

**A144 TREATMENT OF COLLAGEN-INDUCED ARTHRITIS WITH LENTIVIRAL BIP IMPROVES CLINICAL PARAMETERS OF DISEASE**

A M Shields, P H Wooley, S J Thompson, L S Klavinskis, G S Panayi, M Antoniou, V M Corrigan *School of Medicine, King's College London, UK*

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Rheumatoid arthritis (RA) is a chronic autoimmune disease manifesting primarily as an inflammatory polyarthritis of the synovial joints. Gene therapy has the potential to permit the

delivery of therapeutic genes specifically to sites of rheumatological pathology through the specific transfection or transduction of joint-trafficking cells or via transcriptional targeting, thus minimising systemic immunosuppression.

Immunoglobulin binding protein (BiP) is a 78 kD endoplasmic reticulum (ER) stress protein with multiple intracellular roles regulating the ER stress response. At times of stress, BiP may leave the cell and exert potent anti-inflammatory effects on myeloid lineage cells. When administered to mice with collagen-induced arthritis (CIA), recombinant human BiP (rhuBiP) protein can prevent arthritis when administered prophylactically and treat ongoing arthritis when administered therapeutically.

A clone of the murine (m) BiP gene was modified to remove the 3' KDEL ER localisation signal, facilitating protein secretion. The mutant mBiP gene was subcloned into ubiquitous-chromatin opening element (UCOE) enhanced mammalian expression vectors and protein synthesised from permanently transfected 293T cells. mBiP produced in a mammalian expression system demonstrates similar biological activity to bacterially synthesised rhuBiP *in vitro*. Both proteins induce interleukin (IL)6 (rhuBiP vs mBiP – 153±51 pg/ml vs 63±18 pg/ml), tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) (rhuBiP vs mBiP – 162±21 pg/ml vs 148±19 pg/ml) and interferon (IFN)  $\gamma$  (rhuBiP vs mBiP – 562±177 pg/ml vs 204±65 pg/ml) from naïve DBA/1 splenocytes after 24 h of stimulation.

HIV-1 based lentiviral vectors containing the mBiP gene were generated for *in vivo* gene delivery in the CIA model. The lentiviral mBiP vector (Lenti mBiP) was active *in vivo*, evidenced by profound antibody responses against the transgene. Lenti mBiP significantly reduced the mean number of arthritic paws in treated mice (2.6±0.3 vs 1.5±0.4 in control vs Lenti mBiP treated animals,  $p>0.05$ ) and demonstrated a trend towards reductions in clinical (6.1±0.6 in control vs 3.7±1.2 in Lenti mBiP-treated animals) and histological scores when mice were treated intraperitoneally with 10<sup>7</sup> infectious viral particles at arthritis onset. The mechanisms underlying the suppressive effect of Lenti mBiP remain unclear; preliminary studies have shown that PPD-induced surface upregulation of CD86 on CD11b<sup>+</sup> monocytes is inhibited in Lenti mBiP compared with control-treated animals (31.5±1.5% vs 48.5±3.6%).

These promising preliminary data suggest that gene therapy using the stress protein BiP is a novel and efficacious therapeutic modality for the treatment of RA.