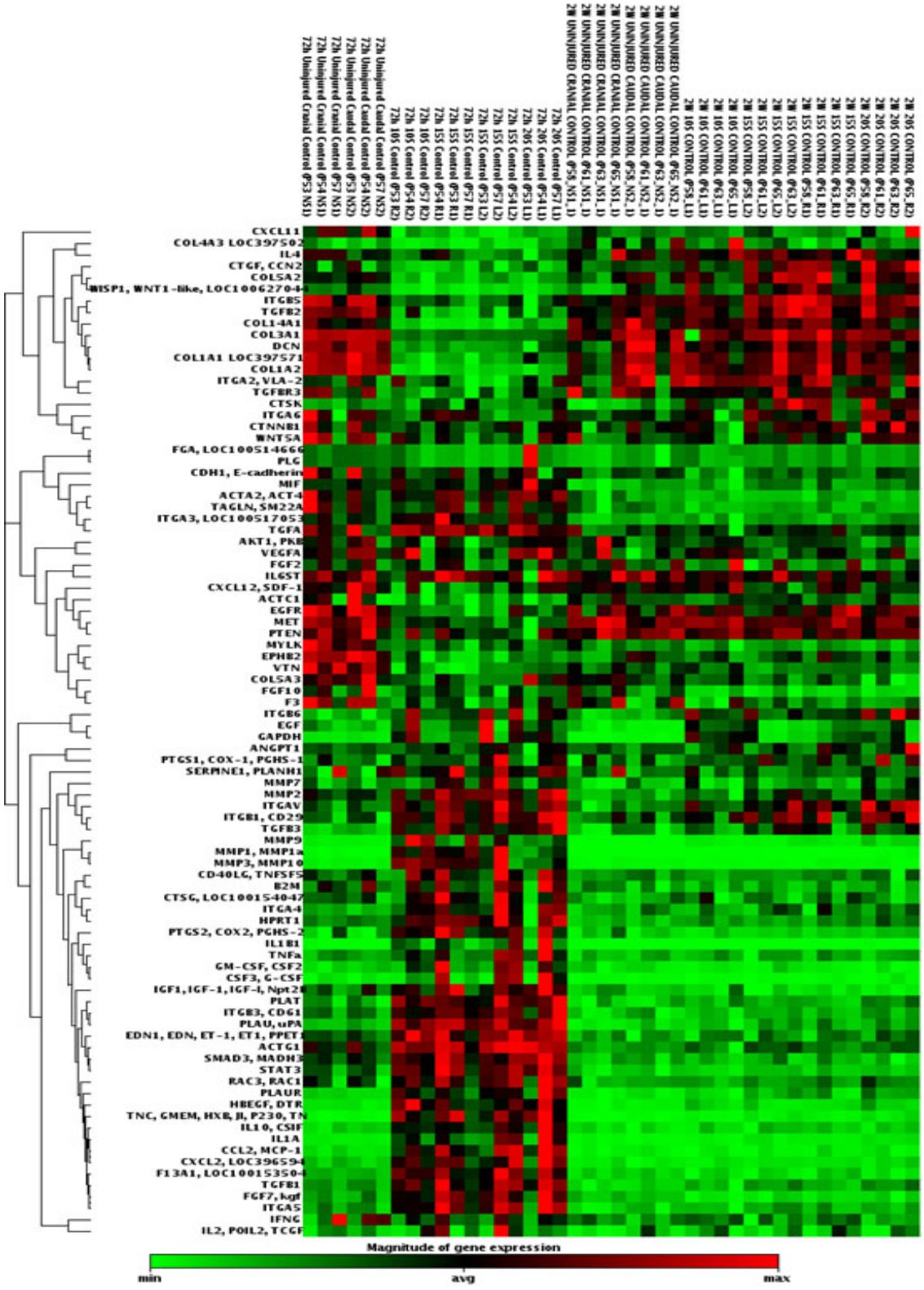
Figure 3 demonstrates the heat map differences between treated (topical p38 MAPK inhibitor) and not treated (vehicle) after two weeks. The three groups are unijured, burn with vehicle treatment, and burn with p38 MAPK inhibitor treatment. One pig in 20 second Vehicle is out of range and will not be used. We were expecting that the treatment group will have deactivation of set of genes in 2 weeks compared to vehicle. This is seen in certain genes such as GAPDH and BAG3. However, the data demonstrated that the treatment has more activation of a set of regulatory genes as compared to vehicle. We have not completed these analyses and the ultimate pathway analyses is pending.

Goal 3: Define the role of p38MAPK in wound healing and scar formation.

Referring to table 2, a significant portion of goal 2 (Define the inflammatory signaling post burn injury and elucidate the relationship between early inflammatory signaling, wound healing, and scar formation) and goal 3 (Define the role of p38MAPK in wound healing and scar formation) has been done. However, final analyses and completion of work is pending.

Table 2	**Assay Status**							
Study ID	**H & E Slides**	**Wound Closure Images**	**Itch Score**	**Wound Contraction Images**	**Wound Healing Profiler RT2-qPCR Array**	**Apoptosis Profiler RT2-qPCR Array**	**Cleaved Caspase3 (CC3) Immuno Histo chemistry**	**Western Blot: p38 MAPK activation, and CC3**
Pg001	Completed- Analysis	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Pg002	Completed- Analysis	n/a	n/a	Completed - Analysis	n/a	n/a	n/a	n/a
Pg003	Completed- Analysis	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Pg004	Completed- Analysis	Completed-Analysis	n/a	n/a	Completed-Analysis	n/a	n/a	n/a
Pg005	Completed- Analysis	Completed-Analysis	subjective inconclusive	n/a	Completed-Analysis	n/a	n/a	n/a
Pg006	Completed- bx tissue processed thru H&E digital images. On hold- image measurements. Pending- western p38 activation results.	n/a	n/a	n/a	Completed- bx tissue biopulverized. On hold-pending western results	Completed- bx tissue biopulverized. On hold-pending western results	Completed- bx tissue processed thru slides On hold-pending western CC3 results	In progress
Pg007	Completed- bx tissue processed thru H&E digital images. On hold- image measurements. Pending- western p38 activation results.	n/a	n/a	n/a	Completed-Arrays. Completed-partial analysis (pending Pg009 arrays completion)	Completed-Arrays. Completed-partial analysis (pending Pg009 arrays completion)	Completed-bx tissue processed thru CC3 IHC digital images. Completed-RO1 analysis Completed-algorithm consult/design NWBS for R01 depth analysis On hold pending-western CC3 results	In progress
Pg008	Completed bx tissue processed thru H&E digital images. In progress- image measurements.		n/a	n/a	Completed-Arrays. Pending- final analysis formatting	n/a	n/a	n/a
Pg009	Completed bx tissue processed thru H&E digital images. On hold- image measurements. Pending western p38 activation results	n/a	n/a	n/a	Completed-bx tissue biopulverized In progress-arrays	Completed-bx tissue biopulverized In progress-arrays	Completed- bx tissue processed thru slides On hold-pending western CC3 results	In progress

Figure 2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72h Uninjured Cranial Control (P54 N51)
72h Uninjured Cranial Control (P57 N51)
72h Uninjured Caudal Control (P53 N52)
72h Uninjured Caudal Control (P54 N52)
72h Uninjured Caudal Control (P57 N52)
72h 105 Control (P53 R2)
72h 105 Control (P54 R2)
72h 105 Control (P57 R2)
72h 155 Control (P53 R1)
72h 155 Control (P54 R1)
72h 155 Control (P57 R1)
72h 155 Control (P53 L2)
72h 155 Control (P57 L2)
72h 155 Control (P54 L2)
72h 205 Control (P53 L1)
72h 205 Control (P54 L1)
72h 205 Control (P57 L1)
2W UNINJURED CRANIAL CONTROL (P58_N51_1)
2W UNINJURED CRANIAL CONTROL (P61_N51_1)
2W UNINJURED CRANIAL CONTROL (P63_N51_1)
2W UNINJURED CRANIAL CONTROL (P65_N51_1)
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IL4
CTGF, CCN2
COL5A2
WISP1, WNT1-like, LOC100627044
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TGFB2
COL14A1
COL3A1
DCN
COL1A1 LOC397571
COL1A2
ITGA2, VLA-2
TGFBR3
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ITGA6
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PLG
CDH1, E-cadherin
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ACTA2, ACT4
TAGLN, SM22A
ITGA3, LOC100517053
TGFA
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VEGFA
FGF2
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MET
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MYLK
EPHB2
VTN
COL5A3
FGF10
F3
ITGB6
EGF
GAPDH
ANGPT1
PTGS1, COX-1, PGHS-1
SERPINE1, PLANH1
MMP7
MMP2
ITGAV
ITGB1, CD29
TGFB3
MMP9
MMP1, MMP1a
MMP3, MMP10
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B2M
CTSG, LOC100154047
ITGA4
HPRT1
PTGS2, COX2, PGHS-2
IL1B1
TNFa
GM-CSF, CSF2
CSF3, G-CSF
IGF1, IGF-1, IGF-I, Npt2b
PLAT
ITGB3, CD61
PLAU, uPA
EDN1, EDN, ET-1, ET1, PPET1
ACTG1
SMAD3, MADH3
STAT3
RAC3, RAC1
PLAUR
HBEGF, DTR
TNC, GMEM, HXB, JI, P230, TN
IL10, CSIF
IL1A
CCL2, MCP-1
CXCL2, LOC396594
F13A1, LOC100153504
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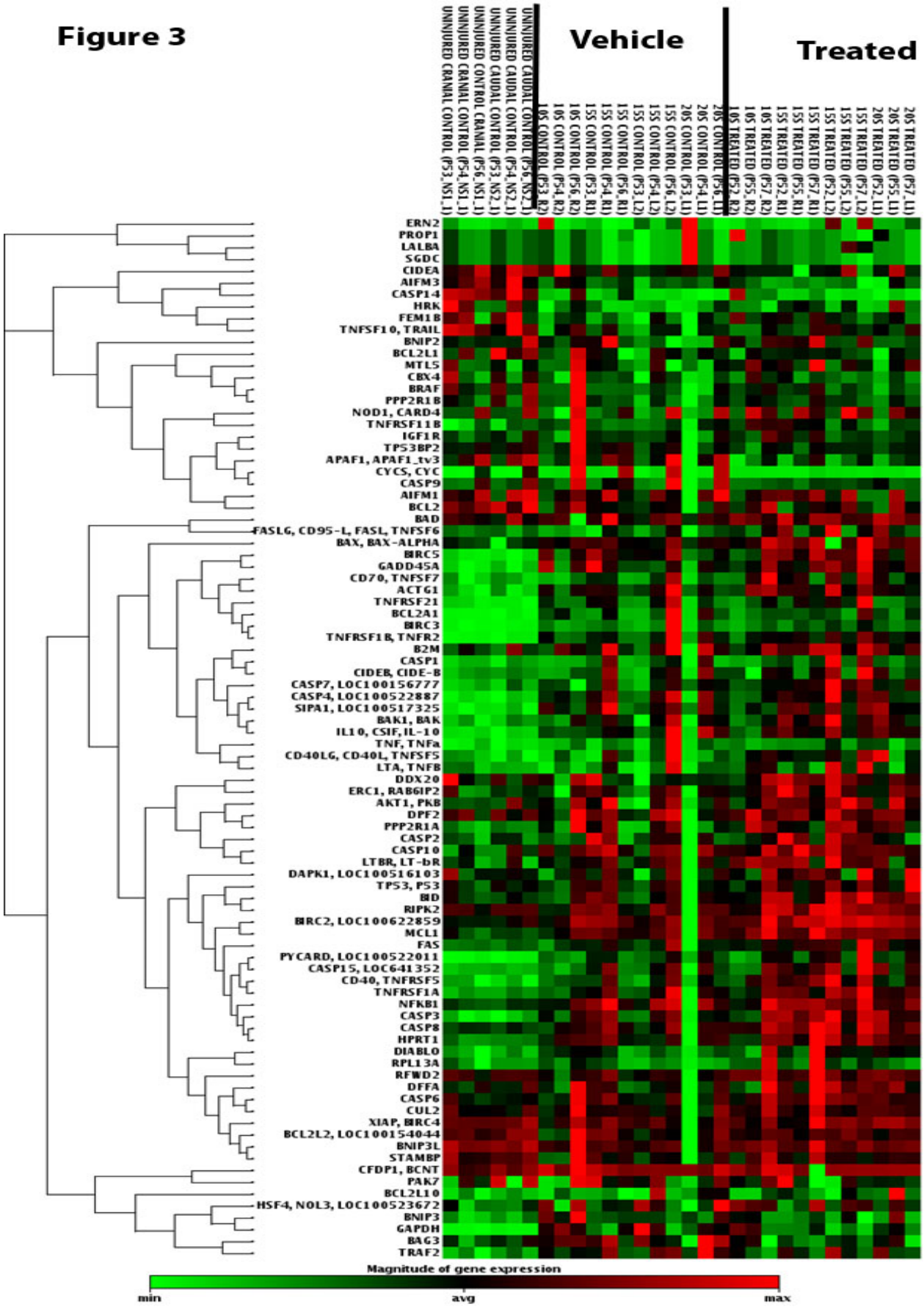
FGF7, kgf
ITGA5
IFNG
IL2, POIL2, TCGF
Magnitude of gene expression
min
avg
max

Figure 3


Vehicle
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10S CONTROL (P53_R2)
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PROP1
LALBA
SGDC
CIDEA
AIFM3
CASP14
HRK
FEM1B
TNFSF10, TRAIL
BNIP2
BCL2L1
MTL5
CBX4
BRAF
PPP2R1B
NOD1, CARD4
TNFRSF11B
IGF1R
TP53BP2
APAF1, APAF1_tv3
CYCS, CYC
CASP9
AIFM1
BCL2
BAD
FASLG, CD95-L, FASL, TNFSF6
BAX, BAX-ALPHA
BIRC5
GADD45A
CD70, TNFSF7
ACTG1
TNFRSF21
BCL2A1
BIRC3
TNFRSF1B, TNFR2
B2M
CASP1
CIDEB, CIDE-B
CASP7, LOC100156777
CASP4, LOC100522887
SIPA1, LOC100517325
BAK1, BAK
IL10, CSIF, IL-10
TNF, TNFa
CD40LG, CD40L, TNFSF5
LTA, TNFB
DDX20
ERC1, RAB6IP2
AKT1, PKB
DPF2
PPP2R1A
CASP2
CASP10
LTBR, LT-bR
DAPK1, LOC100516103
TP53, P53
BID
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BIRC2, LOC100622859
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FAS
PYCARD, LOC100522011
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NFKB1
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HPRT1
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CASP6
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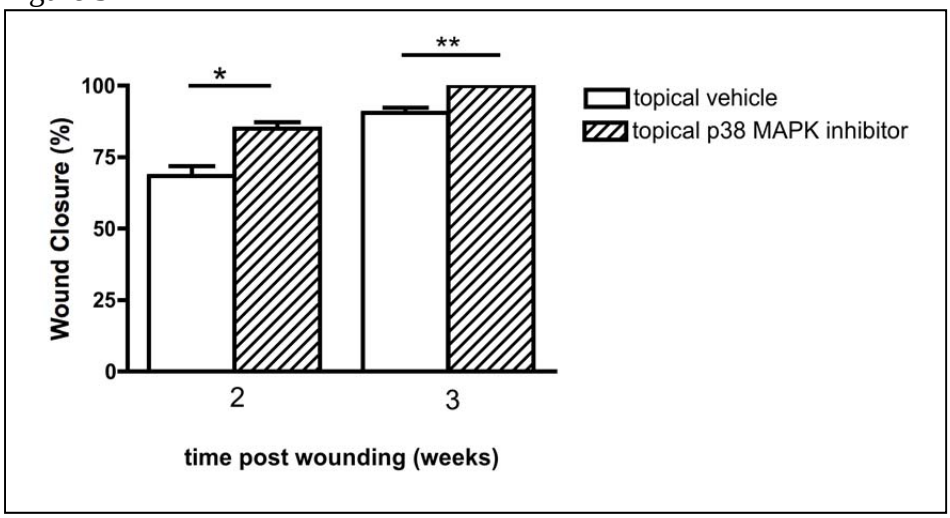
BNIP3
GAPDH
BAG3
TRAF2
Magnitude of gene expression
min
avg
max

Goal 4: Identify the wound healing response to topical p38MAPK inhibition. Demonstrate early wound healing and reduced scar formation with topical p38MAPK inhibition. Define the long-term wound outcome of topical p38MAPK inhibition post-burn injury.

We have demonstrated early wound closure with p38 MAPK inhibition. Using the dermatome model in Pg001 and Pg002, we demonstrated that wounds treated with p38MAPK inhibitor epithelialized faster than control group in 2 and 3 week time-points. Pictures of each wound were analyzed by computer and the area that were epithelialized were measured (Figure 4). The data demonstrated that there was statistical significant closure rate in wounds treated with p38MAPK inhibitor (Figure 5). The burn wound data is collected and the analyses is pending. The scar formation portion of this goal is pending.

Figure 4: Percentage closure was calculated for each individual wound

Figure 5



Goal 5: Identify the optimal timing and duration of treatment for p38MAPK therapy

The duration of p38 MAPK treatment has been set at 72 hours. We have used topical p38 MAPK upto 3 days after injury. There has been no increase in wound infection or delayed wound closure. Therefore, we concluded that 72 hour time point remains optimal. It remains to be seen, if longer time is associated with better outcomes. This goal is accomplished.

Goal 6: By the end of the project, have a well-defined protocol and experimental plan to initiate human subject research to study topical p38MAPK inhibition as a therapy to decrease end-organ dysfunction, improve wound healing, and reduce scar formation in patients with burn injuries.

This is the final goal of the project. We are hoping by the end of the project to develop a human subjects study protocol. This goal is pending.

What opportunities for training and professional development has the project provided?

The collaboration with NWBiospecimen (Univ. of WA) has improved the understanding of apoptotic response in burn injury with both groups.

How were the results disseminated to communities of interest?
There were two presentations at University of Washington, presentation at the Burn annual symposium

What do you plan to do during the next reporting period to accomplish the goals?
Continue with analyses of the data, including the gene expression, apoptosis, and protein expression

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?
We are learning about expressions of genes after burns. More importantly, the reduction of normal function in cells is very interesting.

What was the impact on other disciplines?
The impact of understanding inflammatory response and dermal pathology may be important in treatment of dermatological pathology, such as psoriasis.

What was the impact on technology transfer? Nothing to report

What was the impact on society beyond science and technology?
I hope in the future, we can develop a cream for burn victims.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change
None

Actual or anticipated problems or delays and actions or plans to resolve them
None

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
As previously reported and already approved in the quarterly reports, we have changed the number of pigs and reduce the number. Based on the data, it appears that there is no need to have 24 hours treatment time, since pigs with 72 hours treatment time demonstrated no side effect. This will decrease the number of pigs for AIM 1 and 2 to 44 pigs (previous number was 72 pigs). Aim 3 pig numbers stay the same (8 pigs); therefore, the total pig number will be reduced to 52 for the entire 4 years (reduced from 80). Also the data at 2 weeks is similar to 3 weeks, so we are going to decrease the experimental time from 3 weeks to 2 weeks. The following table is modification of our table 1 in the grant. There is no 24 hours in the treatment frequency and no sacrifice in post-burn day 1.

Table 3	Groups	
	Group 1	Group 2
Burn	Yes	Yes
Number of Burns	3 wounds each side	3 wounds each side

Burn Time	92°C for 10, 15, and 20 sec	92°C for 10, 15, and 20 sec
Treatment	Topical Vehicle	Topical p38 inhibitor
Treatment Frequency	BID topical application	BID topical application
Treatment Duration	72 hours	
	5 days	
Sacrifice	Post-burn day 3	
	Post-burn day 7	
	2 weeks post burn	

Significant changes in use or care of human subjects. Not applicable

Significant changes in use or care of vertebrate animals. No change

Significant changes in use of biohazards and/or select agents. No

6. PRODUCTS:

No products

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Saman Arbabi, MD, MPH
Project Role: PI
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1
Contribution to Project: He will provide the overall supervision and direct the animal studies.
Change in effort: From 10% to 8% as of June 1, 2015

Name: Adelaide Warsen, MS
Project Role: Research Scientist
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 12
Contribution to Project: Direct performance of all the proposed animal research
Change in effort: None

Name: Modou Mbowe
Project Role: Lab Technician

Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1
Contribution to Project: Research Assistance
Change in effort: Added at 50% as of August 18, 2016

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
No changes

What other organizations were involved as partners?
The collaboration with NWBiospecimen (Univ. of WA), Histology Imaging Core (UW), and Fred Hutchinson Cancer Research Center (FHCRC) Experimental Histopathology Shared Resource is going well. We have not had the results yet, and if there are issues, we expect to resolve them with assistance of Dr. Schmechel (Chief of Pathology at Harborview medical Center and the Director for NWBiospecimen histology core).

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: None

QUAD CHARTS: Attached

9. APPENDICES

None

Topical modulation of the burn wound inflammatory response to improve short- and long term outcomes

2b. Accelerated wound healing Award #W81XWH-14-1-0401

PI: Sam Arbabi, MD, MPH **Org:** University of Washington

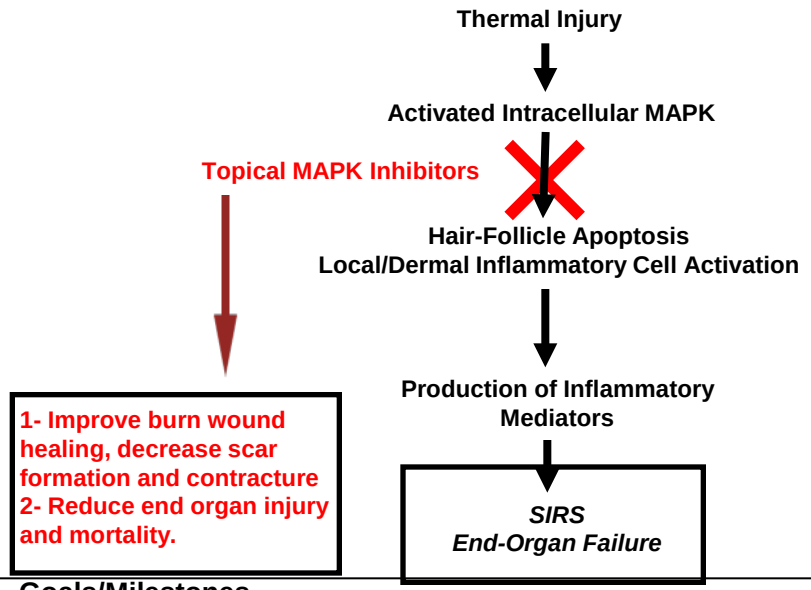
Award Amount: $1,497,377

Study/Product Aim(s)

• The magnitude and impact of burns associated with warfare can be devastating. We employ a gel formulation of a powerful p38MAPK inhibitor that is ideal for early topical intervention on the battlefield, ready to use, and can be rapidly applied to wounds by self, buddy aid, and/or first responders. This topical treatment would aid in preservation and stabilization of systemic homeostasis, mitigating short and long term deleterious consequences of severe wound injuries, such as secondary organ damage, scar formation, and burn contracture.

Approach

- In the current application, we propose to continue our wound healing studies in an animal burn model that resembles human wound healing. We will use the red Duroc pig burn wound model that resembles human wound healing and scar formation.



Timeline and Cost

Activities / FY	14-15	15-16	16-17	17-18
Aim 1: Determine the effect of topical p38MAPK inhibition on wound healing gene expression in the female red Duroc pig model of burn injury				
Aim 2: Determine the effect of topical p38MAPK inhibition on early wound healing post-burn injury				
Aim 3: Define the long-term wound outcome of topical p38MAPK inhibition post-burn injury.				
Estimated Budget ($K)	367	373	377	381

Updated: October 2016

Goals/Milestones

FY 14-15 Goals –

☑ Establish the red Duroc pig burn model

FY 15-16 Goals–

☑ Define the inflammatory signaling post burn injury

☑ Identify the optimal timing and duration of treatment for p38MAPK.

FY16-17Goals –

☐ Demonstrate early wound healing, decreased burn wound depth, and reduced inflammatory response with topical p38MAPK inhibition.

FY 17-18 Goal –

☐ Demonstrate decreased scar formation with topical p38 MAPK inhibition.

Comments/Challenges/Issues/Concerns

- If timelines change, comment here.

Budget Expenditure to Date

Projected Expenditure: $190,000

Actual Expenditure: $187,074