Seamless Multiscale Imaging and Computational Modeling of Molecular Communication in the Osteoarthritic Knee Joint

Lauren Kark, Ph.D.¹, Lucy Armitage ¹, Dan Hageman, B.S.¹, Roy K. Aaron, M.D.², Melissa L. Knothe Tate, Ph.D.¹.

¹University of New South Wales, UNSW Sydney, Australia, ²Brown University, Providence, RI, USA.

Disclosures: L. Kark: None. L. Armitage: None. D. Hageman: None. R.K. Aaron: None. M.L. Knothe Tate: 3C; bioz Ltd., Australia.

Introduction: Osteoarthritis (OA), the most common joint disease worldwide, is characterized by loss of joint structure and function. Loss of structure is associated with loss of articular cartilage (AC) and changes to subchondral bone (SCB) which worsen with age and result in significant pain and disability (i.e. loss in function). In a previous study we demonstrated the intrinsic molecular sieving behavior of the knee joint’s respective bounding tissues, which effectively serve as gatekeepers for molecular communication [1]. Here, as a first step toward understanding the role of exercise in molecular communication, we carried out a coupled in vivo experimental and computational study to (i) observe transport in the anaesthetized GP and (ii) predict transport in virtual GP knees. The Dunkin Hartley Guinea pig serves as an in vivo animal model of naturally occurring OA with increasing age. We hypothesized that molecular transport is significantly affected by molecular size, animal age (and progression of OA), as well as mechanical loading.

Methods: Two different molecular weight (MW) fluorescent-tagged, neutral dextrans were injected in a single bolus (10kDa: rhodamine green 70kDa: Texas red; Life Technologies, Invitrogen) into the heart of anaesthetized animals (IACUC approved) per previous protocols [1-3]. After circulation for 5 minutes while maintaining body temperature, knee joints were resected and immediately cryopreserved in liquid nitrogen cooled OCT medium (TissueTek, Sakura Finetek, Torrance, CA). High resolution, episcopic cryoimaging (BioInvision, Middlefield Heights, OH) was carried out to obtain cell scale resolution, three dimensional (3D) image stacks in cohorts of young adult (6 mo), middle aged (12 mo) and aged (18 mo) animals (n = 3 per cohort). Image stacks were imported into Mimics software (Materialise, Leuven, Belgium) and segmented into volumes of bone, cartilage, meniscus, ligament, and muscle, after which they were rendered in 3D for voxel counts of respective tissue volumes and tracer distributions. The three dimensional reconstructions were then meshed for import into finite element (FE, Ansys 4.5, Canonsburg, PA) software, allowing for prediction of tracer displacements under mechanical loads.

Results: Molecular communication within the knee joint depends on animal age, disease state, and physical activity (simulated exercise). Specifically, transport decreased with increasing age (Fig.). Furthermore, the number and volume of OA associated lesions increased significantly with increasing age. FE modeling predicted significant shifts in molecular distribution within the respective tissue compartments of the knee joint that were also related to molecular size, as well as GP age and disease state.

Discussion: Based on the experimental data and computational predictions, molecular transport is significantly affected by molecular size, animal age (and progression of OA), as well as mechanical loading. Seamless multiscale imaging and computational modeling enable assessment of molecular
communication in the OA knee joint and interactions between molecular communication and exercise. Follow on studies with simulated exercise (controlled loading under anaesthesia) and gait protocols may enable the development of prescriptive physiotherapy protocols to prevent and/or slow the progression of OA.

**Significance:** Current treatments for OA focus on easing of symptoms and reduction of disability, since the etiology of the disease has yet to be elucidated. The current studies aim to elucidate the role of the respective tissues and interfaces of the joint as a gatekeepers in osteochondral communication and to understand changes in molecular communication in association with exercise as well as progression of OA.

Figure: 3D, cell scale resolution images of the Guinea pig knee joint exhibiting distribution of 50kDa (red) and 10 kDa (green) molecules in 12 mo (A, 1000s exposure time) and 18 mo (B, 2000s exposure time required due to significantly reduced red and green emission intensity) animals. OA lesions (white arrow) are evident in the knees of the older cohort. C. 3D reconstruction of the tissue compartments of the GP knee joint. D. Finite element mesh of knee joint compartment, exhibiting meniscus (red) as well as patellar (yellow) and collateral (blue) ligaments allows for elucidation of interactions between molecular transport and mechanical loading.