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学位論文内容の要旨
Abstract of the dissertation

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学位論文題名
The title of the doctoral dissertation

Pentosan polysulfate: an effective treatment for model of rheumatoid arthritis and a novel candidate for inhibition of cytokines-induced osteoclastogenesis
多硫酸ペントサン：関節リウマチの効果的な治療法およびサイトカイン誘発破骨細胞分化制御の新規薬剤としての検討

Inflammatory joint diseases characterized by abnormal synovial proliferation and destruction of articular cartilage and bone. The degree of joint damage in inflammatory joint diseases such as, rheumatoid arthritis (RA) correlates with the number of synovial macrophages and inflammatory mediators appeared in the thickened synovial lining and synovial fluid. Comprehensive investigation of biological reaction of inflamed synovial joints is essential for implementing the treatment strategies by considering pathological changes. This study was constructed based on two major purposes. Primary objective was to identify the differentiation potential of synoviocytes and osteoclast; key effector cells in RA and second is to study the effectiveness of pentosan polysulfate (PPS) over the osteoclastogenesis and inflammation-related arthritis.

The synovial membrane (SM) is the central area of pathology of osteoarthritis (OA), RA and other inflammatory joint diseases including canine common knee injuries such as cranial cruciate ligament rupture (CCLr) and medial patella luxation (MPL). Findings of current study showed, differentiation capability of SM-derived multipotent stem cells varies with inflammatory severity occurring in CCLr and MPL. Further, current study was able to emphasize that pre-activated MSCs by inflammatory factors might offer a method of improving the potency of these cells without the need for additional cell number.

Several studies have shown that RA synovial cells release proinflammatory prostaglandins and cytokines, such as interleukin (IL)-1, tumour necrosis factor alpha (TNFα), and IL-17, all of which are known to promote

osteoclastic bone resorption. Osteoclastogenic properties of inflammatory cytokines at different time-points of osteoclastogenesis were identified. This study might be a manifesto for future investigation of finding other factors involved in the IL-1β–induced inhibition of canine osteoclastogenesis and to unveil the rationale of MMP9 downregulation by IL-17 in addition to determine the mechanisms of action of IL-17 in bone erosion.

Pentosan polysulfate sodium is a semi-synthetic sulfated polysaccharide drug manufactured from European beech-wood hemicellulose by sulfate esterification. From the results of previous *in vitro* and *in vivo* studies, the spectrum of pharmacological activities exhibited by PPS would qualify it as disease-modifying osteoarthritis drug (DMOAD) because of its ability to preserve the integrity of the articular cartilage and bone while improving the quality of the joint synovial fluid. Findings of current study provide useful preliminary information of inhibitory effect of PPS on OC differentiation and bone resorption by proving treatment option for osteoporosis or other bone diseases associated with excessive bone resorption and provides useful information for future pharmacokinetic studies and clinical trials *in vivo*. Pentosan has been used as a treatment for variety of inflammatory conditions with an excellent long-term safety profile. One of the aims of this study was to investigate potential anti-arthritic activity of PPS in collagen induced arthritis rat. The results of the current *in vivo* study confirmed that PPS upgrades the clinical outcome of RA animal model while conserving structural silhouettes of the joints by possessing its anti-arthritis effect.

Collectively this whole study was able to emphasis that the anti-arthritis and anti-inflammatory effect of PPS in RA animal model while unveiling it's another dimension of mechanism of action on osteoclastogenesis. To achieve this phenomenon, clustered studies including, understanding differentiation potential of synoviocytes and OC at inflammatory background added the contextual value and fundamental theories to the whole study.