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TITLE: Chronic pain following spinal cord injury. The role of immunogenetics and time of injury pain treatment.

PRINCIPAL INVESTIGATOR: Dr. Mark Hutchinson

CONTRACTING ORGANIZATION: The University of Adelaide
Adelaide, AU 5005

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Fort Detrick, Maryland 21702-5012

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14. ABSTRACT . We are one-year into the three-years of our research program into the immunogenetic and drug exposure factors that contribute to chronic pain following spinal cord injury. Owing to the planned data collection timeline of the 2 studies in this program we have no raw data to report, but we have made significant administrative advances. Study 1 comprises two study sites, South Australia (site 1) and New South Wales (site 2). We have received human research ethics approval from the Royal Adelaide Hospital (site 1) and the New South Wales approval is under review. Study 1 has been approved by the Human Research Protection Office (16986.1). Our clinical team at Site 1 (Hampstead Rehabilitation Centre, Royal Adelaide Hospital) has identified 244 patients in their database who fulfill the inclusion criteria for Study 1. They have been processing 20-30 recruitment and questionnaire/sample mail-outs per week. The aim is to have exhausted the Site 1 subject list by the end of 2012 and have begun Site 2 (NSW) recruitment in 2013. Study 2 institutional Ethics approval has been gained and is being reviewed by the Human Research Protection Office (16986.2). We are on track to start Study 2 in 2013 as planned.					
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INTRODUCTION

Spinal cord injury results in significant trauma and inflammation originating at the site of injury as well as from various systemic anatomical compartments. This inflammatory event provides both beneficial activation of repair and clearance systems, but also creates long-term detrimental consequences such as chronic pain. Chronic pain develops after spinal cord injury in more than 65% of the clinical population¹. However, the reasons why some patients develop chronic pain and others do not remains unknown. Chronic neuropathic pain elicits a number of changes in the activity, properties and transmitter content of pain-pathway neurons². This central sensitization to nociceptive stimuli culminates in profound debilitating pain that serves no adaptive purpose for the sufferer. It is now established that spinal inflammatory events resulting from numerous stimuli initiate and maintain chronic neuropathic pain conditions³ and may result from a dysregulation of the spinal immunocompetent cells, glia, and their up regulation of pronociceptive (pain) systems. A key event in the initiation of this inflammatory response is the activation of the innate immune system pattern recognition receptor, Toll Like Receptor 4 (TLR4)^{4,5}. TLR4 is able to detect the presence of endogenous danger molecular patterns resulting in the activation of an inflammatory cascade that results in the expression and release of a myriad of inflammatory signals such as proinflammatory cytokines, chemokines, prostaglandins, reactive oxygen species and nitric oxide. Importantly, these same proinflammatory molecular signals also elicit a pronociceptive, or painful, response that contributes indelibly to the chronic pain state⁵. The prototypic opioid, morphine, is capable of TLR4-mediated proinflammation⁶⁻⁸. As such, exposure to morphine at the time of injury may result in exacerbated proinflammation and hence produce long-term consequences for the pain susceptibility of the individual. In addition, the immune genes that encode these key inflammatory mediators are highly polymorphic. Hence, an individual may have a genetic predisposition to over respond in a proinflammatory fashion to the spinal cord injury and/or to experience inflammation in response to opioid exposure. Critically, this genetic variability may significantly impact the long-term health and quality of life of the individual. Thus both genetics and drug exposure at the time of injury may be contributing factors individually and/or interactively that lead some individuals to develop chronic pain following injury or may protect others from developing a pain pathology. Hence, this project will investigate the impact of both pharmacological agents and genetic variability on the occurrence of chronic pain following spinal cord injury.

BODY

The research management team (Dr Hutchinson, Dr Collier & Dr Clarke) and met between fortnightly to monthly during year 1 of the research project to ensure administrative progress. Now that data collection has begun we have increased correspondence and meetings to weekly of not daily communication.

Our professional research team has grown to include Ms Vicky Staikopoulos, Ms Francesca Alvaro and Ms Kathy Heyman. Vicky is our highly experienced technical research assistant (working 3 days a week) who is working on the lab side of the team to prepare our mail-outs, process DNA samples and receive data back from our analysis centre. Kathy and Francesca form the hands on part of our clinical team who are engaged at the Hospital and the Rehabilitation Centre. They liaise with Dr Marshall and Dr Clarke to coordinate the subject recruitment and consenting. Kathy is a registered nurse and Vicky has many years clinical trials experience. Kathy and Francesca job share approximately a 3-4 day load. This arrangement is working very well to ensure a balance of strict patient information confidentiality at the hospital side and timely outcomes at the lab side. All staff and investigators have completed NIH Human Research training and their details and credentials have been passed onto the Human Research Protection Office.

STUDY 1

Human research ethics for Study 1 Site 1 has been approved by the research ethics committee at the Royal Adelaide Hospital (Site 1: approval no. 111008) and approved by the Human Research Protection Office (16986.1). Study 1 Site 2 ethics has been submitted and is under review for patient recruitment in New South Wales.

The clinical team at Site 1 (Hampstead Rehabilitation Centre, Royal Adelaide Hospital) has identified 244 patients in their database who fulfill the inclusion criteria for Study 1. They have been processing 20-30 recruitment and questionnaire/sample mail-outs per week. The aim is to have exhausted the Site 1 subject list by the end of 2012 and have begun Site 2 (NSW) recruitment in 2013.

Parallel these efforts we are nearing the completion of the processing of DNA samples from the healthy control reference sample population.

Additionally, our clinical team is reviewing the clinical records of the recruited and consented patients from Study 1 Site 1 and this data collection process has begun.

STUDY 2

Study 2 institutional Ethics approval has been gained and is being reviewed by the Human Research Protection Office (16986.2). We are on track to start Study 2 in 2013 as planned.

In order to comply with new HRPO guidelines a research monitor has been appointed to oversee Study 2. Ms Melanie Gentgall has been appointed and approved by the Royal Adelaide Hospital as the Research Monitor for Study 2. Melanie's role and processes that will be followed have been included in the approved Ethics Application which is now under review at the HRPO.

The processing data pipeline has been constructed and is being employed in all data collection to date.

KEY RESEARCH ACCOMPLISHMENTS

- Human research ethics approval granted for Study 1
- HRPO approval gained for Study 1
- Subject recruitment commenced for Study 1
- Human research ethics approval granted for Study 2

REPORTABLE OUTCOMES

Dr Clarke presented an outline of this project entitled "ROLE OF XENOBIOTICS IN SUSCEPTIBILITY FOR NEUROPATHIC PAIN IN SPINAL CORD INJURED PATIENTS" at the World Pain Congress (IASP) in Milan, and at the 51st Annual Scientific Meeting of the International Spinal Cord Society in London. These presentations included some preliminary analysis of old pilot data obtained prior to the awarding of this current grant, but these data had formed the foundation for the hypotheses proposed here. These presentations proved invaluable in sourcing additional peer review of our hypotheses and research plan and facilitated contact with basic researchers and clinicians alike readying them for the future presentation of these exciting results.

When data collection for each study is completed more presentations and communications are planned.

CONCLUSION

Since the awarding of this grant, publications of additional parallel basic mechanistic research by our group and others around the world continues to support the core hypothesis underlying this research program, exposure to drugs, such as opioid analgesics at the time of spinal cord injury may result in profound alternations in the proinflammatory environment within the central nervous system that may produce long-term consequences for the pain susceptibility of the individual. Thus, genetic polymorphisms in the immune genes responsible for this immune response may have a genetic predisposition to over respond in a proinflammatory fashion to the spinal cord injury and/or to experience inflammation in response to opioid exposure. Critically, this genetic variability may significantly impact the long-term health and quality of life of the individual. Thus both genetics and drug exposure at the time of injury may be contributing factors individually and/or interactively that lead some individuals to develop chronic pain following injury or may protect others from developing a pain pathology. The data collected from the 2 studies to be carried out here will provide critical clinical evidence to support these hypotheses

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APPENDICES

1. Approval letter from the RAH Human Research Ethics Committee for Study 1
2. Approval email from the HRPO for Study 1
3. Approval email from the RAH Human Research Ethics Committee for Study 2



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Research Ethics Committee

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Tel: (08) 8222 4139

Fax: (08) 8222 3035

Email: Heather.O'Dea@health.sa.gov.au

13 August 2012

Dr Mark Hutchinson
ARC Research Fellow
Discipline of Physiology
UNIVERSITY OF ADELAIDE

Dear Dr Hutchinson,

Re: "Immune genetic studies of spinal cord injury patients."

RAH PROTOCOL NO: 111008.

Thank you for your recent letter informing us of the changes listed below. These changes have been approved.

- Updated study contact details for participants
- Advertisement, Version 1 (12 July 2012)

Yours sincerely,

Dr A Thornton
CHAIRMAN
RESEARCH ETHICS COMMITTEE

Resent-From: <mark.hutchinson@adelaide.edu.au>
From: "Brosch, Laura R Dr CIV USA MEDCOM USAMRMC" <Laura.Brosch@us.army.mil>
Subject: A-16986.1 HRPO Approval Memorandum (Proposal Log Number SC100231, Award Number W81XWH-11-1-0806) (UNCLASSIFIED)
Date: 7 March 2012 5:25:33 AM ACDT
To: "mark.hutchinson@adelaide.edu.au" <mark.hutchinson@adelaide.edu.au>
Cc: "Brosch, Laura R Dr CIV USA MEDCOM USAMRMC" <Laura.Brosch@us.army.mil>, "Bennett, Jodi H Ms CIV USA MEDCOM USAMRMC" <Jodi.Bennett@us.army.mil>, "Duchesneau, Caryn L Ms CIV USA MEDCOM USAMRMC" <Caryn.Duchesneau@us.army.mil>, "McKean, Joshua Mr CIV USA MEDCOM USAMRAA" <Joshua.McKean@AMEDD.ARMY.MIL>, "Bekirov, Iddil H DoD Af US USA MEDCOM CDMRP" <Iddil.Bekirov@us.army.mil>, "Frank, Melanie A CTR US USA MEDCOM USAMRMC" <melanie.frank1@us.army.mil>, "Katopol, Kristen R Ms CTR US USA MEDCOM USAMRMC" <Kristen.Katopol@us.army.mil>, "Drake, Carrie E Ms CTR US USA MEDCOM USAMRMC" <Carrie.Drake@us.army.mil>

Classification: **UNCLASSIFIED**
Caveats: NONE

SUBJECT: Initial Approval for the Protocol, "Immune Genetic Studies of Spinal Cord Injury Patients," Submitted by Mark R. Hutchinson, PhD, University of Adelaide, Adelaide, Australia, in Support of the Proposal, "Chronic Pain Following Spinal Cord Injury: The Role of Immunogenetics and Time of Injury Pain Treatment," Submitted by Mark R. Hutchinson, PhD, University of Adelaide, Adelaide, Australia, Proposal Log Number SC100231, Award Number W81XWH-11-1-0806, HRPO Log Number A-16986.1

1. The subject protocol, version 3.0/6 February 2012, was approved by the Royal Adelaide Hospital Research Ethics Committee on 14 February 2012. This protocol was reviewed by the U.S. Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) and found to comply with applicable DOD, U.S. Army and USAMRMC human subjects' protection requirements.
2. This no greater than minimal risk study is approved for the enrollment of 225 patients with spinal cord injury (comprised of an equal number of patients who, following their spinal cord injury, developed chronic pain and those who did not) that are currently between 6 months and 10 years post injury.
3. The Principal Investigator has a duty and responsibility to foster open and honest communication with research subjects. The USAMRMC strongly encourages the Principal Investigator to provide subjects with a copy of the research protocol, if requested, with proprietary and personal information redacted as needed.
4. The following are reporting requirements and responsibilities of the Principal Investigator to the HRPO. **Failure to comply could result in suspension of funding.**
 - a. Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review), or a change that could potentially increase risks to subjects.
 - b. All unanticipated problems involving risk to subjects or others must be promptly reported by telephone (301-619-2165), by email (HRPO@amedd.army.mil), or by facsimile (301-619-7803) to the HRPO. A complete written report will follow the initial notification. In addition to the methods above, the

complete report can be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RP, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

c. Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the institutional review board, the institution, the sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.

d. A copy of the continuing review approval notification by the Royal Adelaide Hospital Research Ethics Committee must be submitted to the HRPO as soon as possible after receipt of approval. According to our records, it appears the next continuing review by the Royal Adelaide Hospital Research Ethics Committee is due no later than 14 February 2013. Please note that the HRPO also conducts random audits at the time of continuing review and additional information and documentation may be requested at that time.

e. The final study report submitted to the Royal Adelaide Hospital Research Ethics Committee, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.

f. The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other government agency concerning this clinical investigation or research; the issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any regulatory agencies including legal or medical actions; and any instances of serious or continuing noncompliance with the regulations or requirements must be reported immediately to the HRPO.

5. **Please note:** The USAMRMC ORP HRPO conducts random site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRMC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.

6. Do not construe this correspondence as approval for any contract funding. Only the Contracting Officer or Grants Officer can authorize expenditure of funds. It is recommended that you contact the appropriate contract specialist or contracting officer regarding the expenditure of funds for your project.

7. The HRPO point of contact for this study is Melanie Frank, BSN, RN, Human Subjects Protection Scientist, at 301-619-6766 or melanie.frank1@us.army.mil.

LAURA R. BROSCH, PhD
Director, Office of Research Protections
Director, Human Research Protection Office
U.S. Army Medical Research and Materiel Command

Note: The official copy of this approval memo is housed with the protocol file at the Office of Research Protections, Human Research Protection Office, 504 Scott Street, Fort Detrick, MD 21702. Signed copies will be provided upon request.

Classification: **UNCLASSIFIED**
Caveats: NONE

Resent-From: <mark.hutchinson@adelaide.edu.au>
From: "O'Dea, Heather (Health)" <Heather.O'Dea@health.sa.gov.au>
Subject: RE: PROTOCOL SCI.002
Date: 10 October 2012 5:34:13 PM ACDT
To: "Gentgall, Melanie (Health)" <Melanie.Gentgall@health.sa.gov.au>
Cc: "Marshall, Ruth (Health)" <Ruth.Marshall@health.sa.gov.au>, "Clark, Jillian (Health)" <Jillian.Clark@health.sa.gov.au>, Mark Hutchinson <mark.hutchinson@adelaide.edu.au>, 'Janet Collier' <janet.collier@adelaide.edu.au>, 'Vicky Staikopoulos' <vicky.staikopoulos@adelaide.edu.au>

Dear Mel,

Responses have been reviewed, and both IDSC and REC have been accepted.

The study is now APPROVED, effective 8 October 2012.

An approval letter may be a few weeks, we are very overloaded and behind with approvals.

However, I will proceed with the signatures on the CTN, the latest which was received with the responses 6/8/12 (though the Chairman is interstate this week), and that will be available when signed by HREC and the GM.

Regards,

Heather

Heather O'Dea
Executive Officer || Research Ethics Committee || Royal Adelaide Hospital
Level 3 Hanson Institute, RAH, North Terrace, Adelaide SA 5000
Phone: (08) 8222 4139 || Fax: (08) 8222 3035

From: Gentgall, Melanie (Health)
Sent: Wednesday, 3 October 2012 08:30
To: O'Dea, Heather (Health)
Cc: Marshall, Ruth (Health); Clark, Jillian (Health); Mark Hutchinson; 'Janet Collier'; 'Vicky Staikopoulos'
Subject: PROTOCOL SCI.002

Dear Heather,

Please find attached a copy of the revised documents for the SCI.002 study, as per your email dated 20 August 2012.

A hard copy of all the attached documents has been sent to you via post also.

Please do not hesitate to contact either myself or any of the Investigators at any time if you have any further questions or require additional information.

Kind regards,

Melanie

Melanie Gentgall | Clinical Research Manager
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