

**J. Am Soc Nephrol (2007) Abstracts. In press. (peer reviewed)**

**Chemokine-targeted macrophage depletion ameliorates experimental mesangioproliferative glomerulonephritis.**

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Under the modulation of the CCL2/CCR2 chemokine/receptor axis, activated supernumerary macrophages and T cells play a pivotal role in the decline of organ function and tissue damage in a wide range of renal diseases. Studies of human renal diseases have shown that CCL2 expression is induced in renal cells and leukocytes whereas the cognate receptor CCR2 appears restricted to infiltrating macrophages and some T cells. Several leukocyte depleting agents were found to be efficacious in a number experimental renal disease models. The differential expression of CCR2 in disease and the fidelity of its ligand make it an attractive and selective therapeutic target for the use in a leukocyte-depleting strategy. To this end we designed a fusion protein (OPL-CCL2-LPM) which combines CCL2 as the targeting moiety with the ribosome inactivating protein enzyme (RIP) A1 domain of shiga holotoxin. The CCL2 portion binds specifically to CCR2-bearing leukocytes and is internalized, where the RIP inhibits protein synthesis resulting in cell death. *In vitro* RIP activity and cell-targeted cytotoxicity assays confirmed the bioactivity of OPL-CCL2-LPM. The fusion was tested in a model of Anti-Thymocyte Serum (ATS)-induced mesangioproliferative glomerulonephritis. Male rats were injected with ATS on day 0 and treated intravenously with vehicle, 50 or 100µg/kg of the recombinant protein Q2D from day 2 until day 8. Urine and blood collections were made prior to ATS injection and on days 5 and 9. Animals were sacrificed on day 9. No treatment related effects on body weight or signs of clinical toxicity were observed. Urine protein levels were decreased in treated animals. Histopathological analyses of kidney sections revealed maximum reductions of 31, 36, 24, and 30% for glomerular lesions (H&E), macrophage count (ED-1), fibronectin and α-smooth muscle actin, respectively. The latter two proteins are markers for extracellular matrix synthesis and mesangial cell activation, respectively. These results indicate that OPL-CCL2-LPM was safe and had a significant renal-protective effect in this model of nephritis.