Objectives: Use CRISPR-Cas9, to perturb the COG6 intronic enhancer region and measure the downstream effect on the expression of FOXO1.

Methods: We utilised a modified form of the Cas9 enzyme, dead Cas9 (dCas9), that can precisely target DNA, but will not induce a cut. Using the dCas9 attached to either enhancers (p300) or repressors (KRAB) of expression we investigated how perturbation of the enhancer intronic of COG6 changed the expression of FOXO1.

We designed 3 guides across the COG6 enhancer, and transduced a cell line (HEK293) using a lentiviral dCas9 CRISPR system, with either dCas9-KRAB or dCas9-p300 and each of the three guides. We cultured the cells until 70%–80% confluent, GFP sorted the cells and then extracted RNA. A quantitative PCR was performed (QuantStudio) for both COG6 and FOXO1 gene transcript expression and normalised to housekeeping genes.

Results: Up to 90% of HEK cells were transduced with the dCas9 enzyme and guide, and these were sorted by FACS using GFP to sort the top 60%. The 3 guides gave consistently increased levels of FOXO1 expression with the dCas9-p300, compared to both control and dCas9-KRAB ($p=0.02$). This was particularly evident for guide 3, with a 40% increase (p300) and 10% decrease (KRAB) of FOXO1 expression observed. Expression of COG6 was also perturbed, but in a less consistent manner, with both increase and decrease expression for KRAB and p300.

Conclusions: Over 90% of HEK cells were transduced with the dCas9 enzyme and guide, and these were sorted by FACS using GFP to sort the top 60%. The 3 guides gave consistently increased levels of FOXO1 expression with the dCas9-p300, compared to both control and dCas9-KRAB ($p=0.02$). This was particularly evident for guide 3, with a 40% increase (p300) and 10% decrease (KRAB) of FOXO1 expression observed. Expression of COG6 was also perturbed, but in a less consistent manner, with both increase and decrease expression for KRAB and p300.

REFERENCE:

- [1] Martin P, et al. Capture Hi-C reveals novel candidate genes and complex long-range interactions with related autoimmune risk loci. *Nat Commun* 2015 Nov 30.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.3946

OP0289

INTEGRATION OF CHROMATIN CONFORMATION, TRANSCRIPTOME AND GENOME-WIDE LANDSCAPE OF BRD2 AND BRD4 BINDING MOTIFS IDENTIFIES MECHANISMS OF BET INHIBITOR ACTION IN RHEUMATOID ARTHRITIS SYNOVIAL FIBROBLASTS

S. Nagpal¹, V. Krishna², X. Yin¹, D. Pocalyko², A. Walsh¹, K. Bachman², I. Anderson¹, L. Madakamuti¹. ¹Immunology, ²Discovery Sciences, Janssen Research, Spring House, USA

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by infiltration of immune cells into the synovium and hyperplasia of the synovial lining, resulting in the formation of pannus that degrades cartilage and bone. Fibroblast-like synoviocytes (FLS) are the main cell types of the rheumatoid synovium and possess phenotypic and molecular characteristics of transformed cells. JQ1, an inhibitor of the bromodomain and extra terminal domain (BET) family that includes BRD2, BRD3, BRD4 and BRDT has shown efficacy *in vitro* on RA-FLS proliferation and *in vivo* in a murine model of arthritis.

Objectives: We sought to elucidate the mechanism of action of BET proteins in FLS biology and determine the potential therapeutic utility of targeting BRD2/BRD4 for RA disease treatment and interception.

Methods: To understand the mechanism of JQ1 action, we subjected JQ1-treated RA-FLS to transcriptional profiling by RNA-Seq and determined BRD2 and BRD4 cistromes by identifying global BRD2/BRD4 chromatin binding sites by ChIP-Seq. In addition, Assay for Transposase Accessible Chromatin by high throughput Sequencing (ATAC-Seq) was employed to identify open and closed regions of chromatin in JQ1-treated RA-FLS.

Results: We demonstrate that the active isomer of JQ1 but not its inactive isomer inhibits IL-1b-induced RA-FLS activation and proliferation. Through an integrated analysis of RNA-Seq, ATAC-Seq to profile changes in chromatin accessibility and ChIP-Seq of BRD2/4 and Pol2 proteins, we found that JQ1 inhibited multiple key inflammatory pathways, and altered the genome wide occupancy of crucial transcription factors involved in inflammatory signalling. Specifically, JQ1 treatment resulted in reduced occupancy of both BRD2 and BRD4 in approximately 2000 regions genome-wide, and a loss of Pol2 occupancy in approximately 600 genomic regions. Collectively we found that 105 genes had altered occupancy in all three proteins (BRD2, BRD4 and Pol2) and were also differentially expressed. Most prominently, JQ1 resulted in down regulation of IL6, IL8, p38 MAP kinase and HMGB1/TLR4 signalling pathways. In addition, we have identified BRD2/BRD4 super-enhancer genes and demonstrate that JQ1 altered BRD2/BRD4 occupancy in the IL6 and IL8 super-enhancer regions, and significantly down-regulated IL6, IL8, TLR4 and IL1b expression.

Conclusions: Our results suggest pleiotropic effects of JQ1 on pathways that have been individually targeted and shown to be efficacious for the treatment of RA. These studies provide a strong rationale for targeting of BRD2/BRD4 in RA.

Disclosure of Interest: S. Nagpal Shareholder of: Johnson and Johnson, Grant/research support from: Johnson and Johnson, Employee of: Johnson and Johnson, V. Krishna Shareholder of: Johnson and Johnson, Grant/research support from: Johnson and Johnson, Employee of: Johnson and Johnson, X. Yin Shareholder of: Johnson and Johnson, Grant/research support from: Johnson and Johnson, Employee of: Johnson and Johnson, D. Pocalyko Shareholder of: Johnson and Johnson, Grant/research support from: Johnson and Johnson, Employee of: Johnson and Johnson, A. Walsh Shareholder of: Johnson and Johnson, Grant/research support from: Johnson and Johnson, Employee of: Johnson and Johnson, K. Bachman Shareholder of: Johnson and Johnson, Grant/research support from: Johnson and Johnson, Employee of: Johnson and Johnson, I. Anderson Shareholder of: Johnson and Johnson, Grant/research support from: Johnson and Johnson, Employee of: Johnson and Johnson, L. Madakamuti Shareholder of: Johnson and Johnson, Grant/research support from: Johnson and Johnson, Employee of: Johnson and Johnson

DOI: 10.1136/annrheumdis-2018-eular.7388

FRIDAY, 15 JUNE 2018

PARE abstract session

OP0290-PARE KEEP AN EYE OUT FOR INVISIBLE PAINS – A DANISH CAMPAIGN

C.R. Ziegler. *Gigtforeningen, Gentofte, Denmark*

Background: How does it feel to live with a RMD and have chronic pain? How do you explain pain caused by RMD to your friends and family? How do you make others understand how pain affects your daily life? The communication department of the Danish Rheumatism Association needed to convey living with invisible pains, because it is of such importance to people with RMDs. Based on interviews with the users (people with RMDs) we found the best way of making others understand was to create a film, which illustrated living with invisible pain.

Objectives: We wanted to increase the general understanding of RMDs and living with invisible pain in society. The secondary objective was to brand awareness of the Danish Rheumatism Association and to generate leads for further processing, e.g. signing up for membership.

Methods: Based on a few interviews with users and several posts from Social Media we focused on making invisible pain visible. By choosing the media of a film we could show what the users found difficult putting into words. The film had to be short to make it possible to share, e.g. on Facebook, and by choosing a film without speak we avoided language barriers. Through adverts we retargeted visitors to our website and generated more members of the association.

Results: We launched the film on World Arthritis Day 2017 In 3½ weeks the film reached 1 million users and more than 1000 comments on Facebook, and the number of followers went up by 2000. The total impact of the film will be presented in June 2018.

Conclusions: In the presentation we will show how and why the campaign could be such a success. We will focus on how to follow-up the positive results of generating leads and making invisible pain visible.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.2902

OP0291-PARE RUNNING WITH RHEUMATISM: A 7-WEEK TRAINING PROGRAMME FOR NOVICE RUNNERS WITH INFLAMMATORY RHEUMATIC DISEASE

J.F.M. Holla^{1,2}, J. Brontsema¹, N. Schenk³, R. Jansen⁴, R. Vreenegoor⁵, M. Fluit¹, W.F. Peter¹, I.E. Bultink⁶. ¹Reade, Center for Rehabilitation and Rheumatology, Amsterdam; ²Faculty of Health, Sports and Social Work, Inholland University of Applied Sciences, Haarlem; ³Runner with inflammatory rheumatic disease, Weesp; ⁴Club manager, Athletics Club Phanos, Amsterdam; ⁵Running trainer, Run2Day, Haarlem; ⁶Amsterdam Rheumatology and immunology Center, VU University Medical Center, Amsterdam, Netherlands

Background: In the Netherlands, running is the second most practised sport. Running is also becoming increasingly popular among people with inflammatory rheumatic diseases, according to the growing number of running-related questions to the Dutch Arthritis Foundation and rheumatologists. Frequently asked questions are: 'Am I allowed to run?' and 'How can I start in a safe way?'.

Objectives: Given the increasing demand from the target group, and the potential positive health consequences of high-intensity exercise,¹ we developed a 7 week running programme for novice runners with inflammatory rheumatic disease, and explored its feasibility and safety.

Methods: First we performed a needs assessment among 228 participants with different inflammatory rheumatic diseases. In all, 200 (88%) participants were interested in practicing the sport of running. Then, a rheumatologist, specialised physical therapist, patient representatives and experienced running trainers developed the running programme, based on the proven effective 'Start to Run' programme of the Dutch Athletics Federation. The programme aims to prepare participants in 7 weeks for a 20 min run without breaks, and consists of one supervised group training session and one or two non-supervised training sessions per week. In addition to gradual progression of joint load (by starting with running on soft even surfaces) and running volume, special attention is paid to development of muscle strength and coordination, optimal movement pattern and running at an own comfortable pace. During the programme, the running trainer is in close contact with a rheumatologist and/or specialised physical therapist who can be consulted for advice.

Results: Of the first 24 participants of 'Running with Rheumatism', 12 participants completed the programme successfully, 4 participants developed a running related injury, 1 participant dropped out due to rheumatic symptoms, and 7 participants dropped out due to other reasons (e.g. surgery, infectious mononucleosis, burn-out). Participants indicated that they felt safe and comfortable during the group training sessions, and were surprised to be able to achieve so much progress in a short time period. They felt that they had become stronger and got to know their body and physical capabilities better.

Conclusions: The first running groups were successful. The incidence of running related injuries did not significantly differ from incidence rates reported from

comparable programmes for regular novice runners in the Netherlands. Therefore, we aim for nationwide implementation.

REFERENCE:

- [1] Jong ZD, Munneke M, Zwiderman AH, et al. Is a long-term high-intensity exercise program effective and safe in patients with rheumatoid arthritis? Results of a randomized controlled trial. *Arthritis & Rheumatism* 2003;48:2415–24.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.3782

OP0292-PARE THE CREATION OF THE 'AQUA RE-ACTION'. A METHODOLOGICALLY BASED AQUATIC PHYSICAL INTERVENTION/REHABILITATION PROGRAM FOR PEOPLE WITH RMD'S

A. Iacovou. Cyprus League Against Rheumatism, Limassol, Cyprus

Background: As an Aquatic Instructor and an OA patient myself, I faced with other RMD patients the demand for an aquatic physical conditioning program that can meet our needs. After contacting with Patient Leagues and Aquatic Fitness Training Organisations, I found out that there was no such a specific program and it was essential to create one.

Objectives: My first objective was to get trained and create an aquatic program that could improve the quality of life through improving the ROM, muscular strength, flexibility, balance and aerobic capacity. My next objective was to accommodate people with variables like having or not fear of water, with minimum or increased joint mobility, with different affected joints and connective tissues. Hence to that I had to approach and convince Rheumatologists, Orthopaedics, Physiotherapists and patients for the benefits of this specific Aquatic program and have it as an option to their rehabilitation. Moreover, I had to use water as my basic instrument and use its principles (Laws of physics) to estimate the programs intensity. Finally I decided to offer that knowledge through an Instructor course.

Methods: In order to get trained, I followed specific training in Aquatic fitness and Rehabilitation by International Aquatic Organisations like the Aquatic Exercise Association, International Aquatic Therapy Faculty and BECO Academy and spending hours in the pool testing exercises and designing the program. Methodologically, I implemented the Principles of Aquatic Environment like buoyancy, hydrostatic pressure, inertia, and biomechanics like, hydrodynamics, movement speed, levers, to estimate the exercise in low to medium intensity and I emphasised on the quality and the execution of the movement. The program was focused on no pain moves in the biggest possible ROM, using all joints and muscle groups, working on muscle flexibility strength and aerobic capacity. I created a shallow and a deep water program in order to classify participants based on certain criteria.

I contacted meetings with Physicians, and the Cyprus League Against Rheumatism. Published article about Aquatic workout benefits to RMD's at the Cyprus League Against Rheumatism (Cyplar) Journal, I gave lectures and special offer to Cyplar members.

The creation of the Instructors course, needed to start from registering a name, logo and manual. It was also essential to build a business structure to obtain financial and human resources.

Results: Based on the participants testimonies there was an improvement on quality of life, their joints range of motion, muscle strength, flexibility and aerobic capacity. Hence to that they mention less pain, move quality night sleep and generally better social life with out depression. All the above was mentioned also from their Physicians and therapists that lead to increasing their trust towards the program benefits. Hence to that our collaboration with CYPLAR continued by organising a joined annual Swimming charity event.

AQUA Re-Action is the registered name of the program, and Logo and Manual are in an ongoing process of final registrations.

Conclusions: Having an active lifestyle through an aquatic physical conditioning program, which is under the guidance of a specialised Aquatic Instructor, for at least 3 times per week, can lead to a significant improvement on patients Quality of life within few weeks.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.1674