Potential Role of Regulatory Cell Therapies in Transplantation: Where are we Now?

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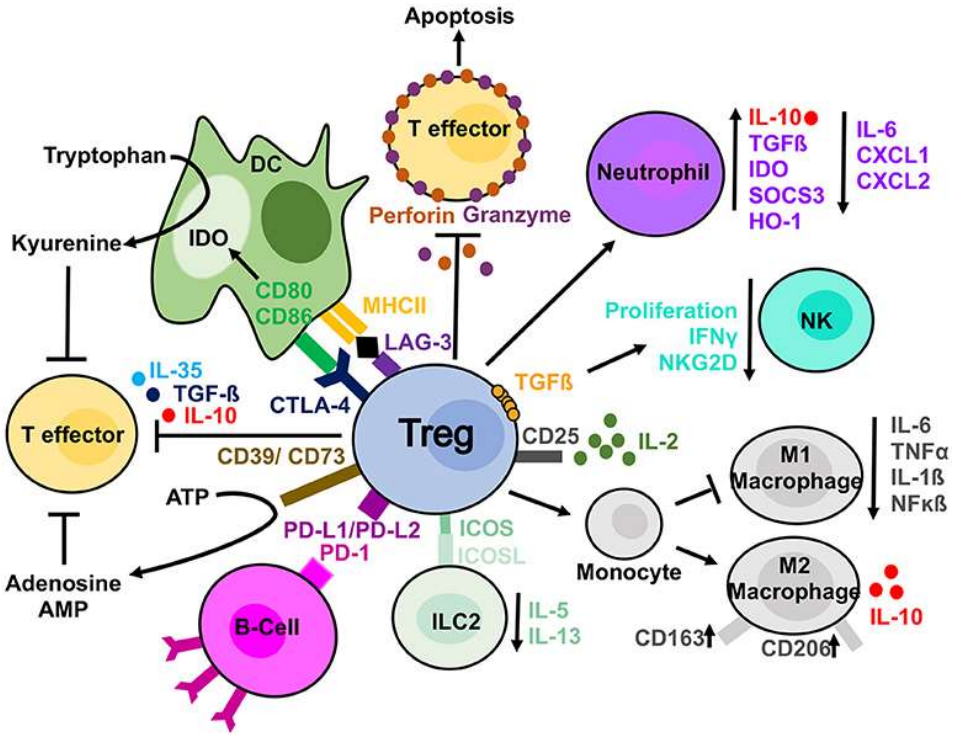
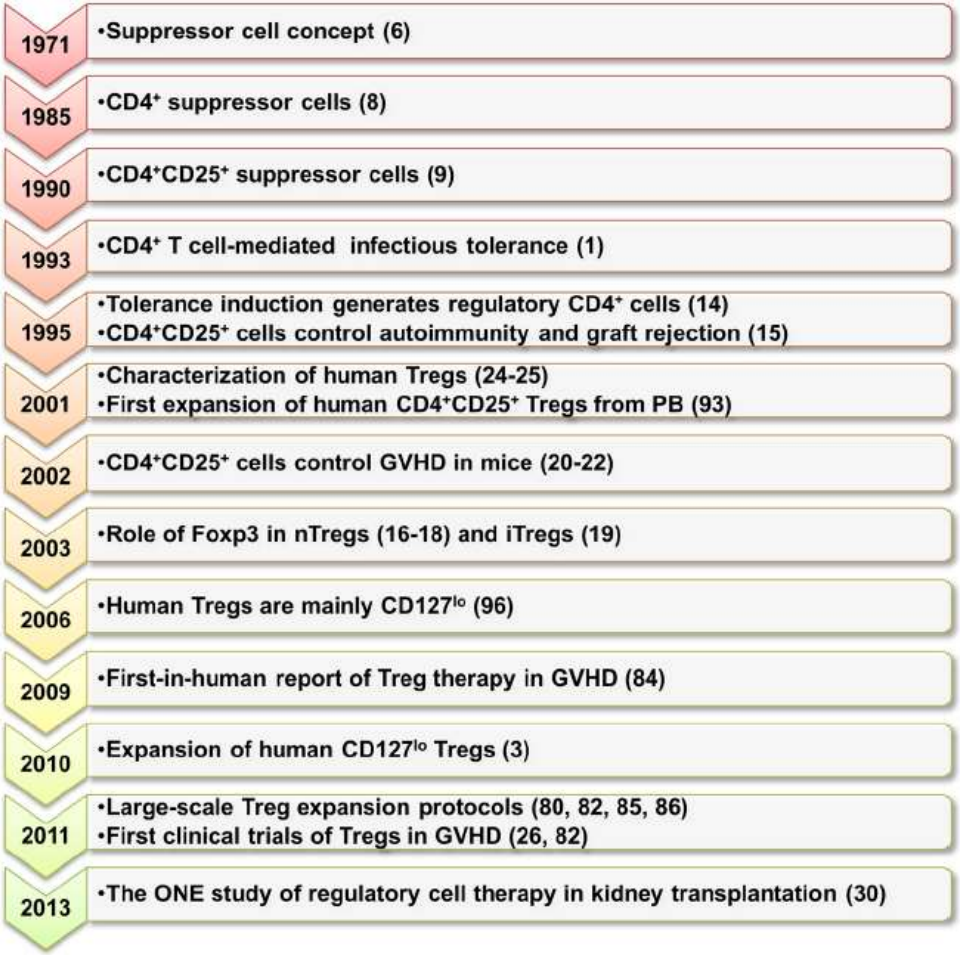
What are the main immunological challenges in transplantation?

- Non-specific immunosuppression
- Rejection – acute and chronic
- Poor long-term outcomes

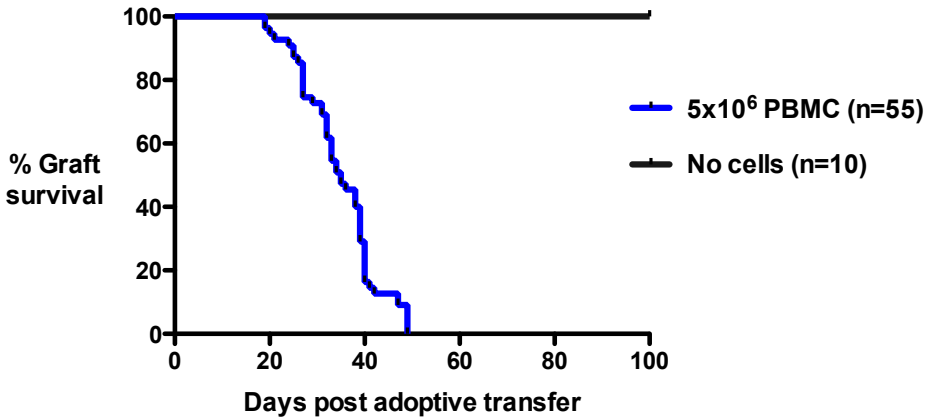
Regulatory T cells may be able to address these challenges

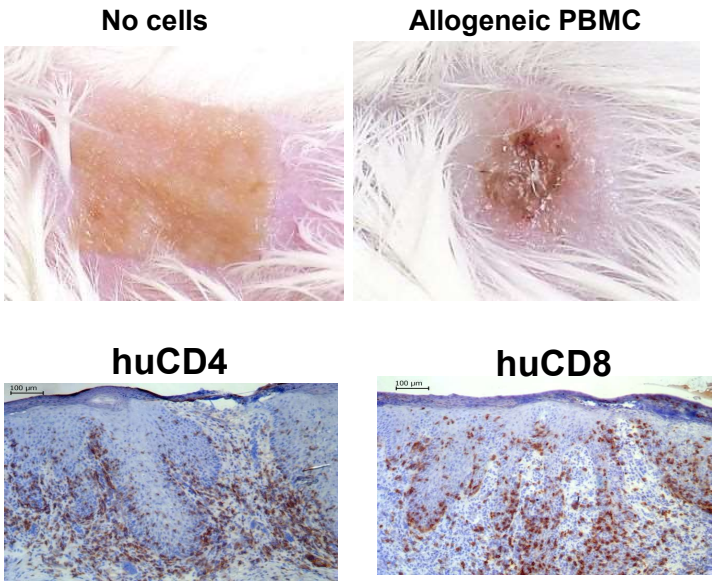


Romano et al. *Front Immunol* 2022


1971
•Suppressor cell concept (6)
1985
•CD4+ suppressor cells (8)
1990
•CD4+CD25+ suppressor cells (9)
1993
•CD4+ T cell-mediated infectious tolerance (1)
1995
•Tolerance induction generates regulatory CD4+ cells (14)
•CD4+CD25+ cells control autoimmunity and graft rejection (15)
2001
•Characterization of human Tregs (24-25)
•First expansion of human CD4+CD25+ Tregs from PB (93)
2002
•CD4+CD25+ cells control GVHD in mice (20-22)
2003
•Role of Foxp3 in nTregs (16-18) and iTregs (19)
2006
•Human Tregs are mainly CD127lo (96)
2009
•First-in-human report of Treg therapy in GVHD (84)
2010
•Expansion of human CD127lo Tregs (3)
2011
•Large-scale Treg expansion protocols (80, 82, 85, 86)
•First clinical trials of Tregs in GVHD (26, 82)
2013
•The ONE study of regulatory cell therapy in kidney transplantation (30)

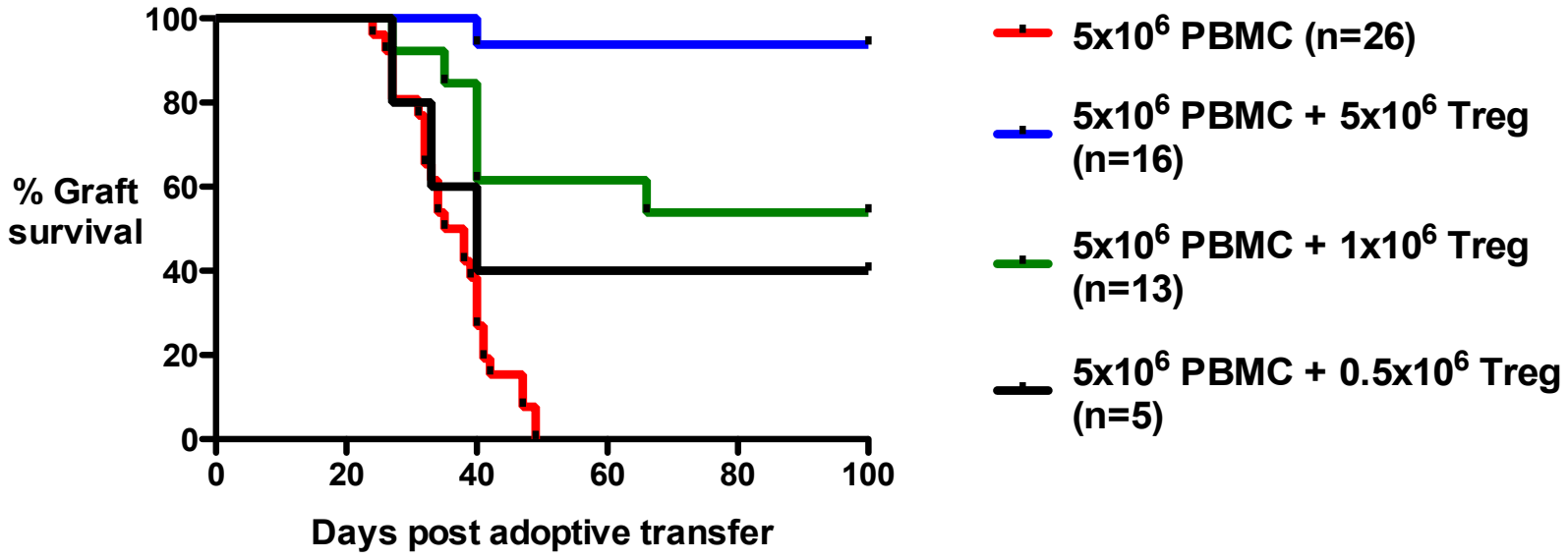
In vivo human alloimmunity model



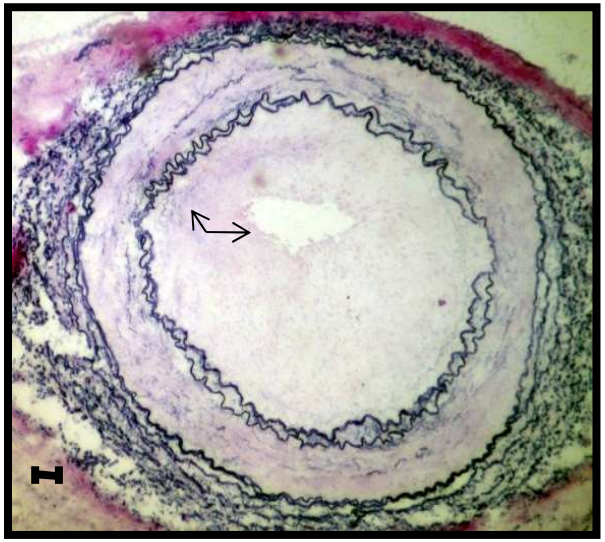


Issa et al. *Transplantation* 2012
Adigbli et al. *Transplantation* 2020

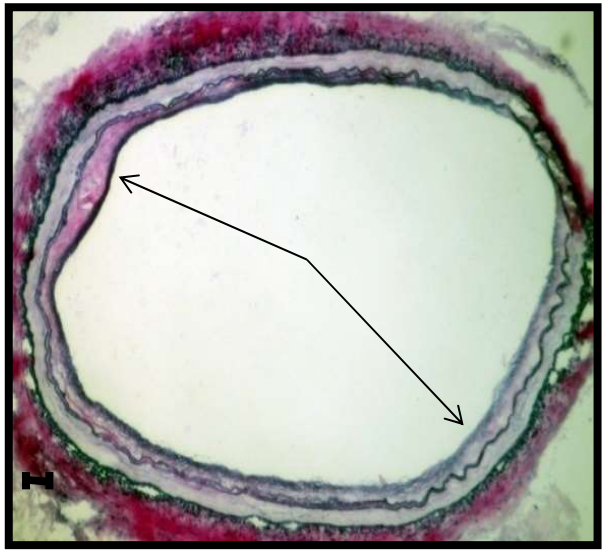
Human Treg therapy prevents acute transplant rejection



Human Treg therapy prevents transplant vasculopathy

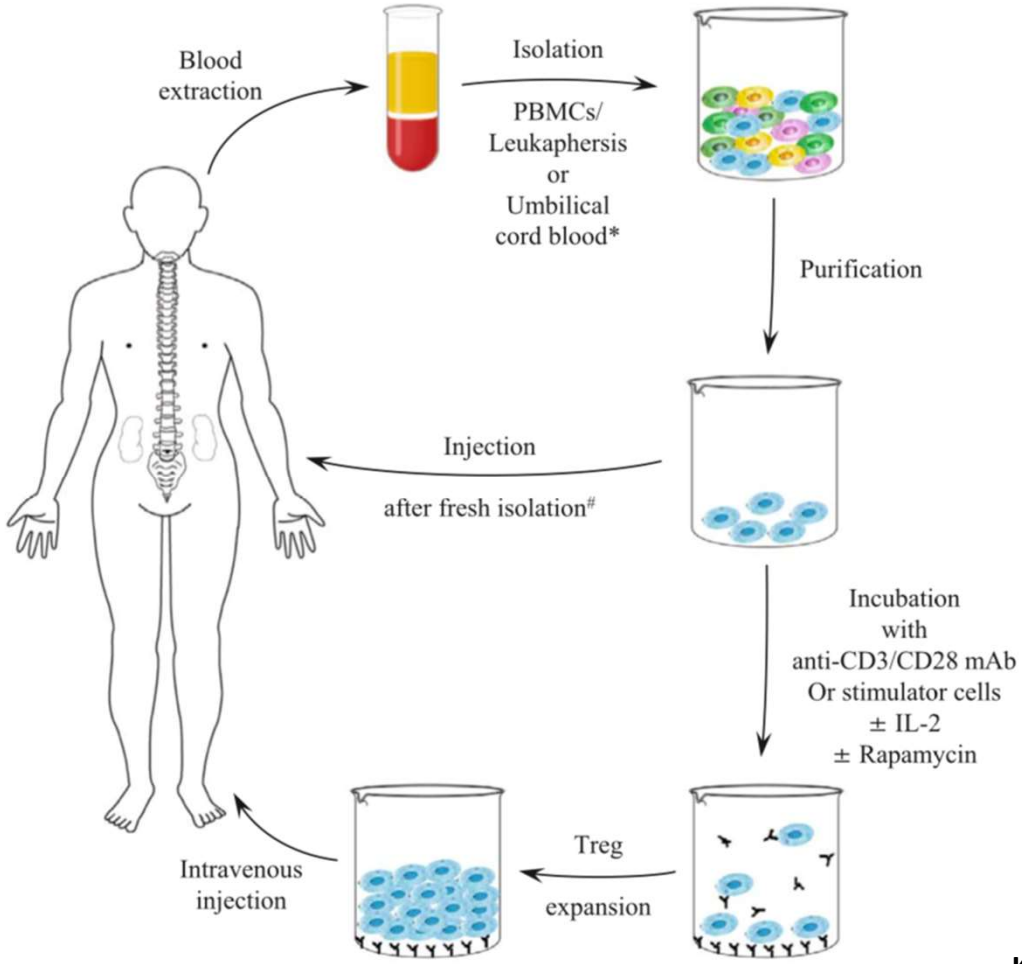


Effectors only



Effectors + Tregs

Nadig et al. Nat Med 2012

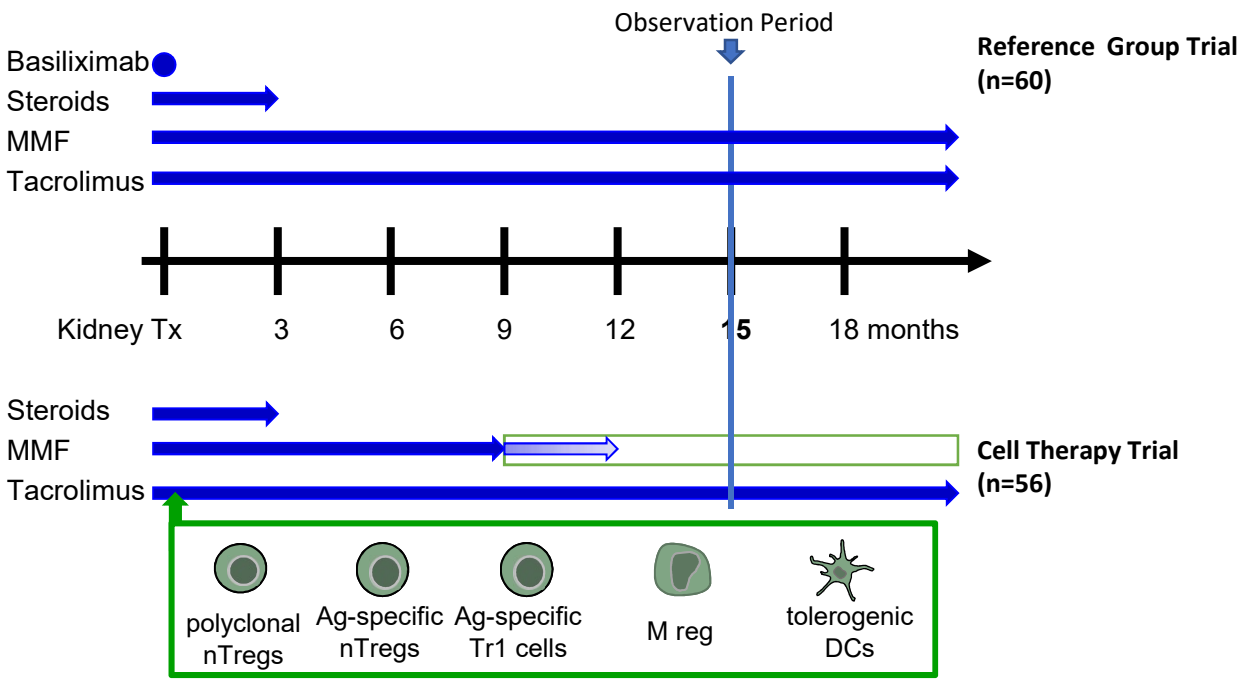


Kawai et al. *Human Immunol* 2018

ONE STUDY

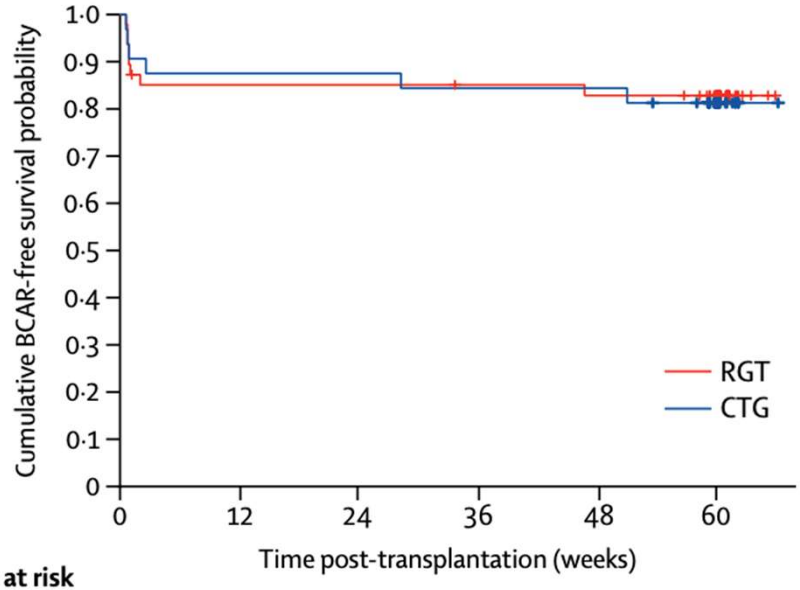
SAN FRANCISCO
BOSTON

LONDON
BERLIN
OXFORD
REGENSBURG
NANTES
MILAN



Sawitzki et al. *Lancet* 2020

Rejection-free survival

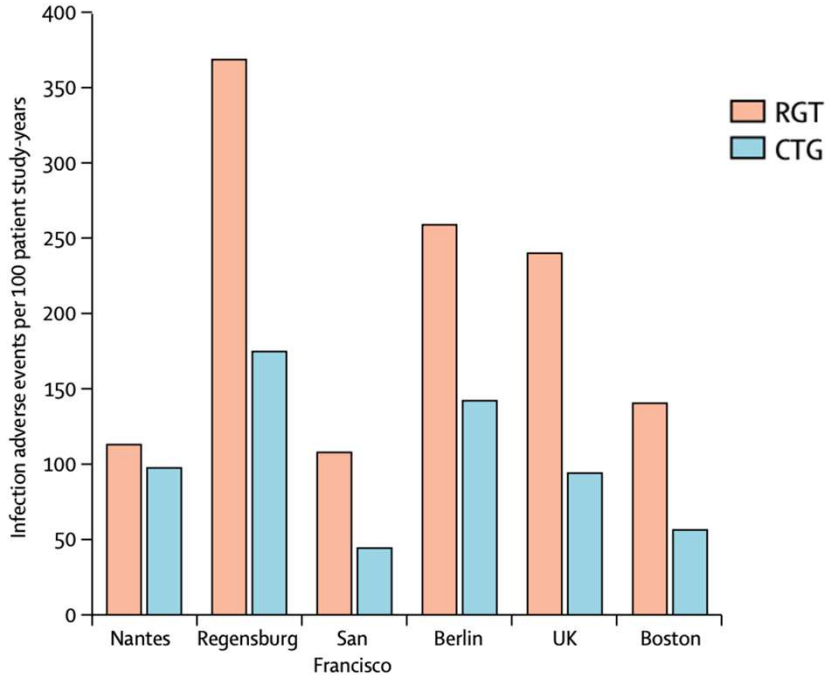


Number at risk

RGT	47	39	39	38	37	23
CTG	32	28	28	27	27	10

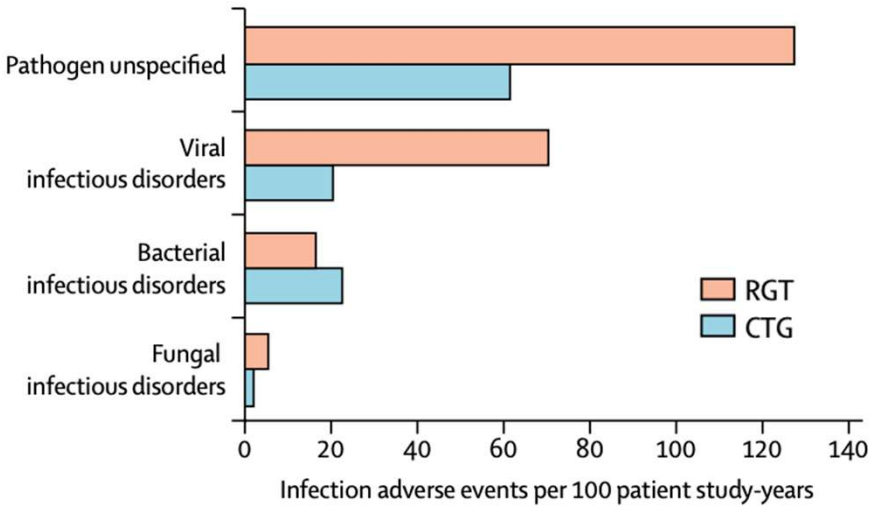
Sawitzki et al. *Lancet* 2020

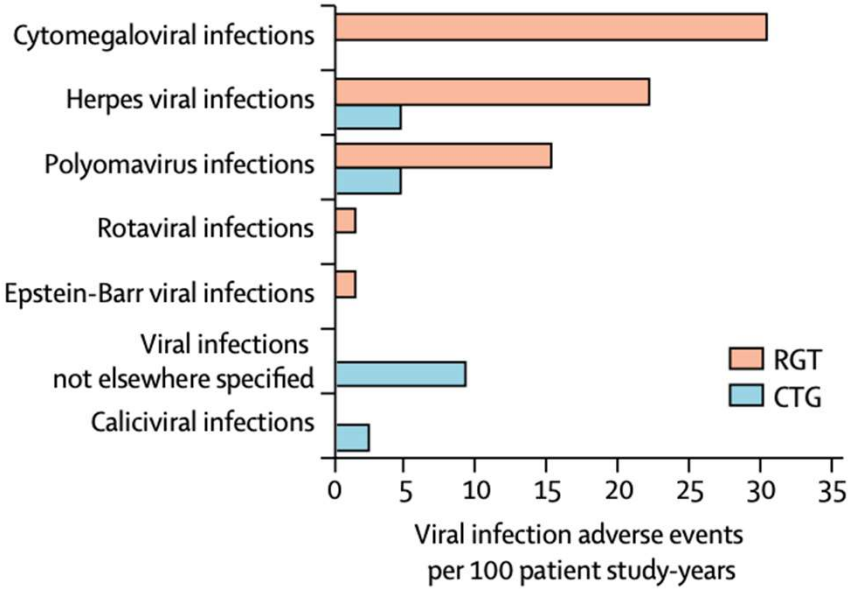
Infection events



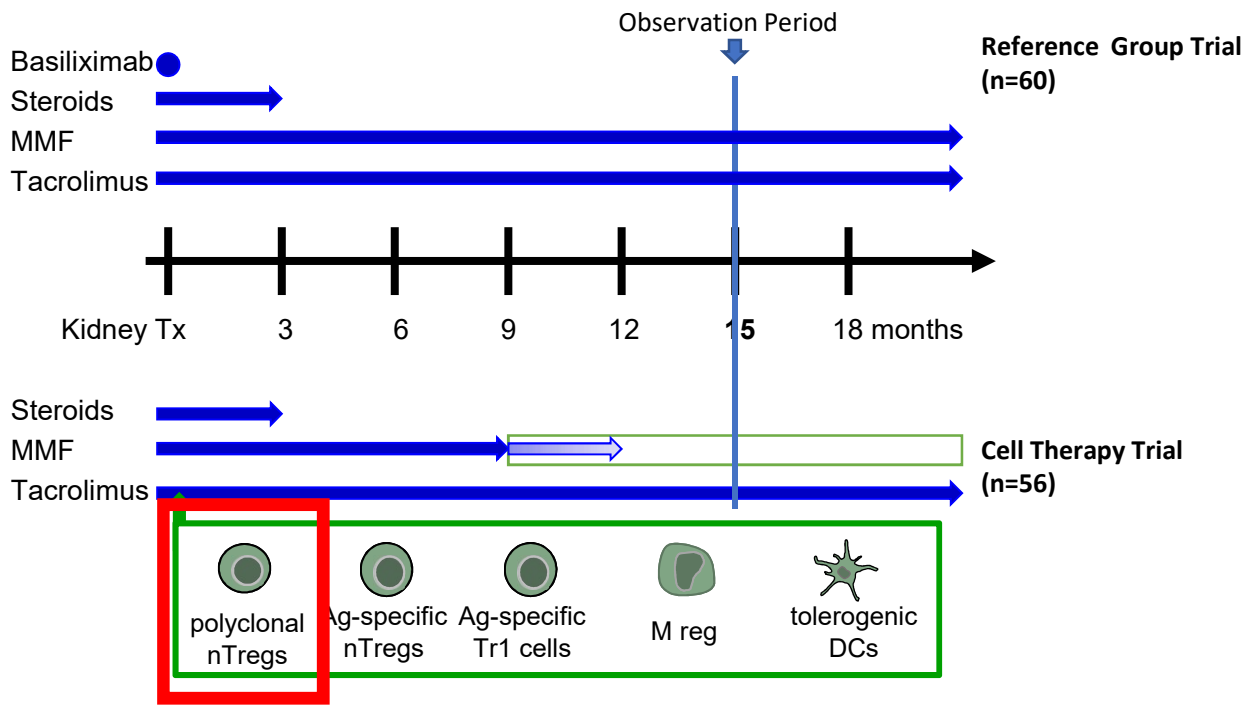
Sawitzki et al. *Lancet* 2020

Infection events

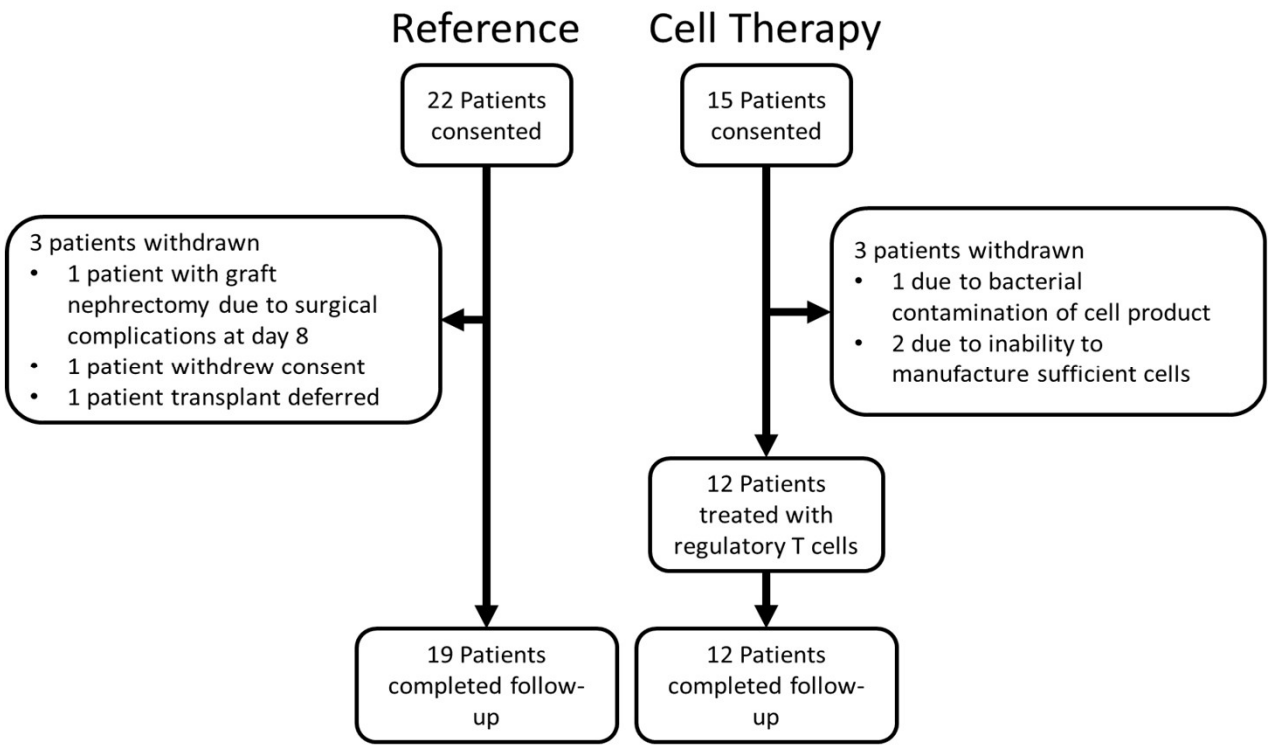




Sawitzki et al. *Lancet* 2020

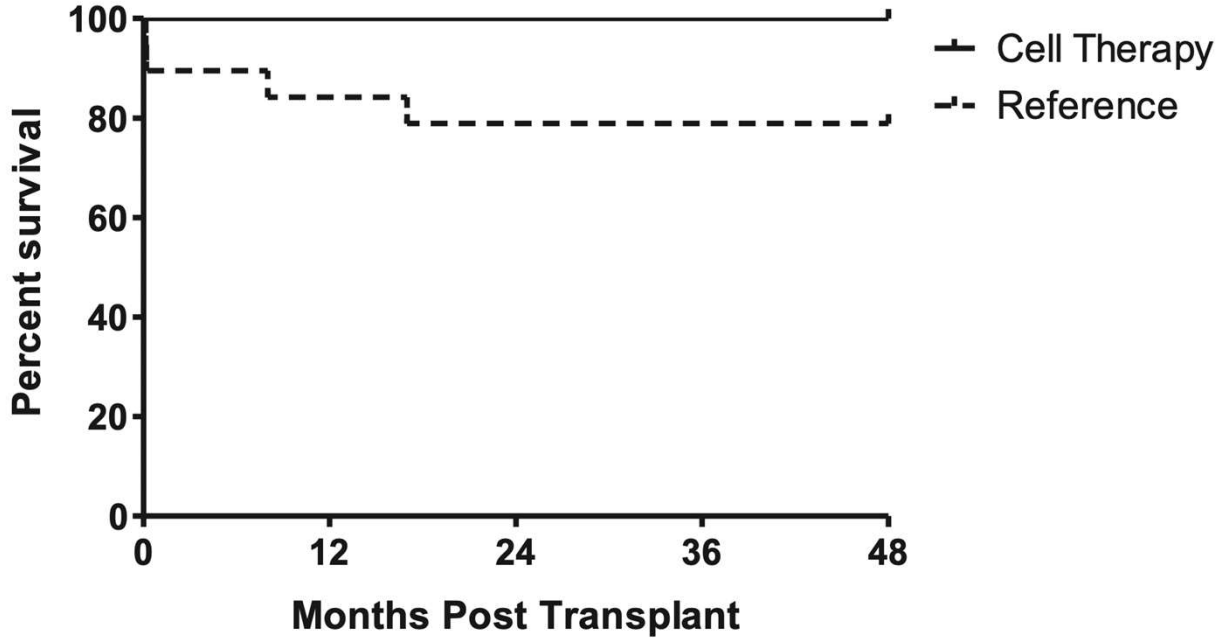

Observation Period
Reference Group Trial
(n=60)
Basiliximab
Steroids
MMF
Tacrolimus
Kidney Tx
3
6
9
12
15
18 months
Steroids
MMF
Tacrolimus
Cell Therapy Trial
(n=56)
polyclonal nTregs
Ag-specific nTregs
Ag-specific Tr1 cells
M reg
tolerogenic DCs

The ONE Study – UK experience



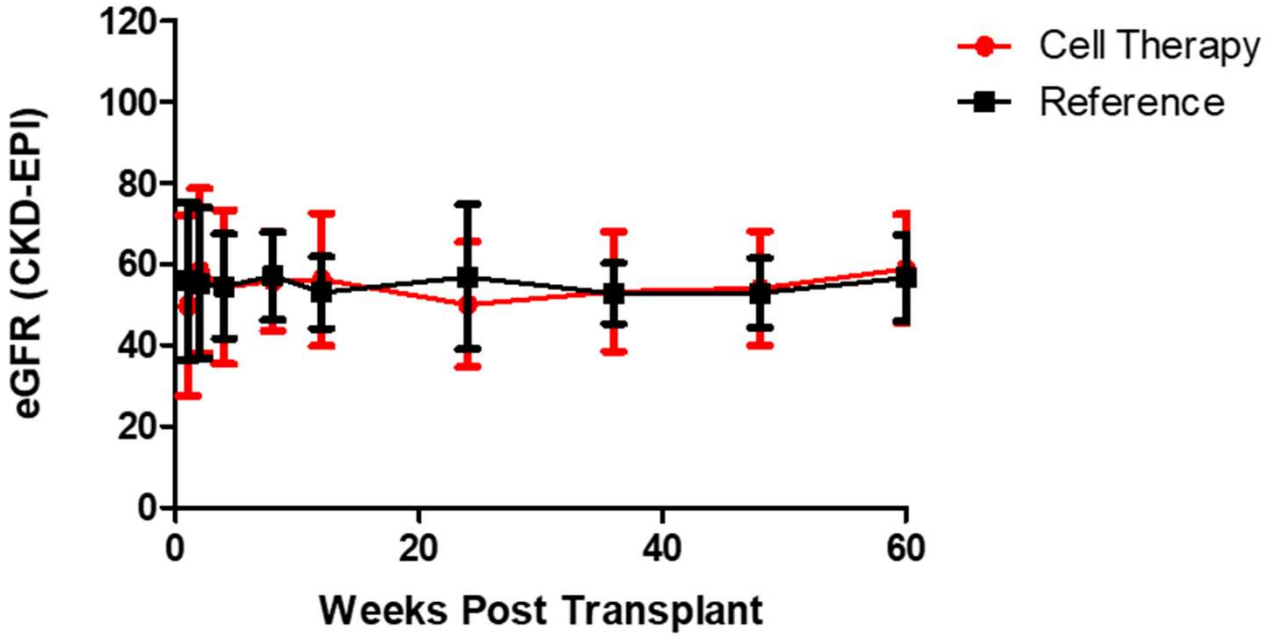
TRIG

Rejection events



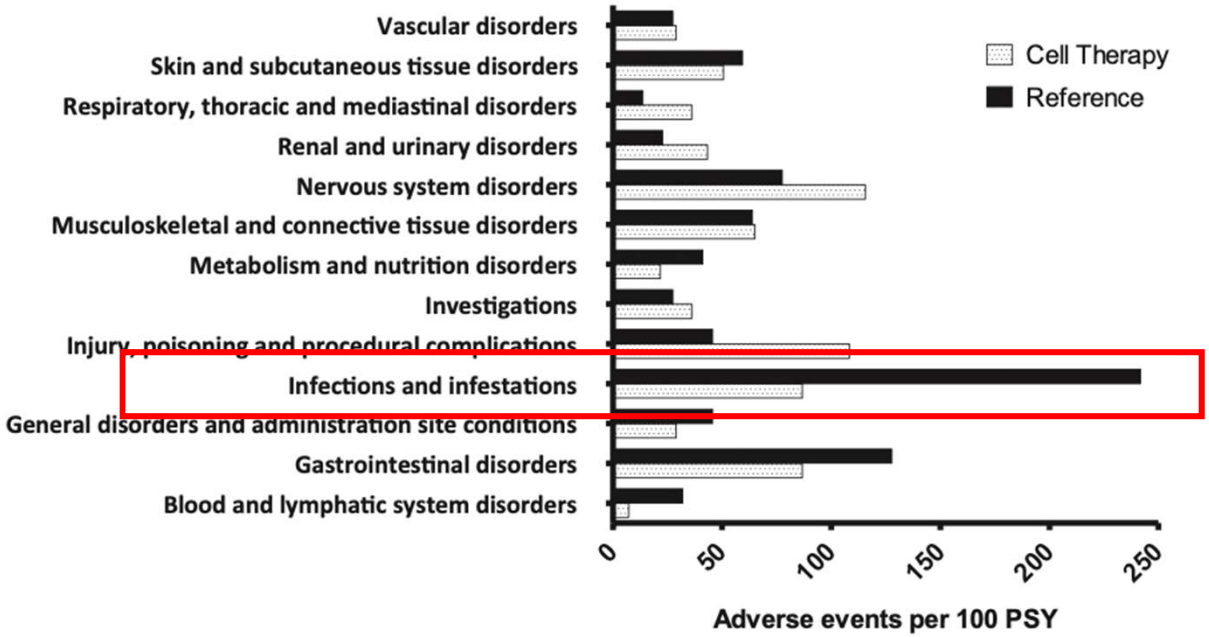
Harden et al. *AJT* 2021

Graft function



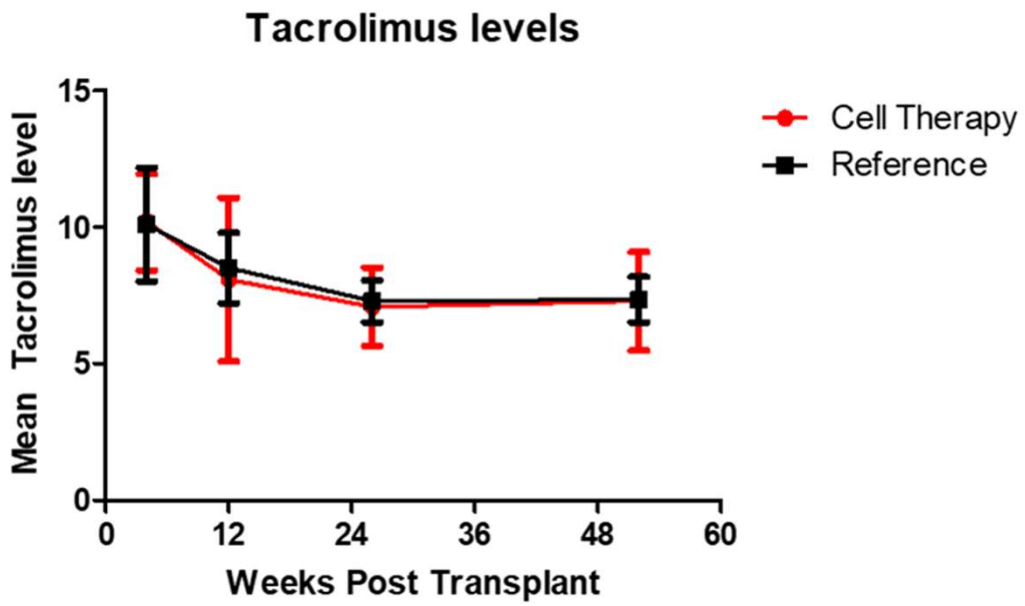
Harden et al. *AJT* 2021

Adverse events



Harden et al. *AJT* 2021

Immunosuppression

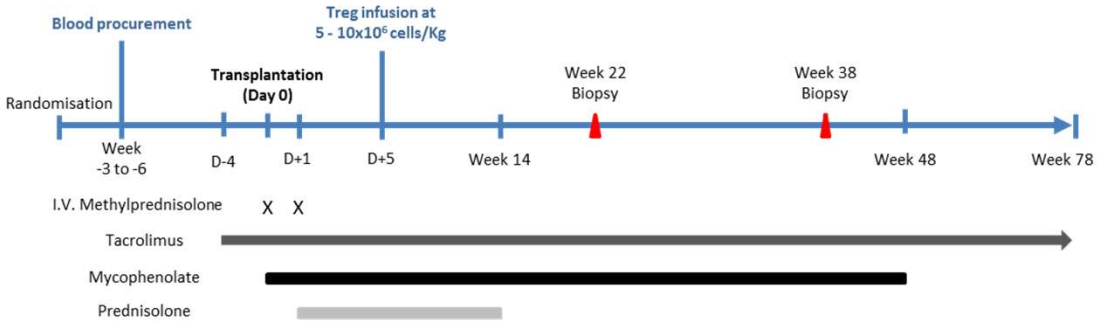


4 cell therapy patients currently maintained on tacrolimus monotherapy

Harden et al. *AJT* 2021

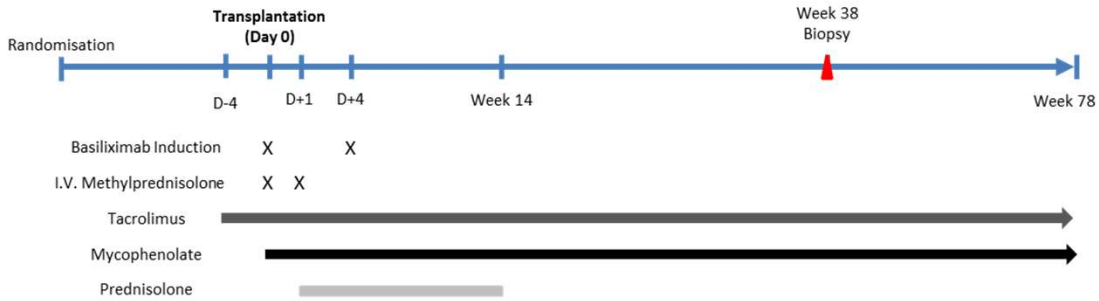
TWO STUDY

Regulatory T cell arm



18 months (78 weeks)
Primary endpoint analysis- Incidence of biopsy proven acute rejection episodes

Control arm



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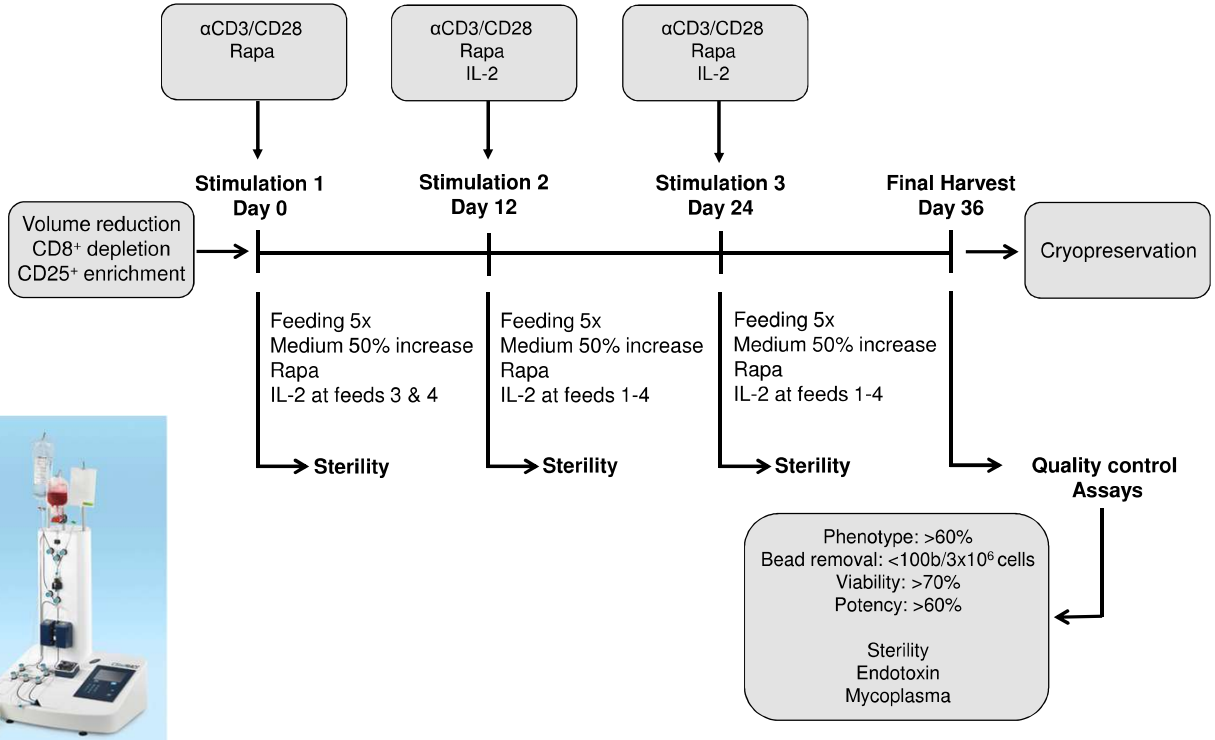
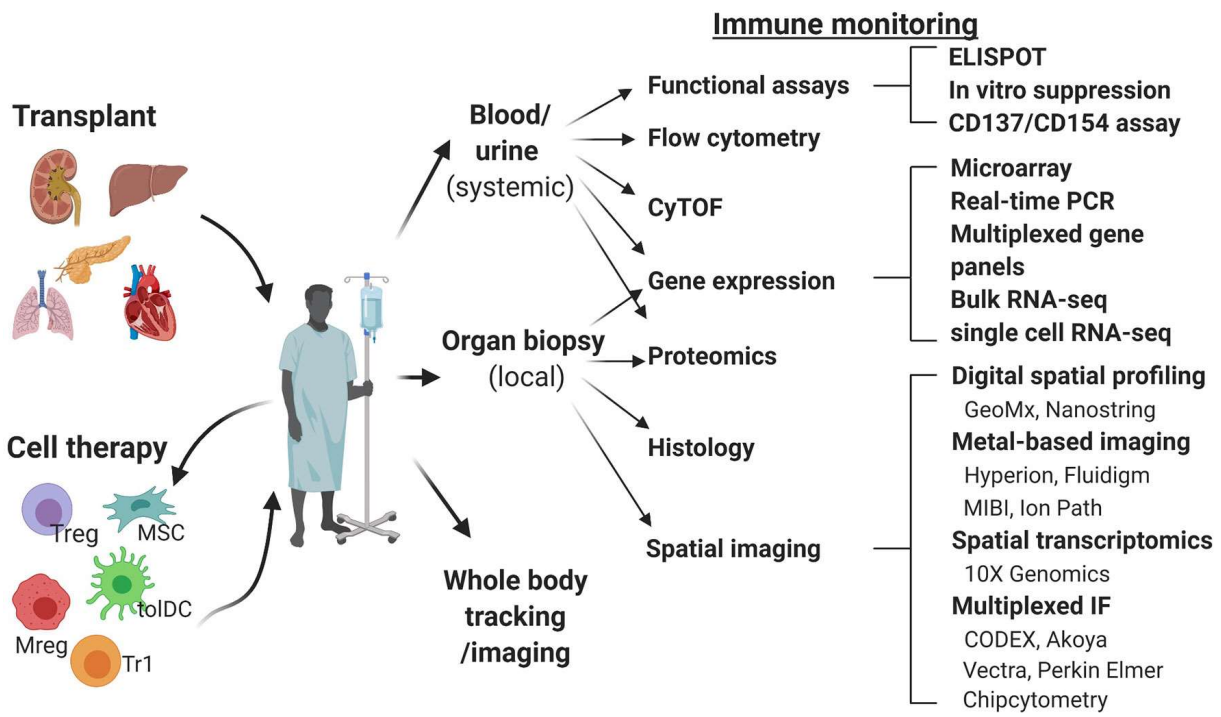


TRIG

Fraser et al. *Mol Ther* 2018

Immune monitoring

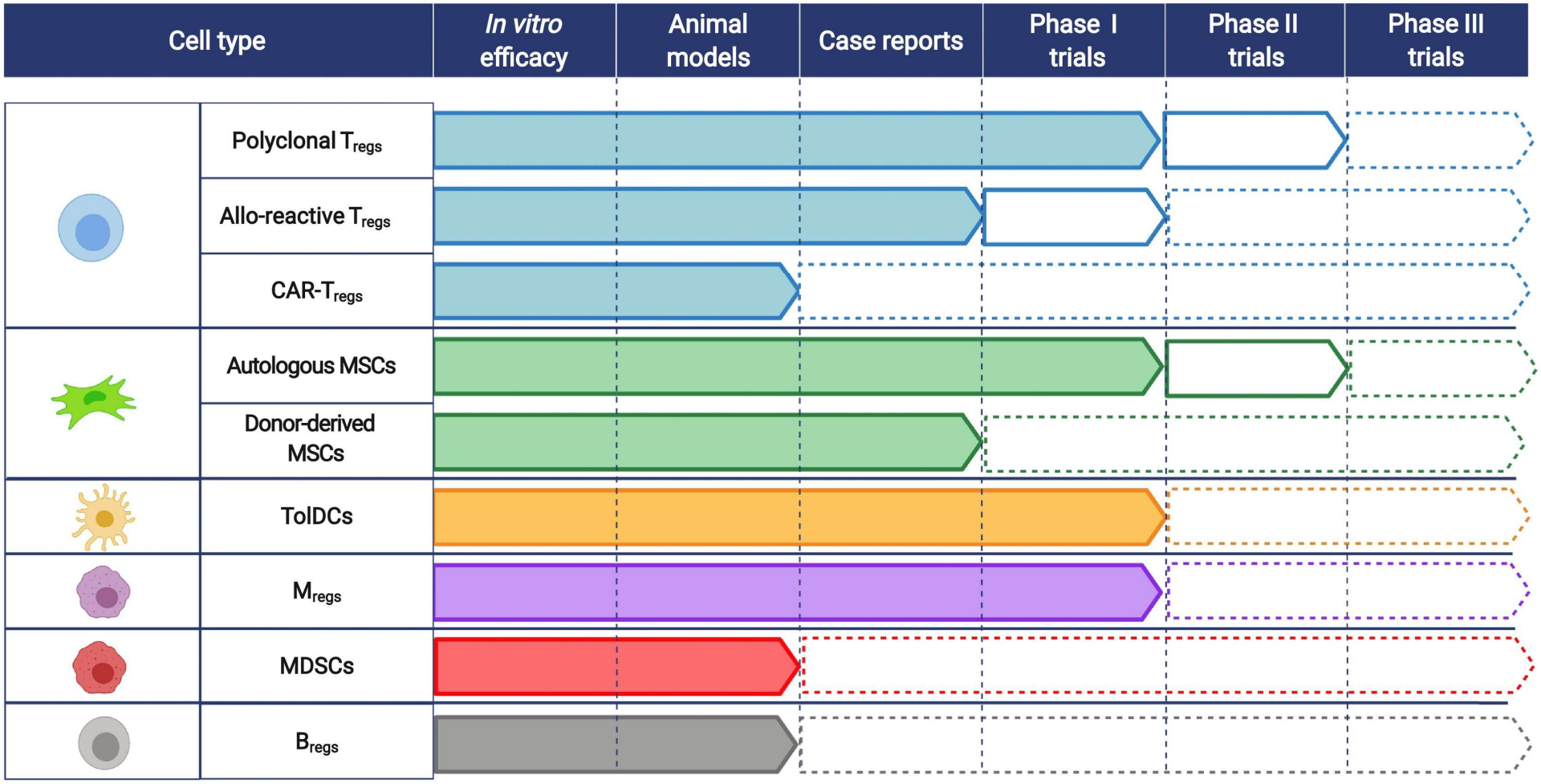


Mengel et al. *AJT* 2020

Stark et al. *Front Immunol* 2021

Treg cell therapy

- Early phase data are encouraging
- Emerging data and experience continues to inform trial design
- Immune monitoring is crucial for understanding the impact of treatment and will likely be important in identifying who to treat



Trends in Immunology

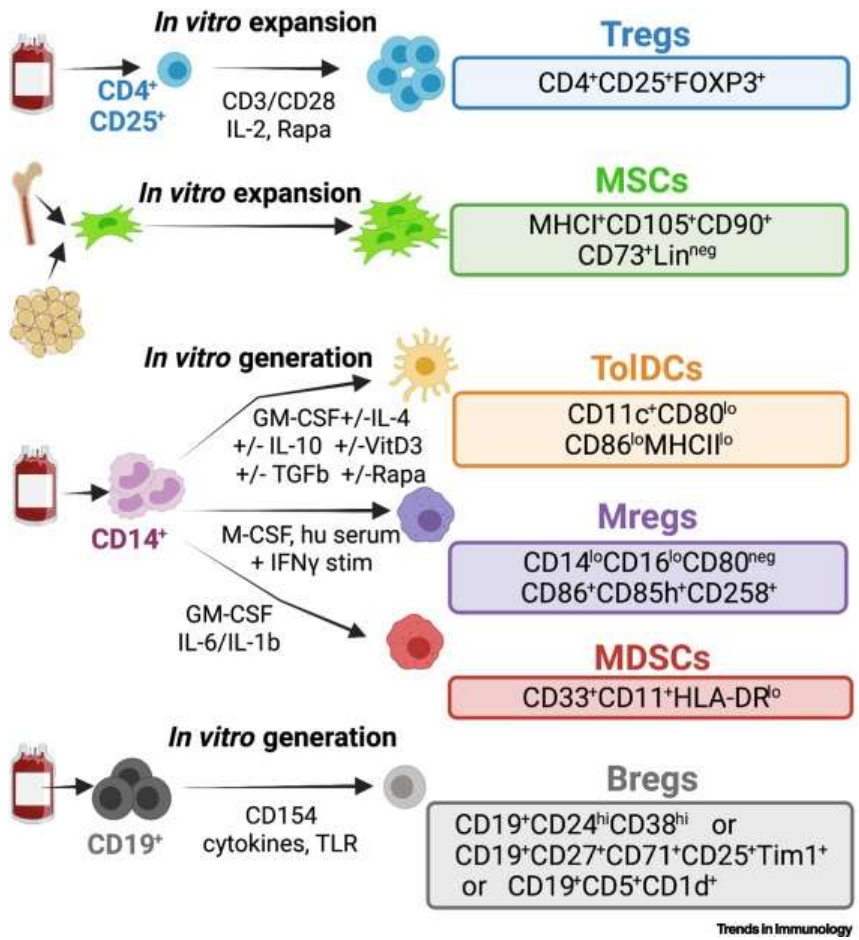
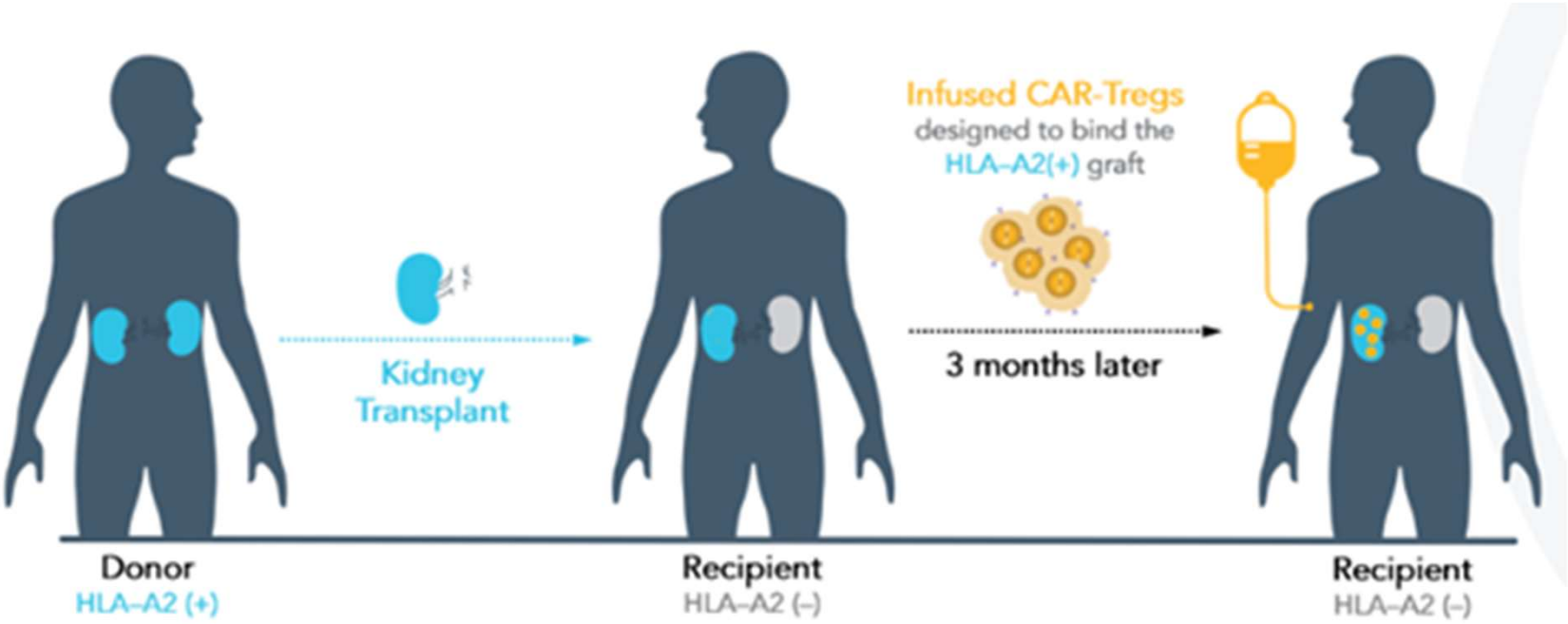

In vitro expansion
CD4+
CD25+
CD3/CD28
IL-2, Rapa
Tregs
CD4+CD25+FOXP3+
In vitro expansion
MSCs
MHCI+CD105+CD90+
CD73+Linneg
In vitro generation
GM-CSF+/-IL-4
+/- IL-10 +/-VitD3
+/- TGFb +/-Rapa
TolDCs
CD11c+CD80lo
CD86loMHCIIlo
CD14+
M-CSF, hu serum
+ IFNγ stim
Mregs
CD14loCD16loCD80neg
CD86+CD85h+CD258+
GM-CSF
IL-6/IL-1b
MDSCs
CD33+CD11+HLA-DRlo
In vitro generation
CD19+
CD154
cytokines, TLR
Bregs
CD19+CD24hiCD38hi or
CD19+CD27+CD71+CD25+Tim1+
or CD19+CD5+CD1d+
Trends in Immunology

Table 1. Overview of the design and principal outcomes of published clinical trials of Treg cellular therapy in human organ transplantation

Study ID Study name (number of patients treated)	Cell product	Timing after transplantation and dose	Setting[a]	Trial Phase	Outcomes[a]
NCT02129881[xi] ONE Study (UK) (n = 12)	Polyclonal, autologous Tregs (frozen)	d + 5, 1–10 × 10^6/kg	LDRT. Tregs as replacement for induction therapy (aCD25). At 48w Tac monotherapy.	I/II	Reduced rates of BPAR, fewer infections. Safe and feasible. Phase II study commenced (TWO Study, EudraCT 2017-001421-41[xii]).
NCT02371434[xiii] ONE Study (Charité) (n = 11)	Polyclonal, autologous Tregs (fresh)	d + 7, 0.5–3 × 10^6/kg	LDRT. Tregs as replacement of induction therapy (aCD25). At 48w Tac monotherapy.	I/II	Immunosuppression reduction to low dose Tac monotherapy in eight out of 11 patients. Safe and feasible.
NCT02145325[ii] TRACT Study (US) (n = 9)	Polyclonal, autologous Tregs (fresh)	2 m, 500–5000 × 10^6	LDRT, aCD52 induction. At 1m Tac converted to Rapa.	I	Safe and feasible. No increase in infections or BPAR up to 2 years. Phase II study commenced.
NCT02088931[iii] TASKp Study (US) (n = 3)	Polyclonal, autologous Tregs (fresh)	>6 m post-transplantation, 320 × 10^6	Subclinical inflammation in renal transplant biopsies. No change to immunosuppression.	I	Safe; feasible to produce Tregs in patients on immunosuppression. Tregs detected for 4 weeks post infusion.
UMIN000015789[xiv] Todo group (Japan) (n = 10)	Treg-enriched co-culture with donor antigen.	d + 13	LDLT, cyclophosphamide induction. Immunosuppression cessation at 18m.	I/II	Seven patients immunosuppression free, three patients developed mild acute cellular rejection during weaning.
NCT02166177[xv] ThRIL Study (UK) (n = 3 + 6)	Polyclonal, autologous Tregs (frozen)	3 m or 4 m post enrolment, 1–4.5 × 10^6/kg	DCD or DBD LT, thymoglobulin induction. Low Tac and Rapa 1.5–4m pre-Treg infusion.	I/II	Safe; early protocol not clinically feasible, late protocol feasible.

[a]Abbreviations: aCD25, basiliximab; aCD52, alemtuzumab; BPAR, biopsy-proven acute rejection; DBD, donation after brain death; DCD, donation after cardiac death; LDLT, living donor liver transplantation; LDRT, living donor renal transplantation; LT, liver transplantation; Rapa, rapamycin; Tac, tacrolimus; d, days; w, weeks; m, months.

HLA A2 Car T regulatory Cell Trial TX200



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