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Chemokine regenerative therapy for chronic fibrotic kidney disease: translational studies

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Chronic Kidney Disease (CKD) is a common, progressive disease that afflicts both human and veterinary patients with a higher prevalence in women than men. The underlying pathology is chronic tubule-interstitial fibrosis, irreversible, and has no cure. There is a marked shortage of transplantable kidneys. Widespread clinical use of tissue engineered kidneys or cell therapy for CKD is years in the future. The goal of this study is to test the use of the cell-signaling chemokine CXCL12 on restoration of kidney structure and function in both a preclinical cat model of renal fibrosis and in a pilot study using cats with naturally-occurring CKD.

Preclinical Study**:** Adult female cats with established ischemia/reperfusion (I/R) - induced renal fibrosis were used to test the effects of intra-renal injection of 100, 200, or 400 ng (n=6/dose) of CXCL12 on renal structure in the affected kidney. Baseline blood/urine renal function tests were performed at the time of I/R Injury, Day 42, Day 70 (Treatment Injection), and then monthly for 4 months post-injection. Necropsies were performed and tissues harvested for histological evaluation. I/R increased collagen content and increased collagen fiber width in the affected kidney. Both the mid and high doses of CXCL12 restored kidney collagen content and collagen fiber width in the I/R kidney ($p<0.05$ vs. untreated). Because only one kidney was damaged, only minimal changes could be detected in BUN, creatinine, or urine specific gravity (USG) ($p>0.05$).

Field Study**:** Fourteen cats with clinical Stage 2 CKD were divided into Control vs.Treatment group. Treated cats received the 200 ng dose of CXCL12 in both kidneys using ultrasound guidance. Baseline blood/urine renal tests were performed prior to injections and repeated monthly for 12 months. CKD staging, serum creatinine, SDMA (symmetric dimethylarginine), and USG were measured. Bilateral intra-renal injection of CXCL12 using ultrasound guidance in cats with CKD was feasible and safe in a general practice clinical setting with no obvious side effects noted during the follow-up period.

Successful testing of this regenerative approach would introduce a potential novel therapy to treat chronic fibrotic kidney disease that affects both animals and humans that would be easy to administer, cost effective, and readily available to patients in a variety of geographic and economic situations.

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