Learning from failure

By Lev Osherovich, Senior Writer

Transplanted kidneys live on borrowed time, with many grafts eventually succumbing to immune attack or recurrence of the original kidney disease. Now, a gene expression study by a Canadian team has identified a set of biomarkers associated with graft failures.¹ The findings are a big step toward unraveling why some patients lose their grafts and could help nephrologists adjust immunosuppressant regimens and anti-fibrosis therapies.

The findings have spurred the launch of **Transcriptome Sciences Inc.**, a new diagnostic services company. Meanwhile, **Stromedix Inc.** hopes to use the gene expression data to help interpret the effects of its fibrosis drug candidate.

The presentation and progression of kidney graft failure can vary from person to person, noted Philip Halloran, lead author of the study and university professor and director of the Transplant Applied Genomics Center at the **University of Alberta**. The team also included researchers from **The University of Arizona** and the **University of Minnesota**.

"Some people have recurrence of disease but it doesn't progress to graft loss," he said. "It's useful to know who will deteriorate. In some cases you might be able to adjust treatment to stabilize them."

"The dream is to get patients very early in the course of graft loss or even in advance of it, then to identify the patients who will have a rapid course of disease," said Stromedix CEO and founder Michael Gilman.

Better than protein

To look at the molecular details of graft failure, Halloran's team collected kidney biopsies from 105 transplant patients who were showing signs of graft rejection. Of these patients, 30 quickly progressed to graft failure during the subsequent 32 months.

The group used microarrays to compare gene expression from patients who quickly progressed to failure with that from patients whose initial signs of rejection appeared to be held in check. The analysis identified a set of 409 genes that were significantly overexpressed in failed grafts compared with grafts that survived ($p < 0.0001$). Among these was a set of 30 genes whose expression collectively predicted the likelihood of graft failure.

The researchers then used this subset of genes and levels of expression to assign a graft loss risk score to each biopsy and to another set

of kidney biopsies independently gathered by the collaborators at the University of Minnesota. High-risk scores proved more effective at predicting graft loss than conventional clinical markers for graft failure such as increased protein levels in the patient's urine.

Halloran hopes to develop a microarray-based diagnostic using the findings, which were published in *The Journal of Clinical Investigation*. To do so, his team next needs to validate the gene expression index in a prospective trial.

He also hopes to improve the test's predictive power for biopsies taken shortly after transplantation.

The diagnostic IP in the study is exclusively licensed to Transcriptome Sciences, which is a spinout of the University of Alberta.

Dean Zaragoza, VP of business development at Transcriptome and business development associate at the university's technology transfer office, said the gene expression data are only a part of the picture Transcriptome hopes to provide to clinicians.

"We initially envisioned this as a stand-alone diagnostic product used in the lab to predict graft loss," he said. "But it's not as simple as a molecular profile. We need to use a number of clinical and molecular parameters, including histopathology and antibody data, to provide a comprehensive readout. Now we are on a service model where we provide the readings and diagnostic services."

Zaragoza said the company is still working out the specific parameters for the diagnostic. Transcriptome plans to seek venture financing within a year.

Surrogate markers

The longer-term value of the study may be in identifying proteins upregulated in failing kidney grafts that could be targeted to slow down graft loss. On this front, Stromedix has been collaborating with Halloran's team to understand the cascade of events leading to fibrosis in transplanted kidneys.

Stromedix's STX-100, a mAb against integrin $\alpha_v\beta_6$ licensed from **Biogen Idec Inc.**, is in Phase IIa testing for chronic allograft nephropathy.

According to Gilman, Halloran's study points to genes downstream of integrin $\alpha_v\beta_6$ activation as major players in graft loss.

Integrin $\alpha_v\beta_6$ is a cell surface receptor that "is expressed on epithelial cells at low levels in healthy tissue but is dramatically upregulated in injured tissue in the kidney, lung, liver and other specialized epithelia," said Gilman. Aside from integrin $\alpha_v\beta_6$ itself, many of the genes picked up in Halloran's profile were tissue injury response factors and cytokines that are activated by the receptor.

"Integrin $\alpha_v\beta_6$ is among our top genes," said Halloran. "It could be targeted by antibodies, so there's a potential for intervention."

Halloran's studies jibe well with Stromedix's internal work that "allowed us to identify a transcriptional gene signature that we believe represents integrin $\alpha_v\beta_6$ -regulated genes," said Gilman.

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—Michael Gilman, Stromedix Inc.

He added that Stromedix has validated many of the genes upregulated in Halloran's studies in mouse models of kidney fibrosis and plans to monitor the gene set in the upcoming Phase IIa trial of STX-100.

In principle, blocking integrin $\alpha_v\beta_6$ with a mAb should turn off many of the genes identified in Halloran's study. Preselecting patients with greater expression of integrin $\alpha_v\beta_6$ and its downstream effectors may improve the odds of a successful trial of STX-100, Gilman told *SciBX*.

"In our Phase IIa trial, the endpoints are safety and tolerability as well as gene expression," he said. "We will biopsy before and after STX-100 treatment to see if we can intervene to normalize gene expression. The real question, though, is whether this will help the patients."

Gilman said that showing a correlation between outcomes and the gene expression profile might also allay concerns about larger-scale interventional trials for kidney graft loss.

"Data like these reduce the risk of future investment," said Gilman.

"Here's a gene signature with correlation to graft failure. If we know that our drug impacts that signal, it will be easier to write the check for a Phase III trial."

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