Selected Renal Cells Improve Function in a Canine Model of Chronic Kidney Disease

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INTRODUCTION | BACKGROUND

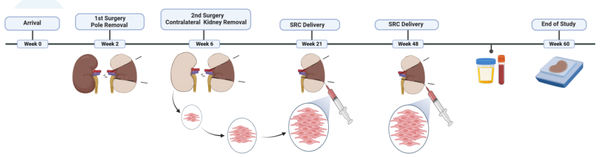
- Selected renal cells (SRCs) manufactured from rodent, canine and human kidney biopsies express renal reparative and restorative markers including *cdh1*, *cubn*, *neph*, *epo*, and *pecam*[1]
- In rodent models of chronic kidney disease (CKD) cortical administration of SRCs[2-5] is associated with
  - restoration of renal microarchitecture
  - extended survival
  - preservation of both glomerular and tubular functions

GOAL

To evaluate the effects of autologous SRCs (REACT®/rilparencel) in a clinically relevant, canine model of CKD

METHODS

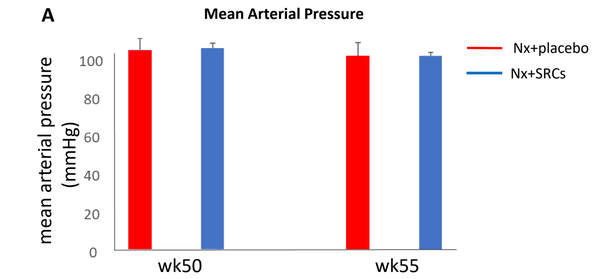
Canine Model of Sub-total Nephrectomy (Nx)

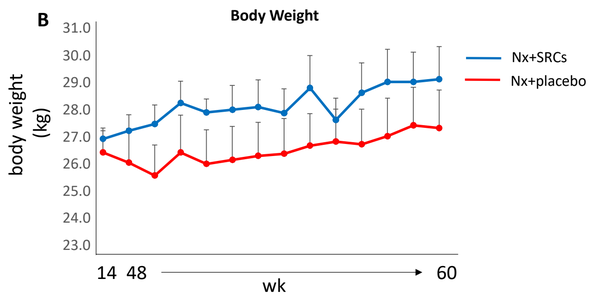


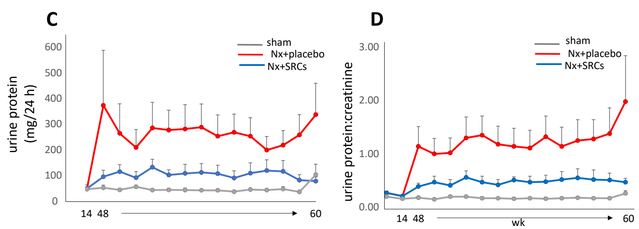
- Study protocol (# 09-10-262) approved by the Medical College of Georgia (Augusta, GA); study conducted under supervision of the institutional veterinarian
- Male, age-matched (>24 mo old) mongrel canines subjected to 2-step 70% Nx procedure (weeks 2 and 6)[6] and fed a high protein and high NaCl diet
- SRCs prepared from the excised, contralateral kidney and delivered (5 mL DPBS; $6x10^6$ cells/g tissue; n=4 canines) via a flank incision to the cortex of the remnant kidney at weeks 16 and 48 after renal polar ablation. The Nx+placebo cohort (n=4 canines) was administered DPBS. A sham cohort comprised surgically intact canines (n=2)
- Canines were weighed, and blood samples and 24 hr urines (metabolic cages) collected weekly. Creatinine clearance (CrCl) was determined using the formula urine creatinine x urine volume / serum creatinine. Mass-adjusted CrCl was determined by multiplying CrCl with body mass[7]. Post-randomization CrCl and mass-adjusted CrCl were plotted as difference from pre-randomization. Radiotelemetry was used to collect data on systolic and diastolic blood pressures and mean arterial pressure calculated
- At sacrifice (week 60), kidneys were retrieved for histopathologic analyses. Evaluation of Masson's trichrome-stained remnant kidney parenchyma was performed using light microscopy and by an observer blinded to the treatment groups. Histological sections were graded on a worsening severity 0-4 scale[8]
- Data are expressed as mean±standard error of mean. Treated vs. placebo differences were analyzed by one way analysis of variance followed by Scheffe's post hoc test. Correlation between various variable were plotted and fitted using MS-Excel, the Pearson product moment, r, calculated and its p-value determined. A p<0.05 was considered statistically significant

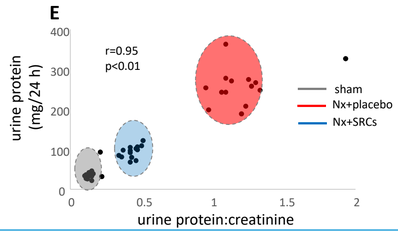
RESULTS

- In this canine model of CKD accompanied by progressive renal impairment, intervention with SRCs was associated with
  - no change in mean arterial pressure
  - increased body weight
  - improved urine protein levels, urine protein:creatinine profiles and serum albumin profiles
  - An improved creatinine clearance profile
  - preservation of glomerular and tubular microarchitecture

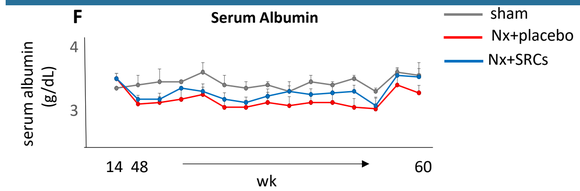


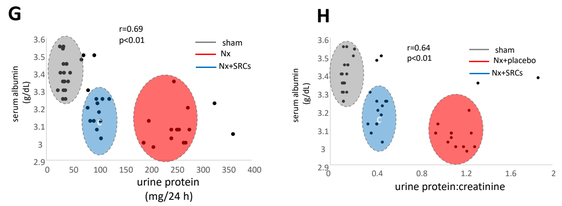


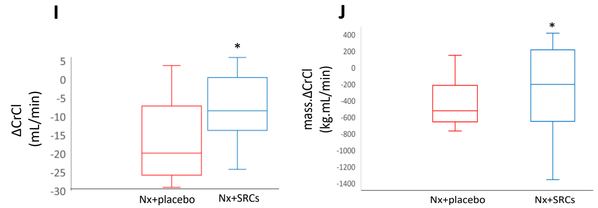


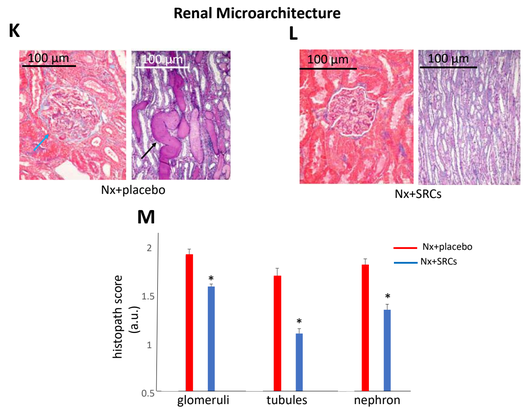


RESULTS CONTD.









A. There was no effect of SRCs on hemodynamics. B. Increased body weight was observed in the Nx+SRCs cohort ($p < 0.01$ vs. Nx+placebo). C-E. Compared to the sham cohort, Nx+placebo canines exhibited an increase in 24-hr urine protein and urine protein:creatinine levels ($p<0.01$ vs. sham). Treatment with SRCs was associated with improvement in these profiles ($p<0.01$ vs. Nx+placebo). Urine protein vs. urine protein to creatinine ratio revealed a robust direct correlation and distinct clustering of cohorts. F-H. Serum albumin was reduced in the Nx+placebo cohort ($p<0.01$ vs. sham) whereas treatment with SRCs was associated with an improved serum albumin profile ($p<0.01$ vs. Nx+placebo). Inverse correlation, and cohort clustering were found between serum albumin and urine protein, and urine protein to creatinine ratio. I, J. Compared to the Nx+placebo cohort, treatment with SRCs was associated with a reduced decline in CrCl and mass adjusted CrCl through the evaluation period ($p=0.03$). K-M. Representative Masson's trichrome-stained sections of renal parenchyma from Nx+placebo and Nx+SRC cohorts. Glomerular hypertrophy (blue arrow) and deposition of tubular casts (black arrow), inflammation and scarring observed in the Nx+placebo cohort are markedly reduced in the Nx+SRCs cohort (*, $p<0.01$ vs. Nx+placebo)

DISCUSSION

- This is the first report describing interventional benefit with autologous SRCs in a clinically relevant, canine model of CKD
- In canines submitted to Nx, treatment with SRCs was associated with improvements in multiple readouts of renal filtration and improved renal glomerular and tubular microarchitecture absent any hemodynamic change
- External validation of SRC activity in a clinically relevant model of CKD
- These results are consistent with expression of reparative and restorative markers by SRCs[1], a standalone autologous cell-based platform for therapeutic intervention in CKD

CLINICAL STATUS

- Preliminary data[9-10] from patients with advanced diabetic kidney disease (CKD Stage 3A-4) suggest that administration of SRCs (REACT®/rilparencel) is associated with preservation of kidney function
- REACT®/rilparencel is currently being evaluated in a global Phase 3 registration trial[11] for treatment of CKD and has been awarded Regenerative Medicine Advanced Therapy Designation by Food and Drug Administration

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