Gene Therapy: Treating the Transplanted Kidney and Beyond

The goals for gene therapy are becoming both more ambitious and yet more practical as the field matures. The field will show continued advances in 2012.

In one line of research in mice, gene therapy shows promise in delivering agents that cannot be given systemically—either because of side effects or poor pharmacokinetic properties—to reduce chronic transplant dysfunction.

In the early days, researchers envisioned replacing defective genes to completely cure hereditary diseases, efforts that have largely come up short. But meanwhile, less heroic strategies have been progressing, using genes to treat symptoms, or provide short-term therapy rather than a long-term cure. If there is a near-term role for gene therapy in renal disease, it may be of the latter kind, according to Leo Deelman, PhD, director of clinical research for Stanford University’s Division of Nephrology and chair of the ASN’s Comparative Effectiveness Task Force. Randomized clinical trials, seen as the gold standard, have historically excluded chronic kidney disease patients and often do not reflect the “real world” of everyday clinical practice.

In contrast, CER methods focus on trials done in normal settings with larger, more diverse populations, and compare “usual care” groups (instead of the typical placebo group) with groups receiving interventions.

Several research projects exemplify the spirit of CER by using clinical or common-munity settings and testing new strategies against usual care, said Ebony Boulware, MD, associate director for the Welch Center for Prevention, Epidemiology, and Clinical Research at Johns Hopkins. These research projects include a nurse coordinated care model, a computerized drug-alternation program, and a randomized trial for erythropoiesis-stimulating agent (ESA) treatment in nondialysis chronic kidney disease.

Systematic reviews also fit under the CER umbrella. Steve Brunelli, a nephrologist and renal epidemiologist at Brigham and Women’s Hospital, analyzed the past year’s many studies focusing on dialysis. Many asked more questions than they answered. This year will likely see more studies designed to clarify best practices for dialysis patients in modality and access choice, timing of treatment initiation, and management of infections and comorbidities.

Watch for news from the Patient-Created Outcomes Research Institute (PCORI) this year. Created through an appropriation in the Affordable Care Act, PCORI is unique in that, although federal monies were appropriated, it acts as a private foundation, and sets priorities and raises money through a Board of Governors. While not directly funding CER, PCORI will be responsible for improving health care delivery through funding projects that help develop methodologies for CER to ultimately guide patients to make informed decisions based on “high integrity, evidence-based information,” said Neil Powe, MD, a member of the Institute of Medicine’s (IOM) Committee on CER Prioritization and vice chair of medicine at the University of California San Francisco.

Interest in this type of research is soaring. The first call for proposals in November 2011 received 1,400 applicants for 40 available awards. Hopes are high that this new organization will be able to take a focused patient and stakeholder-centered approach to refining, creating, and testing methods that can ultimately be used as practice models for CER.

Winkelmayer, Brunelli, and Powe all spoke about CER and its use in nephrology practice during the public policy sessions at Kidney Week 2011.

“Gene transfer could help, if we selectively express immunosuppressant molecules in the kidney to prevent rejection,” Deelman said. Delivery of the gene to the target organ has always been a major stumbling block for gene therapy, and so the transplanted kidney is, in some ways, an ideal gene therapy target, since it can be treated in isolation before implantation. If there is a near-term role for gene therapy in renal disease, it may be of the latter kind, according to Leo Deelman, PhD, assistant professor of medicine at the University of Groningen, the Netherlands. One strategy is to use gene therapy to provide local immune suppression for renal transplantation.

“Transplantation is the first choice for end stage renal disease,” Deelman said at Kidney Week 2011, “but it is associated with a lot of problems,” including rejection and acute lack of function. Early on, there is ischemia-reperfusion damage, contributing to loss of function and acute rejection. In the long term, nephron loss, inflammation, and fibrosis may occur, leading to chronic failure. “There are also side effects of systemic immunosuppressant therapy. Toxicity is a big problem.”

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“The problem he encountered is that the kidney is relatively poorly stocked with the cellular receptors that the virus binds to enter the cell. The solution, he found, was to modify the virus so that it binds to another receptor that is plentiful on kidney cells, increasing its uptake.

In an initial study meant to explore the potential of the gene transfer system, Deelman worked with mice in which the donor and recipient were the same strain, to minimize acute rejection. A kidney from the donor was removed and placed on ice, and then perfused with solution containing the virus, which carried a reporter gene. After 20 minutes, the kidney was washed with saline to remove excess virus, and then implanted in the recipient. He found that there was a high transfection rate, with intestinal fibroblasts expressing the transfected gene most strongly. Initial expression of the reporter gene was high, but dropped off after two weeks to only 7 percent of the original level. The kidney showed only mild levels of cytopathic lymphocytes, indicating the virus was tolerated reasonably well.

Next, Deelman introduced immunomodulator genes into the virus, and used mice of different strains for donor and recipient. He first tried the gene for interleukin-13 (IL-13), “a potent anti-inflammatory molecule,” which reduces proinflammatory cytokines and inhibits macrophage function. As part of the experiment, he compared gene therapy on the kidney alone to injection of the adenovirus intramuscularly into the recipient. “The aim was to see whether this local therapy with IL-3 was as effective as systemic therapy,” he said.

Local therapy led to high expression of IL-13 in the kidney at day 8 after transfaction, and some reduction of renal damage markers consistent with an immunomodulatory effect. The results were “similar or better than for intramuscular treatment,” he said. “Local gene therapy is a feasible alternative to systemic therapy.”

The second gene he tried was for 2,3-indoleamine dioxygenase, or IDO. IDO is the rate-limiting enzyme in the catabolism of tryptophan, and high expression depletes tryptophan. The enzyme is abundantly expressed in the placenta during pregnancy, and protects the fetus against rejection. It is also expressed in tumor cells, as a mechanism to escape the immune response. It inhibits naïve T cell proliferation and induces T cell apoptosis, while stimulating regulatory T cells. IDO has been used to prevent acute rejection in diverse organs, including skin, heart, and pancreatic islets, as well as to suppress airway inflammation.

“The aim was to determine whether gene therapy with IDO could have an effect on acute rejection of the transplanted kidney.” To test this, both kidneys in the recipient were removed before transplantation, in order to assess the function of the transplanted kidney alone.

The gene was expressed at high levels, and led to a “dramatic reduction” in plasma creatinine versus control, “and a complete normalization of kidney function.” Biomarkers of inflammation and renal damage were all lower in the treated mice, and there was less macrophage infiltration and less fibrosis. “This is really quite impressive,” Deelman said.

Deelman’s group is now examining IDO’s potential to reduce chronic transplant dysfunction. Their initial results indicate that at three months, treated mice have no proteinuria, lower blood pressure, and better body weight, compared to controls.

The long-term benefit was not due to continued expression of IDO, since, as before, gene expression was largely absent after two weeks. Instead, Deelman said, early treatment with IDO may protect cells from immune surveillance in the critical early period, or may induce tolerance. Whether local therapy will prove superior to systemic therapy in humans “remains to be shown,” Deelman said.