DMM-induced OA mice showed that administration of 10 mg/kg THC by oral gavage also reduced mechanical allodynia (n=10/group) without modifying animal locomotion or anxiety. In vitro, THC treatment of human OA FLS and chondrocytes (n=3 each) increased Annexin V positivity starting at 2.5μM, but not with 1μM THC, as determined by flow cytometry. In cultured OA FLS (n=4), 73 genes were differentially expressed (35 upregulated, 38 downregulated) after treatment with THC compared to vehicle treatment (≥1.5-fold), as determined by RNA sequencing (Figure 1D). Similarly, in OA chondrocytes RNA sequencing (n=6/group), 21 genes (9 upregulated, 12 downregulated) were differentially expressed (≥1.5-fold) after THC treatment. Computational analyses indicated that ECM-related pathways were enriched in the upregulated genes in both fibroblasts and chondrocytes, while lipid/steroid/cholesterol-related pathways were enriched by the downregulated genes in both cell types. 22 common putative transcription factors were also identified as potential regulators of the fibroblast and chondrocyte genes reduced through THC treatment.

Conclusion: Oral administration of 10 mg/kg THC reduced cartilage degeneration and synovitis in DMM mouse knee joints and modified pain responses in DMM and MIA models. JR, AM, HFF share equal first author contribution.

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OP0201 INTRA-ARTICULAR INJECTIONS OF TWO LIPOSOMAL ADENOSINE FORMULATIONS PROVIDE SIGNIFICANT PAIN RELIEF AND GAIN IN FUNCTION, IMPROVE COMFORTABLE RANGE OF MOTION AND SLOWED RADIOLOGIC PROGRESSION IN A PRECLINICAL CANINE MODEL OF OSTEARTHrosis

Keywords: Osteoarthritis, Cartilage, Pain

D. LI1, B. N. Cronstein2, J. Cook3, C. Bozynski3, S. Ansel3, 1Regenostics, Inc., Princeton Innovation Center, Princeton, United States of America; 2New York University, School of Medicine, New York, New York, United States of America; 3University of Missouri, School of Medicine, Columbia, United States of America

Background: Osteoarthritis (OA) affects 10% of global population and its effective non-surgical treatments represent significant unmet need. There has been a rapid escalation in the annual number of arthroplasties, placing a significant burden on patients and healthcare systems. We previously demonstrated that adenosine and its A2A receptor play critical roles in maintaining joint homeostasis. Adenosine treatment prevents structural progression and preserves articular cartilage in rodent models of OA.

Objectives: To test the new, more stable and long-lasting formulations of liposomal adenosine in the treatment of post-traumatic OA in a preclinical canine model.

Methods: OA was induced by arthroscopic medial meniscus release (MMR) in 21 purpose-bred hounds (10M, 11F). Evidence of OA was documented at two months after MRR (pre-Tx). Knees were injected with 3ml of RgnA09M, RgnA09N (3mg/ml Adenosine; N=7 each) or saline (9mg/ml NaCl; N=7) for a total of 3 intra-articular (IA) injections each carried out one month apart. RgnA09M and RgnA09N comprised identical lipid composition but varied in particle size and liposome lamellarity. Blinded assessments for knee pain, function and effusion were performed using validated visual analogue scale (VAS) scoring by a board-certified veterinary surgeon. Comfortable range of motion (CROM) was measured using a standard goniometer and radiographic assessments of knee joints were also performed. Results presented are before surgical induction of OA (pre-MR), at pre-Tx, at 4 months (post-Tx) and the time of humane euthanasia (6 months post-Tx) for histology and histopathology. Blood for biomarkers and synovial fluid were collected at same time points. MRIs were used to evaluate cartilage structure and integrity at pre-Tx and 6 months post-Tx. Wilcoxon matched pair signed rank test was used for statistical analyses.

Results: There was a demonstrable symptomatic knee OA at pre-Tx with a 26.3% loss in function, increased joint pain score (2.0±0.9 vs 0 at pre-MR), 10% loss of CROM, development of radiographic OA (1.2±0.5 vs. 0 at pre-MR), observable OA on MRI (3.9±0.9 vs. 0 at pre-MR) and joint effusion (2.3±0.9 vs 0 at pre-MR). Saline treatment provided no benefits. The IA administration of RgnA09M, led to a steady decrease in pain by 65.0% and 74.3%, at 4mo and 6mo post-Tx respectively, with a corresponding 30.9% and 61.8% gain in function. In comparison, the injection of RgnA09N led to decrease in pain by 80.9% at 4mo but a loss of effect to 74.7% at 6mo post-Tx. A corresponding trend was observed in the gain of function, with an overall gain of 39.7% at 6mo post-Tx (Figures 1A and 1B).

Moreover, injections with RgnA09M, improved CROM to near-normal values at 6mo, while RgnA09N significantly improved it at 4mo (Figure 1C). Compared to saline, both RgnA09M and RgnA09N improved radiographic scores of OA by up to 42.6% at 6mo post-Tx (Figure 1D). In saline-treated dogs there was an improvement in the size of effusions initially, but a loss in benefit as time progressed. In contrast, the magnitude of the change was much greater in those treated with both formulations, and it continued to improve over time (Figure 1E). Finally, at 6mo post-Tx, MRIs showed significant slowing in the progression of OA with RgnA09M by 55.3% and with RgnA09N by 42.6% (Figure 1F). Histology and biomarker results are pending.

Conclusion: Three IA injections of RgnA09M and RgnA09N were associated with improved symptomatic knee OA including gain in function and decrease in pain and OA progression compared with saline. The persistent improvement lasted 6 months, indicating symptomatic and mechanistic benefits of the treatment. Moreover, liposomal adenosine injections slowed the progression of OA as observed on radiographs and MRIs. These findings provide the first evidence that IA injection of liposomal adenosine improves pain relief, gain in function, CROM, and prevents radiologic progression in a large animal model of post-traumatic OA.

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Understanding Treatment response and novel treatment approaches in RA

Keywords: Rheumatoid arthritis, -Omics

S. Yamada1, Y. Nagafuchi2, M. Wang3, M. Ota1,2, H. Hatano1,4, Y. Takeshima1,2, M. Okubo5, S. Kobayashi1,2, Y. Sugimori5,6, M. Nakano7,7, R. Yoshida1, N. Hanata1, Y. Suwa1, T. Tsunoda1, Y. Iwasaki1, S. Sumitomo1, K. Kubo1, K. Shimane6, K. Setoguchi7, T. Azuma1, H. Kanda1,10, H. Shoda1, X. Zhang3, K. Shimane6, K. Setoguchi7, T. Azuma1, H. Kanda1,10, H. Shoda1, X. Zhang3, K. Yamamoto1, K. Ishigaki2, Y. Okamura2, K. Fujio1, Graduate School of Medicine, the University of Tokyo, Department of Allergy and Rheumatology, Tokyo, Japan; 2Graduate School of Medicine, the University of Tokyo, Department of Functional Genomics and Immunological Diseases, Tokyo, Japan; 3Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Clinical Immunology Center, Graduate School of Peking Union Medical College, Chinese Academy of Medical Sciences and Peking Union Medical College, Department of Rheumatology, Beijing, China; 4Center for Integrative Medical Sciences, RIKEN, Laboratory for Human Immunogenetics, Kanagawa, Japan; 5Tokyo Metropolitan Geriatric Hospital, Department of Medicine and Rheumatology, Tokyo, Japan; 6Tokyo Metropolitan Bokutob

OP0202 IMMUNOMICS ANALYSIS OF RHEUMATOID ARTHRITIS IDENTIFIED PRECURSOR DENDRITIC CELLS AS A KEY CELL SUBSET OF TREATMENT RESISTANCE

Keywords: Rheumatoid arthritis, -Omics

S. Yamada1, Y. Nagafuchi2, M. Wang3, M. Ota1,2, H. Hatano1,4, Y. Takeshima1,2, M. Okubo5, S. Kobayashi1,2, Y. Sugimori5,6, M. Nakano7,7, R. Yoshida1, N. Hanata1, Y. Suwa1, T. Tsunoda1, Y. Iwasaki1, S. Sumitomo1, K. Kubo1, K. Shimane6, K. Setoguchi7, T. Azuma1, H. Kanda1,10, H. Shoda1, X. Zhang3, K. Yamamoto1, K. Ishigaki2, Y. Okamura2, K. Fujio1, Graduate School of Medicine, the University of Tokyo, Department of Allergy and Rheumatology, Tokyo, Japan; 2Graduate School of Medicine, the University of Tokyo, Department of Functional Genomics and Immunological Diseases, Tokyo, Japan; 3Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Clinical Immunology Center, Graduate School of Peking Union Medical College, Chinese Academy of Medical Sciences and Peking Union Medical College, Department of Rheumatology, Beijing, China; 4Center for Integrative Medical Sciences, RIKEN, Laboratory for Human Immunogenetics, Kanagawa, Japan; 5Tokyo Metropolitan Geriatric Hospital, Department of Medicine and Rheumatology, Tokyo, Japan; 6Tokyo Metropolitan Bokutob


Background: To date, there have been no comprehensive studies of the immune cells that play a pivotal role in treatment-resistant rheumatoid arthritis (RA).

Objectives: We performed large scale transcriptome analyses of immune cells in peripheral blood prior to treatment in a total of 55 patients with RA to identify the gene expressions and subsets that predict treatment resistance.

Methods: We isolated 18 peripheral blood immune cell subsets of 55 pre-treatment RA patients and 39 healthy controls, and performed RNA sequencing (Figure 1A). Transcriptome changes in RA and treatment effects were systematically characterized. Association between immune cell gene modules and treatment resistance was evaluated. We validated predictive value of identified parameters for treatment resistance using quantitative polymerase chain reaction (qP CR) and mass cytometric analysis cohorts. We also characterized the identified population by synovial single cell RNA-seq analysis.

Results: Immune cells of RA patients were characterized by enhanced interferon and IL6-JAK-STAT3 signaling that demonstrate partial normalization after treatment. A gene expression module of plasmacytoid dendritic cell (pDC) reflecting the expansion of pre-dendritic cell (pre-DC), which is recently identified subpopulation of DCs (1), exhibited strongest association with treatment resistance (Figure 1B-D). Type I interferon signaling was negatively correlated to pre-DC gene expression. qPCR and mass cytometric analysis validated that the pre-DC associated gene expression and the proportion of pre-DC were significantly higher before treatment in treatment-resistant patients (Figure 1E, F). A cluster of synovial DCs showed both features of pre-DC and proinflammatory conventional DC2s (Figure 1G).

Conclusion: Treatment resistance can be predicted by an increase in pre-DC in the peripheral blood of RA patients prior to starting therapy. This result shows the potential for realizing a stratified therapy of RA based on analysis of pre-DC in peripheral blood.

REFERENCE:

OP2003

IMMUNOPHENOTYPING OF RHEUMATOID ARTHRITIS STRATIFIES FIVE GROUPS THAT HAVE DIFFERENT RESPONSES TO MOLECULAR TARGETED THERAPY

Keywords: Adaptive immunity, Rheumatoid arthritis, Disease-modifying drugs (DMARDs)

S. Kubo1, S. Nakayama2, Y. Miyazaki3, Y. Fujita4, R. Kanda2, K. Kusaka1, Y. Todokoro2, H. Miyata2, K. Sonomoto5, S. Fukuyo6, K. Hanami7, Y. Tanaka8

1University of Occupational and Environmental Health, Japan, Department of Molecular Targeted Therapies (DMTT), Kitakyushu, Japan; 2University of Occupational and Environmental Health, Japan, Department of Clinical Nursing, Kitakyushu, Japan

Background: Different molecular targeted therapies affect immune cell phenotypes and signals differently due to their modes of action[1]. Theoretically, it is possible to use these drugs based on a stratification of rheumatoid arthritis (RA) patients. However, despite innovations in the treatment of RA, precision medicine with the development and application of personalized treatments by molecular targeted therapy is still far from its achievement. At least, precision medicine by a single biomarker is not known to be possible[2].

Objectives: To investigate the possibility of precision medicine based on the immune phenotype of peripheral blood, we stratified RA patients by comprehensive flow cytometric immunophenotyping and evaluated the response to targeted therapy.

Methods: This study enrolled 96 healthy controls (HC) and 533 bio-naive RA patients with moderate to severe disease activity according to CDAI. The Human Immunology Project, a NIH/FICIS-developed flowing cytometry immune cell profiling method on T cells, B cells, NK cells, dendritic cells, and monocytes, was used to stratify the patients using cluster analysis (Ward and UMAP methods). Inverse probability weighting with propensity scores was used to control for patient characteristics and CDAI was used to measure remission achievement after 6 months of targeted therapy for each stratified subgroup.

Results: The mean age was 63.5 years old, and the disease activity was CDAI 27.1. In comparison to HC, CD4 T cell differentiation was noticeably affected in RA patients, with elevated effector T cell and effector memory T cells re-expressing CD45RA (TEMRA). Meanwhile, there was no meaningful change in the...