Priority Statement Title: **Multi-level Exploration of Osteoarthritis**
Priority Statement Code: CJ3C

Domain: Body/Joint/Tissue/Cell

Priority Statement

Background and Relevance

Biomechanics is the key to understanding Osteoarthritis (OA). While the symptoms of OA are well known (pain, joint space narrowing, cartilage fibrillation and eburnation, subchondral bone cysts), scientists are still uncovering the root causes of the disease. **A leading cause of disability in the United States, OA is one of the most urgent research challenges of twenty-first century medicine.** The primary opportunities and outcomes associated with this priority area are to reduce disability, pain, and the cost of care while improving function and quality of life of persons suffering from OA.

Objectives

- Conduct epidemiology studies that are coupled with biomechanical and biological data to establish and/or confirm risk factors for onset and progression of OA.
  - OA has been associated with 3 primary biomechanical factors: (1) increased BMI, (2) injury, and (3) malalignment. This knowledge came from large sample size epidemiology investigations (MOST, OAI, Johnston County Project, etc). To develop a deeper understanding of OA, epidemiology that incorporates biomechanical and biological data is needed.
- Develop improved methods for **early detection** of OA.
  - Baby boomers are anticipated to need a significantly increased number of total joint replacements. Still, TKR recipients do not have normal gait, even at several years post-op. Younger people with obesity and/or malalignment and athletes with injuries (eg. ACL or meniscal tears) may have the most to gain from an OA initiative.
- Development of sensitive biomechanical, biological, and clinical biomarkers to serve as an endpoint for investigations of disease onset and progression, treatment effectiveness, and diseasse prevention.
  - Since OA is multi-factorial --- a multi-dimensional endpoint maybe required.
- Design and conduct comprehensive, multi-factorial investigations of OA to reveal the relationships between aberrant structure (alignment, BMI, and injury), abnormal biomechanical function (impairment, functional limitations, and disability), and joint pathophysiology (catliage, meniscus, and bone integrity; synovial or serum factors of inflamtion of cartilage matrix breakdown) at a multi-scale level.
  - Although certain biomechanical markers (eg adductory knee moment) have been implicated in knee OA it's not clear how these markers are related to soft tissue (eg. cartilage) integrity, pain, and joint pathophysiology. Single outcome studies do not permit these associations.
- Develop subject specific models for understanding OA onset, progression, and treatment effectiveness
  - Joint stress maybe the underlying offensive agent in OA yet it can't be measured by current experimental methodologies in vivo. Validated subject specific models can assist in revealing these factors and how they're effected by risk factors and treatment. In addition, experiments are needed to determine the structural and material properties of the tissues and cells within the diarthrodial joint to enhance the accuracy of predictive models and reveal the differences between healthy individuals and those afflicted with OA. Methods are needed to predict the response of a patient to treatment to more efficiently and effectively manage the patient with OA.
- Conduct clinical trials that assess the response of disease to perturbation or treatment at multiple time points and for multiple functional activities (walking, sit to stand, stair ascent and descent, etc) to provide an improved understanding of the mechanism(s) of disease progression.
  - Clinical outcomes of both conservative (eg. viscosupplements, pharmaceutical, nutraceutical, orthoses, physical therapies) and surgical (eg. reconstructive and realignment surgery, cartilage transplantation, resurfacing, joint fusion, partial and total joint replacement) procedures are essential to determine which approaches are palliative for pain relief and which, if any, are disease modifying. New and effective therapies or approaches to prevention are likely to result from understanding how the patient with OA responds to existing treatments at a multi-domain level.

These objectives will require bridging multiple domains (whole body, joint, tissue, and cellular) . This recommendation will require a translational approach to be successful. Data from the whole body, joint, tissue, and cellular levels must be integrated towards the goal of developing truly successful treatments that can slow down or eliminate disease progression as well as effectively prevent OA in the patient at risk.

Recommended Actions
Develop RFPs to address the previous objectives. Establish a national/international database of biomechanical, biological, and clinical data that maybe shared between clinicians and laboratories.