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► **To cite this version:**

Jessy Pr sumey, Gabriel Courties, Louis-Marie Charbonnier, Virginie Escriou, Daniel Scherman, et al.. Targeted delivery to inflammatory monocytes for efficient RNAi-mediated immuno-intervention in auto-immune arthritis. 6th european workshop on immune-mediated inflammatory diseases, Nice, France. BioMed Central, 9 (Suppl 2), pp.P38, 2011. <inserm-00643966>

HAL Id: inserm-00643966

<http://www.hal.inserm.fr/inserm-00643966>

Submitted on 23 Nov 2011

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POSTER PRESENTATION

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Targeted delivery to inflammatory monocytes for efficient RNAi-mediated immuno-intervention in auto-immune arthritis

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From 6th European Workshop on Immune-Mediated Inflammatory Diseases
Nice, France. 23-25 November 2011

Inflammatory mouse Ly6C^{high} monocyte subset and its human counterpart, defined as CD14⁺ CD16⁻, represent a valuable cellular target for innovative immunotherapeutic strategies against immune-mediated inflammatory disorders (IMID). However, delivery systems able to differentially target both subsets in vivo are still missing as well as demonstration for efficient immuno-modulation. The present work aims at providing evidences for the selective delivery of a siRNA-containing lipid formulation to the Ly-6C^{high} monocyte population and at evaluating the therapeutic potential of targeting this subset as well as their human counterpart for immuno-intervention in a prototype IMID like rheumatoid arthritis (RA). The pre-B-cell colony enhancing factor (PBEF/visfatin/Nampt) is an essential enzyme in the NAD biosynthetic pathway that exerts a key role in the persistence of inflammation through the induction of the expression of the TNF- α and IL-6 pro-inflammatory cytokines and is highly expressed in patients with a variety of IMID. Mice with collagen-induced arthritis (CIA) display Ly-6C^{high} monocytosis in the circulation that infiltrate into the inflamed joints. The systemic delivery of siRNAs formulated with the cationic liposome DMAPAP provides specific and functional down-regulation of PBEF within inflammatory monocytes. Moreover, decreased production of the PBEF-induced pro-inflammatory cytokines TNF- α and IL-6 was evidenced in both mouse and human inflammatory monocytes. PBEF gene silencing within Ly-6C^{high} monocytes resulted in reduced disease severity in mice

with CIA, associated with an overall systemic immuno-modulation of the effector T cell balance. These results identify PBEF as a critical target to modulate autoimmune responses and inflammation in arthritis and provide novel evidence that silencing of a master gene within inflammatory monocytes is a promising strategy for future therapeutic intervention in the context of IMID.

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Published: 23 November 2011

doi:10.1186/1479-5876-9-S2-P38

Cite this article as: Présumey et al.: Targeted delivery to inflammatory monocytes for efficient RNAi-mediated immuno-intervention in auto-immune arthritis. *Journal of Translational Medicine* 2011 **9**(Suppl 2):P38.

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