

Transplantation Tolerance Through Therapeutic Cell Transfer: Where Do We Stand?

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I have financial relationship(s) with: Novartis – Grant Support Regenerex – Grant Support Astellas – Speakers Bureau Veloxis – Speakers Bureau TRACT Therapeutics - Founder

<u>AND</u>

My presentation includes discussion of the investigational use of FCRx, a cell based therapy being developed by Regenerex LLC, and TregCel, a cell therapy being developed by TRACT Therapeutics



10 Years Graft Survival after Kidney Transplant Living Vs. Deceased donor



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Tolerance

A state of fully functional graft in the absence of immunosuppressive treatment.

Allograft Survival without the need for drugbased immunosuppression in the absence of a deleterious allogeneic immune response

Auchincloss H Jr. Am J Transplant 2001;1:6–12.

Why is the pursuit of tolerance so compelling?

- Better control of the immune system: potential for "one organ transplant for life"...
- Financial Costs
- Compliance ... pediatric patients



 Better long term patient survival if IS can be discontinued



Adapted from Levitsky J. *Liver Transpl.* 2011;17(3):222-32.

Billingham, Brent and Medawar

In 1953 published on actively acquired tolerance to foreign cells in *Nature*:



Used neonatal injections of donor hematopoietic and lymphoid cells.

The injected mice developed sustained <u>chimerism</u>, defined as persistence of donor hematopoietic cells in the recipient

Adult mice failed to reject skin grafts from the donor strain while rejecting third-party skin grafts . Loss of chimerism resulted in the loss of immune tolerance.

Relevant questions regarding chimerism and tolerance

Is establishment of durable chimerism <u>sufficient</u> to achieve clinical transplantation tolerance?

Is establishment of durable chimerism <u>necessary</u> to achieve clinical transplantation tolerance?

Does the end justify the means?

Can we identify biomarkers in chimeric, tolerant subjects that would predict operational tolerance in others?

Early Strategies To Achieve Clinical Transplantation Tolerance Based Upon The Use Of Donor-Derived Cells

Donor specific blood transfusions: Developed in the 1970s; often led to better renal allograft acceptance in well matched D/R pairs but sensitization in often in others.... Recent data suggesting dynamic immune regulation (Tregs) plays a role (Claas et al)

Donor derived bone marrow/HSC: Monaco et al (1976), Barber (1991) show reduced rates of acute rejection and improved early allograft survival; Ciancio et al (2001) – reduced chronic rejection with bone marrow infusion in cadaver kidney recipients – direct immunoregulatory effects of bone marrow (Miller J & Mathew J et al, multiple refs)

Operational Tolerance in Solid Organ Transplant Recipients

Deliberate IS withdrawal versus "Russian Roulette" (patient noncompliance)

Trials of IS withdrawal somewhat successful in liver transplant recipients – tolerogenic effect of the liver allograft? Has not been translatable to other solid organs

Operational tolerance as a dynamic process based upon immune regulation versus elimination of alloreactivity (clonal deletion).



Identifying Transplant Recipients with Operational Tolerance



Functional assays: donor specific hyporesponsiveness – MLR, Elispot Signatures of tolerance: proteomics, genomics, immunophenotypic analyses

Retrospective data in very few subjects – no prospective validation Little confirmation with histology in the allograft

Stability of signature over time?

Prospective trials currently being planned (Immune Tolerance Network, CTOT)

Third International Workshop For Clinical Tolerance

September 8th-9th, 2017 Stanford University



Current Interventional trials for tolerance induction

Center	HLA	Protocols	n
MGH	Match	Full or mixed chimerism(for myeloma kidney)	10
	Mismatch	Mixed (transient) chimerism	12
Stanford	Match	Mixed chimerism	29
	Mismatch	Mixed chimerism	23
Northwestern	Match	Alemtuzumab and donor HSC infusion	20
	Mismatch	Durable chimerism	42 enrolled 37 transplanted
	Mismatch Mismatch	Durable chimerism Regulatory T cells (TRACT)	42 enrolled 37 transplanted 9
Johns Hopkins	Mismatch Mismatch Mismatch	Durable chimerism Regulatory T cells (TRACT) Full chimerism	42 enrolled 37 transplanted 9 1
Johns Hopkins Sam Sang University (South Korea)	Mismatch Mismatch Mismatch Mismatch	Durable chimerism Regulatory T cells (TRACT) Full chimerism Mixed chimerism	42 enrolled 37 transplanted919

Major Hurdles in Applying mismatched HSC to Solid Organ Transplant

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•••



- Conditioning
- GVHD
- Engraftment
- Donor/Recipient HLA Disparity

MGH



*rituximab added in subjects 4-10 Day -7, -2

Kawai et al. *N Engl J Med. 2008;358(4):353-61.* Kawai et al. N Engl J Med. 2013; 368(19):1850-2. Kawai et al. *Am J Transplant.* 2014 ;14:1599-611.

MGH

10 haplotype matched kidney/HSCT subjects

- 9 of 10 exhibited "ENGRAFTMENT SYNDROME" at week 2
 - Capillary leak syndrome
 - Elevated creatinine (mean 7.6 ± 4.4 mg/dl)
 - Fluid retention
 - Acute tubular injury
 - Interstitial edema
 - Hemorrhage

Farris et al, *Am J Transplant* 2011; 11(7): 1464-1477

MGH (HLA mismatched)

Results

10/10 Transient mixed chimerism (< 21 days)

- 7/10 Taken off IS
- 4/7 Remain off IS for 5-12 years

5/10 C4d+ staining on biopsies

3/7 Back on IS at 5, 7 and 8 years due to chronic rejection or recurrent disease

Stanford



Stanford HLA-Matched Protocol Current Status

29 transplanted

24 mixed chimeras withdrawn from immunosuppression

- > 23 without subsequent rejection (up to 9 years)
- > 1 developed acute rejection at 4 years off drug
- > 8 of the 23 have not lost mixed chimerism
- > 15 of the 23 lost mixed chimerism after year 1
- 5 did not achieve mixed chimerism

Maintained on immunosuppression

1 recent graft loss to recurrent disease (SLE)

1 failing graft due to what is probably recurrent membranous

Medeor Therapeutics advancing approach into Phase 3 trial

Stanford HLA Mismatched Tolerance Induction: Summary

HLA Haplotype-Matched Protocol (N=23)

- No immune graft loss
- Increase proportion of pts with sustained mixed chimerism at 1 year with T cell dose escalation
- Minimization of immunosuppression to low dose tacrolimus monotherapy is possible
- Immunosuppression-independent chimerism with complete withdrawal of immunosuppression not yet <u>achieved</u>

Clinical tolerance trials Northwestern Transplant Center

- Simultaneous kidney/HSC in HLA mismatched related and unrelated recipients (FCRx)
- Sequential kidney/HSC in HLA-matched related recipients

 Adoptive therapy with Treg adoptive cell transfer (TRACT) in living donor kidney transplant recipients (Phase 1)

Hypothesis:

Use of a bioengineered donor derived HSCT (FCRx) with low intensity conditioning will allow for the establishment of <u>durable donor macrochimerism</u> and donor specific tolerance, with a minimal risk of GVHD



Chimerism and Tolerance Without GVHD or Engraftment Syndrome in HLA-Mismatched Combined Kidney and Hematopoietic Stem Cell Transplantation Joseph Leventhal *et al. Sci Transl Med* **4**, 124ra28 (2012); DOI: 10.1126/scitransImed.3003509

www.ScienceTranslationalMedicine.org 7 March 2012 Vol 4 Issue 124 124ra28

KIDNEY TRANSPLANT

Chimerism and Tolerance Without GVHD or Engraftment Syndrome in HLA-Mismatched Combined Kidney and Hematopoietic Stem Cell Transplantation

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The toxicity of chronic immunosuppressive agents required for organ transplant maintenance has prompted investigators to pursue approaches to induce immune tolerance. We developed an approach using a bioengineered mobilized cellular product enriched for hematopoietic stem cells (HSCs) and tolerogenic graft facilitating cells (FCs) combined with nonmyeloablative conditioning; this approach resulted in engraftment, durable chimerism, and tolerance induction in recipients with highly mismatched related and unrelated donors. Eight recipients of human leukocyte antigen (HLA)–mismatched kidney and FC/HSC transplants underwent conditioning with fludarabine, 200-centigray total body irradiation, and cyclophosphamide followed by posttransplant immunosuppression with tacrolimus and mycophenolate mofetil. Subjects ranged in age from 29 to 56 years. HLA match ranged from five of six loci with related donors to one of six loci with unrelated donors. The absolute neutrophil counts reached a nadir about 1 week after transplant, with recovery by 2 weeks. Multilineage chimerism at 1 month ranged from 6 to 100%. The conditioning was well tolerated, with outpatient management after postoperative day 2. Two subjects exhibited transient

The Facilitating Cell

• CD8+



- αβ/γδ TCR-
- Distinct from Stem Cell (HSC)
- Promotes engraftment
- Prevent GVHD
- Human FC Characterization: AJT 2016
- Immunomagnetic selection/enrichment for FC/HSC:FCRx
- FDA approval: IDE#13947

Simultaneous FCRx + Kidney Transplant NCT00497926

- Donor stem cell graft manipulated to enrich for facilitating cells (FC), which promote engraftment and reduce risk of GVHD
- Collaboration with Regenerex LLC/University of Louisville launched in 2006, Phase 2 trial ongoing since 2009
- 37 subjects transplanted (36 NMH, 1 Duke)

FCRx/FCR001

 FCR001 is an allogeneic somatic cell therapy product derived from mobilized peripheral blood cells collected from the donor by apheresis. The product contains a minimum of hematopoietic progenitor cells (CD34+), Facilitating Cells (CD8+/αβTCR-), and a specified number of αβ T cells.



* Recipients undergo autologous mobilized apheresis and cryopreservation for potential autologous rescue

Kidney + FCRx Trial Algorithm



Patient characteristics (n=37)

- Male/Female 30/7
- Age (Mean yrs) 39.2 (range 18-64)
- LURD 17
- LRD 20
- Re –Tx 2
- ESRD cause
 PKD 9; IgAN 7; Reflux 4; DM 3; HTN -3;
 Membranous 2; Chronic GN-3; Alports-2; FSGS 2;
 Unknown 2

FCRx trial to induce donor chimerism and tolerance:

- Durable chimerism established in 27 of 37 subjects; the majority (24/27) developed "full" (>98%) whole blood / T cell chimerism.
- 26/37 subjects fully weaned off of immunosuppression (5 93 months drug-free)
- Subjects with transient chimerism can be successfully weaned to monotherapy
- First successful demonstration of durable chimerism and tolerance in mismatched kidney transplant recipients
- <u>Chimeric subjects regain immune competence and undergo robust immune reconstitution</u> (<u>Transplantation 2015</u>); no evidence of immune defect ...
- Biomarkers in urine and biopsy identified in tolerant subjects (ATC 2017, JASN 2018)
- <u>Significantly better renal function and reduced rates of HTN/HLD at 3 and 5 yrs post-Tx in</u> tol subjects as compared to SOC matched subjects (ATC 2018, submitted)
- 2 graft losses related to post-transplant infections
- 2 cases of GVHD
- 2 deaths (steroid resistant GVHD/CMV (mo 11), lung cancer (yr 4.5)



Immune Reconstitution/Immunocompetence in Recipients of Kidney Plus Hematopoietic Stem/Facilitating Cell Transplants

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> Nineteen subjects have more than 18 months follow-up in a phase IIb tolerance protocol in HLA-mismatched recipients of living donor kidney plus facilitating cell enriched hematopoietic stem cell allografts (FCRx). Reduced intensity conditioning preceded a kidney allograft, followed the next day by FCRx. Twelve have achieved stable donor chimerism and have been successfully taken off immunosuppression (IS). We prospectively evaluated immune reconstitution and immunocompetence. Return of CD4⁺ and CD8⁺ T central and effector memory cell populations was rapid. T-cell receptor (TCR) Excision Circle analysis showed a significant proportion of chimeric cells produced were being produced de novo. The TCR repertoires posttransplant in chimeric subjects were nearly as diverse as pretransplant donors and recipients, and were comparable to subjects with transient chimerism who underwent autologous reconstitution. Subjects with persistent chimerism developed few serious infections when off IS. The majority of infectious complications occurred while subjects were still on conventional IS. BK viruria and viremia resolved after cessation of IS and no tissue-invasive cytomegalovirus infections occurred. Notably, although 2 of 4 transiently or nonchimeric subjects experienced recurrence of their underlying autoimmune disorders, none of the chimeric subjects have, suggesting that self-tolerance is induced in addition to tolerance to alloantigen. No persistently chimeric subject has developed donor-specific antibody, and renal function has remained within normal limits. Patients were successfully vaccinated per The American Society for Blood and Marrow Transplantation guidelines without loss of chimerism or rejection. Memory for hepatitis vaccination persisted after transplantation. Chimeric subjects generated immune responses to pneumococcal vaccine. These data suggest that immune reconstitution and immunocompetence are maintained in persistently chimeric subjects.

Features of Immune Reconstitution/Immune Competence in Chimeric Subjects

- Lineage reconstitution of memory T cell subpopulations, B cells, NK cells, and monocytes occurs within a year; naïve T cells up to 24 months, consistent with other published reports on allo-HSCT
- TCR repertoire diversity is comparable to pre transplant donors/recipients, not different than transiently chimeric subjects undergoing autologous reconstitution (97% is new and unique from pre-transplant donor/recipient)
- Persistence of pre-transplant immunity to childhood vaccines despite full donor chimerism; chimeric subjects can be safely and successfully vaccinated without loss of engraftment/tolerance
- No late serious opportunistic infections in chimeric subjects off of IS
- Majority of AE/SAE occurred while subjects still on IS

OK...But what about Graft Versus Host Disease?



GvHD Experience in FCRx Trial

- 2 cases of biopsy proven GVHD (Day 95 and Day 134 post-Tx)
- Both occurred in highly HLA mm LURDTx from multiparous female donors (4/6, 5/6)
- First case associated with CNI conversion for nephrotoxicity steroid responsive Grade 2 skin/GI GVHD. Associated GI CMV infection. Full resolution of acute skin/GI GVHD but development of grade 1-2 ocular/musculoskeletal GVHD... Pt remains off CNI and MMF.
- Second case of Grade 3 GI CMV/GVHD colitis, diagnosed late related to delayed reporting of symptoms with presentation to local non-transplant center hospital
- Treatment resistant, failed steroids and multiple 2nd/3rd line agents; associated GI CMV.
- At ~11 mo post-transplant, condition deteriorated with pulmonary process of undetermined etiology, ultimately developing septic shock which progressed to multi-organ failure and death

Patient Safety

- Low intensity conditioning well tolerated: integration of HD eliminates potential ESRD-related drug toxicities
- Post-transplant nadir period is brief (< 2 weeks) and easily managed on an outpatient basis ; limited need for blood product support
- Clinical interface with subjects is more robust than for SOC KTx
- Chimerism has been stable following IS withdrawal; no DSA, no allograft rejection. Peripheral blood chimerism represents a good noninvasive biomarker of tolerance

Optimization of FCRx Protocol: 2009-2017

- FCRx graft engineering
- Strict Adherence to Conditioning Regimen
- Exclusion of Highly Sensitized Subjects
- Enhanced Subject Follow-up
- Exclusion of Female > Male Gender MM in unrelated D/R pairs
- Weekly contact with subjects to ensure prompt reporting of any/all symptoms
- Overall Patient Survival: 94.6%
- Overall Death Censored Graft Survival : 94.3%

Tolerance is associated with improved renal function

Comparison of durably chimeric and transiently chimeric FCR001 with SOC (5 year Follow-up)						
Total Cohort	FCR001 n=37		SOC n=132			
Cohort reaching 5-year follow-up	n=19		n=132			
Survival	94.7%		93.2%			
Graft survival	88.8%		83.3%			
Sub-cohort+	Durably Chimeric (n=11)	Transiently Chimeric (n=5)	All			
eGFR (mean \pm SEM)	75.8 ± 5.55	65 ± 5.17	53.1 ± 1.98			
eGFR Chimeric vs. SOC (two tailed t - test)	p = 0.0017	p = 0.33	n/m			
BPAR	0	40%	34.8%			
Hypertension	18%	60%	82.8%			
Hyperlipidemia	9%	40%	43%			

SEM = Standard Error of Mean

⁺ = number of subjects with \geq 5 years of follow-up

Barriers to Entry:

Paradigm shift in patient management: "its simply too complicated to be practical in thousands of SOT recipients..."

Annual Number of Transplant Recipients in the US by Transplant Type

Transplant Surgery <u>Hematology/Stem Cell Transplant</u> Transplant Nephrology/Hepatology/Cardiology Infectious Disease Radiation Oncology Blood Center/Leukopheresis Nurse Coordinators/Mid Level Practitioners Immune Monitoring Laboratory

Multi-Disciplinary Approach to Combined SOT/HSCT

Regulatory T cells

Regulatory CD4+CD25+FoxP3+ T cells

- Derived from the thymus and/or peripheral tissues have been demonstrated to broadly control T cell reactivity.
- Control immune responsiveness to allo and auto antigens
- Contribute to operational tolerance in transplantation models
- Role in controlling inflammatory conditions

Tregs for Adoptive Cell Transfer (TRACT)

- Development of new therapies to minimize or eliminate the need for antirejection drugs and their associated morbidity is of great interest to the transplant community
- Research over the past two decades has highlighted the ability of specialized cells called regulatory T cells (Tregs) to control immune responses.
- Human Tregs can be isolated and expanded to large numbers while maintaining purity and potency
- Thus, the potential of therapeutic cell transfer using Tregs as an alternative, non-pharmacological mechanism to reduce or eliminate graft rejection is ready to be translated from the bench to the bedside

Potential ways of manipulating regulatory T cells in transplantation

Wood KJ and Sakaguchi S. Nat Rev Immunol. 2003 Mar;3(3):199-210.

The ONE Study Consortium

SCIENTIFIC **REP**CRTS

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OPEN A Phase I Clinical Trial with *Ex Vivo* Expanded Recipient Regulatory T cells in Living Donor Kidney Transplants

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There is considerable interest in therapeutic transfer of regulatoryT cells (Tregs) for controlling aberrant immune responses. Initial dinical trials have shown the safety of Tregs in hematopoietic stem cell transplant recipients and subjects with juvenile diabetes. Our hypothesis is that infusion(s) of Treqs may induce transplant tolerance thus avoiding long-term use of toxic immunosuppressive agents that cause increased morbidity/mortality. Towards testing our hypothesis, we conducted a phase I dose escalation safety trial infusing billions of ex vivo expanded recipient poly donal Tregs into living donor kidney transplant recipients. Despite variability in recipient's renal disease, our expansion protocol produced Tregs which met all release criteria, expressing >98% CD4+CD25+ with <1% CD8+ and CD19+ contamination. Our product displayed >80% FOXP3 expression with stable demethylation in the FOXP3 promoter. Functionally, expanded Tregs potently suppressed allogeneic responses and induced the generation of new Tregs in the recipient's allo-responders in vitro. Within recipients, expanded Treqs amplified circulating Treq levels in a sustained manner. Clinically, all doses of Treq therapy tested were safe with no adverse infusion related side effects, infections or rejection events up to two years post-transplant. This study provides the necessary safety data to advance Treg cell therapy to phase II efficacy trials.

Kidney transplantation is the treatment of choice for most causes of end stage renal diseases^{1,2}. While transplantation is effective in replacing the non-functional kidney, disparity between donor and recipient major histocompatibility antigens results in massive activation of the recipient's immune system that, if left unchecked, leads to subsequent rejection of the organ. To prevent this, patients must take immunosuppressive drugs (IS) for life, generally a combination of agents including a calcineurin inhibitor (CNI), and corticosteroids3-6. However, dependence on IS tempers the substantial benefit obtained from transplantation1-13. Specifically, CNIs are nephrotoxic, a side effect of significant concern in transplantation while steroids exacerbate osteoporosis and hyperlipidemia, and cause avascular osteonecrosis. Development of alternate therapies that help to minimize the need for lifelong immunosuppression, or to eliminate them entirely through the induction of tolerance, are therefore of great interest.

Regulatory CD4+CD25+T cells (Treg) derived from the thymus and/or peripheral tissues have been demonstrated to broadly control T cell reactivity14. Importantly, Tregs have been shown to control immune responsiveness to alloantigens and contribute to operational tolerance in pre-clinical transplantation models¹⁵⁻²⁰. Initial efforts to evaluate the therapeutic effects of Tregs in humans have focused upon stem cell transplant recipients in an effort to control graft versus host disease (GVHD) or to treat autoimmune diseases21-24. There have been

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Expansion and Profile of expanded Treg products

- (A) GMP expansion protocol. GM = growth medium
 (B) Cell Numbers in Treg products; bar = median (n=9).
- (C) Phenotyping Scheme for CD4+CD25+FOX P3+ cells.
- (D) Mean (±SD) expression of Treg (CD4, CD25 & FOXP3) and non-Treg (CD8, CD20 & CD127) markers (n=9).

Treg Percentage Change in Peripheral Blood of Phase 1 Expanded Treg Trial Patients

- All expanded cell products met release criteria
- There were no infusion related serious adverse events with <u>up to 5 billion cells per patient</u>
- Analysis of subjects shows a sustained increase in circulating Tregs following Treg infusion
- First in Human use of Tregs in de novo living donor kidney transplant recipients
- Have received FDA approval to conduct a Phase 2 trial
- <u>Pursuing grant funding and commercialization path</u> (TRACT Therapeutics Inc) to advance technology

- Pharmacologic inhibition of non-Tregs (mTOR, PI3K? inhibition)
- IL2 stimulation requirement
- Polyclonal vs. antigen-specific expansion?
 - Allo-specific B cells: as APCs? CD40L-activated?
 - Chimeric antigen receptors (CARs)?

Conclusions

- Long-term renal allograft survival is still an ongoing problem.
- Induction of immunological tolerance is a promising approach to avoid long-term immunosuppressive medication use.
- Where pharmacologic approaches to tolerance induction have been unsuccessful, cell based therapies show promise
- Long term follow-up is required to better assess the risk/benefit ratio of different cell therapy strategies.

Barriers to Entry 2

"I need to have a 5 star transplant program... its too risky to enroll my patients ..."

Continued advancement in our field demands "safe zones" for clinical innovation involving high risk/high reward interventional approaches

Conclusions

- Single center success needs multicenter validation: Phase 3 trial
- Need to develop approaches applicable to deceased donor transplantation
- Biomarkers for tolerance can provide opportunities in selecting and monitoring tolerance recipients.

DELAYED TOLERANCE FOR DECEASED DONOR TRANSPLANTATION

Deceased Donor Organ and Vertebral Body (VB) Procurement

VBM processing and cryopreservation for FCRx ? Expansion of HSC & FC...

SOT and Recovery

Elective Conditioning + FCRx Infusion

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Questions?