Pre-ARC Proposal ***"Biomechanics and Osteoarthritis"***

Pre-ARC Director: David Felson MD MPH, Professor of Medicine and Epidemiology

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Overview of Goals and Mission

Osteoarthritis is the most common form of arthritis with the disease currently affecting an estimated 26,000,000 persons in the United States. Most commonly affected joints are hands, knees and hips. While some treatments alleviate the pain that comes with osteoarthritis, there are no known treatments which slow the gradual deterioration of the joint. Rates of osteoarthritis have been rising based in part because of the aging of the population and its increasing ponderosity. Knee replacement rates for example have risen 800% in the last 25 years in the United States. A better understanding of the pathogenesis of disease and its relation to symptoms and an identification of treatments which might delay structural and symptom progression are badly needed.

Osteoarthritis is widely regarded as an end-stage failure of multiple tissues within the joint. The disease begins in a focal fashion, often with hyaline cartilage loss or, in the case of the knee, a meniscal tear or extrusion. This focal defect then triggers a cascade of pathologic events driven in part by asymmetry or malalignment across the joint which increases load in focal areas across the joint, generating further focal damage.

There is extensive evidence that osteoarthritis is mechanically driven. In almost all animal models of disease, mechanical insults are used to cause disease development. Plus, injuries to human knees like meniscal tears lead to very high rates of later osteoarthritis in affected joints. Other evidence for the mechanical pathophysiology of osteoarthritis includes that joints which are rarely affected by osteoarthritis such as the ankle get disease only when subjected to major injury producing mechanical aberrancies. Lastly, even disease symptoms are mechanical, with joint pain produced by activities which load the joint.

Attempts to correct mechanical abnormalities in hip and knee osteoarthritis and in other joints affected have not to date been successful. For example, studies of wedges which alter the load in the shoe, which then produces changes in the distribution of load across the knee, have failed to relieve knee pain. This is either because they have not changed load sufficiently or because loading effects are inconsistent across affected persons. While pathomechanics appear to account for osteoarthritis symptoms and

structural deterioration, there are no biomechanically based treatments with proven effects on both structure and pain..

The overall goal of this pre-ARC is to assemble scientific investigators with clinical and/or engineering backgrounds to create collaborative studies which focus on the mechanical pathophysiology of structural deterioration in osteoarthritis, to develop novel therapeutic approaches and to evaluate these approaches using sophisticated imaging and engineering approaches.

The pre-ARC has focused initially on femoroacetabular impingement, a developmental abnormality in the hip that occurs in young adults and which predisposes to early adulthood hip osteoarthritis. The reasons for this focus are both intellectual and practical. Intellectually, this is a potentially preventable form of hip osteoarthritis but if osteoarthritis is not prevented in young affected persons, they can be disabled from hip osteoarthritis in their 20's or 30's, long before they are good candidates for hip replacement. Second, many of the pre-ARC investigators in our team focus on hip disease and hip osteoarthritis, including Dr. Young-Jo Kim, an engineer and orthopedist at Children's Hospital whose practice involves carrying out surgery to correct femoroacetabular impingement. In addition, the research of Dr. Cara Lewis the Peter Paul Assistant Professor at Boston University, focuses on developing corrective exercise and movement patterns for persons with femoroacetabular impingement. Lastly, Dr. Guoan Li, an engineer at MGH has developed a fluoroscopically based technique to evaluate contact stresses across joints during activity and can evaluate both femoroacetabular impingement in vivo and its potential correctability both with surgery and with exercise.

It is hoped that the pre-ARC with its other collaborators will move from hip to knee, where similar opportunities exist. An additional element of this collaboration has been an interest in evaluating the molecular changes that occur with impingement and with stress across the joint. This is the focus of Dr. Alan Grodzinsky, an engineer at MIT, a world leader in the study of the structural biologic changes in cartilage that occur with static and dynamic compression of joint tissue. These investigators all work with Dr. Felson, who is a clinical osteoarthritis investigator with a long-standing interest in both hip and knee osteoarthritis prevention and treatment.

Agenda for the Pre-ARC

The goals of the pre-ARC are:

1) To develop collaborative research protocols that will help address important questions initially in hip disease and then moving to knee disease. To develop more explicit goals for the ARC.
2) To decide whether other collaborators would enrich and bring additional valuable collaborations into the group.
3) To identify funding opportunities.
4) To invite speakers who could inform and enrich this collaboration.

A collaborators group has been meeting roughly every month for the past six months, rotating sites from Boston University Medical Campus to Children's Hospital, MIT and MGH. At each site the home investigator reviews their ongoing research. A collaborative project on femoroacetabular impingement has been developed and received IRB approval. Initial patients are being recruited for movement strategies and exercise therapies by Dr. Lewis from Dr. Kim's clinic practice with a study design informed and overseen by Dr. Felson. The plan is to expand that study to include Dr. Li's dual fluoroscopic evaluation to see if the movement strategies and exercises recommended by Dr. Lewis are in fact lessening the impingement seen on fluoroscopy during activity. The subjects being studied are all scheduled for surgery by Dr. Kim to correct their impingement. During the surgery Dr. Grodzinsky will obtain synovial fluids and other specimens to evaluate effects of impingement on molecular markers. ARC resources would enable this project to expand, would enable preliminary data on knee studies to be acquired, would fund visiting investigators or speakers and would help provide support staff for the integration of these cross-institutional studies. It is clear that interventions especially in the knee, will need to be refined, developed and tested and additional engineering other input regarding how to do this is needed and will probably require the ARC to be expanded. Ultimately, both industrial and federal funding will be sought.

A list of current investigators in the ARC are below.

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