Osteoarthritis: A Perspective from the Arthritis Foundation

We Need a Base Hit

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Introduction

Osteoarthritis (OA) affects 27 million Americans. This leading cause of disability results in 632,000 joint replacements each year, accounts for approximately 5% of overall health care costs, and is expanding rapidly as the population ages and deals with the obesity epidemic [7, 9]. This is a bad situation now and unless remedial action is taken it will get a lot worse soon.

Despite its personal and societal impact, relatively little attention has been directed at OA. Moreover, our pharmaceutical companies are discouraged from developing new interventions because present outcome measures are very insensitive. To change this picture, we need vigorous efforts in public health to increase awareness of OA and encourage life styles that do not promote OA. We need public policies that effectively combat obesity and encourage healthy behavior. And, we need research that will lead to an understanding of how to detect and reverse OA at its earliest stages.

Arthritis Foundation Contributions

The Arthritis Foundation is addressing these needs in several ways. In partnership with the Centers for Disease Control and Prevention, a National Public Health Agenda for Osteoarthritis has been developed [12]. To implement

this agenda, the Arthritis Foundation has taken a leadership role in forming the OA Action Alliance [15], which is a consortium of 45 organizations that have agreed to work together to implement the Public Health Agenda for OA. In public policy, the Arthritis Foundation is advocating strongly for increased funding for arthritis research and seeking passage of the Arthritis Act in congress. We have also worked with the Department of Defense to develop new funding for studies of post-traumatic arthritis.

In research, the Arthritis Foundation has provided over \$400 million in support of studies aimed at gaining a better understanding of diseases that affect joints and understanding how a joint functions as an organ. Much of this investment has been specifically directed at learning how OA can cause a joint to fail. This knowledge has now advanced to the point that it is time to place more emphasis on learning how to intervene in this disease.

One approach to an effective intervention for OA is through regenerative medicine. Here stem cells will be used to repair damaged tissues of joints such as cartilage, ligaments, and tendons (see the article by Gordana Vunjak-Novakovic in this symposium). Arthritis Foundation funded stem cell research has advanced to the point that clinical studies in large animal models are ready to begin [6]. While this approach provides great hope for people with advanced OA, the ultimate goal is to prevent the onset of OA or halt its progression at the earliest stages. Here, an entirely different approach is required to develop methods to diagnose OA at the earliest stages prior to onset of symptoms.

The Arthritis Foundation has recognized this need. Consequently, our major flagship initiative in OA is focused on discovery and validation of new measures (biomarkers) that can detect OA at its earliest stages and predict its outcome. This investment has been made in conjunction with the foundation for the National Institutes of Health (NIH) to support the Osteoarthritis Biomarker Consortium, an international effort to assess the ability of 16 different

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molecular measures and seven imaging technologies to predict OA development and progression among the patients enrolled in the NIH's OA initiative cohort (see the article by Virginia Kraus in this symposium). Hopefully, this analysis will detect one or more signals that correlate with outcome in OA. Such candidates might be refined as tools for the clinical evaluation of patients in future studies.

SNOW IV: Barriers and Opportunities for New Interventions in OA

It is important that we look beyond diagnostics and begin to contemplate new treatments. To approach this challenge, the Arthritis Foundation convenes leading international authorities in OA to identify the barriers and opportunities for developing new interventions for OA at its Segal North American Osteoarthritis Workshop (SNOW). At SNOW IV, which was held in March 2011, several key concepts were established:

- It is important that we define specific types of OA such as that associated with aging [10], obesity [4], and trauma [3] and to understand how they differ in terms of causative mechanisms [2].
- A number of potential therapeutic compounds for OA are known [11] (Table 1).
- Plain X-rays (the gold standard accepted by the FDA) are an inadequate clinical trial outcome measure to monitor joint structure [5].
- Pharmaceutical companies are discouraged with drug development for OA because of the costs imposed by current regulatory hurdles.
- Anterior cruciate ligament (ACL) injury is an ideal model for early events in OA [5].
- In this injury, biochemical measures show articular cartilage breakdown commencing immediately and continuing for one or more years thereafter [16].
- Qualitative changes in the involved cartilage following ACL injury can be detected with new MRI technologies (dGEMRIC, T1rho, and T2) within the first several weeks [1] and persist for months [8, 14].

Some of these points should contribute to the efforts in planning the way ahead.

Table 1 Drug targets and compounds potentially useful for treatment of OA

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- Inflammatory cytokines (biological inhibitors of IL-1, TNF α , IL-6)
 - Apoptosis (small molecule inhibitors of caspases)
 - Cartilage repair (growth factors BMP-7, FGF-2, FGF-18, IGF-1)
 - Cartilage matrix (inhibitors of MMPs, aggrecanases, cathepsins, etc.)
 - Oxidative injury (antioxidants)
 - Lubrication (lubricin, hyaluronan)
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Adapted from Lotz, M.K., and Kraus, V.B. 2010. New developments in osteoarthritis. Posttraumatic osteoarthritis: pathogenesis and pharmacological treatment options. *Arthritis Res Ther* 12:211 with permission from BioMed Central

We Need a Base Hit!

Now let's consider the proposition that halting or reversing established OA – a home run by any standard – may be beyond our grasp, at least at the moment. Rather than being discouraged with our inability to hit the ball over the fence, let's focus on an intermediate step. The available information suggests that it should be possible to pharmacologically stabilize the cartilage matrix after a joint trauma, such as an ACL disruption that is so well known to lead to OA. Current data indicate that we can detect this stabilization with new imaging techniques and molecular biomarkers. Putting it in athletic terms so appropriate for a conference at the Hospital for Special Surgery with its ability to sustain athletes in their endeavors, the demonstration that we can modulate cartilage matrix in a joint at risk and measure that intervention would be a clutch base hit. This would put us in "scoring position" and serve as a major morale booster for all members of the team who are striving to find a better solution for OA. In fact, it might help change outcome measures at the FDA, and it might encourage our colleagues in the pharmaceutical industry to re-engage efforts to develop products for OA.

Game Strategy

Recent workshops focusing on biomarkers in OA hosted by the Osteoarthritis Research Society International (OARSI) have reviewed the state of the art of how to assess OA [13, 17] (see the article by Timothy McAlindon in this Supplement). Similarly, recent workshops hosted by the American Orthopedic Society for Sports Medicine (AOSSM) have focused on the potential of the acutely injured knee as a model for studying OA [1]. Their discussions make it clear that several advantages exist to the ACL model as a strategy for getting this crucial base hit in OA. With this clinical model the exact time of onset of the disease is known. The subject is typically young and healthy, a single joint is involved, and present studies indicate a high risk of subsequent OA whether or not the joint is repaired surgically. In short, with this model we know exactly when the disease process begins. We can study its evolution largely free of confounding pathology, and, as noted above, we have the technology to track pathophysiological processes as they evolve. We just need to get the bat on the ball.

A New Research Initiative for the Arthritis Foundation

In 2012, the Arthritis Foundation will select a new Flagship Initiative (a term we use to refer to our major large scale and highly cooperative research ventures) in OA research. The help of the OA community is required in planning this initiative and in ensuring that we follow the pathway most likely to lead to an improved quality of life for people with, or at risk of, OA. Specifically, do you support an effort to demonstrate that the cartilage matrix can be pharmacologically stabilized following

joint trauma as a worthwhile intermediate step — to go for a base hit — toward developing an intervention for OA?

Summary: How You Can Help

Advice from the community regarding this initial proposal will be of great value. The challenge we face is great, the resources at hand are limited, but collective wisdom is a source of great power. Our questions include:

- Are there better approaches to moving the OA field toward therapeutics? If not,
- What patient population should be studied? Is the ACL model the right one?
- How might an appropriate interventional trial be designed at this time?
- What interventions should be tested now?
- What are the outcome measures and how should they be assessed.
- What is the time frame over which a meaningful alteration in outcome should be sought?
- Given the fact that such a trial is likely to be costly and the expense born only partially by the Arthritis Foundation, how might full funding be developed?

Your advice will be of great value. We invite you to post comments and suggestions to the Arthritis Foundation.

Disclosures The author certifies that he has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements) that might pose a conflict of interest in connection with the submitted article.

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