8. Towards novel therapeutic strategies

A158 TOWARDS GENE THERAPY FOR THE TREATMENT OF RHEUMATOID ARTHRITIS: PRODUCTION AND BIOACTIVITY OF INTERFERON β IN FIBROBLAST-LIKE SYNOVIOCYTES TRANSDUCED WITH ADENO-ASSOCIATED VIRUS TYPE 5 EXPRESSING HUMAN INTERFERON β

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10.1136/ard.2010.149013.1

Background and objectives The authors are developing local intra-articular gene therapy for the treatment of rheumatoid arthritis (RA) using human interferon β (hIFN β) as therapeutic gene expressed under control of an inflammation-inducible promoter and recombinant adeno-associated virus type 5 as vector (ART-I02). To evaluate hIFN β expression by ART-I02 and bioactivity, fibroblast-like synoviocytes (FLS) from RA patients and different animal species were transduced with ART-I02 and the culture medium was analysed. Since most RA patients in their future phase I trial will be on methotrexate (MTX) treatment, the authors investigated the influence of MTX on transduction efficacy.

Methods Primary human, monkey, mouse and rat and non-primary rabbit FLS were transduced with ART-I02 (MOI 200.000). To activate the nuclear factor- κ B promoter, cells were stimulated with tumour necrosis factor (TNF) (1 ng/ml) with or without interleukin 1 β (IL-1 β) (10 ng/ml) 4 or 24 h post-transduction. In addition, human FLS were incubated in medium with MTX (10 nM, 1 μ M, 100 μ M) added pretransduction and post-transduction. Supernatants were harvested 48 h after stimulation. Production of hIFN β was measured by ELISA. Bioactivity was established by analysing the effect on pro-inflammatory cytokine (IL-6, IL-8) and matrix metalloproteinases (MMP) production by ELISA and with a quantitative gene reporter bioassay.

Results Human IFN β production was detectable in supernatants of FLS of all species, with comparable levels in human and monkey FLS. In human FLS transduced with ART-I02, the inhibition of IL-8 (80%) and MMP3 (60%) secretion was most pronounced after stimulation with TNF 24 h after transduction ($p < 0.05$). IL-6 production was significantly ($p < 0.05$) reduced by hIFN β in cells stimulated with both TNF and IL-1 β . Monkey FLS expressing hIFN β showed a 40% decrease in IL-8 secretion ($p < 0.01$) after stimulation with TNF. No effect of hIFN β on cytokine and MMP secretion was observed in rabbit and rodent FLS. Human IFN β produced by both human and monkey FLS showed robust levels of bioactivity in the gene reporter bioassay. MTX treatment did not influence hIFN β production by ART-I02 or bioactivity.

Conclusion Transduction of FLS with ART-I02 resulted in significant hIFN β expression in FLS of all species. Moreover, hIFN β produced by ART-I02-transduced cells is bioactive in human and monkey FLS. This study supports the use of non-human primates in a non-clinical pharmacology-toxicity programme and represents a next step towards a phase I clinical trial in RA patients.