A Novel Cellular Therapeutic Approach to Replacing Toxic Immunosuppressive Drugs in Kidney Transplantation

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A recognized leader in transplantation and immunology, Dr. Chandraker is currently working on alternatives to immunosuppressive drugs currently used to prevent rejection of transplanted organs. His innovative approach is able to suppress the immune system response to a transplant without causing non-specific immunosuppression.

While kidney transplantation is usually viewed as a successful treatment, long term transplant survival has not greatly improved in many years and kidney transplant patients often require multiple transplants. The situation is even more critical for other types of transplants; median survival for a lung transplant, for example, is around 6 years. Immunosuppressive drugs needed to sustain transplants increase the risks of cancer, infection, heart disease and toxicity to the kidney (Fig 1).

Cellular therapy with T-regulatory cells (Tregs) is a promising strategy to control immune responses and restore immune tolerance in a variety of immune-mediated diseases, such as transplant rejection and autoimmunity. Multiple clinical trials are currently testing this approach, typically by using polyclonal Tregs that have been expanded prior to transplantation. However, evidence from animal models of Treg therapy has clearly shown that antigen-specific Tregs are vastly superior to polyclonal cells. Another disadvantage of the polyclonal approach is that it is essentially limited to living donation, which excludes the majority of kidney transplant recipients as well as recipients of other organs such heart, lung, pancreas and most liver transplants.

We have developed an approach that entails expanding donor antigen specific T regulatory cell enriched lines (ASTRLs) from human kidney transplant recipients. These ASTRLs can be expanded ex vivo using donor specific peptides (Fig 2). ASTRLs have been shown to significantly prolong transplant survival in a kidney transplantation animal model and demonstrate 'linked suppression' while preserving the immune system's ability to respond to infections and cancer (Fig 3). The goal is to use ASTRLs to decrease reliance on conventional immunosuppression. This approach has several advantages compared to competing technologies; it is relatively inexpensive, less complex, applicable to all types of transplants and may have application in autoimmune diseases.

We have advanced pre-clinical studies, solid IP, and are now transitioning the work from academic discovery to NewCo formation. We are working on pre-IND studies and targeting completion of our Phase I kidney trial by mid 2023.

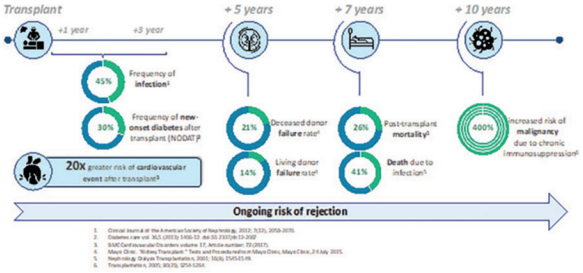

Figure 1. Current immunosuppression is the Achilles heel of transplantation. Lack of precision leads to serious toxicities and poor survival outcomes. Critical to balance immunosuppression to prevent rejection and maximize safety.

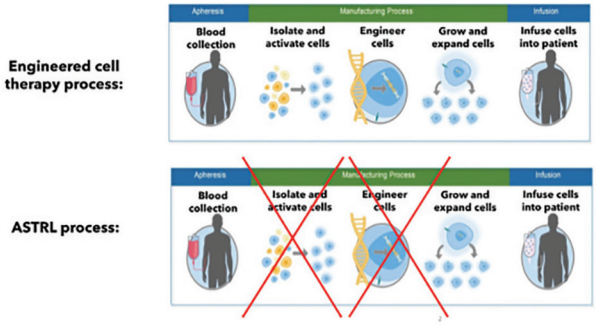

Figure 2. ASTRL manufacturing is simpler than engineered cell technologies. No cell sorting or engineering creates time and cost efficiency.

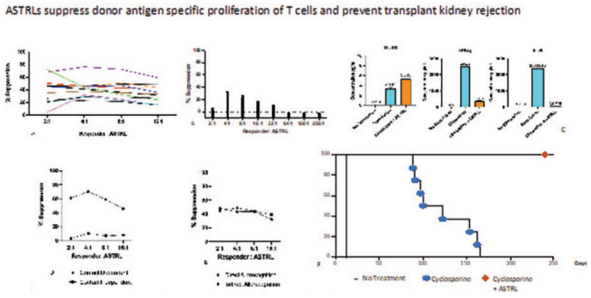

Figure 3. A.) ASTRLs from patients suppress donor antigen specific proliferation of T effector cells. B.) One ASTRL cell can suppress many T cells. C.) Inflammatory cytokine production is reduced by ASTRLs. D.) Suppressive ability of ASTRL is contact dependent. E.) ASTRL manufactured with one donor antigen suppress all donor antigen responses. F.) ASTRL prolong transplant survival in a rat kidney transplant model.