# ANSWERING REVIEWERS

May 09, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16979-edited.doc).

**Title:** Epigenetic targets of RA
Editorial

**Author:** Ghazi Chabchoub

**Name of Journal:** *World Journal of Rheumatology*

**ESPS Manuscript NO:** 16979

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer 00505817

References have been replaced and updated (beyond 2008).

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Rheumatology*.

Sincerely yours,

Signé Par
Dr CHABCHOUB Ghazi

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## Dear Chief Editor,

**We corrected the following sentences:**

1) There is increasing evidence that epigenetic mechanisms play a role in regulating TNF expression LPS stimulation causes phosphorylation of Serine of histone H3 and demethylation of Lysine at the TNF promoter in the monocyte or macrophage cell line[24].

**Corrected: There is increasing evidence that epigenetic mechanisms play a role in regulating TNF expression. Phosphorylation of Serine (S)$^{10}$ of histone H3 and demethylation of Lysine (K)$^{7}$ has been observed at the *TNF* promoter in THP-1 cells, following LPS stimulation [24].**

2) HDAC inhibitor application, FK228 decreased TNF, along with IL-1β, expressed in the joint and suberoylanilide hydroxamic acid (SAHA) and MS-275 decreased IL-6 and IL-1β levels in the serum suggesting an important role for HDAC in regulating production of pro-inflammatory cytokines[31,32].

**Corrected: Various studies using topical application of suberoylanilide hydroxamic acid (SAHA), MS-275 and FK228 established their potential to decrease serum IL-6, IL-1β and TNF levels suggesting an important role for HDAC in regulating production of pro-inflammatory cytokines[31,32].**

3) Incubation of fibroblast-like synovial cells (FLS) from RA patients with phenylbutyrate, TSA and FK228 caused increased acetylation at the promoters of p16INK4 and p21CIP1, associated with increased expression of both these proteins indicates the involvement in HDAC inhibitors promoting cellular senescence in synovial fibroblasts[35].

**Corrected: Treatment of RA synovial fibroblasts (RASF) with phenylbutyrate, TSA and FK228 causes histone hyperacetylation at p16$^{INK4}$ and p21$^{CIP1}$ promoters associated with expression of these two proteins which involved in the reduction of RASF numbers [35].**

4) An age-associated increase in methylation at the OP-1 promoter has been shown and combined with the finding that the demethylating agent, 5-azacytidine, causes an increase is OP-1 production demonstrates that this might be a mechanism contributing to age related cartilage loss in osteoarthritis[37].

**Corrected: Osteogenic protein-1 (OP-1) is a potent anabolic growth factor for articular chondrocytes, an aging-related increase in OP-1 promoter methylation that leads to decreased expression may contribute to cartilage loss seen with aging and in particular with the progression of osteoarthritis in older adults[37].**

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