AWARD NUMBER:  W81XWH-14-2-0190

TITLE:  Testosterone Combined with Electrical Stimulation and Standing: Effect on Muscle and Bone

PRINCIPAL INVESTIGATOR(S):  GAIL F. FORREST, Ph. D.

CONTRACTING ORGANIZATION:  Kessler Foundation
West Orange, NJ  07052

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Fort Detrick, Maryland  21702-5012

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The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.
The study is a prospective, randomized, double blinded, controlled, multi-site clinical trial to determine the efficacy of a tri-combination intervention to improve musculoskeletal gains in men with subacute to chronic SCI with low circulating testosterone levels. Participants will be enrolled at Kessler Foundation (KF), the University of Louisville-Frazier Rehab (UoL), the James J. Peters VA Medical Center (JJPVAMC). During year 2 the Study Team (Drs. Forrest, Bauman, and Harkema) established a new partnership with a pharmaceutical company (AbbVie) to supply Drug and Placebo for all potential study participants. During Year 2, all FDA requirements were satisfied for the acquisition of the IND number for all sites. The drug/placebo has been manufactured and shipped to the Kessler site (10/23/16). Kessler, JPVAMC and UoL received HRPO approval 8/18/16, 9/1/16 and UoL HRPO approval (3/17/17) respectively. In Year 3 JPVAMC, and UoL received training for drug/placebo and electrical stimulation intervention at Kessler on 11/16/16 and UoL (1/17/17—1/18/17), respectively. Data is entered into ITW database as per grant procedures and SOW. All three sites started screening and enrollment. To date, Kessler, UoL and JJPVMVC have prescreened 68 individuals, screened consented onsite 18, 3 are currently screening, 2 have completed 5 months intervention phase, one is currently training. Two are in follow-up of phase of protocol.
Table of Contents

1. Introduction........................................................................4
2. Keywords..............................................................................4
3. Accomplishments..............................................................5
4. Impact..................................................................................9
5. Changes/Problems..............................................................9
6. Products.............................................................................11
7. Participants & Other Collaborating Organizations...............12
8. Special Reporting Requirements........................................14
9. Appendices..........................................................................14
1. INTRODUCTION

This study is a prospective, randomized, double blinded, controlled, multi-site clinical trial to determine the effectiveness of a tri-combination Activity-Dependent Rehabilitation Model on improving musculoskeletal gains in men with subacute to chronic SCI who have low serum testosterone levels. A total of 56 research participants will be enrolled across 3 clinical sites: Kessler Foundation Research Center, the University of Louisville-Frazier Rehab and the James J. Peters VA Medical Center (Bronx, NY). Each site will recruit 19 participants over 3 years or 6-7 subjects per year. Eligibility will be determined by the site physician and site PI. Research participants will be randomized into one of four groups: 1) Stand Training only; 2) Stand+Electrical Stimulation; 3) Stand Training+Testosterone; 4) Stand Training+Testosterone+Electrical stimulation. Each research participant will complete 60 sessions of training.

The model involves intense training with testosterone replacement therapy and electrical stimulation on multiple muscles. Our primary focus is to examine the change in muscle, but we will also look at the change in bone. This tri-combination Activity-Dependent Rehabilitation Model can easily be adapted to a clinic based model.

2. KEYWORDS

Testosterone, multi-muscle electrical stimulation, dynamic standing protocol, muscle volume, MRI, bone mineral density, DXA, QCT scans, metabolic bone markers, subacute SCI, chronic SCI.

3. ACCOMPLISHMENTS

- What were the major goals of the project?

Aims of Proposal

The overall aim of this proposal is to determine the interaction of testosterone, ES of multiple leg muscles and stand training or loading (bearing of the body weight) in individuals with subacute to early chronic SCI who are wheelchair reliant at least 75% of the time in a phase I/II multi-site randomized clinical trial (n=56, recruited at 3 training sites) on bone and muscle.

Our primary aim is to assess the effects of our novel tri-combination Activity-Dependent Rehabilitation model approach on muscle volume of the lower limbs.

Our secondary aims are:

i) To better define the mechanisms that contribute to changes in muscle.

Secondary outcome measures associated with this aim will further assess whether the tri-combination of stand training with TRT and ES will lead to increased muscle strength and contractile elements of muscle as shown by an increase in muscle torque, an increased expression of PGC-1α and its downstream targets in the lower limb and an alteration in myostatin signaling. Preliminary data from animal studies have shown increased expression of Activin receptor IIB and increased nuclear localization of Smad2 and Smad3 after SCI and that these adverse changes are reversed by androgens. Additional studies will examine mRNA levels for myostatin, its receptor and its inhibitors (e.g., follistatins) and determine nuclear levels of Smad2 and Smad3. We will also measure resting energy expenditure to confirm that changes in muscles mass correspond to anticipated metabolic effects.

ii) To evaluate the changes in bone and bone structure with Stand Training with TRT and ES.

Secondary outcome measures of this aim will include BMD of the proximal tibia and distal femur; these are the most common sites for fracture and may also respond faster to intervention. Other secondary outcome measures will be BMD at the hip, cortical and trabecular bone with 3-D volumetric measurements, and bone markers for formation and resorption.
• What was accomplished under these goals?

In Year 1, a significant obstacle was encountered where we were informed that Watson Laboratories had been acquired by a company that would not be able to supply drug and placebo (the fill details are described on Pages 8-9; in addition, the sequential timeline to a positive solution for acquisition of drug/placebo is also provided on Pages 8-10). Therefore the major accomplishment in Year 1 was on November 10th, 2015 we received notification from Abbvie that they will provide the drug and placebo at no cost to the study. Drs. Forrest and Bauman contacted Dr. Henry on November 11, 2015 to notify her of our final solution. All of these details are described on Page 8-10. In year 1, local IRB at Kessler for original protocol was accomplished, but we placed all IRB submissions and resubmissions on hold until we organized a suitable solution for drug acquisition.

In Year 2, the major accomplishments were: i) the establishment of the contractual agreement between Kessler and Abbvie, Inc. for drug acquisition according to study protocol and at no cost to the study; ii) the manufacturing of drug and placebo; iii) the shipping of drug to Kessler Pharmacy (arrived 10/17/16); iv). Local IRBs were approved with all changes to satisfy Abbvie and FDA requests for Kessler, JJPVAMC, and UoL; v) HRPO IRB approval at Kessler (8/18/16), JJPVAMC (9/1/16); vi). Kessler established a pre-screen list and a screen consenting list for potential subjects to be recruited.

In Year 3, after the drug arrival at Kessler (10/17/16), JJPVMVC and Kessler completed their training of drug administration (Dr. William Bauman) and ST+ES training procedures (Gail F Forrest) and testing procedures at Kessler (11/21/16). UoL completed their training and testing procedures meeting at Kessler (1/17/17—1/18/17). Protocol for data collection and database entry for all sites [Kessler, JJPVMVC (11/21/16) and UoL (1/17/17—1/18/17)] were also completed. Kessler and JJPVMVC officially started screening of subjects. Regular biweekly conference calls (Kessler, UoL, JJPVAMC) are ongoing to discuss study protocol, training, and testing. All three sites started screening and enrollment. To date Kessler, UoL, and JJPVMVC have prescreened 68 individuals, screened consented onsite 18, completed training intervention period 2, enrolled 3 for training and currently screening 4 participants.

Dr Gail Forrest requested a No Cost Extension for 2 years (8/28/17). A full 2-year budget was requested and was submitted (11/6.17). Decision is pending.

Specific Aims: (1) To examine the effectiveness of stand training with testosterone and electrical stimulation to induce positive changes in muscle volume. Our secondary aims are: i) To better define the mechanisms that contribute to changes in muscle. ii) To evaluate the changes in bone and bone structure with Stand Training with TRT and ES.

Note: IRB submissions were modified to show new protocol changes.- see below.

<table>
<thead>
<tr>
<th>As per SOW</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Task 1: Adapt TRT to ES protocol: Complete IRB</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Subtask 1: Prepare Regulatory Documents and Research Protocol for Study 1</strong></td>
<td></td>
</tr>
<tr>
<td>Sites for IRB completions submitted</td>
<td></td>
</tr>
<tr>
<td><strong>Milestone Achieved:</strong></td>
<td>Kessler-12/4/15 JJPVMC-1/20/16 UoL 10/27/16</td>
</tr>
<tr>
<td>i) Initial Local IRB approval for Kessler, JJPVAMC, UoL</td>
<td></td>
</tr>
<tr>
<td><strong>Amendments:</strong></td>
<td>3/3/16</td>
</tr>
<tr>
<td>FDA IND number completed (4/29/15).</td>
<td></td>
</tr>
<tr>
<td>Amended and resubmitted to reflect drug changes.</td>
<td></td>
</tr>
<tr>
<td>Final FDA IND number approved 3/3/16.</td>
<td></td>
</tr>
<tr>
<td>Amendment to local site IRBs</td>
<td></td>
</tr>
<tr>
<td>Note: In accordance with FDA Request. Each site was required to include a study physician as a co PI. The change is made to each site’s IRB.</td>
<td></td>
</tr>
</tbody>
</table>
- Review eligibility criteria, exclusion criteria, screening protocol
- Finalize amendments to consent form & human subjects protocol
- Coordinate with Sites for IRB protocol resubmission
- Coordinate with Sites for IRB completions of all amendments. Kessler approval 4/11/16; JJPVAMC approval 1/20/16; UoL 10/27/16

<table>
<thead>
<tr>
<th>Sites for IRB completions submitted to HRPO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Milestone Achieved:</strong></td>
</tr>
<tr>
<td>i) HRPO approval for Kessler, JJPVAMC</td>
</tr>
<tr>
<td>(Kessler submitted IRB to HRPO - 5/18/16)</td>
</tr>
<tr>
<td>ii) UoL HRPO IRB submitted 10/31/16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major Task 2: Training of protocol at Kessler</th>
<th>3-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manual of Operations (MOP) and Standard Operating Procedures for TRT and Case Report Forms completed</td>
<td>6/28/14</td>
</tr>
<tr>
<td>Forrest and Harkema trained site PTs on Combination ST+ES. Additional set up of training software and hardware at Kessler for PTs Completed repeatability testing on ES ramping, training procedures to be applied at all sites</td>
<td>4/28/15</td>
</tr>
<tr>
<td>JJPVAMC Training meeting for ST+ES training procedures at Kessler</td>
<td>6/15/16-6/30/16</td>
</tr>
<tr>
<td>Dr William Bauman (WB) will train sites to administer testosterone gel based on Standard Operating Procedures.</td>
<td>11/21/16/ Ongoing</td>
</tr>
<tr>
<td>Regular biweekly Conference calls (Kessler, UoL, JJPVAMC) established to discuss study protocol, training and testing.</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

**Milestone Achieved:**

- Kessler and UoL Research staff already trained in standing and ES protocol. ES program automated. JJPVAMC 11/21/16

<table>
<thead>
<tr>
<th>Major Task 3: Participant Recruitment, Therapy, Participant Evaluation</th>
<th>3-6 after IRB approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtask 1: Data set up with initial subject at each site.</td>
<td>6/28/14</td>
</tr>
<tr>
<td>Coordinate with sites for all study steps, data collection and database requirements’ - will occur at Training Session at Kessler for JJPVAMC</td>
<td>11/21/16</td>
</tr>
<tr>
<td>Set up assessment measurements (already established at 2 sites – Kessler, UoL). JJPVAMC will have kick off meeting 11/21/16</td>
<td>11/21/16/ Ongoing</td>
</tr>
<tr>
<td><strong>Begin and continue subject recruitment for recruitment and randomization. Numbers below.</strong></td>
<td>9/15/16/ Ongoing</td>
</tr>
<tr>
<td>Milestone: Evaluate and assign participants to one of the four randomized groups at Kessler</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

**Milestone Achieved:** Kessler and JJPVAMC sites: Study begins Kessler 9/15/16; JJJPMC11/21/16

**Milestone Achieved:** 1st participant screen consented ay Kessler
performance or progress of the study (e.g. slow enrollment, large dropouts, or adverse events) for the above HPRO approved protocol.

- As explained above, our study progress has been hindered because of the need to acquire a replacement study drug/placebo.
- Abbvie supplied the drug (Gel) and placebo. Contract was signed (6/24/16). Abbvie drug delivery 10/17/16
- Start-up meetings for training procedure for drug, ST+ES protocol, and all testing procedures for screen and main consenting procedures completed (11/21/16 and 17/17-18/17).
- Screening has occurred at all sites.
- Kessler has pre-screened 35 participants, UoL have pre-screened 25, JJPVAMC have pre-screened 8.
- Kessler screened consented 5 for enrollment (one withdrew), UoL screened 10, and JJPVAMC screened consented 3.
- Kessler enrolled 2, UoL enrolled 1 into main study.
- Two participants have completed 80 sessions of training and are in follow up-period.
- Kessler is currently training 1 participant currently.
- Kentucky is currently screening 3 participants
- Kessler has 1 participant awaiting to be screened.
- Kessler had one SAE (reported in Quarter 3 report) where Kessler had one subject “on medical hold” 4/28/2017- 6/5/2017. Therefore, this stopped his training schedule. Issue was resolved and individual continued training phase.

<table>
<thead>
<tr>
<th>Site</th>
<th>Prescreen</th>
<th>Waiting to screen</th>
<th>Screen consented (Screen Consent and T consent)</th>
<th>Screen in progress</th>
<th>Failed Screen</th>
<th>Passed screen Screen/waiting to enroll</th>
<th>Main Consent</th>
<th>Training</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kessler</td>
<td>35</td>
<td>2</td>
<td>5 (1 withdrew)</td>
<td>4</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>JJPVAMC</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>UofL</td>
<td>25</td>
<td>3</td>
<td>10 (T-screen)</td>
<td>3</td>
<td>14</td>
<td>1 (1 withdrew)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

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

  In Year 3 – study teams across all sites were involved in professional development:

  - Training in Year 3 involved Kessler PTs continued work on the training protocol for the multi-muscle stimulators to set up all ES training programs and procedures as automated software for all sites before training first participant.
  - In Year 3 –UoL completed “on site” training at Kessler for complete testing and training protocol, including drug application and NMES (ES training protocol). Currently sites are actively involved in all aspects of study (enrollment, testing, training).

- 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?
In the next year we are actively prescreening and screening to enroll subjects into the intervention phase as per our SOW (4.25.16).

Note: ***The time line in the SOW (submitted 4.25.16) below was revised in the “No Cost Extension” request. No Cost Extension was submitted 8.28.17. A new budget was requested and submitted 11/6/17. Approval pending:***

<table>
<thead>
<tr>
<th>Major Task 1: Adapt TRT to ES protocol: Complete IRB</th>
<th>Time line (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submit amendments, adverse events and protocol deviations as needed</td>
<td>As needed</td>
</tr>
<tr>
<td>Coordinate with Sites for annual IRB report for continuing review</td>
<td>Annually</td>
</tr>
<tr>
<td><strong>Milestone Achieved: Local IRB approval at Kessler, UoL, JJPVAMC</strong></td>
<td>3</td>
</tr>
</tbody>
</table>

**Major Task 2: Training of protocol at Kessler**

| Training for ES and drug at Kessler site for JJPVAMC | 11/21/16 |
| Dr William Bauman (WB) will train all sites on testosterone gel | 11/21/16 |
| Forrest, Harkema and Bauman will continually instruct all sites on protocol description per MOP | 11/21/16 and ongoing |
| **Milestone Achieved: Research staff trained** | 11/21/16 and ongoing |

| Subtask 2: Site Visit to review training | 4-5 |
| Drs. Forrest will visit the Bronx VAMC study site to provide review and potential additional instruction of the procedures for Stand Training with ES (December 2016, January, 2017 and as required). This will be followed by ongoing conference calls. | 4-5 |
| **Milestone Achieved: Maintained protocol training and follow up at all sites.** | 4-5 |

**Major Task 3: Participant Recruitment, Therapy, Participant Evaluation**

| Subtask 1: Continue Data set up with subjects at each site | Timeline after IRB approval |
| Continue to Coordinate with sites for all study steps, web data collection and database requirements: | 4-6 |
| Continue with assessment measurements at all sites | 4-6 |
| **Milestone Achieved: 1st participant consented, screened enrolled at all sites** | 4-6 |
| Kessler completed first screen in 2016; JJPVAMC completed first screen in 2017 after 11/21/16 meeting; UoL and Kessler has enrolled and completed training on one participant. Participants are in follow up period (full report below). | 4-6 |
| **Milestone Achieved: All sites Study begins** | 4-6 |
| Continue subject recruitment | 4-30 |
| Continue Screen potential participants | 4-30 |
| Evaluate and assign participants to one of the four randomized groups | 4-30 |
| Outcome measures assessment at each time point continues | 4-30 |
| At all sites: Research participant complete 80 sessions of training frequency of 4 times per week (1.5-hour) followed by post testing and follow up (MRI, DXA) | 4-33 |
| **Milestone Achieved: Record data for year 1, 2, 3, into ITW database; Report** | 4-33 |
4. IMPACT

Nothing to report

5. CHANGES/PROBLEMS

- Changes in approach

There was no change in approach in Year 1 or Year 2. In Year 3, the total number of stand training hours was extended to 80 hours within the overall intervention period. Documents were sent to HRPO (6/28/17) and approved (7/11/17).

- Actual or anticipated problems or delays and actions or plans to resolve them

During the reporting period in Year 1 there were significant delays associated with acquisition and delivery of drug/placebo. These delays were reported in the quarterly reports. The delays are outlined in detail below. Note for any delays in Year 3 – these are highlighted in RED

As reported in Quarter 1, year 1 report the main problem to address for Quarter 1 in year 1 was that we were informed that Watson Laboratories had been acquired by a company that would not be able to supply drug and placebo for our proposed placebo-controlled RCT. For the Year 2, Quarter 1 report we proposed our final solution to the TRT/Placebo issue.

- At the time of submission of our grant, Watson Laboratories had provided a letter of support which stated that this company would provide TRT patch and matching placebo for our study. The support being offered by Watson Laboratories was a continuation of previous collaboration with the company for similar work that was completed by Dr. William A. Bauman, co-principal investigator on the current grant, which addressed the safety and efficacy of TRT patch in a population of persons with chronic spinal cord injury at the James J. Peters VA Medical Center and The Kessler Institute for Rehabilitation, work which was published in *Hormones and Metabolic Research* in 2011. In our Quarter 1, Year 1 report we reported that Watson Laboratories was obtained by Actavis Pharmaceuticals, and management at the new company had informed us that they had decided not to provide study drug for our RCT, nor for any other RCTs at this time. It was inferred that their policy decision was based on a change in philosophy toward research initiatives which took into account the total cost of supplying matching placebo and the assumption of risk for any new study.
After careful consideration and in discussion with Patricia Henry, PhD, Science Officer (discussions: 2/17/2015 and 4/1/2015) Drs. Forrest, Bauman, and Harkema addressed the problem in a satisfactory manner to maintain the study as designed and to make no changes to the SOW.

In Quarter 1, we reported that the FDA approved New York based compound pharmacy “Metro Drugs” would be supplying the drug (Gel) and placebo to the sites, and we provided a letter from the company confirming this agreement. Shortly after we submitted the Quarter 1 report, we were informed by the New York State (NYS) DEA that the only suitable and legal option to supplying drug and placebo to our 3 study sites was FDA approved pharmacy that was located outside NYS because of stringent laws that prohibited the dispensing of any controlled substances by an appropriately licensed NYS pharmacy outside of the state. In actual practice, the testosterone/placebo preparation would be sent by the FDA pharmacy directly to the subjects.

As you may appreciate, identifying a FDA compound pharmacy that has the experience and resources to supply both study drug and placebo, with an appropriate dispensing system in place, was an onerous task, and this was, at the time, our main difficulty with being able to initiate the study. A pharmacy was located and agreed to provide the investigators with drug and placebo. To do so required the investigators to pay for the cost of topical generic testosterone preparation (at approximately 25% the cost of Androderm) and for a placebo gel. The cost of these preparations had been provided in a previous email, as well as the other associated costs, including those of the cost of dispensing ($10,920), repacking ($6006), and shipping ($24,570), with a total final cost of the pharmacy to provide us with drug/placebo of over $100,000, an expense that were not budgeted prior to Watson Laboratories withdrawing their support for our proposal. Of note, the investigators decided that intramuscular preparations of testosterone were not physiologic (peaks and valleys in pharmacokinetics) and in the SCI population would be associated with a heightened risk of autonomic dysreflexia, potentially a life-threatening complication, if the injection is delivered below the level of lesion; administration of the intramuscular injection above the level of lesion may be associated with pain and discomfort upon transfers, which may limit mobility, reduce drug/placebo compliance, and increase drop-out rates. A total of 56 research participants is proposed to be studied in our proposal.

The source of the drug was Belmar Pharmacies, a licensed non-resident pharmacy (license #30,649) and that is licensed with the DEA. The letter was provided in the Quarterly report dated 7/14/15. The pharmacy would have supplied the patient-specific compounded testosterone or placebo, directly to patients based upon a valid prescription. To date, this company had been the only viable option after an exhaustive search of both Clinical Trials.gov and reaching out to other pharmacies. Drs. Forrest and Bauman worked with the company to set up the standard of operation procedures for dispensing the drug/placebo to study participants.

Drs. Forrest and Bauman had been in discussions via several email correspondences and conference calls (6/9/15; 6/15/15; 6/16/15) with Patricia Henry, Ph.D., Science Officer, regarding the potential of additional funds to cover the additional cost of the drug. Based on our discussions, Dr. Henry instructed us to submit a formal request for additional funding (6/18/15).

Drs. Forrest and Bauman submitted a formal request to the DOD for additional funding on 6/23/15. Please see letter in report dated 7/14/15.

Of note, in January 2015, the investigators submitted a request to Abbvie to provide testosterone gel and matching placebo for the study. We considered this “option” to be a real possibility, albeit somewhat unlikely if one considers the length of time that our request had languished without resolution. However, our proposal continued to be actively considered. We suggested in
our previous quarterly report (7/14/2015) that if this company approved our request, then the
investigators would proceed with the clinical trial without the need for additional financial
support from the DoD.

- Fortunately, on November 10th, 2015 notification was received from Abbvie that the company
  had agreed, in principle, to provide the drug and placebo at no cost to the study. Drs. Forrest
  and Bauman contacted Dr. Henry on November 11, 2015 to notify her of our final solution. Dr.
  Henry had requested that Dr. Forrest submit a revised SOW to Dr Henry on 11/23/15. Based on
  the revised SOW (4/25/16. Year 1 Final report) – we have amended the protocols at all
  institutions to comply with our proposed changes in drug formulation (e.g., patch to gel
  application), dosage, and origin of agent/placebo.

- **During the reporting period in Year 2:**
  - Abbvie Inc. have manufactured drug/placebo at no cost to the grant. Final contractual agreement
    between Kessler Foundation and Abbvie was signed 6/26/16 (details Q3, Year 2).
  - All details associated with shipping of drug to each site, storage of drug, administration have
    been addressed in Q2, Year 2.
  - Final delivery to drug to Kessler has occurred on 10/23/16.
  - An additional delay to final IRB approval in Year 2 was the acquisition of the IND number from
    the FDA and the modification protocol, as requested by the FDA. This was accomplished by
    3/3/16 at Kessler.

- **During the reporting period in Year 3:**
  - All sites have started pre-screening, and screening. All screen procedures, randomization, drug
    acquisition, testing and training protocols are operational. Sites have completed training of
    subjects. Currently these subjects are in follow-up phase.
  - Kessler had one SAE (reported in Quarter 3 report) where Kessler had one subject “on medical
    hold” 4/28/2017- 6/5/2017. Therefore, this medical event stopped his training schedule. The
    issue was resolved, and individual continued the training phase.

- **Changes that had a significant impact on expenditures**
  - Because of the unanticipated delay in our obtaining of drug/placebo, the projected funds for Year
    1 and Year 2 have not been expended. These details were outlined both in our financial and
    quarterly reports.
  - **With the No Cost Extension – A revised SOW and Budget have been submitted.**

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

  No significant change to human subjects

6. **PRODUCTS**

None to report
7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- 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 individuals have worked on the project?

In Year 3 period individuals’ have worked primarily on training sites, pre-screening, screen consenting and training of subjects. In addition, Physical Therapists and technicians have worked on the establishment of the automated ES program for the standing +ES protocol. In Year 3, PT and study team have increased their amount of time charged to grant because of training and testing procedures.

Overall Submitting PI: Gail F Forrest Ph.D.  
Co-PI: William A. Bauman, M.D.

Individuals that have worked for at least 1 month (~160 hrs) in year 1.

Name: Gail Forrest  
Project Role: PI  
Nearest person month worked: 1.5  
Contribution to Project: Dr Forrest has worked in overall management of grant and with the study teams at all sites.

Name: Milda Woods  
Project Role: Study Coordinator, consultant  
Nearest person month worked: 1.5 months  
Contribution to Project: Ms. Woods has worked continually with Dr Forrest in year 3:  
   i) On the setting up of the reports to the FDA and material related to adverse events.  
   ii) On material for submissions to the HRPO for all IRB approvals.

Name: Leighann Martinez  
Project Role: Site Study Coordinator  
Nearest person month worked: 1.5 months  
Contribution to Project: Ms. Martinez has worked continually with Dr Forrest in year 3:  
   i) On the setting in house IRB documents.  
   ii) On screening, administration and coordinating subjects’ attendance.

Name: Erica Garbarini  
Project Role: Physical Therapist  
Nearest person month worked: 1.5 month.  
Contribution to Project: Ms Garbarini has worked continually with Dr Forrest in year 3  
   i) On training of participants at Kessler as well as coordinating testing at Kessler.  
Other Support: New Jersey on Spinal Cord Injury Research, Rehabilitation Engineering Research Centers (RERC) National Institute on Disability, Independent Living and Rehabilitation Research
**What other organizations have been involved as partners?**

<table>
<thead>
<tr>
<th>Site 2: University of Louisville (UoL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frazier Rehab Institute</td>
</tr>
<tr>
<td>220 Abraham Flexner Way, Suite 1506</td>
</tr>
<tr>
<td>Louisville, KY 40202</td>
</tr>
<tr>
<td>Site PI: Susan Harkema Ph.D.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site 3: James J. Peters VA Medical Center (JJVPA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>130 West Kingsbridge Road</td>
</tr>
<tr>
<td>Bronx, NY 10468</td>
</tr>
<tr>
<td>Site PI: Ann Spungen, EdD.</td>
</tr>
<tr>
<td>William Bauman.</td>
</tr>
</tbody>
</table>

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Provided below:

Gail Forrest Ph.D

**90RE5021 (Folds, PI) Project PI**

<table>
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<tr>
<th>9/30/15 – 9/29/21</th>
<th>.24 CM (2%)</th>
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<tr>
<td>NIDILRR</td>
<td>$995,821 (Total Award)</td>
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Title: Exoskeleton and Spinal Cord Stimulation for SCI” under Prime Award Title: “RERC Program on Robotics and Exoskeletons

Role: PI - project

**W81XWH-14-2-0170 (Spungen, PI)**

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Title: A Randomized, Crossover Clinical Trial of Exoskeletal-Assisted Walking to Improve Mobility, Bowel Function and Cardio-Metabolic Profiles in Persons with SCI

**W81XWH-14-2-0190 (Forrest, PI)**

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<tr>
<td>USAMRAA/CDMRP/DoD</td>
<td>$1,834,554 (Total Award)</td>
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Title: Testosterone Combined with Electrical Stimulation and Standing: Effect on Muscle and Bone”

$1,834,554 (Total Award)

**CSCR14ERG007 (Pilkar, PI)**

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<td>$194,976 (Total Award)</td>
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Title: Development of Signal Processing Toolbox for Assessing Neuromuscular Response during Electrical Stimulation”

Role: Co-I

**W81XWH-15-1-0614 (Bloom, PI)**

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<td>USAMRAA/CDMRP/DoD</td>
<td>$116,087 (Total Award Year 3)</td>
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</tbody>
</table>
8. SPECIAL REPORTING REQUIREMENTS

QUAD CHARTS submitted in appendices

9. APPENDICES

Pls Bio has been included.
BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Gail F Forrest

eRA COMMONS USER NAME (credential, e.g., agency login): gfforrest

POSITION TITLE: Associate Director, Human Performance and Engineering (HPE).

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)

<table>
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<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>Completion Date MM/YYYY</th>
<th>FIELD OF STUDY</th>
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<tbody>
<tr>
<td>Bachelor of Applied Science RMIT, Melb., Australia</td>
<td>B. App. Sc</td>
<td>12/1979</td>
<td>Mathematics/Computing</td>
</tr>
<tr>
<td>Temple University, Philadelphia</td>
<td>Ph.D.</td>
<td>1/2001</td>
<td>Biomechanics</td>
</tr>
<tr>
<td>Post Doctoral Fellow, Kessler Foundation</td>
<td></td>
<td>1/2001-12/2002</td>
<td>Biomechanics</td>
</tr>
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</table>

1 B. Positions and Honors

Prior to 1989 Mathematics and Computer Science Senior Level Teacher, Australia.
1989-1992 Corporate Consultant to Four Season Hotels (Daikeyo Corporation), Australia and Japan.
1991-1992 Victoria University, Melbourne, Australia, Grad Dip. Biomechanics
1995-1997 Teaching Assistant - Human Anatomy and Biomechanics, Temple University.
1997-1998 Biomechanics Lecturer and Coordinator, Temple University.
1998-1999 Teaching Assistant – Physiology, Biomechanics, and Anatomy, Temple University
2000-2002 Post Doctoral Fellow, Kessler Medical Rehabilitation Research and Education Corporation, West Orange, NJ.
2003-2007 Research Scientist II, Kessler Medical Rehabilitation Research and Education Corporation, West Orange, NJ.
2007-2012 Interim Director, HPMAL, Kessler Foundation Research Center, West Orange, NJ.
2012-2014 Assistant Director Human Performance Laboratory, Kessler Foundation.
2014 - Current Associate Director Human Performance and Engineering, Kessler Foundation.

University Appointments

5/2000-9/2000 Adjunct Professor Biomechanics, Physiology, – Temple University, University of Pennsylvania
1/2001-6/2005 Instructor, University of Medicine and Dentistry of New Jersey / New Jersey Medical School
7/5/05-present Assistant Professor University of Medicine and Dentistry of New Jersey/New Jersey Medical School
2011-Date Affiliated Faculty Department of Biomedical Engineering, New Jersey Institute of Technology, Newark, NJ
2012-Date Member of the Graduate Faculty in Biomedical Science, University of Medicine and Dentistry of New Jersey, Newark, NJ.
2013 –Date Associate Professor Rutgers New Jersey Medical School, Rutgers, the State University of New Jersey

Other Professional Experience

1999 - 2000 Research Assistant Dynamic Control of Head Stability, Agency NIH/NIA (RO3); (Ronita Cromwell, Ph.D., Principal Investigator)
2001 - present Institutional Review Board Member Kessler Foundation
2004 - present  Reviewer for Journal of Neuroengineering and Rehabilitation
2005 - present  Reviewer of Journal of Rehabilitation Research and Development
2005 - present  Reviewer of Journal of Spinal Cord Medicine
2005 - present  Compliance Committee member (subcommittee of IRB)
2005 - present  Committee member for ACRM International task force
2005 - present  Reviewer, RESNA
2009 - present  Reviewer NIH (2014/10 ZRG1 BBBP-Y (05), Motor Function, Speech and Rehabilitation (MFSR) Study Section).
2011-present  Craig H Neilson Foundation
2013-present  Reviewer for Gait and Posture.

2 C. Contribution to Science

1. My dissertation concentrated on understanding the dynamics of walking for older and younger adults using kinematics and muscle activation and intersegmental dynamics of the lower limbs;

2. My postdoctoral fellowship work contributed to the scientific understanding of neural plasticity in the lower limbs after intense locomotor step training intervention using a treadmill with body weight support for both motor complete and incomplete SCI. For all of this dissertation work we utilized a full body kinematic marker set and lower extremity muscle activation to study the effect of the intervention on treadmill gait and as well we studied postural control using kinematics and muscle firing patterns of the lower limb.

3. We evaluated the intense locomotor training intervention in an outpatient clinical program for over 250 patients across seven treatment centers across the USA.
   v. Morrison S, Eskay, CP, Forrest GF, Basso EM. Longitudinal recovery and reduced costs after 120 sessions of locomotor training for motor incomplete spinal cord injury Submitted Archives of Physical Medicine and Rehabilitation.
4. Our more recent research has been concentrated on multi muscle stimulation combined with dynamic stand training using bodyweight support and we studied the neuroplasticity effect of the intervention on kinematics and muscle activation during stepping on the treadmill and overground gait.


5. More recently we have focused on Wearable Robotics research and the effect on gait. We are currently investigating multiple wearable robotic exoskeletons and the training effect on neural and gait recovery both within and outside the exoskeleton as well as investigating the effect on muscle and bone. Our contributions to science encompass the training effect of these devices as a suitable device to be used in the community or as a device that can effectively be used in the clinic or understanding the the health benefits associated with using the powered robots.


6. With much of our previous and ongoing research we are investigating the effects of mechanical, pharmacological and multi muscle electrical stimulation effect on musculoskeletal system and overall health.


Active Research Support
90RE5021-01-00 Rehabilitation Engineering Research Centers (RERC)
Forrest (project PI) 7/1/114 – 12/31/19
Forrest (project PI)
National Institute on Disability, Independent Living and Rehabilitation Research
Site Project: Exoskeleton and spinal cord stimulation for SCI:
We propose that the combination of interventions of the exoskeleton assisted walking (EAW) with transcutaneous lumbosacral stimulation (TLS) would increase the excitability of the cord and afferent input when training in the exoskeleton to increase lower extremity muscle firing and to functionally increase walking speed.
W81XWH-14-2-0190 Department of Defense  PI Forrest 9/1/14-8/30/18
USAMRAA/CDMRP/DoD
Testosterone combined with Electrical Stimulation and Stand Retraining.
A Phase I/II prospective, randomized, double blind, controlled, multi-site clinical trial where the primary aim is to determine the neurological and neuromuscular interaction of testosterone, neuromuscular stimulation of multiple lower limb muscles and loading in individuals with sub acute to early chronic SCI who are non-ambulatory. Ultimately, we are interested in recovery of muscle and bone and the effect on functional motor gain for chronic SCI.
National Institute on Disability, Independent Living and Rehabilitation Research
Christopher Dana Reeves Foundation.

BIG Idea Project: Recovery of Autonomic control of cardiovascular and bladder function and the ability to stand and voluntary leg control movements below the level if injury with epidural stimulation
The objective of the project is to test the hypotheses related to neural control of human movement and cardiovascular function after human spinal cord injury while also obtaining knowledge for optimizing spinal cord epidural stimulation (scES) as a therapeutic intervention that can be immediately translated to larger numbers of patients who now have no treatment options for the secondary consequences of spinal cord injury.
SC140099 Department of Defense PI Bloom; Site PI Forrest 9/1/15-8/30/2019
USAMRAA/CDMRP/Department of Defense

Biomarkers of Spontaneous Recovery from Traumatic Spinal Cord Injury
The objective is to test the hypothesis that levels of some inflammatory biomarkers correlate inversely with functional recovery throughout the first year after spinal cord injury (SCI). The project specific aims are to (1) identify the circulating inflammatory response in patients with SCI, (2) determine the trajectory of spontaneous functional recovery in patients with SCI, and (3) derive a predictive, multiscale model of functional recovery after SCI.
W81XWH-14-2-0170 PI Spungen – Site PI Forrest 9/1/2014-8/30/2018
USAMRAA/CDMRP. Department of Defense

Randomized, Crossover Clinical Trial of Exoskeletal-Assisted Walking to Improve Mobility, Bowel Function, and Cardiometabolic Profiles in Persons with SCI
The primary objectives of this research is to document how long it will take to reach functional gains, such as speed and distance after 36 sessions of training with these devices. Preliminary studies support the goals that walking in the exoskeletons will improve bowel function and body composition.
CSCR13IRG013 Forrest (PI) 6/17/2013-6/16/2018
New Jersey Commission on Spinal Cord Research)

Non-ambulatory SCI walk using a Robotic Exoskeleton: Effect on bone and muscle
The overall purpose of this pilot study is to assess if 5 hours per week for 20 weeks of exoskeleton-assisted walking over ground for persons with chronic SCI will positively affect the musculoskeletal system. In addition we will evaluate the human neuromuscular and mechanic response to the robot.
1R21NS095052-01A1 Jiang T (PI) Forrest (Co-I) 04/01/2016-3/31/2018
NINDS. Major goal is to complete Longitudinal Assessment of Spinal Cord Structural Plasticity using DTI in SCI Patients

CSCR15ERG013NJC: Jiang T (PI) Forrest (Co-I) 6/29/2015-6/30/2018
New Jersey Commission on Spinal Cord injury

New Jersey Commission on Spinal Cord injury
The major goal is assessing Spinal Cord Structural Changes using Diffusion Tensor Imaging in Patients with Incomplete Traumatic Spinal Cord Injury
07-3063-SCR-E-0 Forrest (Co-PI) 01/01/7 – 1/31/18
Center For Disease Control and Christopher Dana Reeves Foundation Neuro Recovery Network grant.
The major goal of this project is to develop specialized centers that provide standardized activity-based therapy care based on current scientific and clinical evidence for people with SCI and other selected neurological disorders.
CSCR14ERG007 Pilkar (PI) Forrest (Co-I) 10/17/2014-9/16/2018
New Jersey Commission on Spinal Cord Research

The goal of this study is to develop a robust signal processing algorithm to extract EMG during ES and study the physiological significance of ES on neuromuscular properties of the stimulated muscle. The outcomes of this study will help in understanding the direct effects of ES on muscles by getting access to high quality EMG during ES and help the clinician or researcher to modify and optimize FES training paradigms based on the target muscle response. This could have a major impact on the field of spinal cord injury research and rehabilitation
3 A. Personal Statement

Dr. Bauman, Director of the National Center of Excellence, is an authority on calcium metabolism and bone disease in persons with SCI. He has been invited to be the primary author of a chapter entitled Skeletal Consequences of Spinal Cord Injury" for the 8th Edition of the American Society of Bone and Mineral Research’s Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. He is the senior author of a chapter entitled Immobilization Osteoporosis for the text entitled Osteoporosis. Dr. Bauman was the initial investigator to formally study the prevalence of vitamin D deficiency and replacement therapy in persons with spinal cord injury. Dr. Bauman is an endocrinologist who has written for medical and rehabilitation journals over the past 34 years, authored over 250 peer-reviewed papers, book chapters, and review articles. He has lectured to national and international audiences on the hormonal aspects of bone disease in spinal cord injury. Dr. Bauman has examined the cellular, biochemical, and molecular effects of paralysis due to spinal cord injury or nerve transaction on muscle and bone. He was invited to be Chairman of the International Endocrinology & Metabolism Basic and the Extended Spinal Cord Injury Data Sets. His efforts have led to nationwide changes in the healthcare of persons with disability, and, in particular, immobilization due to spinal cord injury.

Dr. Bauman received the Excellence Award from the American Paraplegia Society for outstanding leadership and accomplishments in SCI health care. In 2005, he received the Paul B. Magnuson Award from the Department of Veterans Affairs Rehabilitation Research & Development Service, its highest service award. Because of his knowledge and expertise, he was invited to give the 31st G. Heiner Sell Memorial Lectureship at the 2012 Annual Scientific Meeting of the American Spinal Injury Association. Dr. Bauman, along with Dr. Ann M. Spungen, the Associate Director of the Center of Excellence, was awarded the highly prestigious 2014 Samuel J. Heyman Science and Environment Medal.

4 B. Positions and Honors

4.1 Positions and Employment

1982 – 1987  Associate Professor of Medicine, Albert Einstein College of Medicine, Bronx, NY
1983 – 1985  Attending Consultant, Department of Medicine, VA Medical Center, Bronx, NY
1985 – 1989  Physician/Research Associate, Solomon A. Berson Research Laboratory, VA Medical Center, Bronx, NY
1987 – 1989  Associate Professor of Medicine and Rehabilitation, Mount Sinai School of Medicine, New York, NY
1989 – 2003  Director, Spinal Cord Damage Research Center, Mount Sinai Medical Center, New York and VA Medical Center, Bronx, NY
1996 – Present  Professor of Medicine, Mount Sinai School of Medicine, New York, NY
1996 – Present  Professor of Rehabilitation Medicine, Mount Sinai School of Medicine, New York, NY
2001 – Present  Director, VA Rehabilitation Research & Development Center of Excellence for the Medical
4.2 Other Experience and Professional Memberships

1976 – 1977  Medical Internship, New York University Medical Center, New York, NY
1977 – 1979  Medical Residency, Montefiore Hospital & Medical Center, Bronx, NY
1979 – 1980  Endocrine Fellowship, VA Medical Center, Bronx, NY
1980 – 1982  Endocrine Fellowship, Montefiore Medical Center, Bronx, NY
1982 – 1985  NIH SERCA Recipient, Attending, Departments of Medicine and Endocrinology & Clinical Sciences, Montefiore Medical Center, Bronx, NY

4.3 Honors

1972  Honors graduate in English Literature, Harvard University
1982  Recipient of NIH Special Emphasis Research Career Award
1994  Excellence in Medical Research, Medical Service, VA Medical Center, Bronx, NY
2001  William Dock Award for outstanding teaching ability in Internal Medicine/Endocrinology
2002  Excellence Award in Research (American Paraplegia Society)
2005  Paul B. Magnusson Award, VA RR&D Service
2014  Medalist, Samuel J. Heyman Service to America Award, Science & Environment

5 C. Contribution to Science

1. Osteoporosis and fractures present a major problem for persons with SCI. My contributions include defining calcium metabolism and bone disease in persons with SCI. Our publications first suggested a high prevalence of vitamin D deficiency in persons with SCI and proposed an approach for vitamin D replacement therapy. Despite literature that suggested a value to bisphosphonate therapy in those with SCI, possibly because of the work conducted in those with varying completeness of lesion, our work has demonstrated the limited efficacy of bisphosphonates administration in persons with acute complete motor SCI, necessitating the search for more effective therapeutic approaches. Our work in monozygotic twins, discordant for SCI, has suggested that bone loss continues for decades after initial injury, a new and controversial finding. We have shown that bone mass below the level of lesion is directly associated to body fat, and also directly correlated to the serum estradiol levels. Our group has provided evidence of the cellular, biochemical, and molecular effects of paralysis due to SCI or nerve transaction on bone.


2. Although it would appear intuitive that individuals who have adverse body composition and reside at the lowest end of the activity spectrum would have metabolic problems which predispose to cardiovascular disease, prior to our group’s entrance to the field, little had been reported in the literature. My contribution has been to be the first investigator to systematically study carbohydrate and lipid metabolism in persons with SCI and suggest that the abnormalities observed would be anticipated to predispose to premature cardiovascular disease. Prior to this work, it was unclear that persons with SCI had disorders of carbohydrate metabolism, which has since been characterized by a high prevalence of carbohydrate intolerance and diabetes mellitus. The finding of low high-density lipoprotein (HDL) cholesterol in those with SCI was observed by our group and subsequently confirmed by others. By nuclear medicine technology and electron beam computerized tomography, publications demonstrated the likelihood of premature atherosclerotic disease in those with SCI. Recently, we have reported on the blunted action of insulin on the sublesional microvascular.

3. Persons with SCI immediately lose muscle and gain fat after injury. Prior to our work, there had been a paucity of rigorous body composition studies. My contribution to body composition in persons with SCI has been to compare various methodologies to determine body adiposity, develop or apply innovative methodologies, define body composition changes after acute and in chronic injury, and more clearly delineate the relationship of body composition to metabolic derangements. A portion of this work, which was performed in monozygotic twins, one in each pair discordant for SCI, and in cross-sectional studies that have served to define changes in soft tissue mass over decades of life in persons with SCI, has improve our general knowledge in this area of study. The loss of muscle in those with chronic SCI occurs at an accelerated rate both above and below the level of lesion, suggesting a global, or systematic hormonal, process. Depressed levels of anabolic hormones (testosterone and growth hormone/insulin-like growth factor) may partially explain the general adverse changes in soft tissue body composition in individuals with chronic SCI. These articles have shown that testosterone levels are lower with increasing duration of injury and by decade of life in those with SCI than in the able-bodied population. Growth hormone and insulin-like growth factor levels are also depressed in younger individuals with SCI. In our preclinical articles, the influence of androgens on muscle mass and signaling pathways after SCI or nerve transection has been described, as well as the antagonistic effect of androgens on the catabolic effect of glucocorticoids on muscle.


4. Other than some of my above noted contributions to the endocrinology and metabolism of persons with SCI, my contribution to Spinal Cord Medicine have been wide in scope in both the clinical and pre-clinical areas. In clinical medicine, my publications have been in the following areas: GI motility of the esophagus, stomach, small intestine, and, especially, the colon, with interventions to improve colonic motility and evacuation, including the novel drug combination of neostigmine + glycopyrrolate, and strategies to improve cleansing preparation for elective colonoscopy; identifying for the first time obstructive airway disease in persons with SCI and interventions to improve function, defining restrictive airway disease in persons with complete motor SCI and strategies to improve respiratory muscle strength; defined cardiovascular autonomic dysregulation in persons with SCI and interventions to improve hemodynamics, as well as the association of cognitive deficits associated with hypotension; pressure ulcer energy requirements, healing, and intervention to heal the wound. Recently, work has been reported that describes the vertical ground reaction force and oxygen utilization while using the ReWalk exoskeleton. In the preclinical area, our work has addressed the effect of spinal cord injury on skeletal muscle. We have addressed the effect of SCI and nerve transection on muscle mass, and the effect of various anabolic or catabolic interventions on known and newly defined signaling pathways in skeletal muscle.


5.1 Complete List of Published Work in MyBibliography:

D. Research Support
Ongoing Research Support
VA RR&D Service Bauman (PI) 07/01/16-06/30/21
National Center Grant $450,000
Title: Center for the Medical Consequences of Spinal Cord Injury
Specific Aims: To improve the health and quality of life for persons with SCI. The center identified four major program areas: (1) endocrine & metabolic, (2) GI, (3) cardiovascular autonomic, and (4) molecular-musculoskeletal. A study in the Endocrine Program will test the efficacy of a potent antiresorptive agent (denosumab) to prevent bone loss after acute/subacute motor-incomplete SCI. VA Career Development awardees were recruited and trained, as well as other trainees and junior investigators at our medical facility.

Role: Director/Principal Investigator

Grant # 297267
Bauman (PI)
07/01/14 – 06/30/18
Craig H. Neilson Foundation
$598,818
Title: Prevention of Bone Loss after Acute Spinal Cord Injury
Specific Aim: To test a RANKL inhibitor (denosumab) to prevent bone loss in persons with acute motor-complete SCI.
Role: PI

CDMRP #11235809
Forrest and Bauman (PI)
9/01/14-8/30/19
Department of Defense CDMRP
$984,976
Title: Testosterone Combined With Electrical Stimulation & Standing: Effect on Muscle and Bone
Specific Aim: To determine whether standing with or without muscle electrical stimulation with testosterone/placebo will improve muscle mass and bone mass.
Role: Co-PI

Federal #B1313-R
Qin (PI)
10/01/14 – 9/30/18
VA RR&D Service
$885,291
Title: Sclerostin Antagonism and the Osteocyte’s Role: Prevention of Bone Loss
Specific Aim: To evaluate the ability of anti-sclerostin antibody (higher & lower doses) to preserve bone integrity after SCI, and to test whether impairment of osteocyte function is one mechanism by which SCI causes bone loss and whether restoration of normal osteocyte function after administration of anti-sclerostin antibody can prevent or reverse bone loss.
Role: Co-Investigator

VA RR&D pending funding
05/01/2017 – 04/30/2021
IIR Merit Review
$1,098,191
Title: Novel Pharmacological and Non-pharmacological Interventions for Bone Loss in SCI
Specific Aim: To test in rat models of moderate and severe contusion SCI, whether a prolonged course of low intensity vibration (LIV) will preserve bone. Regulation of mechanisms in osteocyte to stimulate bone formation and reduce bone resorption after LIV, in the absence and in conjunction with an anti-RANKL antibody and/or androgen, will be investigated.
Role: Co-Investigator

Completed (last 3 years):

VA RR&D #B8048R
Qin (PI)
09/01/13 – 08/31/16
IIR Merit Review
$621,488
Title: FES and Androgens in Bone Loss after SCI: Synergistic Effects and Mechanisms
Specific Aim: To evaluate the ability of mechanical intervention (functional electrical stimulation) or testosterone administration to reduce or prevent bone loss in a rat model of acute SCI.
Role: Co-Investigator

VA RR&D Service #B9212-C
Bauman (PI)
07/11-06/16
National Center Grant
Title: Center of Excellence for the Medical Consequences of Spinal Cord Injury
Specific Aims: To improve the health and quality of life for persons with SCI. The center identified five major program areas: (1) endocrine & metabolic, (2) pulmonary, (3) GI, (4) cardiovascular autonomic, and (5) molecular-musculoskeletal. A study in the Endocrine Program will test the efficacy of zoledronic acid to prevent bone loss after acute/subacute SCI. VA Career Development awardees were recruited and trained, as well as other trainees and junior investigators at our medical facility.

Role: Director/Principal Investigator
Study/Product Aim(s)

- Primary Aim: To determine the effectiveness and superiority of Stand Training with TRT and ES to induce beneficial changes in muscle mass compared to other combinations of these interventions.

Approach

Three sites will recruit 19 participants over 3 years or 6 subjects per year. Research participants will be randomized into one of 4 training groups: 1) Stand Training only (ST); 2) ST + ES; 3) ST + TRT; 4) ST + TRT + ES. Pre and post training outcome measures (height, weight, muscle volume, Quadriceps muscle torque, myostatin gene expression and BMD for the proximal tibia, distal femur and hip, markers for bone formation and resection, 3-D volumetric measurement of cortical and trabecular bone in the lower limbs, and recting energy expenditure).

Timeline and Cost

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Updated: (1/14/16) - Note Timeline will need changed to due to all the delays. We have submitted a revised 567W with a $5000 Cost Extension. Request: Decision pending.

Figure 1. Chart of Project

Goals/Milestones

2015/2016/17 Milestones - Milestone Achieved: Local IRB and HRPO approval at Keiser UCI, JUVMMC total n=56.

2015/2016 Goals - Training of protocol at Keiser Year 2


2016/2017 Year 3: Recruitment; screening (all three sites), randomization, subject training commenced. All sites have screened 88, screen consented and screened 13, main consent enrolled 3, 2 completed training and in follow-up period. One person is currently training. Comments/Challenges: Issue: Time line delayed due to issues associated with obtaining drug and signing of contractual agreements with drug company (see Problems and Issues in report). Budget expenditure to date: $321,291 total (through 6/30/17).