Reviewer's report

Title: Biomarkers of peripheral muscle fatigue during exercise

Version: 1 Date: 17 July 2012

Reviewer: Randall Keyser

Reviewer's report:

This concept of this manuscript is long overdue and a description of specific biomarkers for fatigue would make a helpful reference. Moreover the classification of biomarkers by the categories suggested in this manuscript would be useful in aiding clinicians and researchers in selecting biomarkers that are appropriate surrogates of potential pathways of interest. However, there are several large concerns that cast doubt on the overall impact of the manuscript.

Major Compulsory Revisions

1. The treatment of the biomarkers discussion does not move beyond classification and identification of by-products and responses. A more detailed characterization of the pathways from which the biomarkers are derived and some insight into expected biological variation reference ranges, and minimally important changes in biomarker activity or concentration for clinical significance would strengthen this paper immensely.

2. Factors that potentially impact the fatigue pathways were not discussed, although disease examples were listed in the first paragraph of the Introduction. Examples of major influences could be age, gender, disease or type of disease, and physical fitness. Each of these is likely to effect fatigue levels and most importantly, may exert an influence on some but not all of the pathways and markers mentioned in the manuscript. Moreover, the specific markers influenced may differ for each of these
conditions and even for different diseases or types of diseases. Sufficient detail and depth in characterizing these influences is critical to the impact of this type of review and would enhance enthusiasm for the manuscript greatly.

3. A common definition of muscle fatigue has not been established. In this manuscript the operational definition is “a reversible loss of muscle force during work over time”. A more important phenotype pertaining to muscle function is that of fatigability or the rate of loss of muscle force over time. In fact, fatigability and recovery, or the rate at which muscle function returns to baseline after becoming fatigued, are interactive determinants of the state of fatigue versus rested. While recovery is mentioned briefly, its contribution to offsetting fatigue is not discussed in the manuscript and as such creates a gap that ignores an important in fatigue severity and perhaps biomarker responsiveness. Recovery and fatigue severity are both influenced by fatigability and the degree to which muscle dysfunction is provoked. Thus a discussion on fatigability and recovery is a necessity for understanding the overall fatigue construct.

4. Some explanation of hypothesized fatigue pathways and mechanisms was divergent with current thought. For example, under “Biomarkers Classified According to the Mechanism of Muscle Fatigue” in the second sentence of the first paragraph, the author suggests that depletion of high-energy substrate is thought to be one of the most important contributors to muscle fatigue. While it is true that there are observable decreases in muscle [ATP] and [CrP] during repetitive or prolonged contraction, a review and 2 manor book chapters (Keyser 2010; Fitts 2006; Brooks 2006) suggest that the decreases in high energy compounds are not nearly enough to result in even a small level of muscle dysfunction. Decreases in these compounds at specific locations or in association with the operation of transporters could potentially contribute to muscle fatigue but much more work is needed to establish this
hypothesis. Meanwhile, even small decreases in muscle pH interfere with
crossbridge binding and ATPase activity due to competitive binding and reduced
enzyme function with even miniscule decreases in pH. Decreased muscle pH also
impairs oxidative enzyme activity and may adversely affect ryanodine receptor
function. ROS are electron scavengers, which not only cause fatigue but
mitochondrial damage. Under and over expressions of selected genes believed
to be
interactive in mitochondrial apoptosis and genesis has been identified in
association
with fatigue severity. A more detailed discussion of the potential mediators of
fatigue
and how the biomarkers associated with these pathways would improve the
understanding of biomarker surrogacy.

**Level of interest:** An article whose findings are important to those with closely
related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a
statistician.

**Declaration of competing interests:**

I declare that I have no competing interests