Regulatory T cell (Treg) therapies in liver diseases

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Institute of Liver Studies
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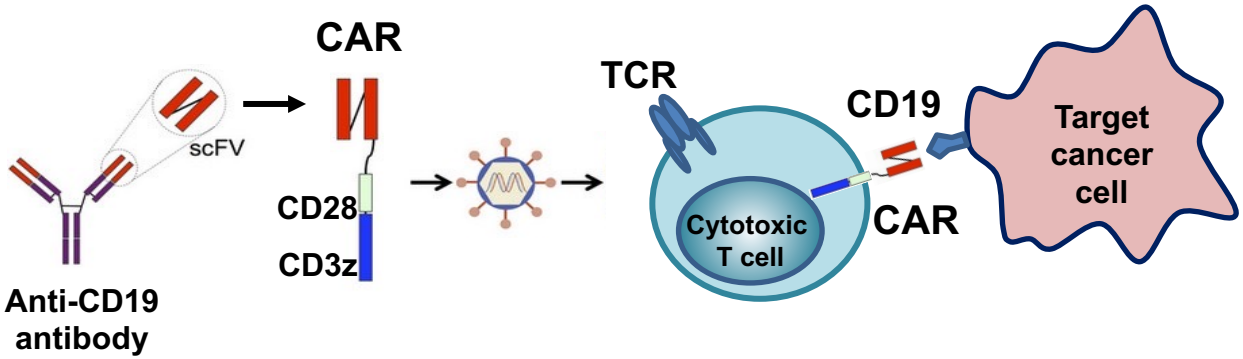
Lausanne, May 2022

DISCLOSURE

- Established in May 2019 through joint investment by Syncona Ltd. and UCL Technology Fund
- Headquartered in London
- c. 100 staff developing engineered T regulatory cell products for immune dysregulation
- UK: MHRA CTA approved in October 2021

The Incredible Story of Emily Whitehead & CAR T-Cell Therapy

2012 first anti-CD19 CAR-T cell treatment
Acute lymphoblastic leukemia



nature medicine

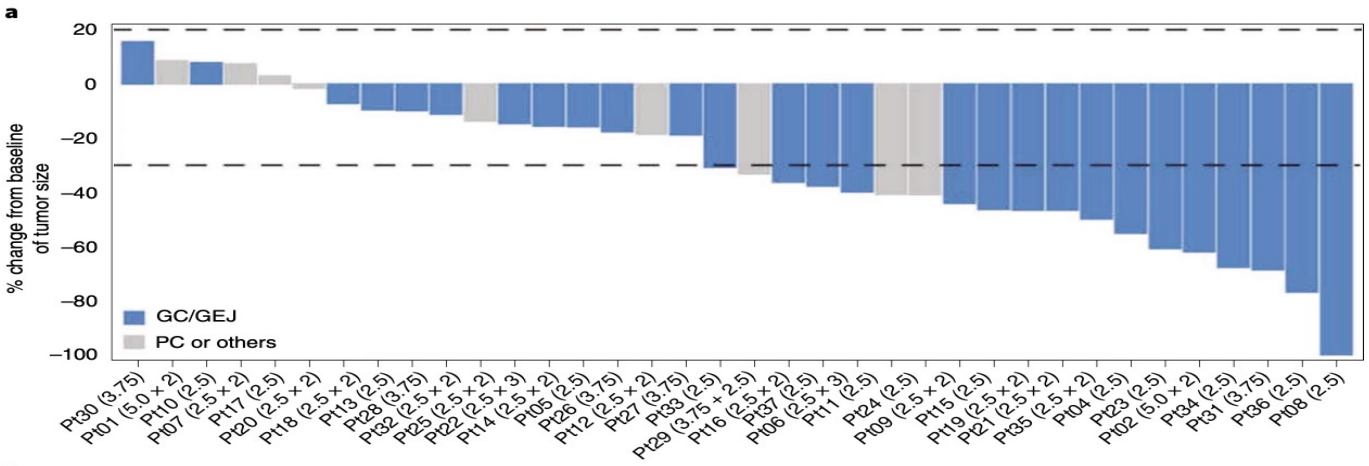
ARTICLES

https://doi.org/10.1038/s41591-022-01800-8

Check for updates

OPEN

Claudin18.2-specific CAR T cells in gastrointestinal cancers: phase 1 trial interim results



Qi et al. *Nat Med* 2022

CD4+CD25+Foxp3+ Tregs: Master controllers of Immune & Tissue homeostasis

Balancing protective immunity vs self-tolerance

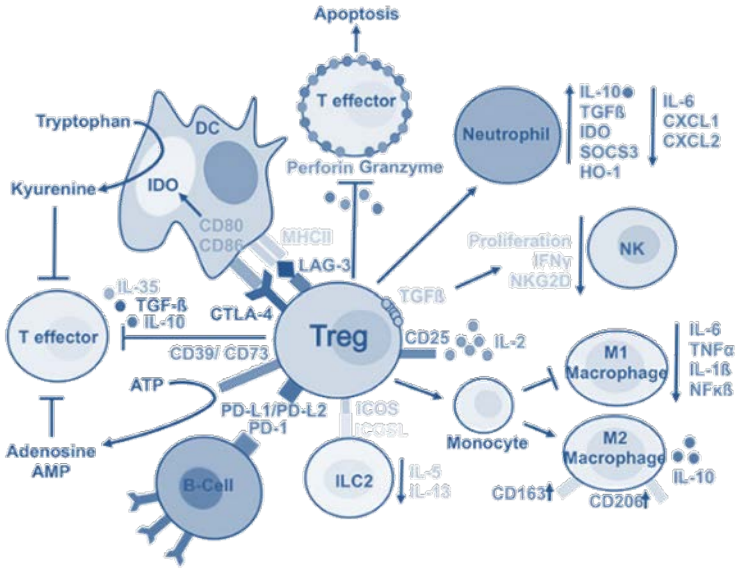
- Mutations in Foxp3 result in systemic autoimmunity (IPEX)
- Several autoimmune disease have a dysfunctional Tregs (e.g. T1D, MS, SLE, IBD)

Suppressing via multiple mechanisms & cell types

- "Poly-pharmacology"Modulate both innate & adaptive immunity
- Drive dominant / infectious tolerance in local immune environment after activation

Function Beyond Immunosuppression

- Promoting tissue repair & tissue homeostasis

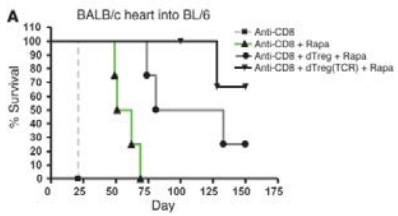


Require activation through their TCR but can exert bystander suppression

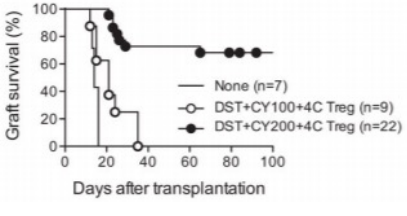
Adoptive transfer of Tregs “resets” immune responses in multiple pre-clinical models

Transplantation

MHC-mismatch heart Tx (*Tsang, Lombardi et al. 2008*)

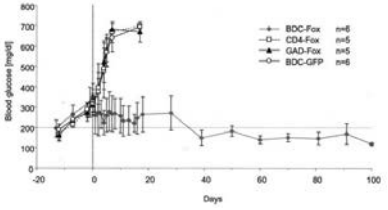


MHC-mismatch islet Tx (*Lee et al. 2014*)

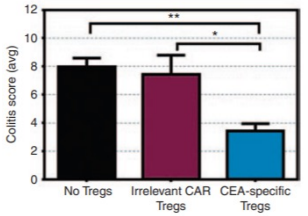


Autoimmunity / Inflammation

Recent-onset diabetes (*Jaeckel et al. 2005*)

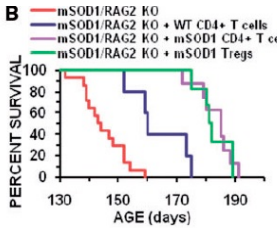


Toxin-induced colitis (*Blat et al. 2014*)

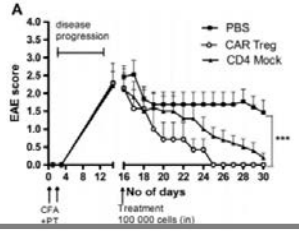


Neuroinflammation

ALS SOD1 model (*Beers et al. 2011*)

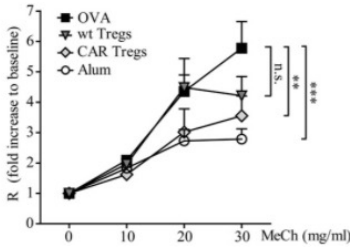


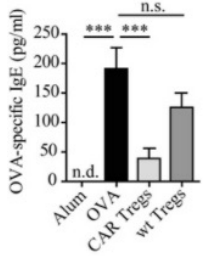
EAE multiple sclerosis (*Fransson et al. 2012*)



Allergy

Experimental Allergic Airway Inflammation (*Skuljec et al. 2017*)





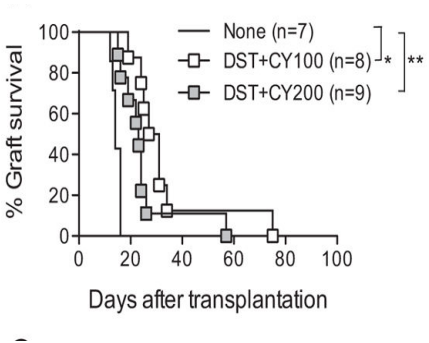
Adoptive Treg transfer in transplantation: rationale

- Transplantation outcomes depend on the balance between effectors and regulators
- Immune Regulation is self-perpetuating
- Local intra-graft regulation (or tissue adaptation) is required for long-term engraftment

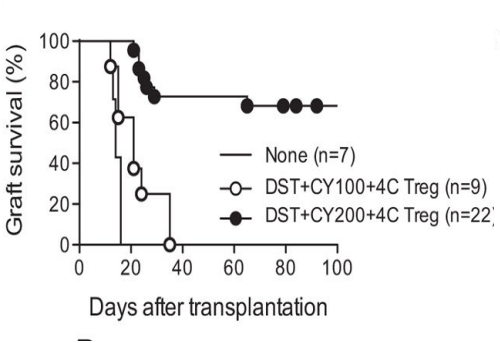
Adoptive Treg transfer in transplantation: dose, specificity and lymphodepletion

Islet allograft, DST, Cy lymphodepletion and Ag-specific Tregs

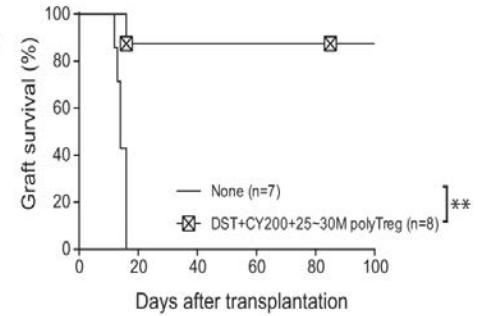
Lee et al. *Am J Transplant* 2014; 14: 27–38



Depletion of Teffs without Tregs

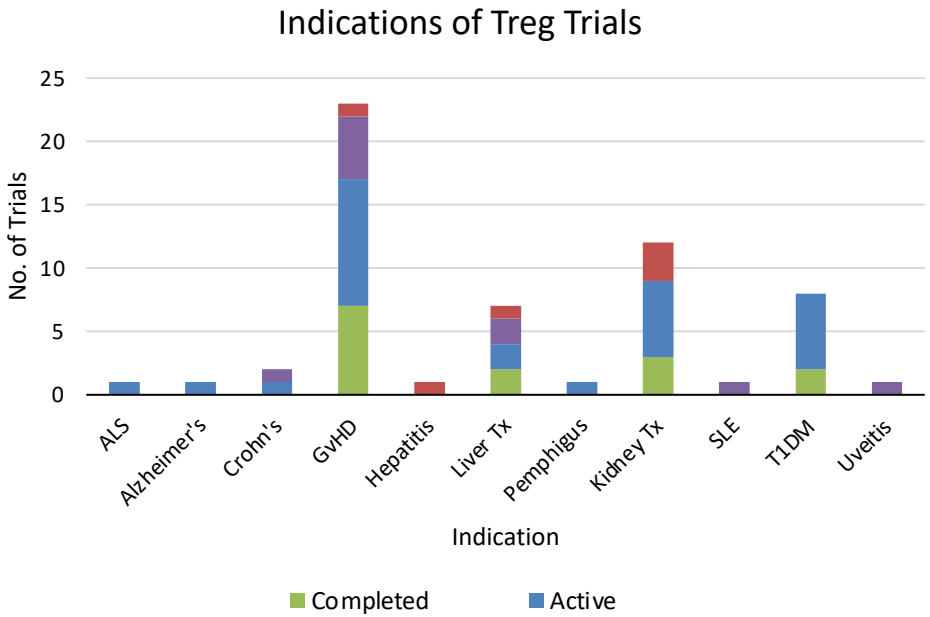


+ 5M of graft-specific Tregs



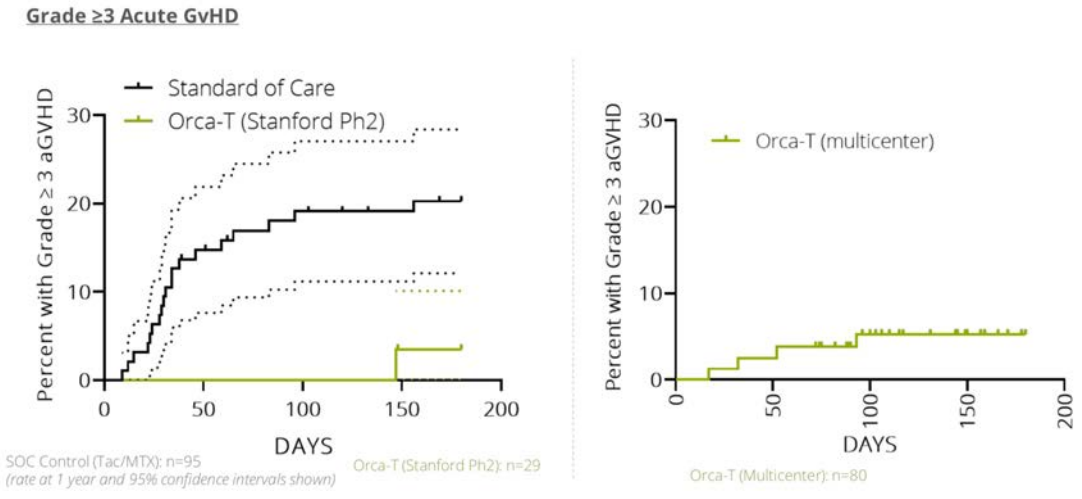
+ 25-30M of polyclonal Tregs

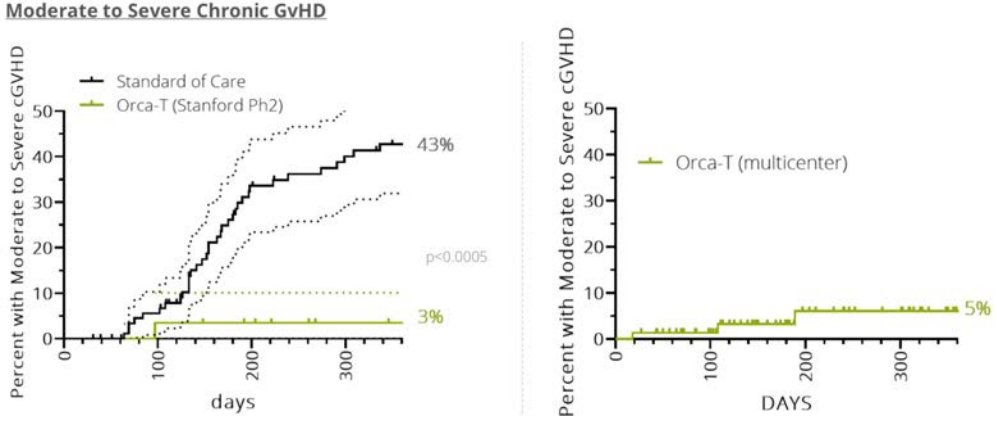
Clinical trials using Tregs (2020)



Source: clinicaltrials.gov

Prevention of GVHD after HSCT using T-cell reduced allografts





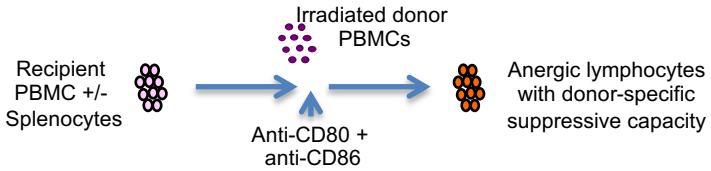
orcabio

E.Meyer, Standford

Phase III trial
in progress

3 million Teff/kg
3 million Tregs/kg

Induction of operational tolerance in living donor liver transplantation

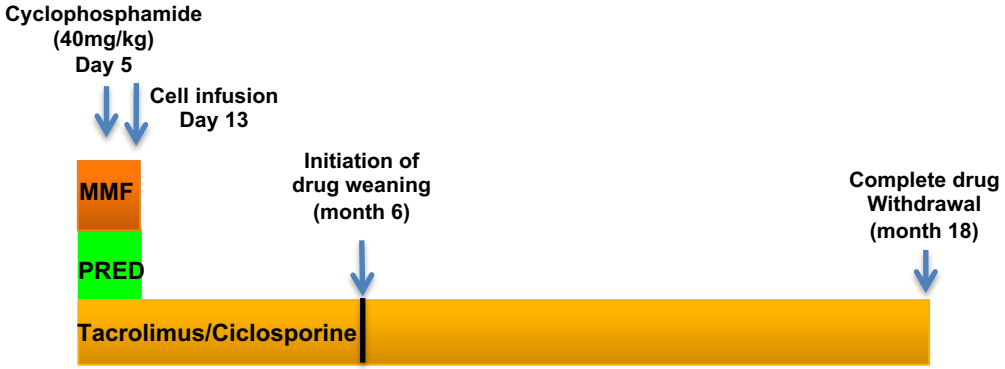


Case	Disease Etiology	CP (mg/kg)	Infused cells Total ($x10^8$)	Infused cells $CD4^+CD25^+$ ($x10^7$)
#1	HCV	50	6.1	3.1
#2	alcoholic	50	25.4	46.6
#3	NASH	30	7.9	9.4
#4	HBV, HCC	40	24.5	44.1
#5	PBC	40	6.3	4.3
#6	PSC	40	11.8	27.2
#7	NASH, HCC	40	25.9	31.8
#8	alcoholic	40	7.0	30.4
#9	PBC	40	5.9	3.3
#10	NASH, HCC	40	12.0	28.9

HEPATOLOGY
AASLD
HEPATOLOGY, VOL. 64, NO. 2, 2016

A Pilot Study of Operational Tolerance With a Regulatory T-Cell-Based Cell Therapy in Living Donor Liver Transplantation

Satoru Todo,[1*] Kenichiro Yamashita,[1*] Ryoichi Goto,[2] Masaaki Zaitsu,[2] Akihisa Nagatsu,[2] Tetsu Oura,[2] Masaaki Watanabe,[2] Takeshi Aoyagi,[2] Tomomi Suzuki,[2] Tsuyoshi Shimamura,[3] Toshiya Kamiyama,[2] Norihiro Sato,[4] Junichi Sugita,[5] Kanako Hatanaka,[6] Hisashi Bashuda,[7] Sonoko Habu,[7] Anthony J. Demetris,[8] and Ko Okumura[7]



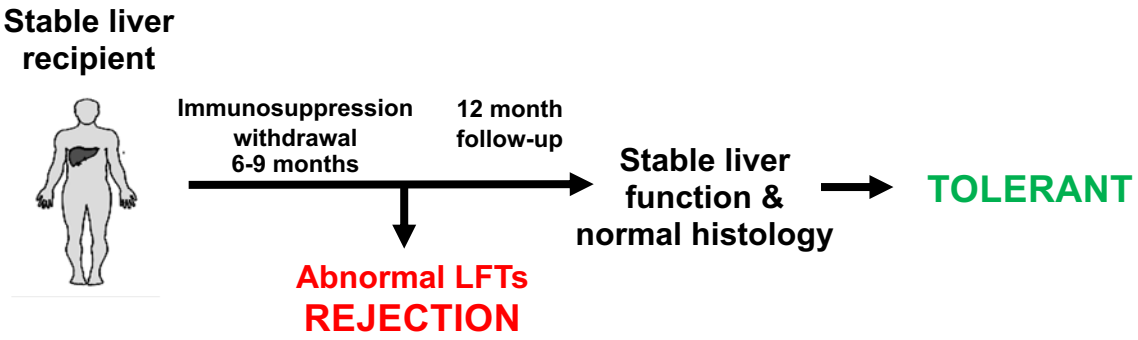
Update 2019: out of the 7 tolerant patients, 1 patient died with normal liver tests; 6 patients are alive and off drugs (longest follow-up: 8 years off medication)

Trials of Immunosuppression Withdrawal and Spontaneous Operational Tolerance in Liver Transplantation

Year	Author	Number of patients	Success (%)	Rejection Acute/Chronic (%)	Graft loss (%)
1997	Mazariegos	95	19	26/0	0
1998/2005	Devlin Girlanda	18	16.7	28/5.6	5.6
2001	Takatsuki	26	23.8	12/0	0
2003/2008	Pons	21	38	22/0	0
2005	Eason	18	5.6	61/0	0
2005	Tryphonopoulos	104	19	67/1.9	0.96
2006	Tisone	34	23.4	76.4/0	0
2007	Assy	26	8	58/0	0
2012	Feng	20	60	35/0	0
2013	Benitez	102	42	58/0	0
2013	Garcia de la Garza	24	62.5	33/0.04	0
2014	Bohne	34	50	44/0	0
2019 AWISH trial	Shaked	76	14	90	0
2020 (IWITH trial)	Feng	88	38	40	0

20% of selected adult recipients

Spontaneous operational tolerance in stable liver Tx recipients: a unique experimental medicine model to study human immunology

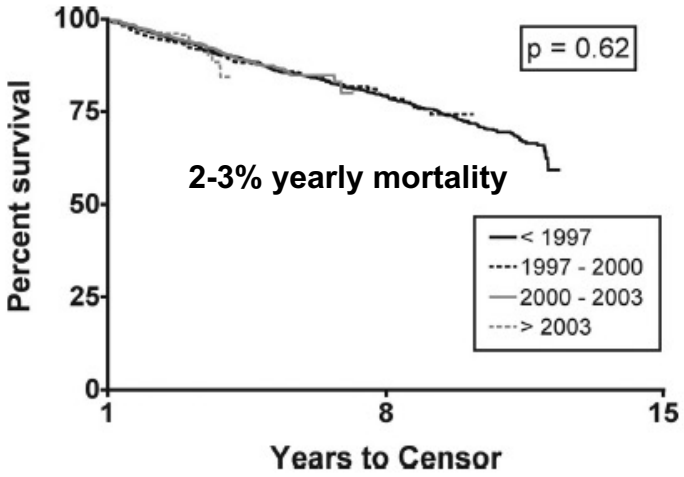


Immune Tolerance Network

1999 Priority:
Tolerance trials in kidney Tx

2022 Priority:
Tolerance trials in liver Tx

Late mortality in liver transplant recipients
(>1 year after transplantation)

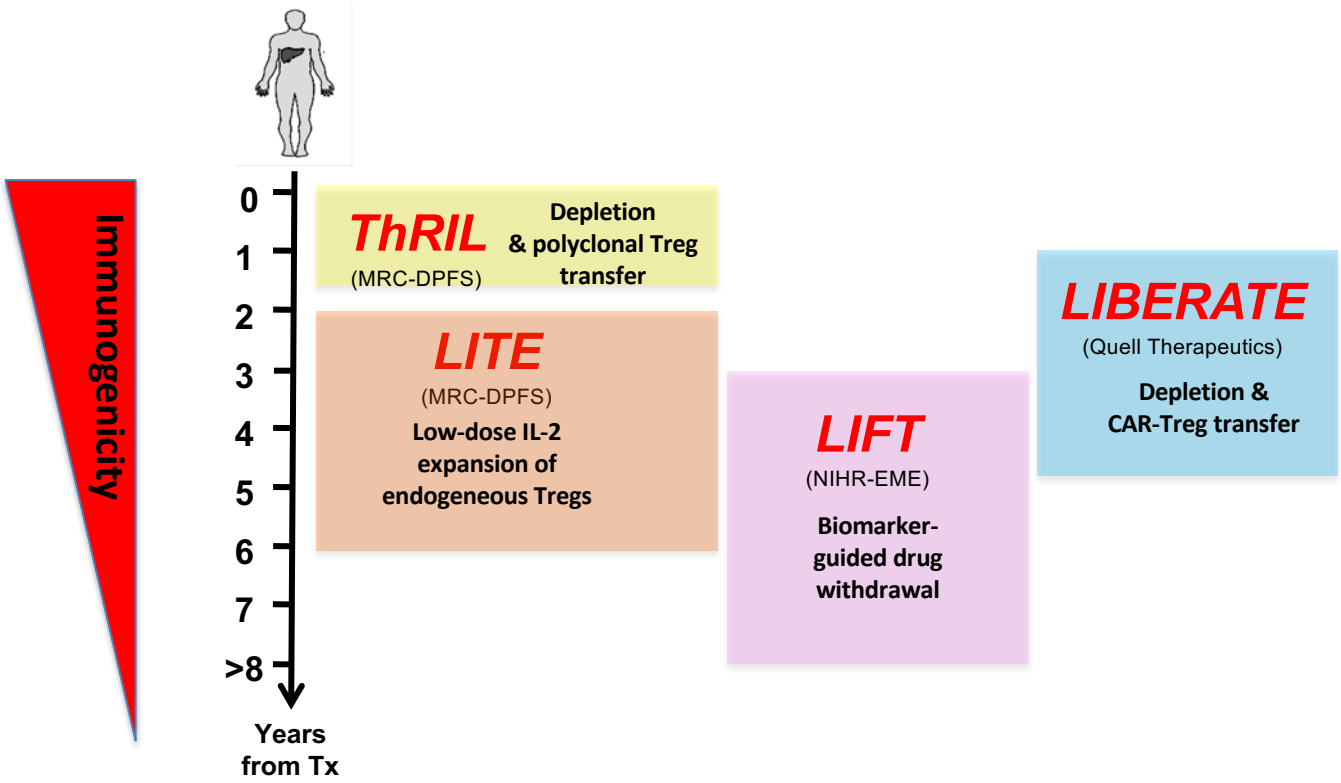


CAUSES OF DEATH **(69% non-liver related)**

- **malignancy**
- **infection,**
- **multisystem failure**
- **cardiac events**
- **graft failure**

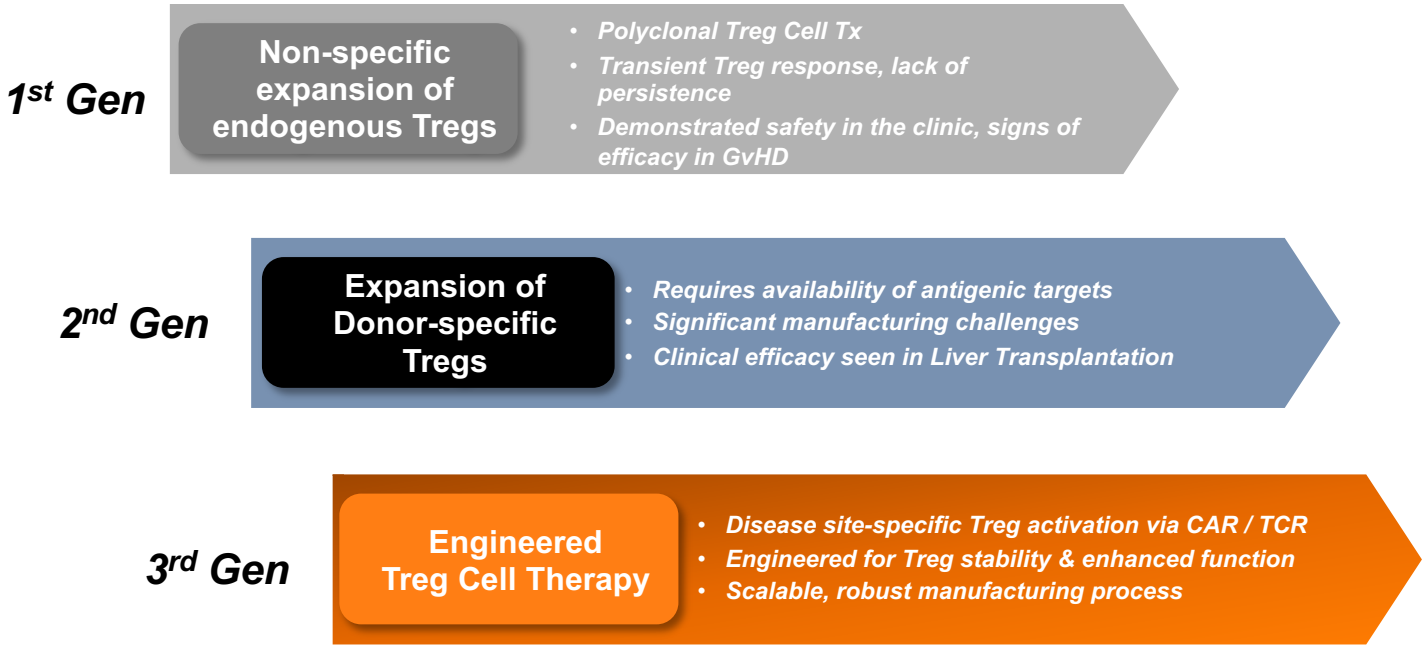
UK Transplant Database
Gelson et al. Transplantation 2011

Clinical trials in liver transplantation tolerance at King's (2014-2022)

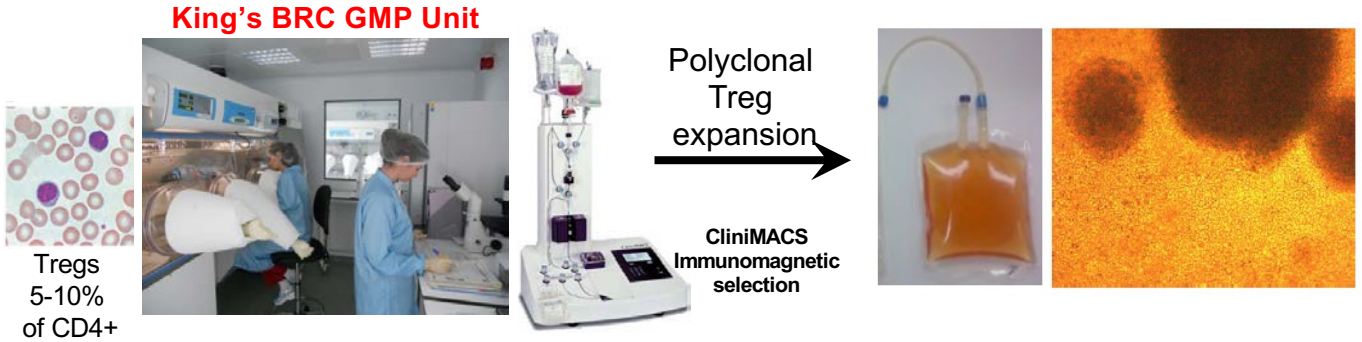


Low immunological risk patients (no autoimmunity / no sub-clinical rejection)

Autologous Treg transfer: manufacture approaches



GMP MANUFACTURE OF POLYCLONAL TREGs AT KING's



Clinical trials:
ThRIL
One Study
Two Study
GameChanger

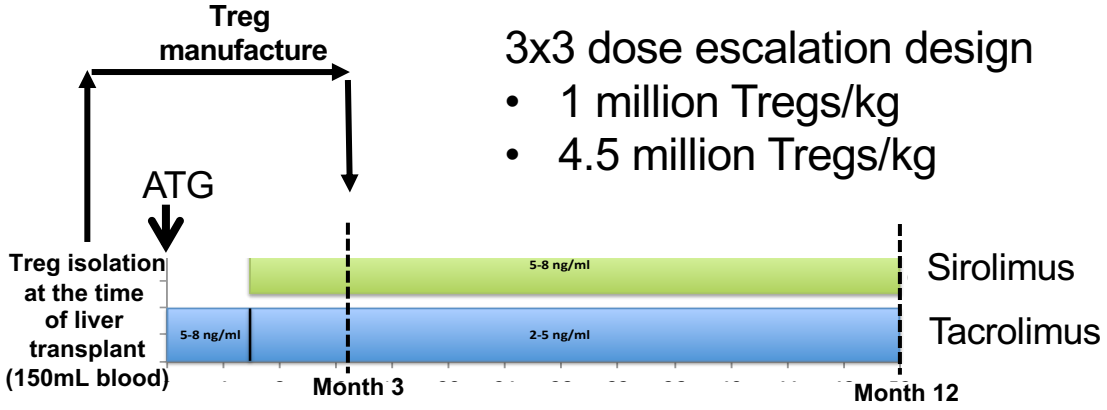
GIOVANNA LOMBARDI

Release Criteria

>60% $CD4^+CD25^+FOXP3^+$ and <10% $CD8^+$)
Bead removal (<100 x 3M)
Suppressive function (>60%)
Viability (>70%)
Sterility

Safinia N. et al. *Oncotarget* 2016;7(7):7563-77

'ThRIL': Single-arm phase I trial assessing the safety and biological efficacy of ex vivo expanded polyclonal Tregs



3x3 dose escalation design

- 1 million Tregs/kg
- 4.5 million Tregs/kg

16 months recruitment period

414 Patients Screened → 32 Patients Eligible → 17 Patients Consented → 7 Patients Transplanted → 3 Patient Dosed

382 Patients Excluded

15 Patients Declined

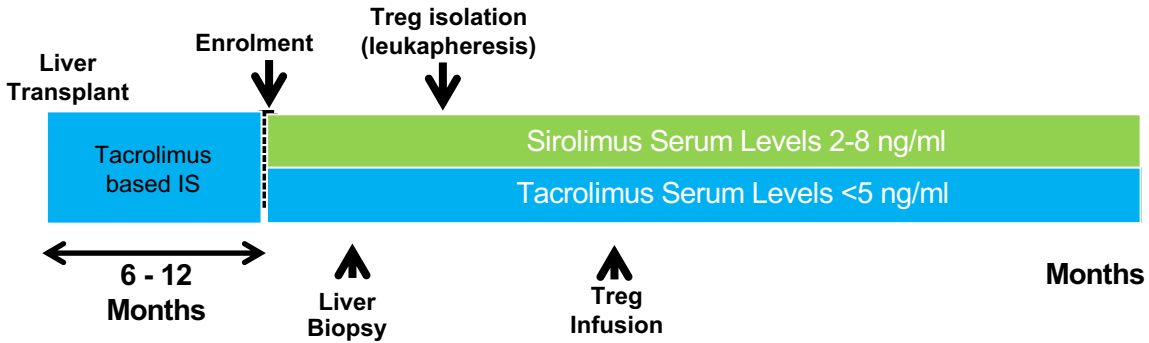
10 Patients Withdrawn	
Logistical reasons	2
Clinical Deterioration	2
Marginal DCD Graft	4
Delisted	2

3 Patients withdrawn	
Complications	2
Failure to manufacture minimum dose	2

Sanchez-Fueyo A. et al. Am J Transplant 2020

'ThRIL': Single-arm phase I trial assessing the safety and biological efficacy of ex vivo expanded polyclonal Tregs

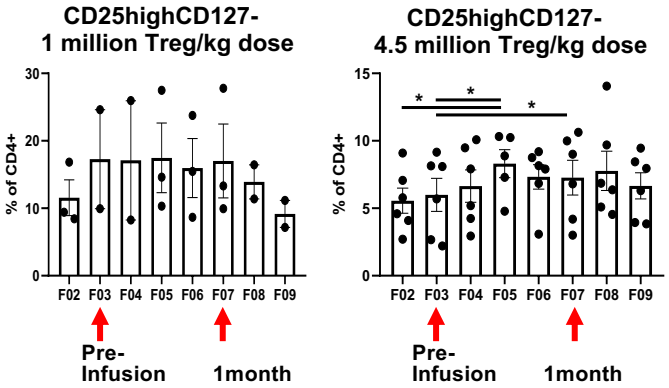
Amended trial design: 6 patients dosed at 4.5 million Tregs/kg



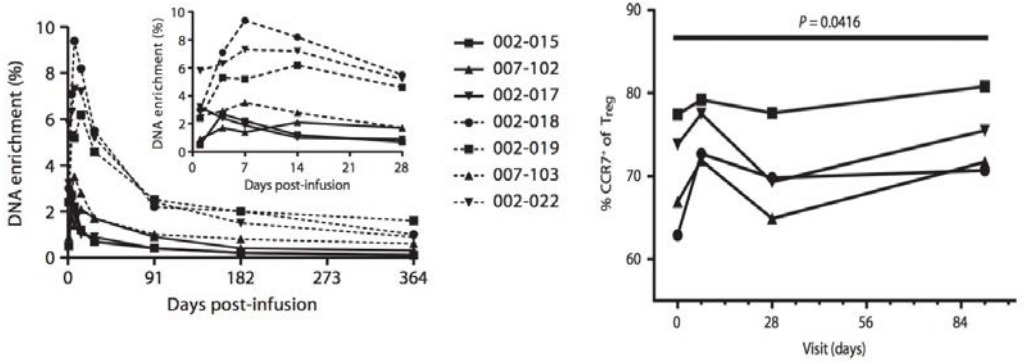
Sanchez-Fueyo A. et al. Am J Transplant 2020

'ThRIL': Immunomonitoring results

CIRCULATING TREGS



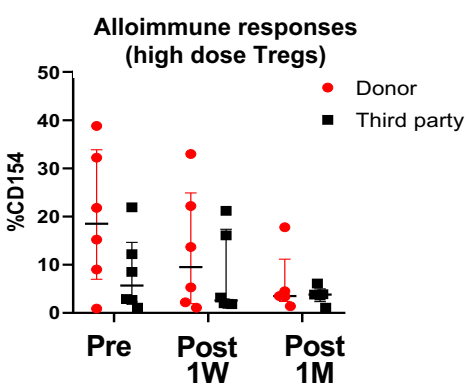
Sanchez-Fueyo A. et al. Am J Transplant 2020

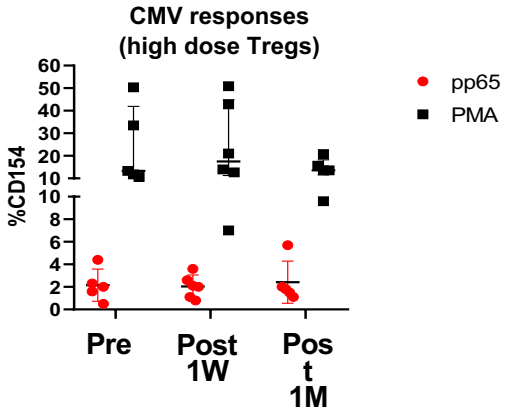


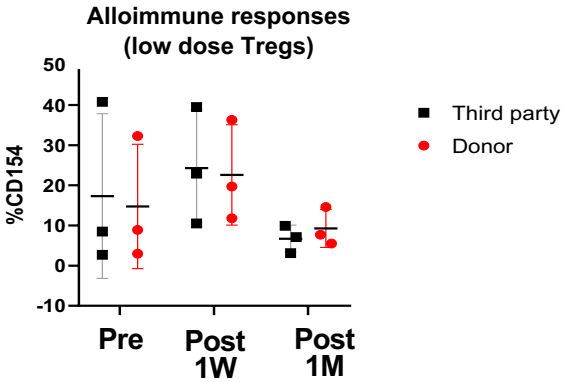
Bluestone J et al. Sci Transl Med 2015

'ThRIL': Immunomonitoring results

DONOR SPECIFIC HYPO-RESPONSIVENESS WITH PRESERVED AND ANTI- CMV T CELL RESPONSES

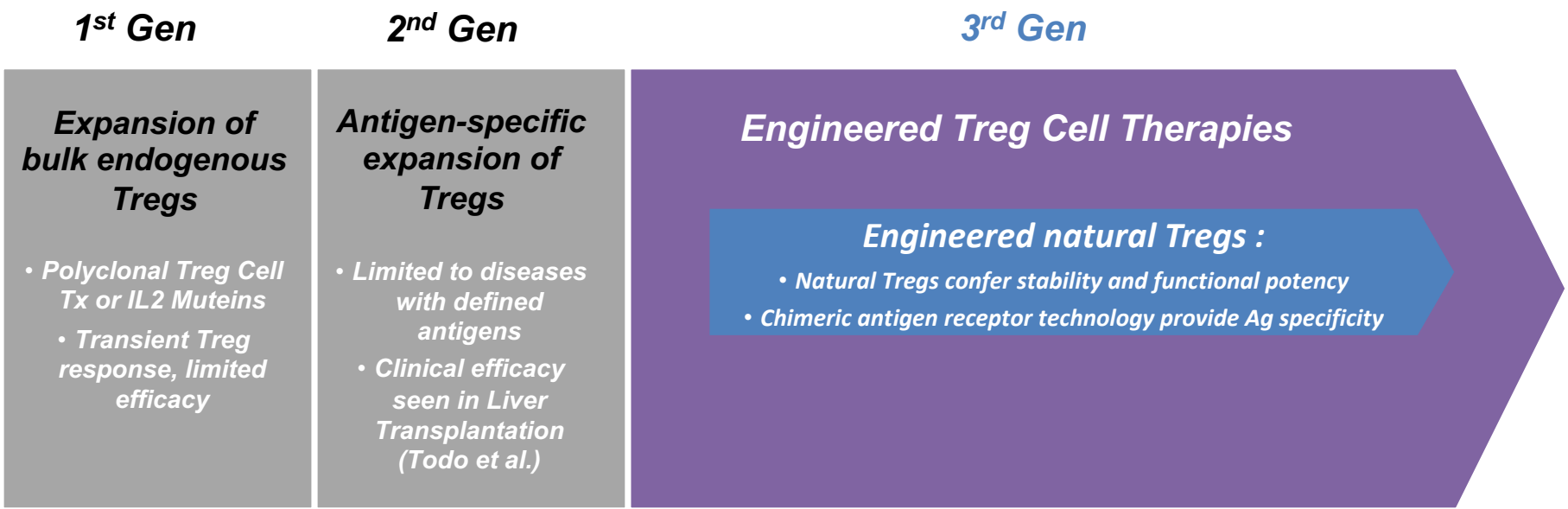




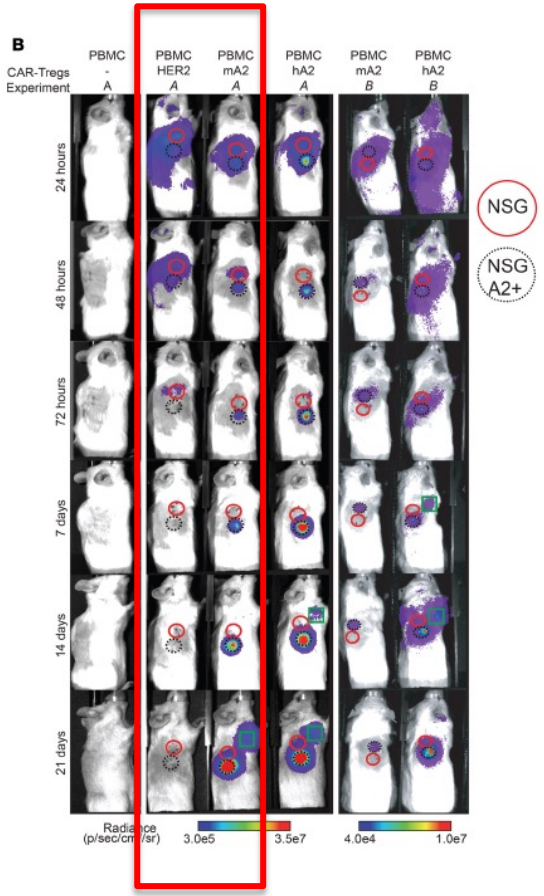


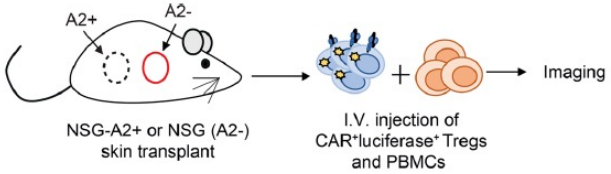
Sanchez-Fueyo A. et al. Am J Transplant 2020

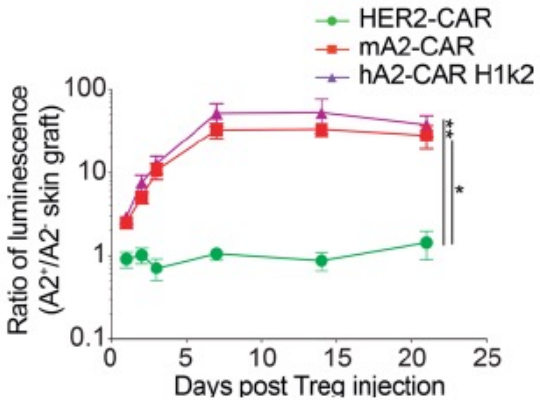
Creating 3rd generation Treg products: multi-modular engineered Tregs



CARs effectively promote the trafficking of Tregs to the target tissue







- **Local accumulation, long-term persistence in <u>lymphopenic</u> host**
- **Unspecific CAR-Tregs also home, but do not persist in the allograft**

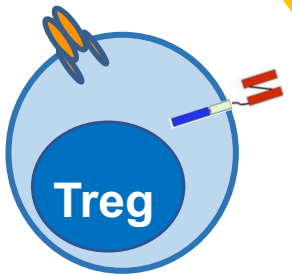
Dawson et al. JCI Insight. 2019;4(6):e123672

Treg engineering: from CARs to TRUCKs & more…

Ag specificity
(TCR, CAR)

Safety
(suicide switch)

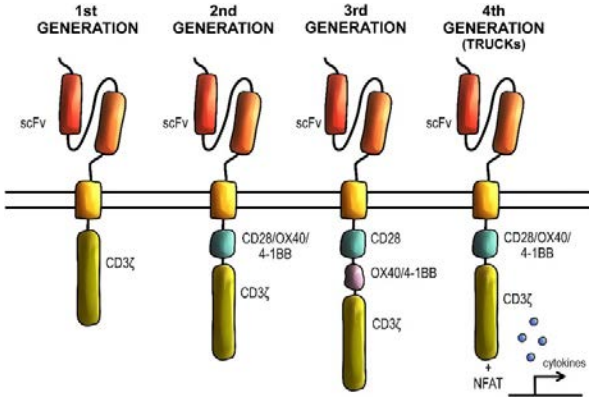
Regulability
(replacement of endogenous TCR , SynNoth technology)



Stability & persistance
(Foxp3 lock, IL-2)

Immunogenicity
(off the shelf)

Functional improvement
(citokines)



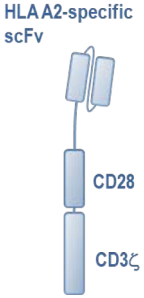
MIT Technology Review

BIOTECHNOLOGY

Genome engineers made more than 13,000 CRISPR edits in a single cell

A team at George Church's Harvard lab wants to redesign species with large-scale DNA changes.

QEL-001 LIBERATE Study: Phase I/II Trial in Liver Transplantation



Megan Levings
VANCOUVER
(MacDonald et al. JCI 2016)

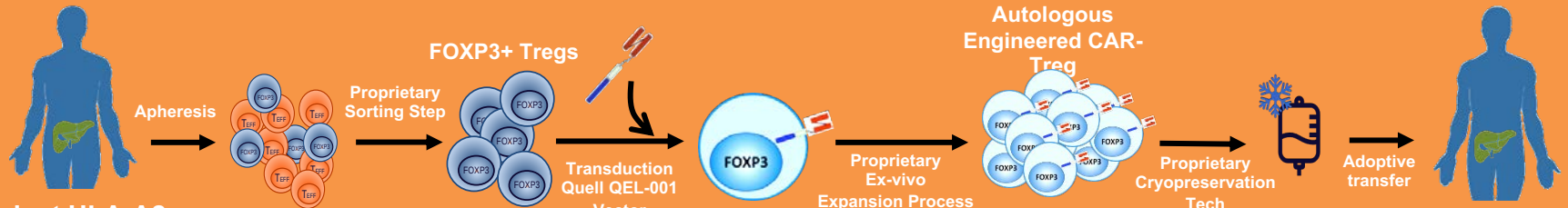
Giovanna Lombardi
KING'S COLLEGE LONDON
(Boardman et al. AJT 2017)

Elmar Jaeckel
HANNOVER
(Noyan et al. AJT 2017)

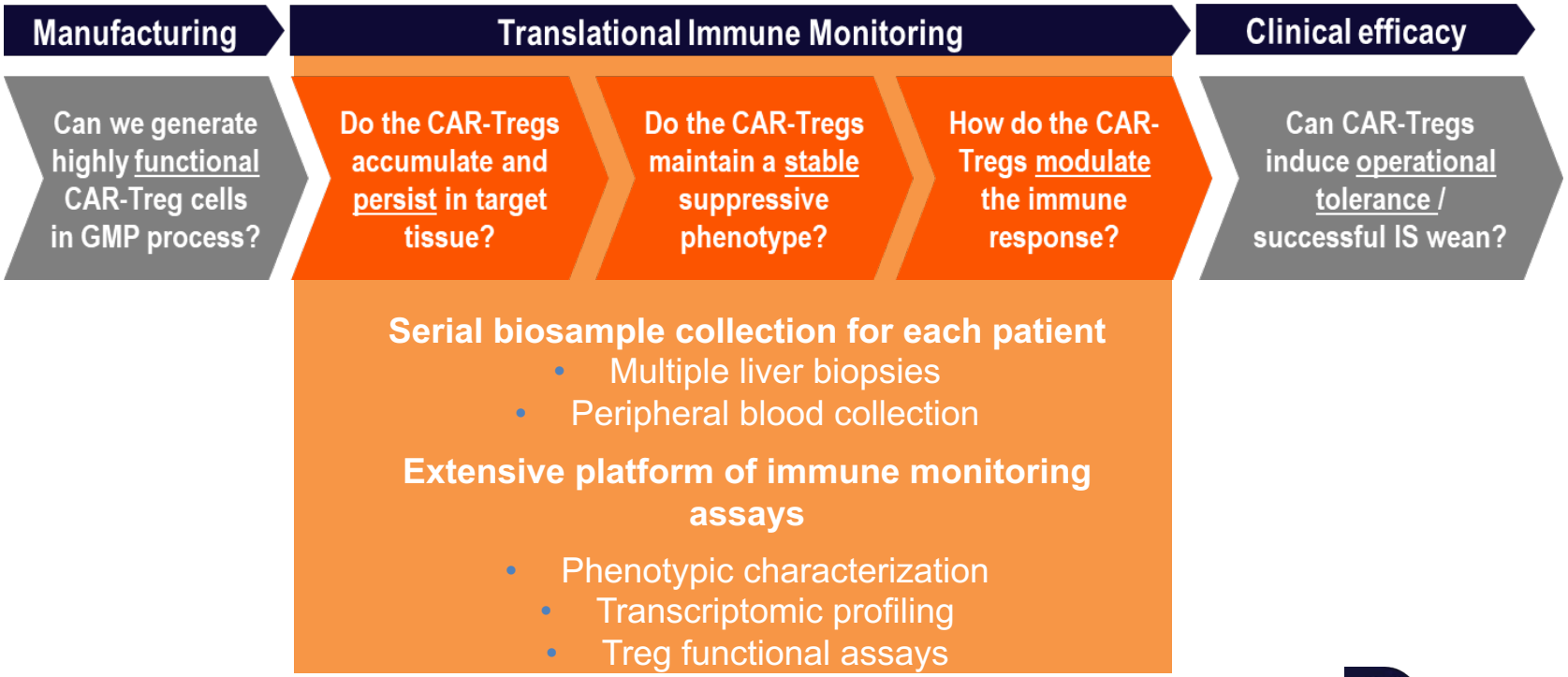
25% of our Tx population – mismatched for HLA-A2

SYSTEMIC IMMUNOSUPPRESSION

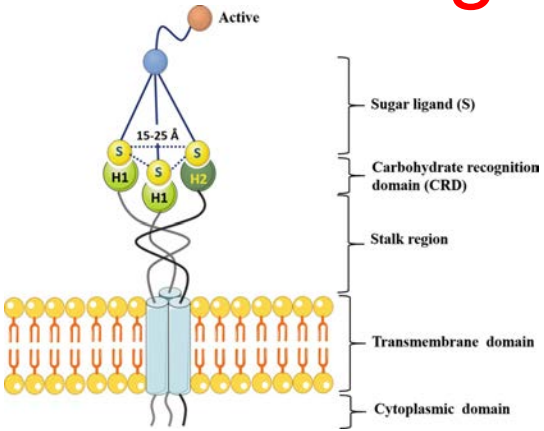
WEAN TO IMMUNOSUPPRESSION FREE



QEL-001 Immune monitoring

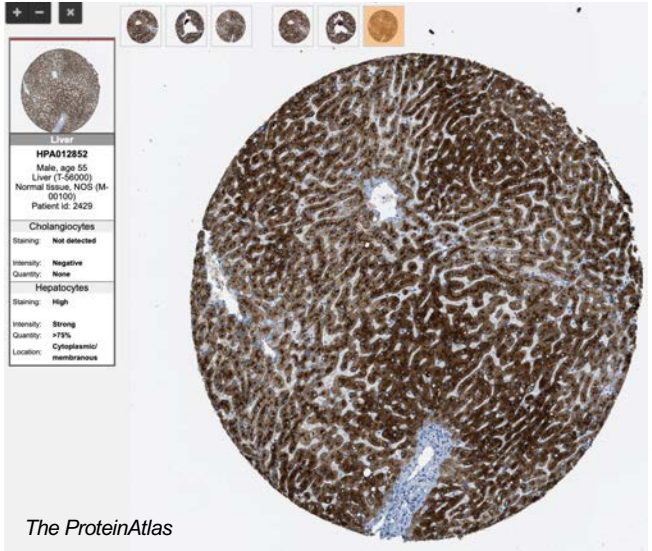


Organ specific CAR-Tregs



- 2 homologous subunits: H1 major, H2 minor
- Expression on sinusoidal surface of hepatocytes
- C-type lectin
- Mediates endocytosis of plasma glycoproteins (with removed terminal sialic acid residue on carbohydrate moieties). Target in autoimmune liver disease.
- Expression in inflammation/cirrhosis: increase in expression (HepG2)

ASGPR1



SUMMARY

- **Liver transplantation** – unique experimental medicine model to investigate the properties of immunomodulatory cell therapies.
- **Safety of polyclonal and antigen-specific Treg preparations**
- **Engineered Tregs** – strong pre-clinical rationale / safety / pleiotropic immunosuppressive properties / manufacturability
- **Questions to be addressed** – cell number, conditioning, trafficking, longevity, overall potency, mechanism of action.

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THANK YOU

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