SUMMARY STATEMENT

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Application Number: 1 F32 AR052608-01

Review Group: ZRG1 F10 (20)
Center for Scientific Review Special Emphasis Panel

Meeting Date: 10/26/2004
Council: JAN 2005 PCC: 2 B
Requested Start: Dual PCC: 4AGERSN
Dual IC(s): AG, HL

Project Title: Effects of chronic hypoxia and aging on skeletal muscle

Requested: 2 years

Sponsor: RICHARDSON, RUSSELL S
Department: MEDICINE
Organization: UNIVERSITY OF CALIFORNIA SAN DIEGO
City, State: LA JOLLA CALIFORNIA

SRG Action: Priority Score: 276
Human Subjects: 30-Human subjects involved - Certified, no SRG concerns
Animal Subjects: 10-No live vertebrate animals involved for competing appl.
Gender: 1A-Both genders, scientifically acceptable
Minority: 1A-Minorities and non-minorities, scientifically acceptable
Children: 3A-No children included, scientifically acceptable
Clinical Research - not NIH-defined Phase III Trial
RESUME AND SUMMARY OF DISCUSSION: Dr. Lowman proposes training with Dr. Richardson to gain expertise in techniques for investigating oxygen transport in human skeletal muscle. During the fellowship period, he will study skeletal muscle performance, oxygen transport and utilization, morphology, and insulin resistance in two age groups where chronic hypoxia may contribute to skeletal muscle dysfunction. Reviewers acknowledged the candidate’s potential and motivation. The Sponsor has the appropriate expertise and provided a well considered training plan. However, reviewers expressed considerable concern regarding group size, which is too small to permit meaningful analysis and interpretation. In addition, data analysis and interpretation related to the effect of exercise on oxygen supply and demand is insufficiently described. Moreover, the funding available to support these studies throughout the fellowship period is unclear. As the discussion concluded, enthusiasm was low.

DESCRIPTION (provided by applicant): The objective of this study is to compare and contrast changes in skeletal muscle O2 transport and utilization in chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF), and to investigate the potential role of insulin resistance in the phenomenon of skeletal muscle dysfunction in two samples of vastly differing ages. COPD and CF often result in impaired pulmonary function, hypoxemia and cachexia, as well as skeletal muscle dysfunction, which plays a significant role in their activity intolerance. The overall hypothesis of this investigation is that COPD and CF, as a result of chronic cellular hypoxia, lead to alterations in both skeletal muscle O2 supply and demand parameters, as well as insulin resistance, and that each of these factors contributes to the syndrome of skeletal muscle dysfunction. Relationships among muscle O2 supply, O2 demand, and insulin sensitivity of an isolated small muscle mass exercise in patients with COPD and CF will be examined by correlating data (molecular biological, biochemical, histological, physiological, and functional performance measures of skeletal muscle) from all three Specific Aims. This research will have a significant impact on understanding the relationships among peripheral O2 transport, skeletal muscle dysfunction, and insulin sensitivity/resistance in these diseases of vastly different age groups and may have direct implications for the clinical management and rehabilitation of these patients.

CRITIQUE 1:

CANDIDATE: John Lowman, Jr. received a BS Ed degree in Exercise Science from Virginia Tech University in 1992 and received an MS in Physical Therapy from Duke University in 1995. He is a licensed physical therapist (PT) and practiced and taught from 1995-1997 at Duke. He is currently finishing his doctoral degree in Physiology at Virginia Commonwealth University under the mentorship of Dr. Roland Pittman; he is scheduled to defend his dissertation this fall and to receive his degree in December of 2004. In formal graduate coursework, Mr. Lowman has performed in the A/B range. Mr. Lowman dissertation is entitled "Effects of emphysema on microvascular oxygen transport and muscle performance in rat skeletal muscle". He has 3 PT related publications from his earlier work at Duke, and his dissertation and other post-baccalaureate work appears to have culminated in three manuscripts that are listed as being 'in preparation'; one of these is from Dr. Pittman's lab.

Mr. Lowman appears to be a quite motivated and independent individual as evidenced by several publications on which he is the sole author. His external letters are good and several underscore the impression that Mr. Lowman is a motivated and independent individual.

SPONSOR AND TRAINING ENVIRONMENT: The environment at UCSD for the type of work proposed is superb. Dr. Richardson is well published in the field and enjoys interaction with the a variety of investigators who, collectively, have make great contributions to our understanding of oxygen transport and utilization in skeletal muscle. Additionally, Dr. Richardson appears to have a significant track record as both a pre-doctoral and postdoctoral mentor. The sponsor is currently supported as a Principal Investigator on an individual project that exists in the context of a P01 grant. This funding will
soon end and one issue of concern is whether or not the mentor will have funding to support the research activities of the trainee.

From examining the application, it appears that the mentor did not have much input in the preparation of key elements of the proposal. While the coordination of the preparation of this proposal was likely confounded by 'coast-to-coast' communication between mentor and trainee, this is disappointing given the stature of the mentor. On one hand, the training plan for Mr. Lowman is quite comprehensive. However, other parts of the proposal are less impressive. Several external letters appear multiple times in the application, and while Dr. Richardson did assemble a brief list of past and current trainees, a section from an institutional T32 was inserted apparently as evidence of his mentoring experience. This left the reviewers to sift through a significant amount of irrelevant (to this application) information about other investigators’ mentoring experience.

**RESEARCH PROPOSAL:** The general aim of determining how COPD and CF affect skeletal muscle O2 supply and demand during exercise in humans is laudable and generally congruent with the applicant’s training in Dr. Pittman’s lab and Dr. Richardson’s considerable expertise. As written, however, it is unclear from the proposal that the measurements being made can really discern between ‘the supply and demand’ elements of the exercise bouts imposed. In addition, the experimental design presented on pp 14 seems to be severely inadequate from an analytical perspective. The analysis of six experimental groups with six-eight subjects per group (three-four men and three-four women) across an incredibly broad age span hardly seems to be amenable to any kind of statistical analysis unless between group differences of geometric magnitude are expected. The proposed experiments will certainly expose the applicant to ‘state of the art’ techniques in the field, but it is unlikely that the experiments will generate any useful information as designed.

**TRAINING POTENTIAL:** The applicant is clearly motivated and suitably trained to embark on his postdoctoral training in Dr. Richardson’s lab at UCSD. Both the trainee and mentor are strong. However, the proposal as written does little to create the mentor-trainee link that is necessary to provide confidence that the training program will be fruitful.

**SUMMARY AND RECOMMENDATION:** The applicant has great potential and seeks to train in a very strong laboratory in a very strong institutional setting. Lacking, however, is concrete evidence that the proposed training program will take advantage of these strengths.

**HUMAN SUBJECTS:** All issues pertaining to subject safety have been addressed adequately.

**INCLUSION OF WOMEN:** Both men and women are included.

**INCLUSION OF MINORITIES:** Adequate. A plan for subject inclusion that is commensurate with the demographics of the San Diego area is proposed.

**INCLUSION OF CHILDREN:** Pre-pubescent children are excluded since the diseases being examined are prevalent in adults.

**TRAINING IN THE RESPONSIBLE CONDUCT OF RESEARCH:** The applicant has taken a formal course on this topic in 2003. In addition, the mentor indicates that the applicant will participate in another course under the direction of Dr. Kalichman while at UCSD. No concerns.

**CRITIQUE 2:**

**CANDIDATE:** Dr. Lowman expects to receive his PhD in December 2004 from Virginia Commonwealth University, where he has worked under the direction of Dr. Roland Pittman. His dissertation work is focused on the effects of emphysema on microvascular oxygen transport and muscle performance in the rat. He now wishes to become proficient in research techniques and
methods needed to investigate oxygen transport in skeletal muscle of humans. He lists three published papers and three manuscripts in preparation in his list of publications. Dr. Lowman appears to have independently produced the research plan with input from his mentor. Dr. Lowman’s letters of support rate his capabilities as excellent to outstanding, indicating that he is highly motivated, intelligent, inquisitive, has a very strong work ethic, and is dedicated to pursuing an academic career.

**SPONSOR AND TRAINING ENVIRONMENT:** The work outlined in this proposal is sponsored by Dr. Russell S. Richardson, Adjunct Associate Professor of Medicine at the University of California, San Diego. Dr. Richardson is well-known for his work regarding exercise adaptation and skeletal muscle dysfunction in COPD in humans and he has published extensively in this area. The facilities available to the applicant in the sponsor’s laboratories are state-of-the-art and sufficient to address the aims outlined in this proposal. Moreover, the environment at the University of California, San Diego is excellent. The training plan outlined for the applicant is comprehensive and should provide Dr. Lowman skills at the organ, cellular and molecular levels and the ability to integrate the information obtained at the organismal level. Formal training in research ethics was completed by the applicant through his enrollment in a course entitled Scientific Integrity.

**RESEARCH PROPOSAL:** The aims of this three year proposal are directed at examining the hypothesis COPD and CF lead to alterations in both skeletal muscle oxygen supply and demand parameters, as well as insulin resistance, as a result of chronic cellular hypoxia. Three Specific Aims are outlined to address this postulate. In the first, single leg oxygen consumption will be determined and the relationships among VO2, muscle fiber-type distribution, fiber size, percent fiber type areas, oxidative enzyme activity and muscle performance (i.e., force production, fatigability) will be examined in human COPD and CF patients to determine the effect of these disorders on skeletal muscle oxygen demand. Studies outlined for the second aim will focus on determinations of blood and oxygenation parameters to calculate leg oxygen delivery and extraction. The relation among these physiological and morphological parameters of oxygen supply will be examined. Finally, the relations among peripheral blood and oxygen supply, body composition, glucose metabolism and skeletal muscle metabolic indicators will be examined as a means to determine the effect of COPD and CF on insulin sensitivity. The research plan is hypothesis-driven, comprehensive, relies on state-of-the-art approaches and techniques, and will provide both descriptive and mechanistic information. However, a major concern relates to the size of the groups for each study, which is far too small to allow for meaningful statistical analysis. A second important concern arises with respect to an inadequate description of how the data will be analyzed and interpreted with regard to the effect of exercise on skeletal muscle oxygen supply and demand in the patient populations to be studied.

**TRAINING POTENTIAL:** Completion of the studies outlined in this proposal will provide Dr. Lowman with excellent training with regard to the study of oxygen transport in skeletal muscle of humans. The training plan is comprehensive, providing Dr. Lowman with extensive experience with a variety of invasive techniques (muscle biopsy, vascular catheterization), physiological measures (cardiopulmonary exercise testing with expired gas analysis, assessing peripheral perfusion, oxygen extraction, vascular resistance and insulin sensitivity), biochemical and molecular biological assays (metabolic enzyme activities, GLUT4 concentration, VEGF and eNOS mRNA and protein expression), and magnetic resonance spectroscopy (to determine ATP, PCr, and Pi levels, myoglobin saturation, and tissue PO2). Completion of the proposed studies should allow Dr. Lowman to take an integrative approach to complex biological questions in humans. In addition, Dr. Lowman will be encouraged to interact with a number of other prominent investigators who share research interest with the sponsor, including Drs. Odile Mathieu-Costello, Peter Wagner, and Michael Hogan.

**SUMMARY AND RECOMMENDATION:** This is an excellent candidate who will work under the direction of an experienced, highly productive, and well-funded investigator in an outstanding environment. The training plan outlined by the sponsor will provide the applicant with training in a wide array of techniques and approaches to study oxygen transport in humans. The research plan is comprehensive and will enable the applicant to pursue an integrative approach involving an attractive
blend of physiologic, biochemical, and molecular biological approaches in humans to study alterations in oxygen delivery and demand, as well as insulin resistance in COPD and CF patients. However, major concerns relate to the size of the groups for each study, which is far too small to allow for meaningful statistical analysis and an inadequate description of how the data will be analyzed and interpreted with regard to the effect of exercise on skeletal muscle oxygen supply and demand in the patient populations to be studied.

**HUMAN SUBJECTS:** The investigators plan for protecting human subjects from research risk is acceptable.

**INCLUSION OF WOMEN:** Both genders will be included.

**INCLUSION OF MINORITIES:** Minority representation is adequate.

**INCLUSION OF CHILDREN:** Prepubescent children will be excluded because they lack musculoskeletal maturation and are more prone to musculo-tendinous injury during maximal exercise bouts. This is acceptable.

**TRAINING IN THE RESPONSIBLE CONDUCT OF RESEARCH:** Provided.

**THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW ADMINISTRATOR TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:**

**PROTECTION OF HUMAN SUBJECTS (Resume): ACCEPTABLE**

**INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE**

**INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE**

**INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE**

**COMMITTEE BUDGET RECOMMENDATIONS:** The budget was recommended as requested.

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NOTICE: The NIH has modified its policy regarding the receipt of amended applications. Detailed information can be found by accessing the following URL address: http://grants.nih.gov/grants/policy/amendedapps.htm
MEETING ROSTER

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ZRG1 F10 (20) L
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