The stimulus-response approach offers the opportunity to increase the accuracy and sensitivity in detecting underlying pathologies that can be elevated in response to specific provocative stimuli. This type of stimulus-response model offers a valuable opportunity to probe the in vivo systems response of osteoarthritis as a framework for the early detection and treatment evaluation.

I-4 SYSTEMS BIOLOGY: BRIDGING THE GAP BETWEEN MOLECULES, ANIMAL MODELS AND OA PATIENTS

W.L. Stanford, Ottawa Hosp. Res. Inst., Ottawa, ON, Canada

OA is a complex disease in which many determinants underlie both the etiology and progression. While reductionist studies have identified many of the molecules and environmental factors involved in OA, the field, and thus patients, could benefit from a more comprehensive systems biology approach. Systems biology seeks to answer biological questions by mathematically modeling the entire system of relevant genes, proteins, cells and other factors. To generate models, various “omics” technologies are applied to generate a comprehensive landscape of the DNA, RNA, protein expression and metabolic state of the cell and/or tissue. Until recently, this approach has relied mainly on simple genetic models, but the invention of induced pluripotent stem cells (iPSCs) has opened up exciting new avenues for the field. iPSCs are powerful embryonic-like stem cells which can be derived from adult blood or skin cells, through genetic reprogramming. iPSCs can be differentiated into many kinds of specialized cells in the laboratory, including cells that are relevant to OA, such as chondrocytes. Using systems biology to study iPSC-derived chondrocytes from multiple OA patients may allow us to identify patient subpopulations with discrete underlying biochemical networks driving the progression of their disease.

This approach could usher in a new generation of personalized OA therapies that target the biochemical networks that are disrupted in individual patients.

I-5 CELL THERAPY OPTIONS FOR OSTEARTHROSIS: STEM/PREGNITOR CELL

A. Reddi, Univ. of California, Davis, Sacramento, CA, USA

The aim of this workshop is to convey an interactive session the current excitement in the area of Stem / Progenitor Cells for potential therapeutic options for osteoarthritis. Morphogenesis is the developmental cascade of pattern formation and establishment of the body plan including the bilateral symmetry of the adult form. Regenerative medicine and Tissue Engineering endeavors to design and restore function to lost or damaged parts due to diseases like arthritis and trauma. The three key elements for tissue regeneration of damaged articular cartilage in synovial joints are signals including morphogens such as BMPs, responding stem cells and a scaffold of extracellular matrix. The discussion of this research area will begin with a presentation by Robert Sah, UCSD on challenges in design, fabrication and functional evaluation of synovial joints. This will be followed by Farshid Guilak, from Duke University on Adipose-derived stem cells for cartilage differentiation. The directed differentiation of adult and embryonic stem cells into articular cartilage will be presented by A. Hari Reddi. The BMPs are lineage directing morphogens that are critical for chondrogenesis. The adult progenitors and stem cells for chondrogenesis are present in synovium, bone marrow, adipose tissue and muscle. The open general discussion will be mutually beneficial and audience participation is strongly encouraged.

I-6 INFLAMMATION AND IMMUNITY IN OA

R. Liu-Bryan, VAMC Med.-Rheumatology, UCSD, San Diego, CA, USA

Articular cartilage degeneration is a major characteristic of OA. Changes in other joint tissues including subchondral bone and synovium are often associated with OA. It is now accepted that inflammation is involved in the development and progression of OA in both early and late stages of the disease. Secreted inflammatory mediators such as proinflammatory cytokines, particularly IL-1β and TNFα, are major players in degeneration of articular cartilage matrix. IL-1β and TNFα, produced mainly by activated synoviocytes, mononuclear cells and chondrocytes, down-regulate the synthesis of major extracellular matrix components (ECM) by inhibiting anabolic activity of chondrocytes, and enhance matrix catabolism by stimulating chondrocytes to release several proteolytic enzymes. In addition, IL-1β and TNFα stimulate articular cells to produce a number of inflammatory mediators including cytokine IL-6 and chemokine IL-8, nitric oxide (NO) and prostaglandin E2 (PGE2), all of which have been implicated in OA pathology.

Inflammation in OA is partly secondary to cartilage and other articular joint tissue damage. Innate immune responses to endogenous danger signals or alarms (danger-associated molecular patterns (DAMPs)) that are derived from damaged articular joint tissues such as low molecular weight hyaluronan (LMW-HA), high mobility group box chromosomal protein 1 (HMGB-1), and members of S100/calgranulin family of proteins are implicated in OA progression by induction of inflammatory mediators. Toll-like receptor (TLR) and receptor for advanced glycation end products (RAGE) signaling can transduce response to these signals and some of these signals (HMGB1, S100A8) activate both of these receptors.

Recent studies demonstrated that activity of AMP-activated protein kinase (AMPK), a master regulator of cell energy homeostasis and metabolism, is decreased in OA cartilage and in chondrocytes following treatment with IL-1β or TNFα. AMPK pharmacological activators attenuate dephosphorylation of AMPKα and pro-catabolic responses in chondrocytes induced by these cytokines. These results suggest that maintenance of AMPK activity supports cartilage homeostasis by protecting cartilage matrix from inflammation-induced degradation.

Further investigation and new therapeutic approaches are needed. New targets that encompass innate immune receptor-mediated signaling, cytokine activity, chondrocyte metabolism, matrix anabolism and catabolism have potential to prevent and therapeutically slow development and progression of OA.

I-7 QUALITATIVE RESEARCH FOR OSTEARTHROSIS: BETTER UNDERSTAND PATIENTS AND CARE PROVIDERS VIEWS AND NEEDS TO IMPROVE MANAGEMENT STRATEGIES

S. Poiraudou, AP-HP, Université Paris Descartes, Paris, France

The patient point of view regarding health status has gained importance in decision-making procedures and has been considered a possible criterion standard to assess treatment efficacy. However, disability and Health-related quality of life are usually recorded using pre-fixed item questionnaires that do not take into account patients priorities. Patients with knee or hip osteoarthritis (OA) and their physician opinions differ on the importance of disabilities. Patients perceive knee OA to be more disabling than hypertension, diabetes mellitus and heart diseases whereas physicians consider these three latter conditions the most important chronic condition. In our study, OA patients and physicians in defining the importance of an illness should lead to a paradigm shift toward more patient-centered approaches. Taking into account patients priorities may lead to a better understanding of what is important to them and therefore to propose more individualized management strategies with increased compliance and efficacy.

Although patients with knee and hip OA and their physicians may differ in their assessment in health and symptoms status, views of patients and practitioners have been seldom studied. Qualitative research is probably the best way to understand patients’ needs and contexts and could improve therapeutic strategies and their assessment. The US Food and Drugs administration has recently proposed guidelines for patient-reported outcomes that emphasize the need for semi-structured interviews of patients to ensure content validity of these instruments. Semi-structured interviews and/or focus groups are widely used methods to constitute qualitative data base and these approaches are of particular interest in chronic conditions. A qualitative study involving semi-structured interviews of German patients with OA, nurses, and general practitioners (GPs) suggested that GPs should focus more on pain and disability and on giving more information about treatments. Using the same techniques, we recently reported data suggesting several ways to improve the patient-practitioner relationship and the efficacy of treatment strategies, probably by increasing their acceptability and compliance. The main factors of improvement we identified are providing adapted, formalized information to patients, adopting more global assessment and therapeutic approaches, and dealing more accurately with patients’ paradoxal representation of drug therapy. We also confirmed that patients’ and practitioners’ views largely differ, and