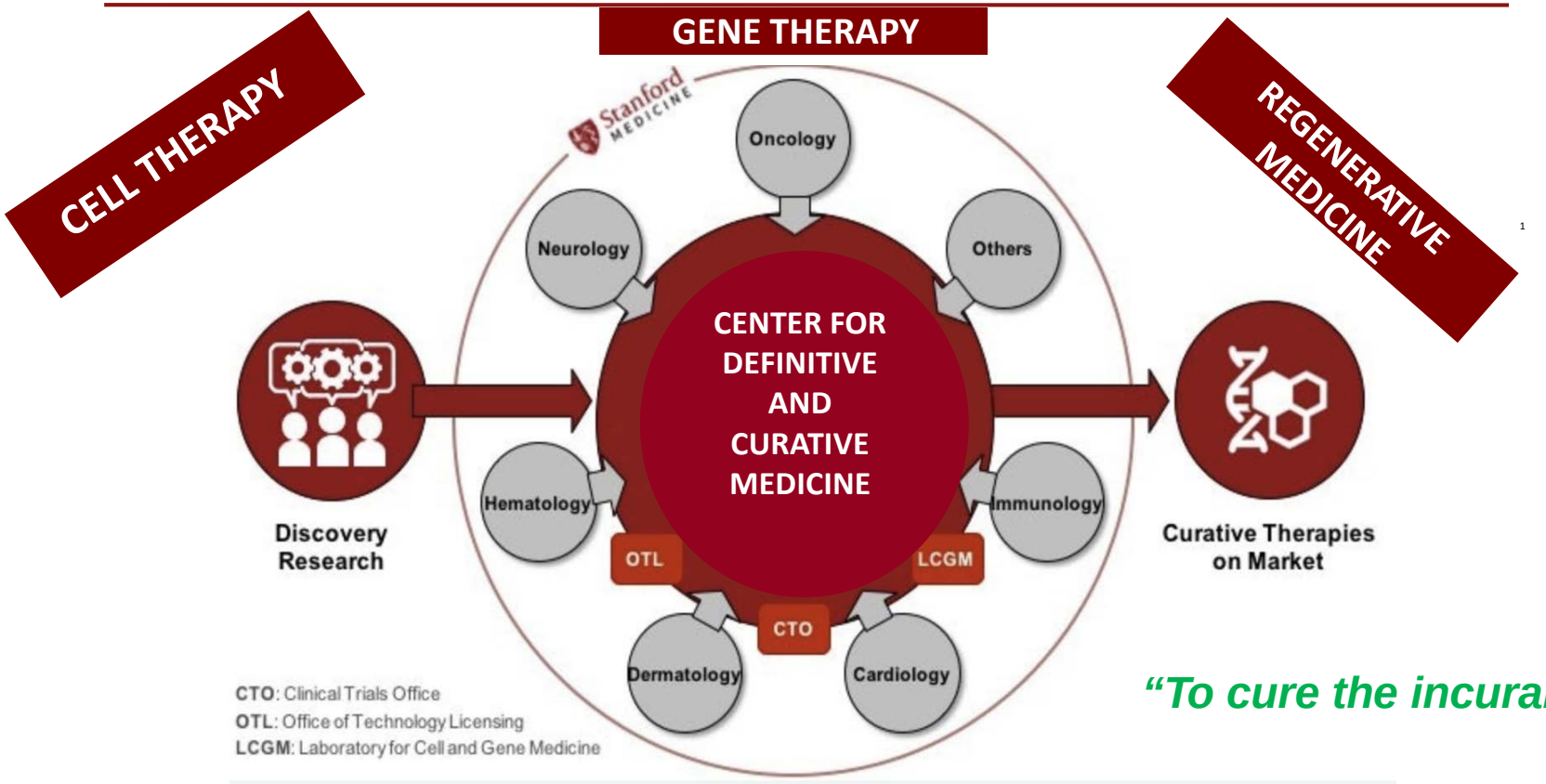
Stanford MEDICINE

Lucile Packard Children's Hospital Stanford

IPEX Syndrome and Gene Therapy Case Study

Rosa Bacchetta, MD
Division of Stem Cell Transplantation and Regenerative Medicine
Department of Pediatrics, Stanford
rosab@stanford.edu

Stanford Pediatric Stem Cell Transplantation, Cell and Gene Therapy, and Regenerative Medicine



"To cure the incurable"

Immune Dysregulation Polyendocrinopathy Enteropathy X-linked (IPEX) Syndrome

Prototype of Genetic Autoimmune Disease

Genetic disease: FOXP3 gene mutation resulting in regulatory T cell dysfunction

Autoimmune Clinical Manifestations: neonatal diabetes, severe enteropathy and eczema

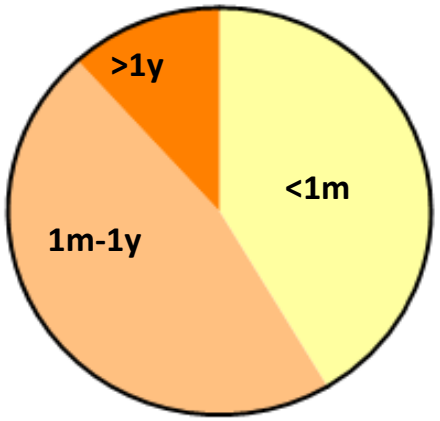
Severe onset and outcome: fatal in infancy

Current treatments: only partial efficacy

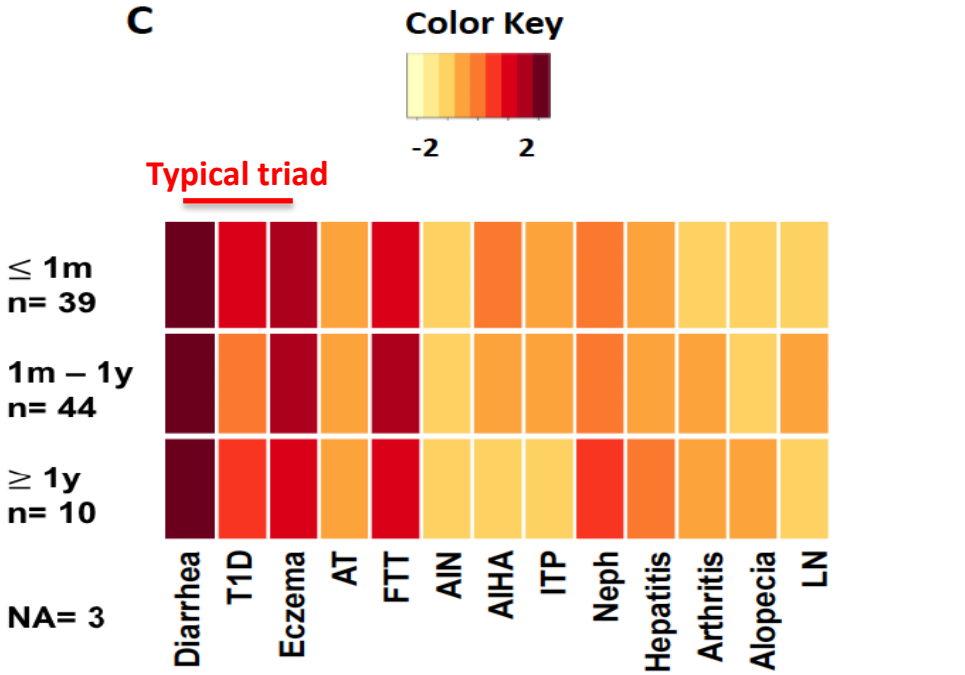
Rare disease with wide distribution-Incidence under estimated

Bacchetta et al, Ann Rev NYAS 2016; Barzaghi et al, JACI 2018

Immune dysregulation Polyendocrinopathy Enteropathy X-likned Syndrome (IPEX): main features at onset



age of onset
N=96 patients



Barzaghi F, Frontiers Immun, 2012
Bacchetta R, NYAS 2016
Barzaghi F, JACI 2018

TWO BROTHERS WITH THE SAME FOXP3 MUTATIONS, BUT DIFFERENT CHANCES TO BE CURED

- **Onset at few weeks of life**, with severe enteropathy, severe weight loss and hepatitis
- **Genetic diagnosis of FOXP3 mutation** at about 4mo, *after already 3 mo in hospitals*
- **Immune suppression over the course of 18 months**: methylprednisolone, tacrolimus, sirolimus, ATG, ATG, tocilizumab, bortezomib, and campath. Overall poor response.
- **αβ T-cell depleted haploidentical HSCT** from the father **at 18 months**
- **Today**: 3 months post HSCT: alive, 100% donor chimerism, no IS, *he is carrying over gut and liver problems.*

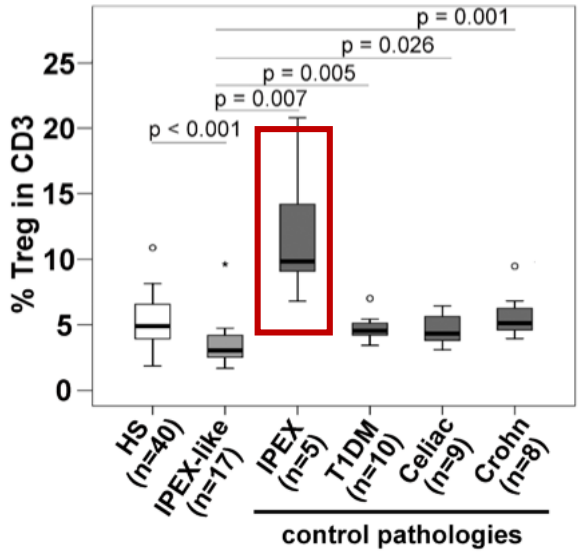
- **Onset at few weeks of life**, admitted to Stanford ER with severe dehydration and weight loss.
- **Immunologic diagnosis within the first month and genetic diagnosis** of FOXP3 mutation confirmed 2 weeks later.
- Presence of autoAb but no clinical manifestations yet.
- **Immune suppression** : methylprednisolone, and sirolimus with good response.
- **αβ T-cell depleted haploidentical HSCT** from the father **at 4 months of age.**
- **Today** 1 month post HSCT: alive, engrafted, no IS, no autoimmune clinical manifestations.

……need for early diagnosis and curative therapy available to every patients

Stanford, Sept 2018

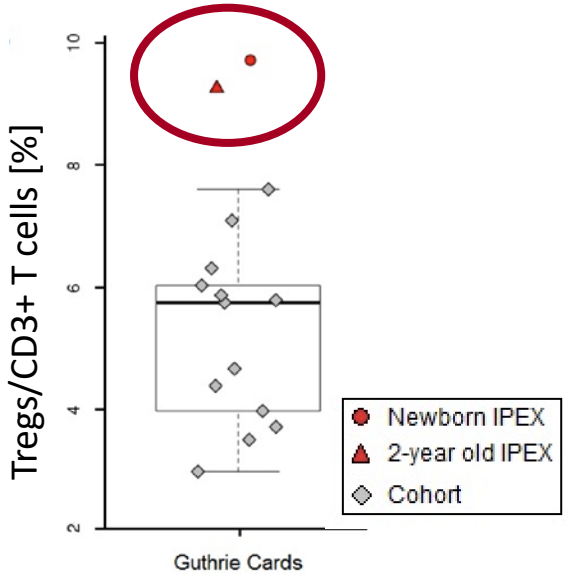
IPEX syndrome can be identify at birth: facilitate approval of tests that can be broadly used to identify the disease

- **Combined epigenetic quantification of TSDR for regulatory T cell and TLSDR for CD3+ T cells allows discrimination between IPEX and IPEX-like patients.**



Barzaghi et al., J Autoim 2012

- **Potential for newborn screening**

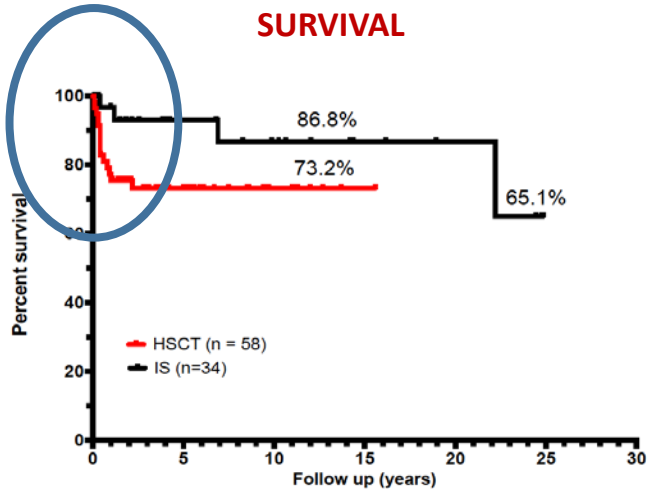


Baron U, Sci Transl Med 2018

What can be plan to improve current treatment outcome

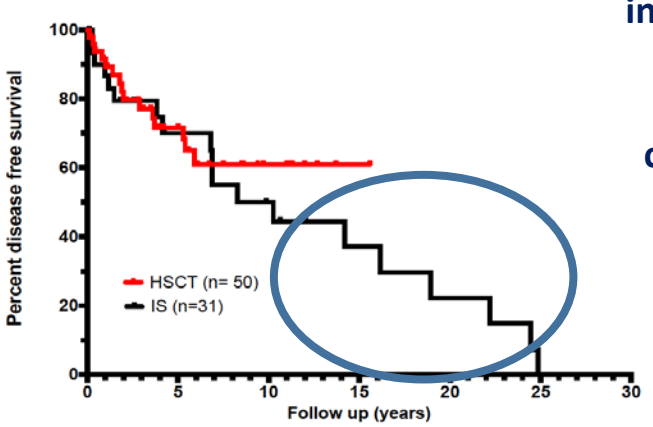
A. Intervene at onset to bridge to transplant or instead of the transplant

SURVIVAL



	Survival probability (%)				
HSCT	82.8	75.5	73.2	73.2	73.2
IS	96.7	96.7	92.9	86.8	86.8
Time	6m	1y	5y	10y	15y

DISEASE FREE SURVIVAL



	Survival probability (%)				
HSCT	93.9	89.3	71.6	61.0	61.0
IS	90.0	83.1	65.1	50.1	37.1
Time	6m	1y	5y	10y	15y

B. Intervene in chronically ill patients to reduce the continue use of immune suppressive drugs

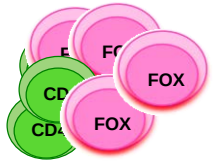
Barzaghi et al. JACI online publication, Jan 2018

Two possible approaches of cell/gene therapy for IPEX syndrome

Cell therapy with LV-engineered T cells to restore tolerance

wtFOXP3 over-expression in conventional CD4+ T cells

LV-FOXP3/NGFR



***in vitro* expansion and selection of transduced cells**

Re-infusion of purified autologous CD4^{LVFOXP3} T cells with normal regulatory function

Gene therapy with CRISPR/Cas9 gene corrected autologous HSPCs to preserve endogenous regulation of FOXP3 gene expression

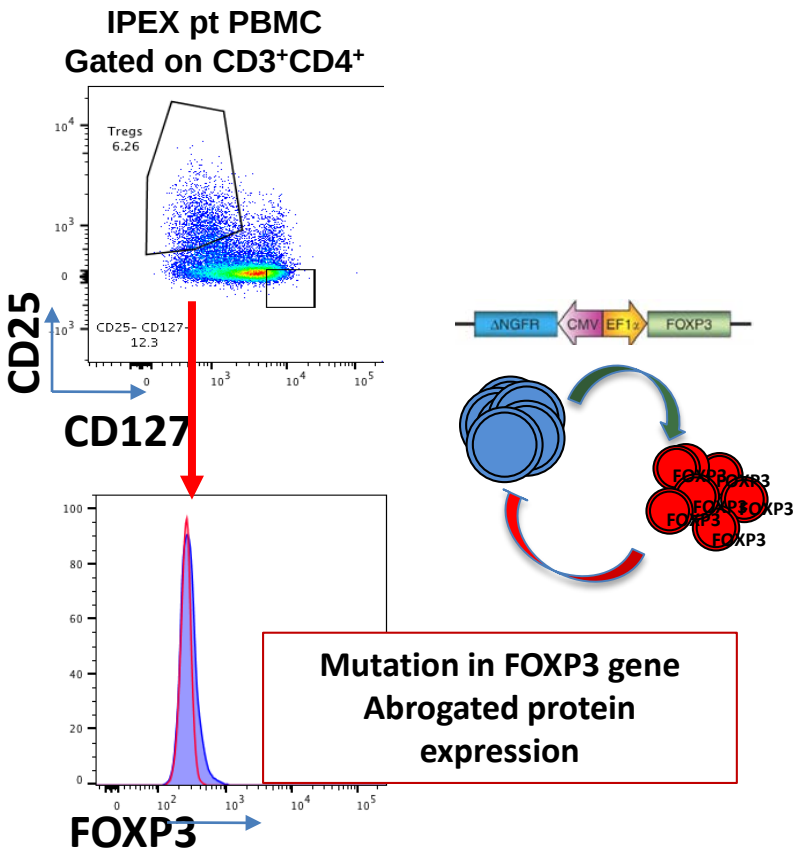
- ***Ongoing studies on best strategy***

Sato Y, Postdoct

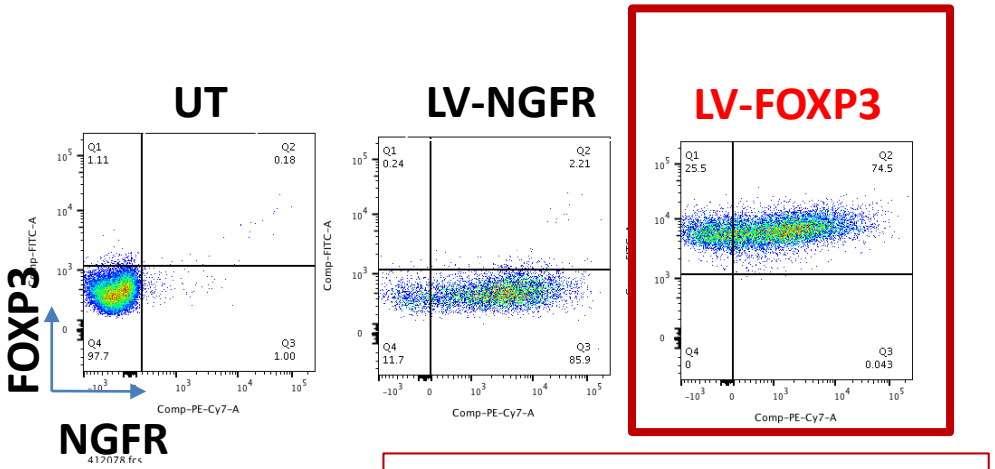
Passerini L et al. STMed 2013

Bacchetta Lab, Stanford

CD4$^{LV\text{-}FOXP3}$ "CONVERTED" Treg CAN BE OBTAINED FROM FOXP3 null T CELLS

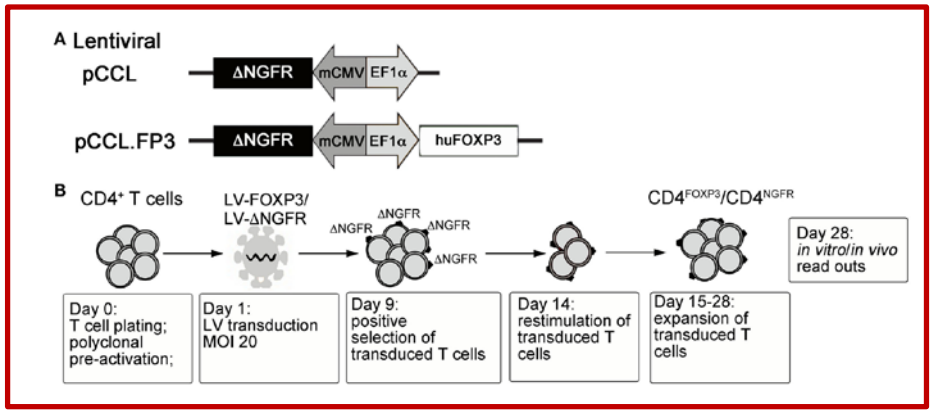


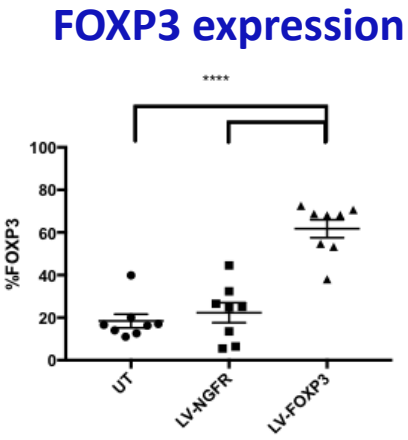
Mutation in FOXP3 gene
Abrogated protein expression

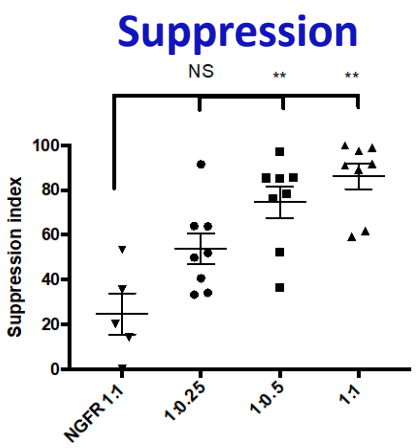


FOXP3 gene protein expression
Restored after LV-FOXP3 "conversion"

DEVELOPING CD4^{LVFOXP3} "CONVERTED" TREG CELLS FOR CLINICAL USE





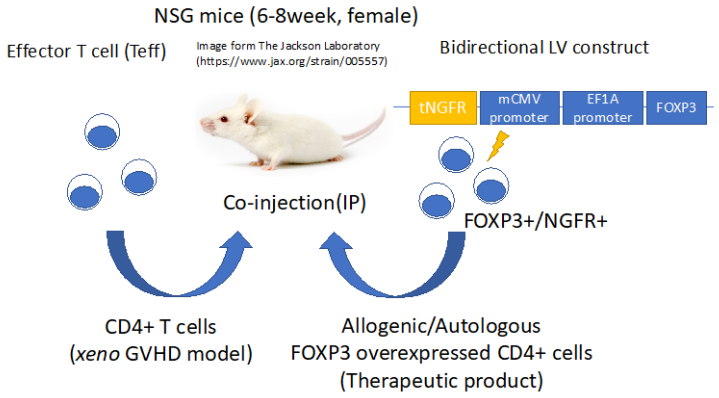


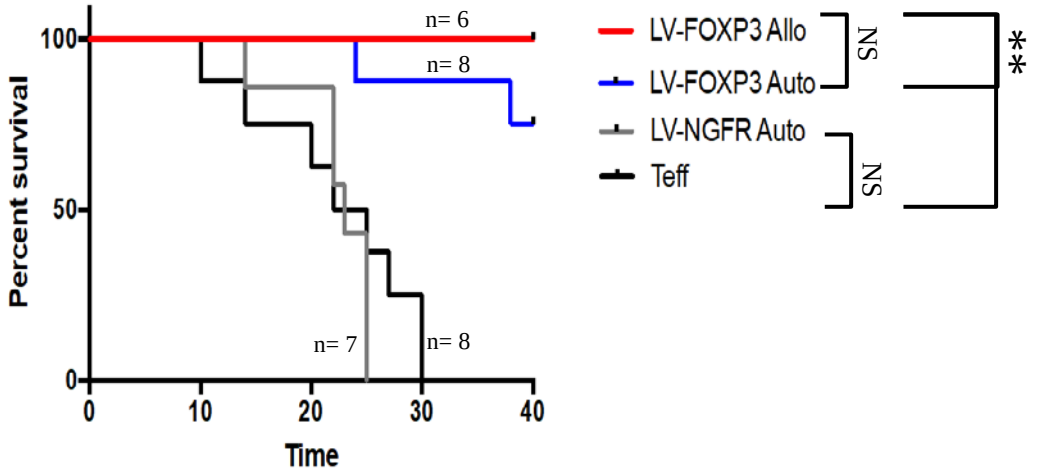
……process is consistent and reproducible among different subjects

Sato Y, Stanford University

DEVELOPING CD4^{LVFOXP3} "CONVERTED" TREG CELLS FOR CLINICAL USE

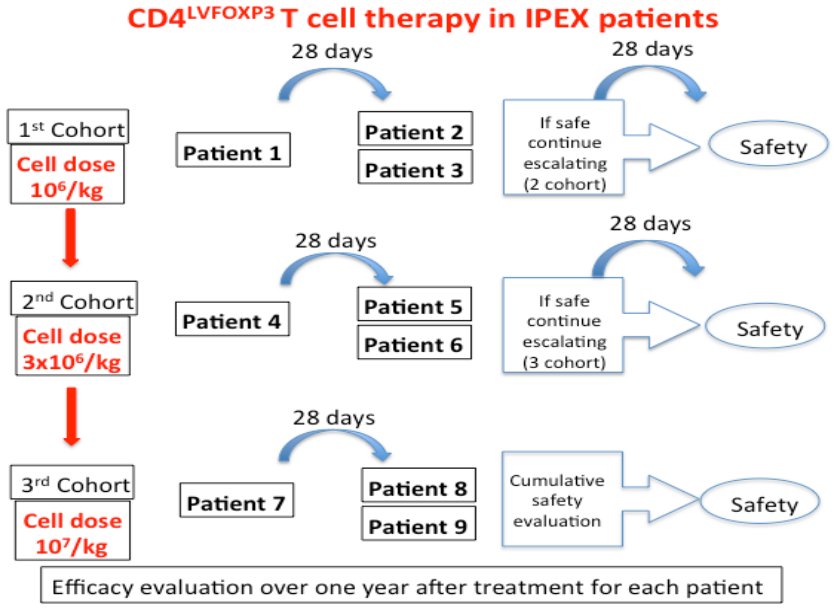
Methods: *in vivo* (xeno GVHD model)





Safety, efficacy, survival tested in hu-mice models

PHASE I CLINICAL PROTOCOL FOR THE CLINICAL USE OF $CD4^{LVFOXP3}$ T CELLS IN IPEX SYNDROME



Primary Objective:

- Asses safety
- Dose ranges and feasibility
- PK and PD of the cell product

Outstanding Questions:

Patient inclusion criteria?

- Disease status
- Age
- Response to prior therapy

Bacchetta &Roncarolo_ Stanford University

KEY QUESTIONS TO EASE THE CLINICAL APPLICABILITY OF PHASE I TRIALS IN IPEX AND SIMILAR BLOOD RARE DISEASES

- **CRITERIA FOR PATIENTS ELIGIBILITY FOR RARE DISEASES**

  Usual criteria for phase 1 study include the presence of clinical manifestation and failed previous therapy: based on clinical history, tools for early diagnosis and disease measurements, *can we aim to treat even before the symptoms arise?*

- **AGE CONSTRAIN FOR PHASE I TRIAL:**

  many of these disease have very early onset, patients can deteriorate very quickly: *can we intervene at early pediatric age?*

- **DISEASE SPECIFIC CRITERIA for evaluating safety and efficacy of a cell/gene product based on preclinical model: what are the expectations from the available preclinical models?**

- **Need to establish a committee to look at the issues related to clinical research in rare disease.**

Pediatric Stem Cell Transplantation and Regenerative Medicine Team, Stanford University

Maria Grazia Roncarolo, MD
Division Chief
C0-directore CDCM

Translational Medicine
Immune Tolerance
Gene Therapy

Matthew Porteus, MD, PhD
C0-directore CDCM

Genome Editing
Hemoglobinopathies
PIDs

Robertson Parkman, MD

Immune Reconstitution
SCT for PIDs

Ken Weinberg, MD

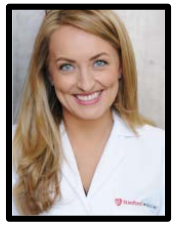
Immune Reconstitution
Viral Specific Immunity
HSC Biology

Rajni Agarwal-Hashmi, MD

Experimental SCT
CAR-T Therapies

Rosa Bacchetta, MD

Genetic Autoimmune Diseases
Tolerance Induction
Genome Editing



Agnieszka Czechowicz, MD, PhD
BMF/Fanconi Anemia
mAb Conditioning

Ami Shah, MD

Quality Control
SCT and Gene Therapy
for Metabolic Diseases

Sandeep Soni, MD

Hemoglobinopathies
Gene Therapy

Katja Weinacht, MD, PhD

Pathophysiology of PID's
Autoimmune Anemias
HSC Metabolism

Alice Bertaina, MD, PhD

Haplo- Transplantation
Experimental SCT

Melissa Mavers, MD, PhD

GvHD Pathophysiology
GvHD Treatment

Julia Chu, MD

Immune Reconstitution
Gene Therapy for PIDs