

patients to currently available drugs underlies the unmet need to identify new therapeutic targets.

**Objectives:** Certain CD4<sup>+</sup>T cell subsets, especially Th17 cells, have been shown to be major drivers of inflammation in patients with RA. The expression of their key transcription factors is controlled by histone modifications which includes acetylation of *lysine residues* mediated by histone deacetylases (HDAC). Indeed, pan HDAC inhibitors have been shown to be a potential therapeutic strategy. However, major side effects limited the clinical use and underline the need of more specific HDAC inhibitors. We therefore addressed the individual role of HDAC1 on the development of collagen-induced arthritis model (CIA).

**Methods:** Mice with a T cell specific deletion of HDAC1 (HDAC1 cKO) were generated by using the CD4Cre/LoxP system. Collagen induced arthritis (CIA) was induced at week 8. Animals were scored for paw swelling and grip strength. After 10 weeks, mice were sacrificed and paraffin sections of the affected joints were analysed for histomorphological signs of inflammation, cartilage and bone destruction. Anti-CII antibody levels were determined by ELISA. Serum samples were analysed for various cytokines by multiplex assays. CCR6 expression in CD4 T cells was analysed by flow cytometry.

**Results:** To address potential effects of HDAC1 in the pathogenesis of RA, CIA was induced in *HDAC1cKO* mice and *WT* mice. Surprisingly *HDAC1cKO* mice were completely protected from the development of arthritis. In line with the clinical data, histological analysis revealed no signs of inflammation, no bone erosion and no osteoclasts in the joints of *HDAC1cKO* mice. Anti-CII antibodies, including total IgG and igG2c were detected in *HDAC1cKO* and *WT* mice. Surprisingly, IL-17 was significantly decreased in the serum of *HDAC1cKO* mice as compared to *WT* mice, suggesting a role of HDAC1 in the development of Th17 cells. To see whether HDAC1 is involved in the regulation of the chemokine receptor 6 (CCR6), the main marker of Th17 cells, we compared the upregulation of CCR6 in CD4<sup>+</sup> T cells from *WT* and *HDAC1cKO* mice. Indeed, CCR6 could not be upregulated in CD4<sup>+</sup> T cells from *HDAC1cKO* mice upon IL-6 *in vitro*. These data support the role of HDAC1 in the regulation of CCR6, an important chemokine receptor, which is necessary for the migration of pathogenic Th17 cells and therefore for the development of arthritis.

**Conclusions:** Our data show the importance of HDAC1 as a key immune regulator in the pathogenesis of T cell driven collagen induced arthritis. Therefore, it might be considered as an interesting novel therapeutic target in RA.

**Disclosure of Interest:** None declared

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THU0085 **CR6086, A NOVEL EP4 ANTAGONIST WITH IMMUNOMODULATORY PROPERTIES, DECREASES BONE LOSS IN THE RAT COLLAGEN-INDUCED ARTHRITIS (CIA) MODEL: A MICROTOMOGRAPHY (MICROCT) STUDY**

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**Background:** CR6086 is a novel PGE2 EP4 receptor antagonist showing favourable immunomodulatory properties, striking DMARD effects in rodents, and an anti-inflammatory activity targeted to immune-mediated diseases and distinct from that of NSAIDs. Besides its role in controlling T cells, PGE2 is implicated in the aggressive bone erosion of rheumatoid arthritis (RA).

**Objectives:** To characterise CR6086 activity on the bone compartment mostly affected by erosion in the CIA model in rats.

**Methods:** 15 male Lewis rats were immunised by intradermal injection with collagen II in CFA. 5 naïve animals were the sham group. 3 days after boost, oedema was assessed and rats assigned to treatment with vehicle or CR6086 (3 or 10 mg/kg qd). Oedema was measured again on days 7 and 14, and hindlimb joints were blindly scored for clinical signs of arthritis (scale 0–4; from normal=0 to maximally inflamed limb with involvement of multiple joints=4). At sacrifice, hindlimb calcaneus underwent high-resolution X-ray microCT (total and cancellous bone), a sensitive method that allows the reduction of experimental animals in compliance with the 3R rule. Parameters were expressed as the mean of left and right paw. Joints were then scored for histological features. Statistics were performed by ANOVA, correlations by Spearman analysis.

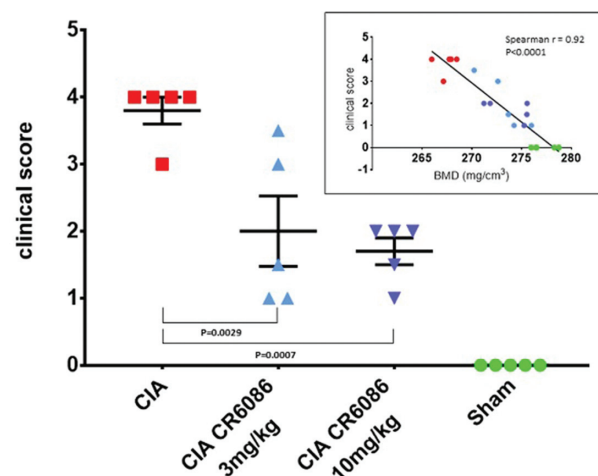
**Results:** CR6086 significantly reduced bone loss in CIA rats (table 1), even at the low dose of 3 mg/kg. The effect on cancellous bone plateaued already at 3 mg/

kg, confirming the sensitivity of the metabolically more active districts of bone to the action of EP4 antagonists.

	Sham-vehicle	CIA-vehicle	CIA-CR6086 3mpk	CIA-CR6086 10mpk
<b>Total bone, mean (SD)</b>				
<b>BMD (mg/cm<sup>3</sup>)</b>	277.20 (1.25)	267.40 (0.95)	273.50 (2.09) p 0.0004#, 0.0167\$	273.90 (2.17) p 0.0002#, 0.0322\$
<b>BV/TV (%)</b>	82.53 (10.11)	60.64 (2.68)	76.02 (5.57) p 0.0005#, n.s.\$ p 0.0004\$	76.77 (5.30) p 0.0003#, n.s.\$
<b>BS/BV (mm<sup>-1</sup>)</b>	6.10 (0.78)	13.64 (0.83)	9.00 (1.48) p 0.0001#, 0.0044\$	8.61 (1.25) p 0.0001#, 0.0134\$
<b>Cancellous bone, mean (SD)</b>				
<b>BMD (mg/cm<sup>3</sup>)</b>	270.44 (2.17)	261.20 (1.20)	267.31 (1.87) p 0.0007#, n.s.\$	266.24 (2.61) p 0.0032#, 0.0225\$
<b>BV/TV (%)</b>	71.09 (4.99)	42.76 (3.74)	61.66 (6.81) p 0.0009#, n.s.\$	58.17 (7.57) p 0.0040#, 0.0165\$
<b>BS/BV (mm<sup>-1</sup>)</b>	14.51 (2.67)	30.31 (1.84)	20.83 (3.30) p 0.0008#, 0.0196\$	21.84 (3.81) p 0.0019#, 0.0067\$
<b>Trabecular thickness (µm)*</b>	143.02 (31.94)	66.94 (4.39)	98.49 (14.38) p 0.0041#, 0.0111\$	94.25 (16.38) p 0.0105#, 0.0055\$
<b>Trabecular separation (µm)**</b>	56.46 (3.51)	90.85 (9.00)	60.51 (8.85) p 0.0004#, n.s.\$	66.85 (9.28) p 0.0023#, n.s.\$
<b>Trabecular number (mm<sup>-1</sup>)</b>	3.64 (0.39)	3.31 (0.10)	4.01 (0.26) p 0.0001#, n.s.\$	3.93 (0.13) p 0.0003#, n.s.\$

\* 2x(BV/BS); \*\* 2x(TV-BV)/BS; \$ vs. sham; # vs. CIA; BMD, Bone Mineral Density; TV, Total Volume; BV, Bone Volume; BS, Bone Surface; mpk, mg/kg

There was a strict correlation between clinical score and bone parameters (BMD; figure 1 inset), confirming that bone erosion in CIA is closely associated with arthritis severity.



**Conclusions:** CR6086 is an EP4 antagonist in clinical development for RA (NCT03163966). Besides its immunomodulatory activity, CR6086 effectively decreases the aggressive bone erosion that characterises both the CIA model and the early phases of human RA.

**Disclosure of Interest:** M. Lanza Employee of: Rottapharm Biotech, G. Caselli Employee of: Rottapharm Biotech, F. Ferrari Employee of: Rottapharm Biotech, A. Grotti Employee of: Rottapharm Biotech, R. Cavagnoli Employee of: Rottapharm Biotech, M. Perrella: None declared, F. Daubine Employee of: Atlantic Bone Screen, V. Ayer Employee of: Rottapharm Biotech, L. Rovati Employee of: Rottapharm Biotech

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