Design of STEADFAST Study Evaluating TX200-TR101: A Chimeric Antigen Receptor (CAR) T Regulatory Cell Therapy for Living Donor Renal Transplant Recipients

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ESOT Congress, 29 August – 1 September 2021

Disclosure of Conflicts of Interest

- I herewith declare the following paid or unpaid consultancies, business interests, grants and research support or sources of honoraria payments for the past three years, and anything else which could potentially be viewed as a conflict of interest:

  Sangamo Therapeutics – full time employee

CAR-T_{REG}: Pioneering a New Frontier with TX200 for Renal Transplantation

TX200
Single infusion

Autologous HLA-A2 specific CAR-T_{REG} cell therapy

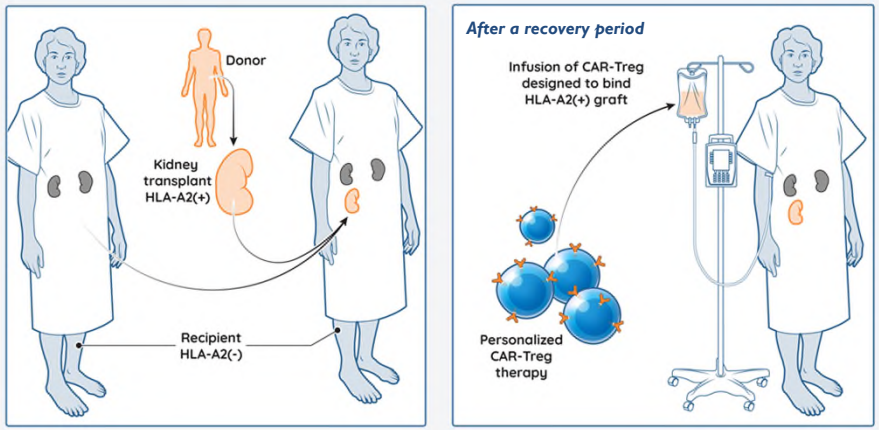
Therapeutic hypothesis and goals:

- Promote immunological tolerance to renal graft
- Help preserve graft function and reduce graft loss
- Reduce need for systemic immunosuppressive therapy

HLA-A2 Mismatched Renal Transplant

~46,000 renal transplantations expected in 2021 (US + EU)[1]

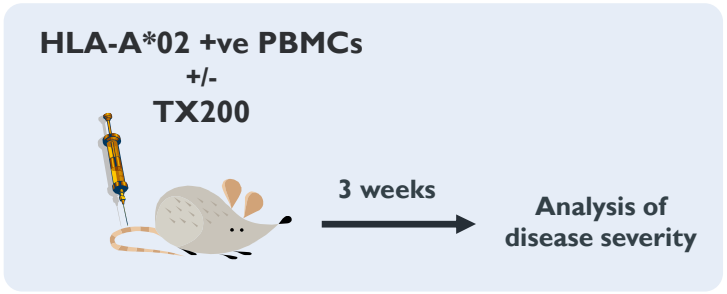
21-26% of transplanted organs are HLA-A2 mismatched[2]



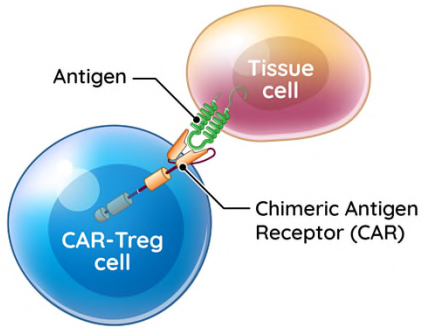
Time from pre-transplant through TX200 administration may be several months

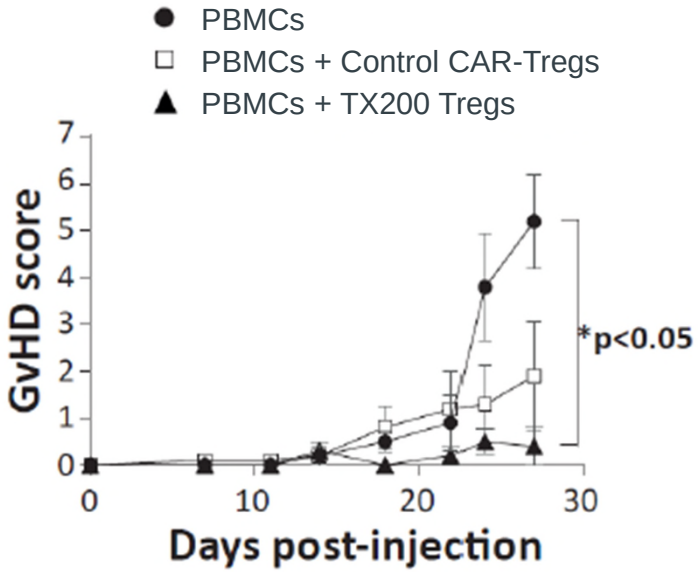
1. IROdat: https://www.irodat.org
2. Barocci et al. 2007; Marrari et al., 2010; Middleton et al., 1985; Schnitzler et al. 1997

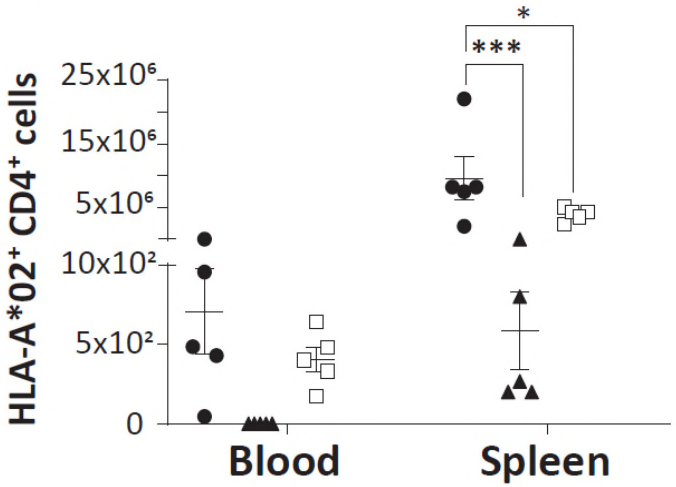
TX200: Robust data from humanised GvHD mouse models demonstrates the immunoregulatory potential of the CAR-Tregs



TX200 CAR-Tregs actively prevent the onset of GvHD by inhibiting the engraftment and expansion of infused proinflammatory human T cells

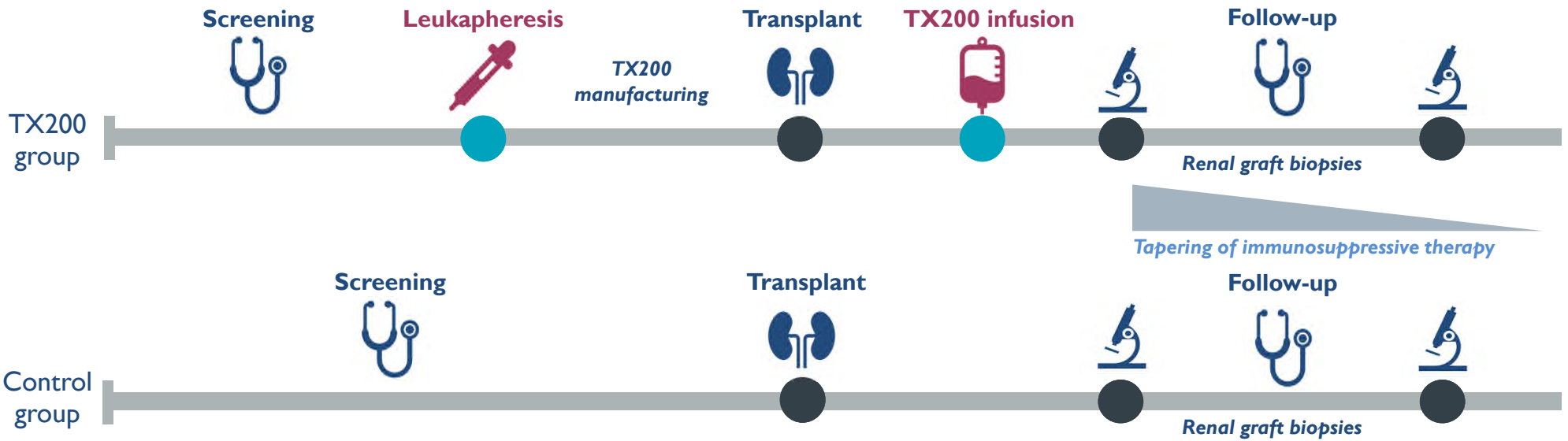






Proics E., David M., Mojibian M. *et al*: Preclinical assessment of antigen-specific chimeric antigen receptor regulatory T cells for use in solid organ transplantation. April 2021 *In revision*

STEADFAST Phase I/IIa Study: Multicentre, open-label, single ascending dose, dose-ranging (NCT04817774)



Rationale for starting dose:

- Number of Tregs in an adult human and estimated number required to prevent graft rejection[1]
- Doses used in previous clinical trials with polyclonal Tregs
- Estimated potency and frequency of antigen-specific Tregs compared to polyclonal Tregs[2-5]

[1]Tang Q, Lee K. *Curr. Opin. Organ Transplant.* 2012; 17(4): 349-54. [2]Duggleby R, Danby RD, Madrigal JA *et al. Front. Immunol.* 2018; 9: 252. [3]Khan MA. *Mol. Med.* 2017; 22: 892-904. [4]Tang Q, Vincenti F. *J. Clin. Invest.* 2017; 127(7): 2505-12. [5]Bacher P, Schink C, Teutschbein I *et al. J. Immunol.* 2013; 190(8): 3967-76.

Eligible Study Population

- Male or female, aged between 18 and 70 years
- A diagnosis of ESRD and scheduled to receive a new kidney from an identified living donor
- Single organ (kidney) recipients and no prior organ transplant
- Low immunological risk
- TX200 group only:
  - Recipients must be HLA-A*02 negative and able to undergo leukapheresis to collect cells
  - Donors must be HLA-A*02 positive
- Control group only:
  - HLA mismatched with donors but mismatch for HLA-A*02 specifically is optional

Primary and Secondary Outcome Measures

PRIMARY

- **Safety and tolerability of TX200-TR101 infusion evaluated by incidence and grade of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs)**
  - Within 28 days post-infusion

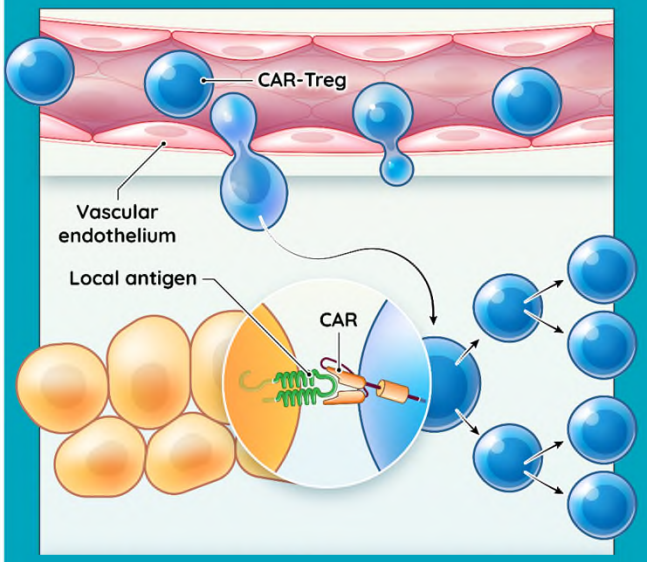
SECONDARY

- **Effect of TX200-TR101 on acute graft-related outcomes (BCAR according to Banff classification criteria) and on long-term safety outcomes (number of transplant recipient subjects with TEAEs, including SAEs)**
  - Day of infusion through end of study (Week 84)
- **Ability to reduce immunosuppression**
  - Day of infusion through end of study (Week 84)
- **Localisation of TX200-TR101 to the graft (biopsy informed)**
- **Effect of TX200-TR101 on chronic graft-related outcomes (chronic graft rejection according to Banff classification criteria and chronic graft dysfunction as measured by estimated glomerular filtration rate)**
  - Day of infusion through end of study (Week 84)

What we expect to learn from the STEADFAST study

- Safety & tolerability
- Proof of mechanism in patients:
  - Localisation and activation of Tregs
  - Stability of Treg function
  - Duration of Treg cells in circulation
  - Impact of Tregs on immune cell composition
- Process development knowledge

STEADFAST



Proposed CAR-T_{REG} homing to target

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Acknowledgements

Sangamo Clinical Sciences
- Katharina Schreeb
- Benjamin Hsu

Sangamo Clinical Operations
- Amy De Sa
- Claire Chapman

Sangamo Preclinical
- Celine Dumont
- Emma Proics

Sangamo Regulatory
- Magali Gibou

Sangamo Communications
- Caroline Courme

Sangamo CMC
- Pierre Heimendinger
- Nadia Lounnas-Mourey
- Herve Bastian
- Marjorie Caron

Sangamo Leadership
- Gillian Atkinson
- Maud Andre
- Duncan McKay

Sangamo Biosample Operations, Supply Chain, Patient Advocacy and the wider Sangamo teams

Previous employees
- Essra Ridha
- Sunita Singh

Our investigators and site teams, vendors and collaborators

The patients

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Thank you