

# Protocol and Baseline Data on Renal Autologous Cell Therapy Injection in Adults with Chronic Kidney Disease Secondary to Congenital Anomalies of the Kidney and Urinary Tract

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## Keywords

CAKUT in adults · Chronic kidney disease · Autologous cell therapy · Preliminary data

## Abstract

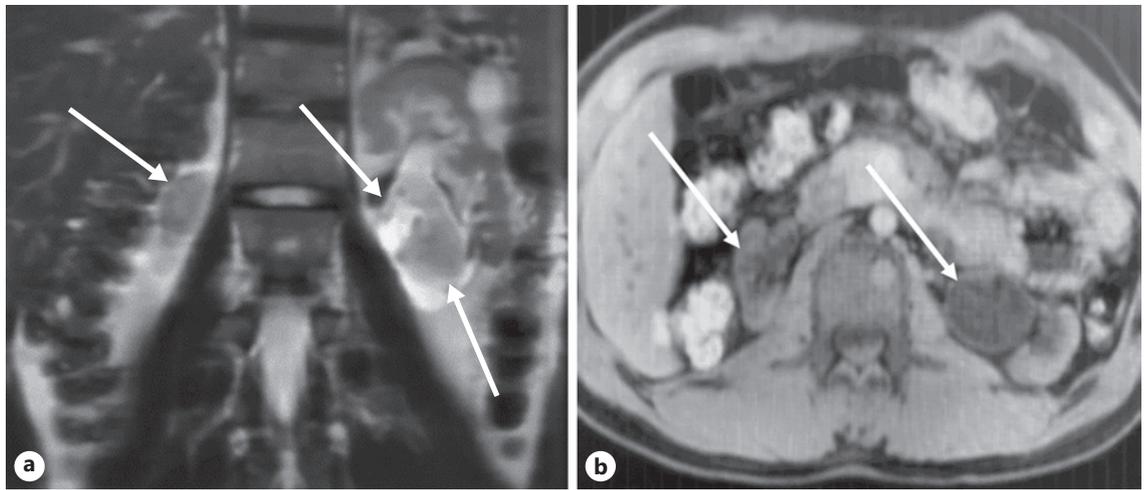
**Background:** Advanced cell therapies with autologous, homologous cells show promise to affect reparative and restorative changes in the chronic kidney disease (CKD) nephron. We present our protocol and preliminary analysis of an IRB-approved, phase I single-group, open-label trial that tests the safety and efficacy of Renal Autologous Cell Therapy (REACT; NCT 04115345) in adults with congenital anomalies of the kidney and urinary tract (CAKUT). **Methods:** Adults with surgically corrected CAKUT and CKD stages 3 and 4 signed an informed consent and served as their “own” baseline control. REACT is an active biological ingredient acquired from a percutaneous tissue acquisition from the patient’s kidney cortex. The specimen undergoes a GMP-compliant manufacturing process that harvests the selected renal cells composed of progenitors for renal repair, followed by image-guided locoregional reinjection into the patient’s renal cortex. Participants receive 2 doses at 6-month intervals. Primary outcomes are stable renal function and stable/im-

proved quality of life. Additional exploratory endpoints include the impact of REACT on blood pressure, vitamin D levels, hemoglobin, hematocrit and kidney volume by MRI analysis. **Results:** Four men and 1 woman were enrolled and underwent 5 cell injections. Their characteristics were as follows: mean 52.8 years (SD 17.7 years), 1 Hispanic, 4 non-Hispanic, and 5 white. There were no renal tissue acquisition, cell injection, or cell product-related complications at baseline. **Conclusion:** REACT is demonstrating feasibility and patient safety in preliminary analysis. Autologous cell therapy treatment has the potential to stabilize or improve renal function in CAKUT-associated CKD to delay or avert dialysis. Patient enrollment and follow-up are underway.

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## Introduction

The global prevalence of chronic kidney disease (CKD) is approximately 10% of the population, with regional and race/ethnicity differences. The most common etiologies of CKD among adults are diabetes, hypertension, glomerular disease, and less commonly congenital anomalies of the kidney and urinary tract (CAKUT). CAKUT



**Fig. 1.** CAKUT MRI: coronal T2 and axial T1 (a, b) weighted MRI shows dilated central collecting system and asymmetric development of the left kidney with thinning of the lateral cortex (arrows). The right kidney is atrophic with a large bowel filling at the renal fossa. Renal volume obtained from the left kidney to determine dose. CAKUT, congenital anomalies of the kidney and urinary tract; MRI, magnetic resonance imaging.

is the most common cause of pediatric-onset CKD, accounting for approximately 50% of cases [1, 2].

CAKUT is the result of a spectrum of defects in the kidneys and outflow tracts which include the ureters, bladder [3], and urethra, and the prevalence of CAKUT has been estimated to be 4–60 per 10,000 births, depending on the registry with some ethnic differences [4]. CKD is a condition with unidirectional progression to end-stage renal disease (ESRD). In the USRDS, adolescents with ESRD have a 10-year survival of >85% [5].

While patients with CAKUT experience slower CKD progression compared to those with glomerular disease [6], ESRD usually occurs in adolescence and young adulthood. While the survival rate of children with ESRD has improved, mortality remains about 30 times higher than that of healthy peers [5]. In the USA, young adult patients with ESRD die due to cardiovascular causes primarily [7, 8], with greater mortality in black patients [9].

Multiple therapies have entered the developmental trial pipeline for CKD; however, most target biochemical or genetic markers for various disease pathways [9–13]. Advanced cell therapies with autologous, homologous cells have shown promise to affect reparative and restorative changes in the CKD nephron and improve glomerular-tubular function in animal data [13] and phase I and ongoing phase II trials in adult diabetic patients with CKD. This manuscript describes our protocol trial and a preliminary analysis of a phase I single-group open-label trial testing the safety and efficacy of Renal Autologous Cell

Therapy/Neo-Kidney Augment (REACT™; NCT 04115345) among adults with CAKUT-related CKD.

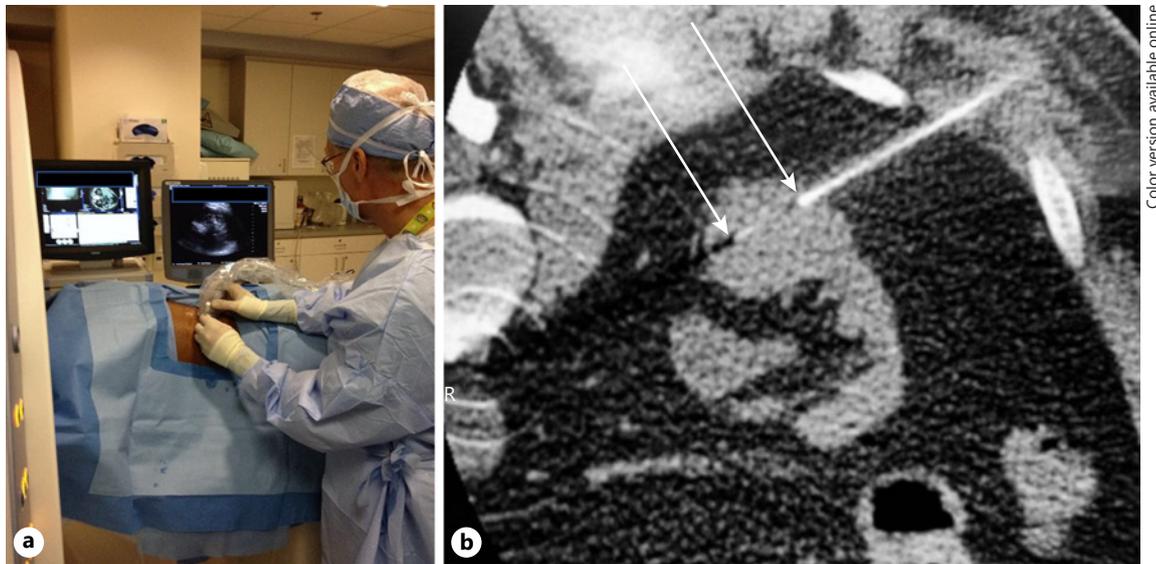
## Methods

### Intervention

The active biological ingredient of REACT is acquired from a percutaneous tissue acquisition from the patient's kidney cortex. The kidney tissue undergoes a Good Manufacturing Practices-compliant process that harvests the selected renal cells (SRC) composed of progenitors for renal repair. Cells are held frozen in liquid nitrogen for future use. Prior to reinjection, SRCs are formulated in a thermolabile gelatin-based hydrogel concentration of  $100 \times 10^6$  cells/mL and injected into the kidney cortex of the donor, with a volume-based dose determined by a noncontrast magnetic resonance imaging (MRI) volumetric analysis of the kidneys (Fig. 1). CAKUT parenchyma and collecting system anatomy is heterogeneous, and optimum injection sites are determined by ultrasound and CT to ensure precision placement in the cortex region (Fig. 2). The cell integration process postinjection into the patient is depicted in Figure 3. Following the REACT injection, the patients return for serial clinical visits and laboratory measurements. Participant timeline from trial entry and tissue acquisition through REACT manufacturing and reinjection is depicted in Figure 4. The patients receive 2 doses administered at 6-month intervals, and each patient serves as their "own" control.

### Patients

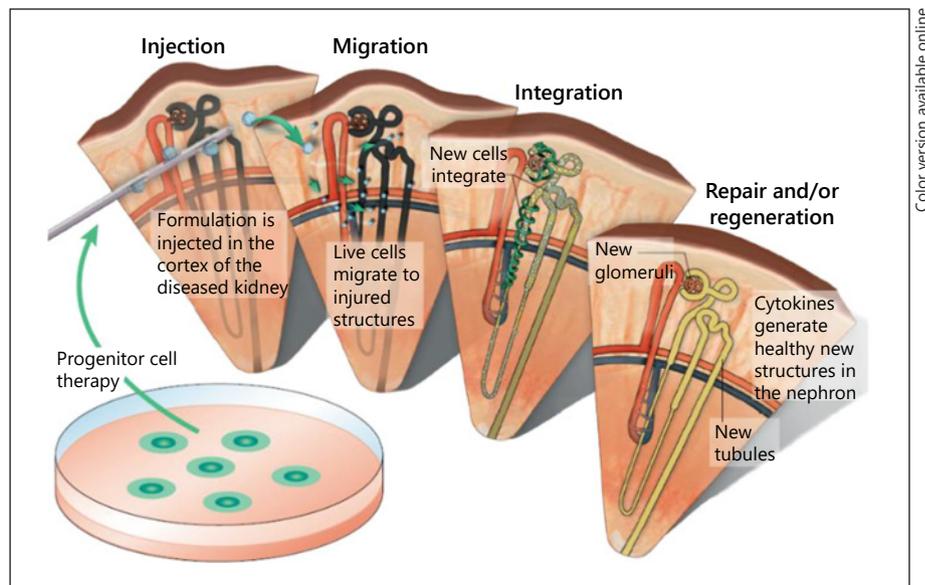
The recruitment goal is 15 subjects. Major inclusion criteria include females or males aged 18–65 years with a documented history of a surgically corrected CAKUT and an estimated glomerular filtration rate (eGFR) of 14–50 mL/min/1.73 m<sup>2</sup> at the time of



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**Fig. 2. a** Cell injection: percutaneous CT and ultrasound-guided needle insertion into the renal cortex assures precision delivery of REACT and allows real-time evaluation of injection-related complications. **b** Axial CT image shows heterogeneous CAKUT morphology with needle system entering the capsule and cortex area

for autologous cell injection (arrows). The small diameter needle platform reduces risks of bleeding and pain. REACT, Renal Autologous Cell Therapy; CAKUT, congenital anomalies of the kidney and urinary tract.

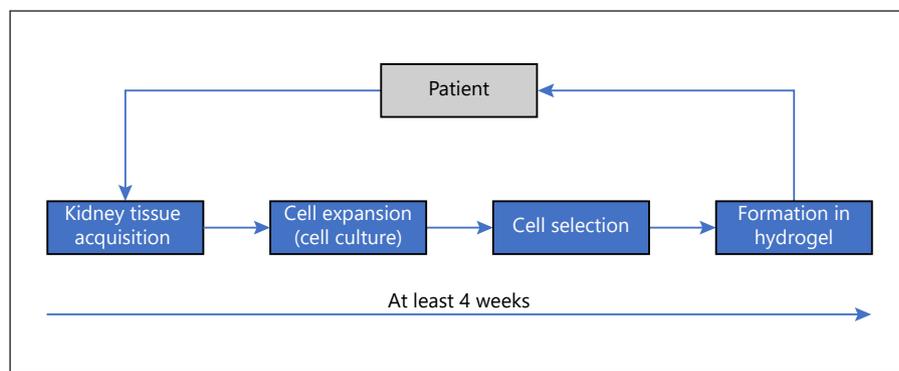


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**Fig. 3.** Autologous cell mechanism of action: cell restoration occurs following REACT injection into the cortex by chemotactic migration to the damaged nephron unit, including tubules in the medullary kidney. Integration into the glomerulus and tubules ensues with cytokine-mediated repair of renal function. (Figure used with permission from *Nature*.) REACT, Renal Autologous Cell Therapy.

screening [14]. These patients' CKD 3/4 must not require dialysis or transplant and must have a defined rate of CKD progression over 24 months with at least 3 eGFR measurements >3 months apart. In terms of clinical parameters, the patients should have blood pressure levels <150/90 mm Hg, ability to refrain from antiplatelet medications and NSAID therapy, and safe bleeding parameter levels for renal interventions (tissue acquisition and cell injections).

Major exclusion criteria are a history of renal transplantation, grade 4-5 hydronephrosis, uncorrected vesicoureteral reflux (VUR), thinned renal cortex disallowing safe biopsy and cell injection, acute kidney injury in last 3 months, allergy to hydrogel formulation constituents, recent urinary tract infections, renal tumors, and cysts or other anatomic masses. Contraindications also include significant medical problems (cardiac, pulmonary, or hepatic conditions), immunocompromised, and pregnancy.



**Fig. 4.** Subject timeline from trial entry and tissue biopsy through REACT manufacturing and reinjection. REACT, Renal Autologous Cell Therapy.

The primary endpoints are improved renal function based upon change in eGFR total slope by CKD-EPI and serum creatinine measurements and incidence of adverse events out to 24 months postinjection. Additional exploratory endpoints are the impact of REACT™ on urinary protein, blood pressure, vitamin D levels, hemoglobin and hematocrit, and kidney volume assessed by MRI.

## Results

We have enrolled 5 patients to date with the following baseline characteristics: 1 woman and 4 men; 5 Caucasians (1 Hispanic and 4 non-Hispanic); mean age 52.8 years (SD 17.7 years; range 22–60 years). The cause of CKD included VUR in all, and one of the men had surgically corrected posterior urethral valves. Comorbidities and their characteristics include the following: all had hypertension and 3 had hyperlipidemia. The woman in our cohort had a mildly elevated baseline blood pressure at 144/88, and all men were normotensive. The cohort's mean estimated glomerular filtration rate by CKD-EPI was 29.5 (range 19–35) mL/min/1.73 m<sup>2</sup>. The mean quality of life score was 81.25 (range 75–100). The mean kidney weight based on MRI measurements was 154 g (SD 72.35 g; range 95–272 g). The mean calculated volume for injection was 2.3 mL (SD 0.91, range 3–8 mL). Six depositions were injected in the 5 patients, as one of the cohorts required 2, with a mean injection volume of 2.3 mL/deposition (SD 0.91 mL; range 1.5–3.5 mL). The mean sedation time was 44.2 min (SD 34.7 min; range 20–105 min), and the mean injection time was 19.6 min (SD 18.61 min; range 7–56 min).

The 5 enrolled patients showed an adequate cortex thickness of >5 mm for safe left-sided kidney tissue acquisition and reinjection on screening ultrasound and MRI. There was normal cell isolation and expansion for

each patient, and 6 cell injections were completed. There have been no biopsy, injection, or cell product-related acute or chronic complications.

## Discussion

In this report, we have documented the feasibility and safety of using REACT, an autologous cell therapy, as a potential cell-based treatment that may durably stabilize renal function in CAKUT-associated CKD. The potential to delay or avert dialysis remains to be demonstrated after long-term follow-up is completed.

CAKUT is diagnosed most often prenatally or during pediatric years with crossover implications into later adulthood. The risks for CKD progression include the onset of comorbidities such as metabolic syndrome, hypertension, and cardiovascular disease [15]. Despite the traditional categorization of patients with CAKUT as being “nonglomerular,” glomerular-tubular changes have been described [16].

CAKUT is a complex renal disease presenting with a broad spectrum of heterogeneous phenotypes and mono- and polygenetic etiologies that may cause long-lasting parenchymal scarring and nephropathy [3]. Despite surgical correction of the gross collecting system abnormality, these patients may progress to ESRD. While there are few histopathological studies in CAKUT patients, renal parenchymal changes, glomerular changes, overt tubule-interstitial changes, and fibrosis is noted to occur with tubule-interstitial or reduction in proximal tubule size [16].

Based on our experience with animal histopathological effects [17], we moved to address the CAKUT population in humans. There is a significant unmet need for clinical strategies to improve renal function and delay the

need for renal replacement therapy in progressive CKD [15].

This current trial uses a percutaneous, image-guided techniques with conscious sedation. The phase I trial of high-risk CKD diabetics who were injected with REACT used a laparoscopically assisted surgical approach and general anesthesia [18]. Furthermore, the cell-based therapeutic could be administered (mean eGFR <30 mL/min) safely in a small cohort [17]. Ongoing phase II clinical trials are exploring additional safety and efficacy (NCT02836574 and NCT03270956) in stage 3-4 diabetic CKD and provide a platform for autologous cell therapy adaptation in additional CKD etiologies.

CAKUT patients are good candidates for autologous kidney cell therapy to stabilize CKD progression or improve it. Following the REACT injection, there is chemotaxis-regulated migration of cells with integration into the glomerular-tubular unit and rebuilding of cellular elements that restore renal function [13], as depicted in Figure 3. Using autologous/homologous cell therapies for CKD has several advantages. In this therapy, the kidney cells that repair and restore nephron structure and function can be effectively expanded in vitro with Good Manufacturing Practices and maintained for future use, with liquid nitrogen preservation. Regardless of the CKD etiology, the kidney late-stage pathology leads to chronic inflammation and fibrosis with damage to glomeruli and tubules.

Potential complications such as radiation exposure during cell injections are rare due to current dose-reduction strategies with focused imaging of the kidneys and awareness of ALARA (As Low As Reasonably Achievable) algorithms. Other complications such as bleeding are avoided by our strict inclusion criteria for anticoagulation assessment that avoids patients at risk for bleeding and use of atraumatic needles in areas of minimal vascular risk in the kidney. No transfusions have been required postprocedure. Sedation in all patients was well tolerated.

REACT is “accepted as self” by the patient, with no identified immunologic and cell transformation consequences. REACT’s active biological ingredient is known to survive in analogous environments from the donor kidney, with a half-life of 6 months. Cell administration methods into the kidney are easily standardized and reproducible with precision placement into the renal cortex using image-guided techniques and small caliber needles to maximize cell deposition in a favorable environment. Procedural injection risks are low and performed in outpatient settings with conscious sedation.

## Conclusions

REACT is demonstrating good feasibility and patient safety at baseline and preliminary analysis. Autologous cell therapy is a novel treatment and has the potential to stabilize renal function in CAKUT-associated CKD and delay or avert dialysis. Patient enrollment is underway.

## Acknowledgements

The authors would like to thank their participants for teaming with them to move this evidence forward and advance this field.

## Statement of Ethics

This trial has been censored by Institutional Review Board approval and participant informed consent.

## Conflict of Interest Statement

Diaz-Gonzalez de Ferris: grants and research support Renal Research Institute, ProKidney. Joseph Stavas, Tim Bertram, Ashley Johns, and Deepak Jain are employees of ProKidney.

## Funding Sources

This research trial is privately funded solely by the sponsor ProKidney. Joseph Stavas, Tim Bertram, Ashley Johns, and Deepak Jain are employed by the sponsor ProKidney. Maria Diaz-Gonzalez de Ferris is a consultant of the sponsor ProKidney.

## Author Contributions

Drs. Stavas, Jain, Diaz-Gonzalez de Ferris, and Bertram and Ms. Johns have made substantial contributions to the conception of the manuscript and drafting and revision of content, agreed to be accountable for accuracy and result interpretation, and approved the final version for publication.

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