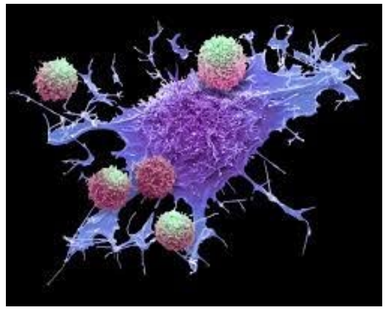
Caso 3:
Terapia celular para la Inducción de Tolerancia Inmunológica

Cell Therapy to Induce Immune Tolerance

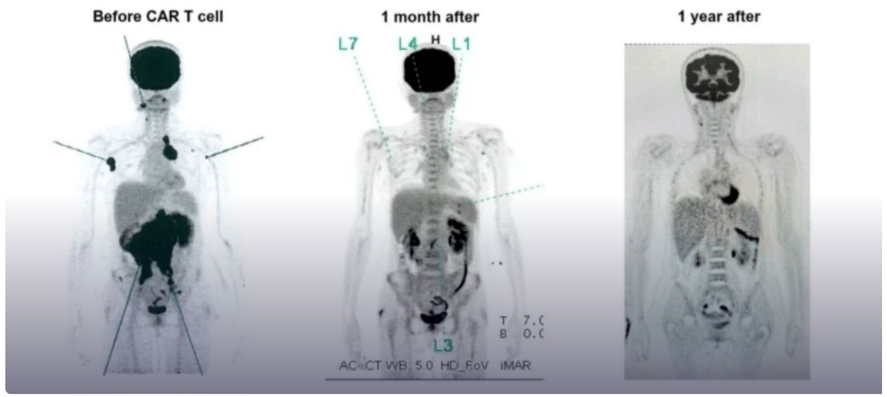
Rafael Correa-Rocha
Instituto de Investigación Sanitaria Gregorio Marañón (IISGM)
THYTECH SL

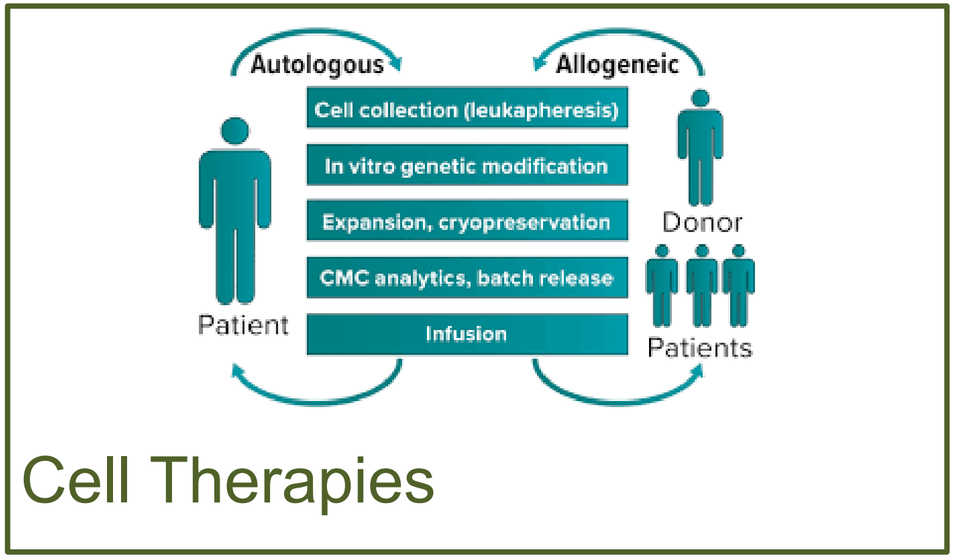
Cell therapies

A revolution in therapeutics



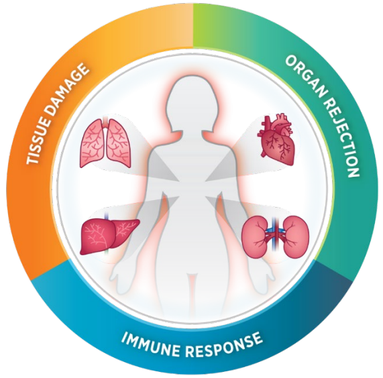
CAR T Cell Therapies





Cell Therapies

ORGAN TRANSPLANTATION



Organ availability

Only 10% of global transplant needs are met worldwide

Immune Rejection

10-20% of patients will experience at least one episode of rejection

Transplant Rejection

an Unmet Medical Need

TRANSPLANT

IMMUNE REJECTION

IMMUNOSUPPRESSANTS

- INFECTIONS
- AUTOIMMUNE DISORDERS
- CANCER

Thanks to them, **transplants can be carried out**

But they have a **pleiotropic action** on the **immune system** (weaken our defenses)

Not 100% Effective preventing rejection

Median graft survival **< 20 years**

82 years

Average Life Expectancy

Adult Patient **< 20 years**

Child **< 20 years**

In **children** **Viability of transplanted organ** is even **further from guaranteeing life expectancy**.

An unmet medical need in our Hospital

Hospital General Universitario Gregorio Marañón

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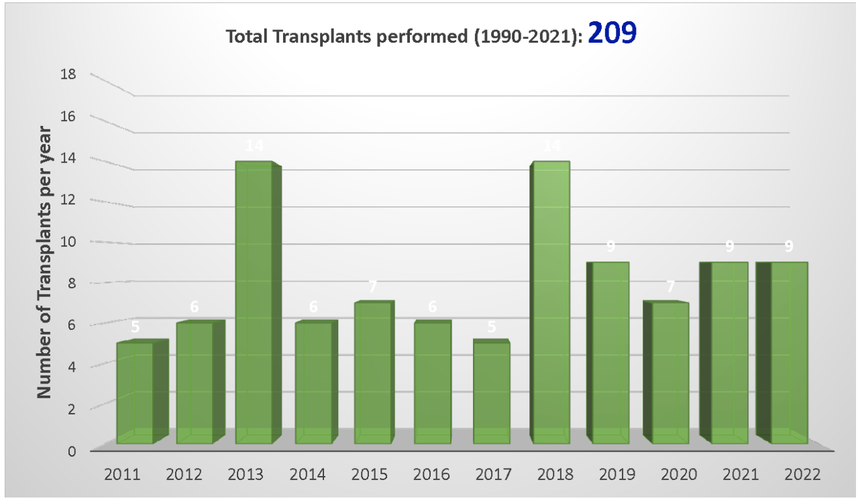
Comunidad de Madrid



Half of transplanted hearts in children are lost before 15 years after transplantation

It is **necessary to develop <u>new strategies</u>** that:

* **Allow allograft survival** (induce **immunological tolerance**).
* **Avoid toxicity** associated with **immunosuppressive drugs.**

Immune balance and regulatory T cells (Treg) in Transplantation

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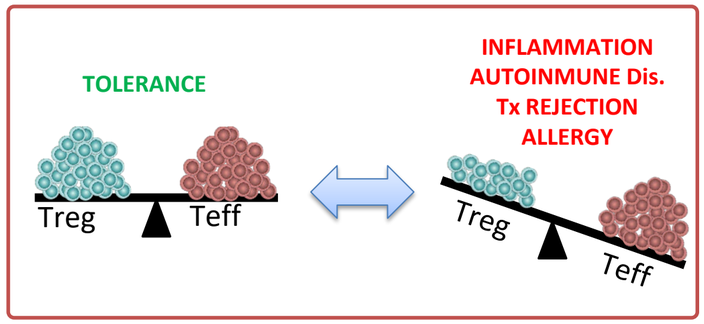
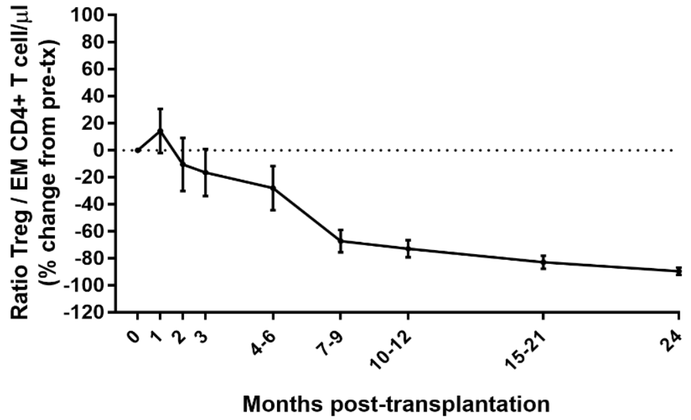
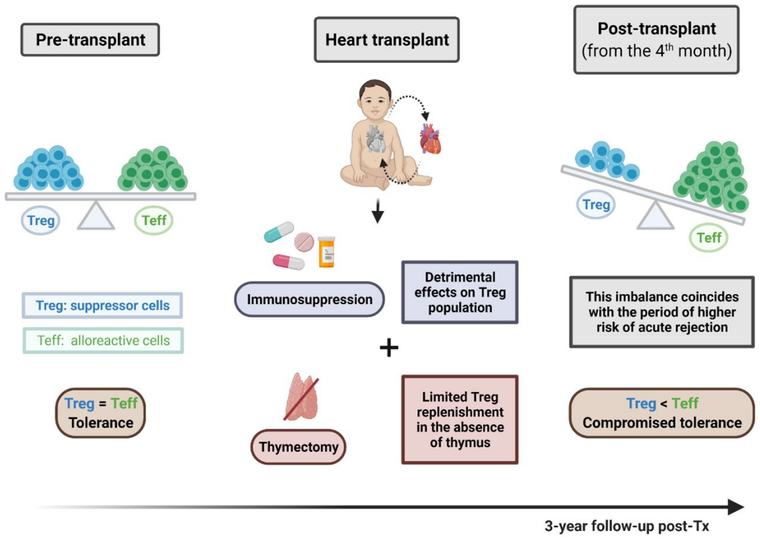
Instituto de Investigación Sanitaria Gregorio Marañón

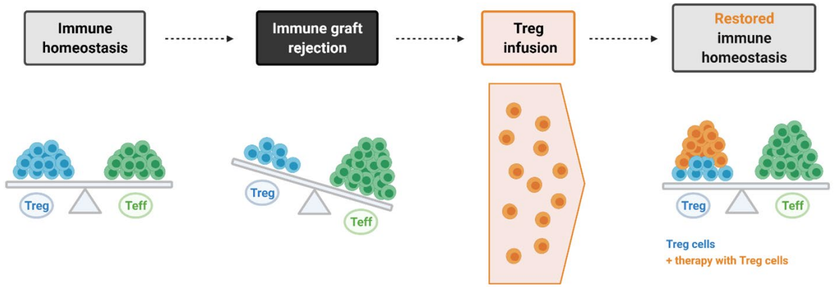


Treg/Teff balance in Heart transplant Children

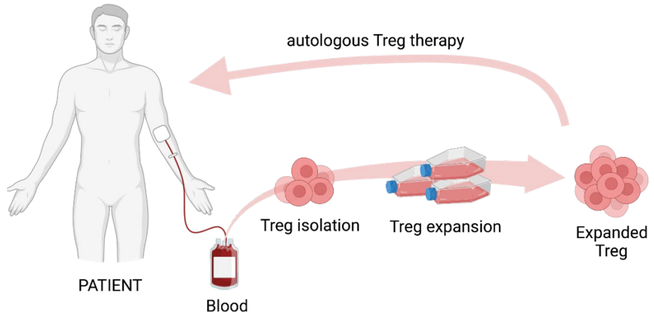




Bernaldo-de-Quiros et al. Transplant Direct. 2021 23;7(5):e693
López-Abente et al. Sci Rep. 2021 11(1):827



Treg therapy Standard approach

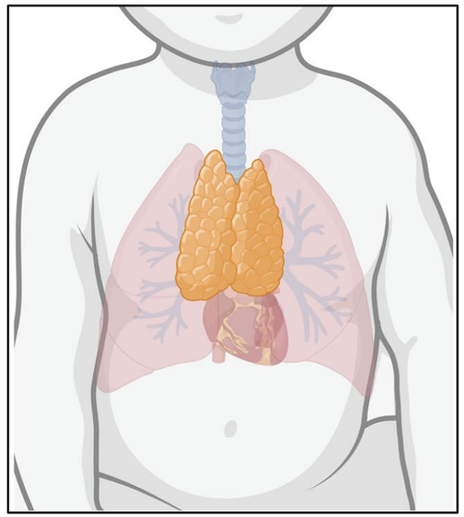


- Safe
- Not definitive conclusions about efficacy
- **Unviable in Children (500ml blood required)**

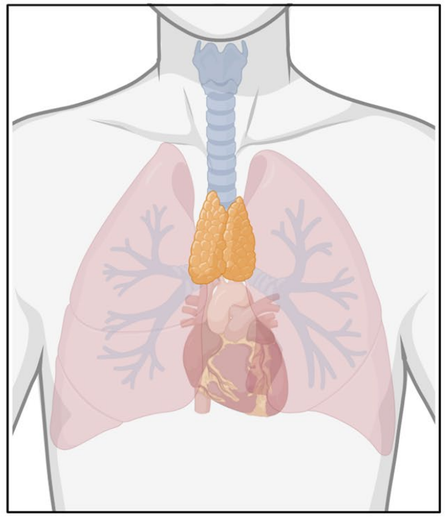
Discarded pediatric thymus as a source of therapeutic Treg

- The **Treg factory (thymus) is routinely discarded during pediatric cardiac surgery**
- Only organ larger in children than adults, due to thymic involution beginning before puberty
- In newborns and young children, surgical access to the heart requires removal of the thymus
- There are more Tregs in a discarded thymus than in the total periphery of an adult (≃ 250 million)

Newborn

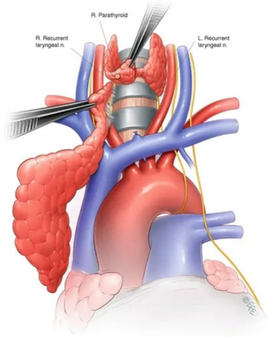


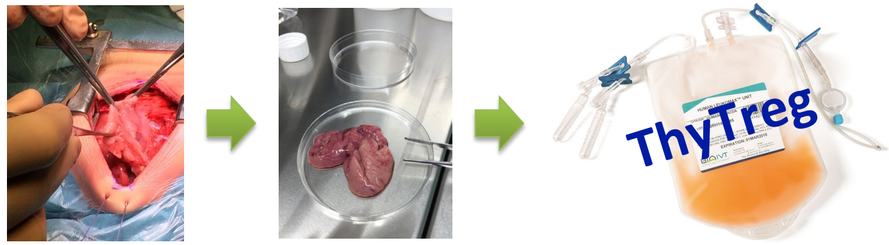
Adult



Treg Source	Yield, Treg cells
Adult peripheral blood apheresis	10 million
Cord blood unit	~5 million
Discarded pediatric thymus	Up to 500 million*

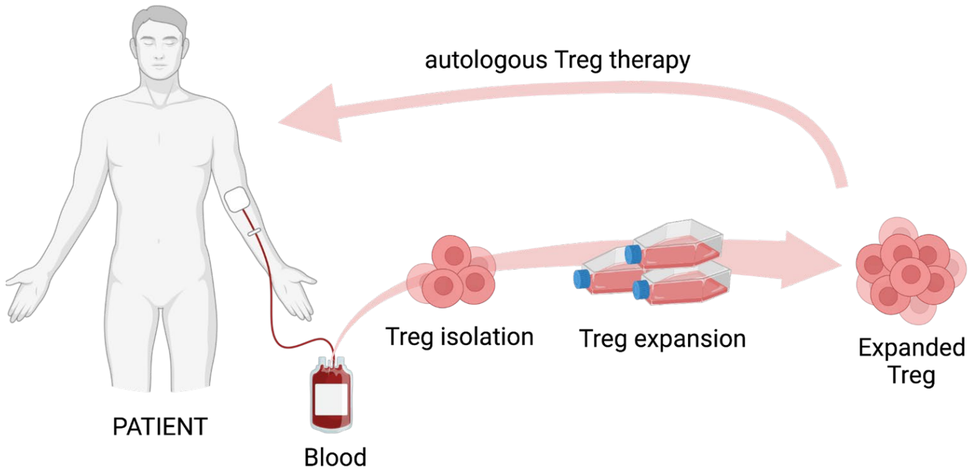
* Bernaldo-de-Quiros et al, Frontiers in Immunology 2022





thyTreg. An Innovative Approach to develop Treg Cell Therapies

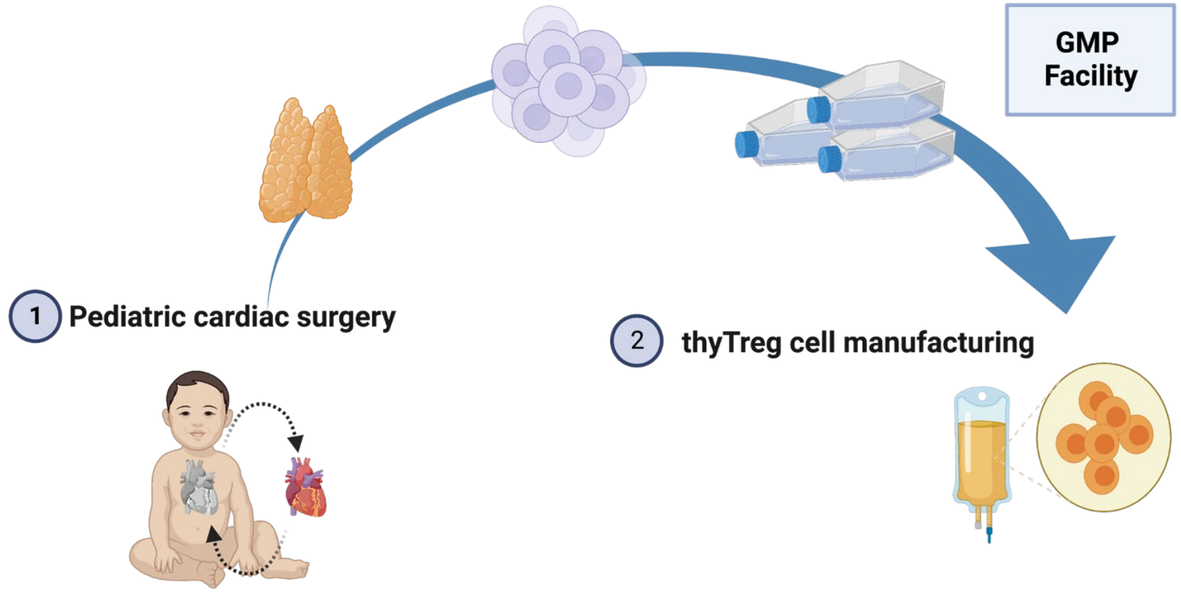
Standard approach



Treg source: BLOOD (500 ml)

- Maximum amount: 10 x10^6 Treg
- Yield: < 1 dose → expansion → **1 dose**
- Treg survival: 0.4 years
- ↓ suppressive capacity
- Unfeasible in pediatric patients
- For autologous use only

thyTreg approach



Treg source: THYMIC TISSUE (25 gr)

- Maximum amount: **500 x10^6 Treg**
- Yield: > 10 → expansion → **> 100 doses**
- thyTreg survival: > 4 years
- **↑ ↑ suppressive capacity**
- Feasible therapy in **children**
- Potential **allogeneic use**

Our experience as an example of existing challenges

The Pathway from the Bench to the Patient …

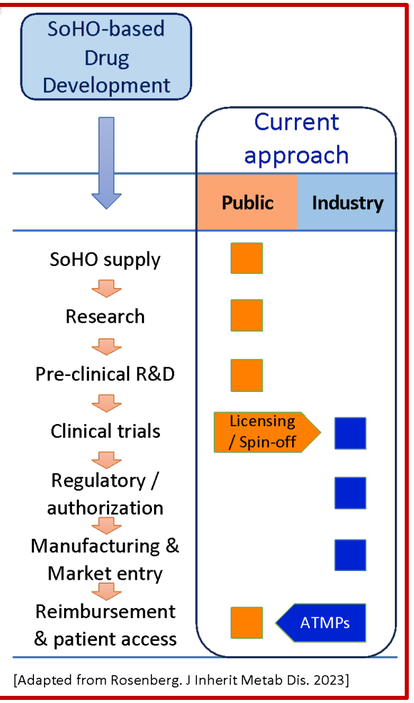
10.12.2007 EN Official Journal of the European Union L 324/121

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

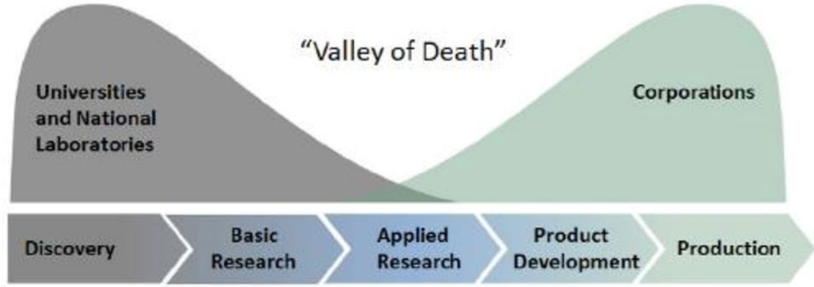
of 13 November 2007

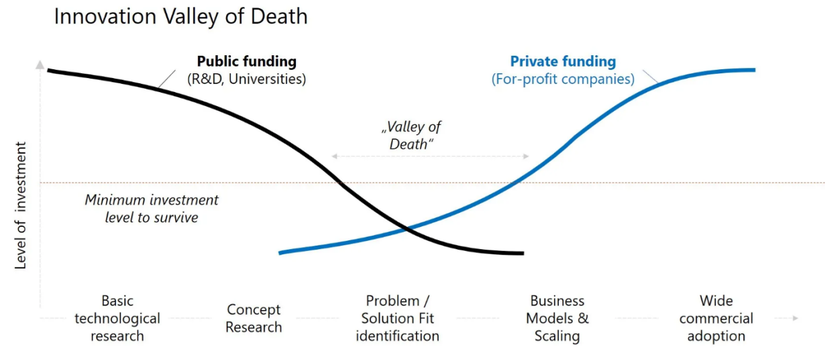
on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

(Text with EEA relevance)



[Adapted from Rosenberg. J Inherit Metab Dis. 2023]





Laboratorio de Inmuno-Regulación

Instituto de Investigación Sanitaria Gregorio Marañón

Treg Research

GMP Protocol thyTreg

thyTreg discovery

2014 **2017** **2019** **2030 ?**

Research → Pre-clinical → CT Phase I → CT Phase II → CT Phase III → Approb. EMA/FDA → PATIENT

From the Bench to the Patient…

Hospital General Universitario Gregorio Marañón
SaludMadrid
Comunidad de Madrid

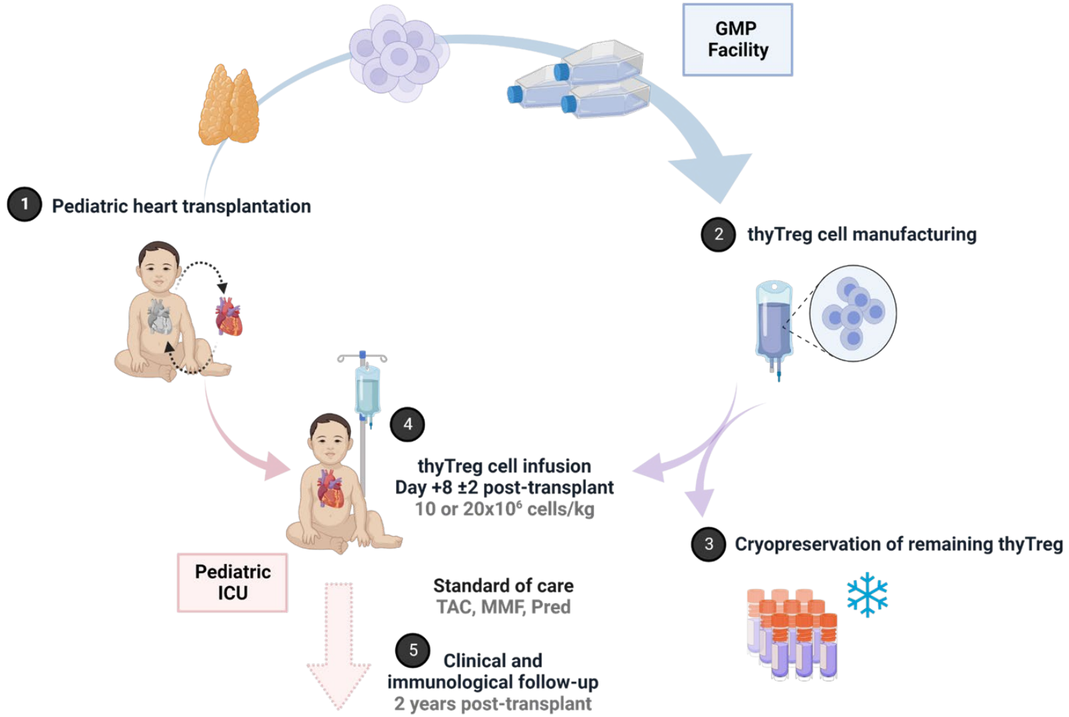
IiSGM
Instituto de Investigación Sanitaria Gregorio Marañón

Laboratorio de Inmuno-Regulación
Instituto de Investigación Sanitaria Gregorio Marañón

Cell Therapy With Treg Cells Obtained From Thymic Tissue (thyTreg) to Prevent Rejection in Heart Transplant Children

- ✓ Eudra-CT: 2018-003574-28 / Clinicaltrials: NCT04924491
- ✓ Authorized by Spanish Drug Agency (AEMPS) (Nov-19)
- ✓ **7 patients treated** (July 2020 – 2023)

1st

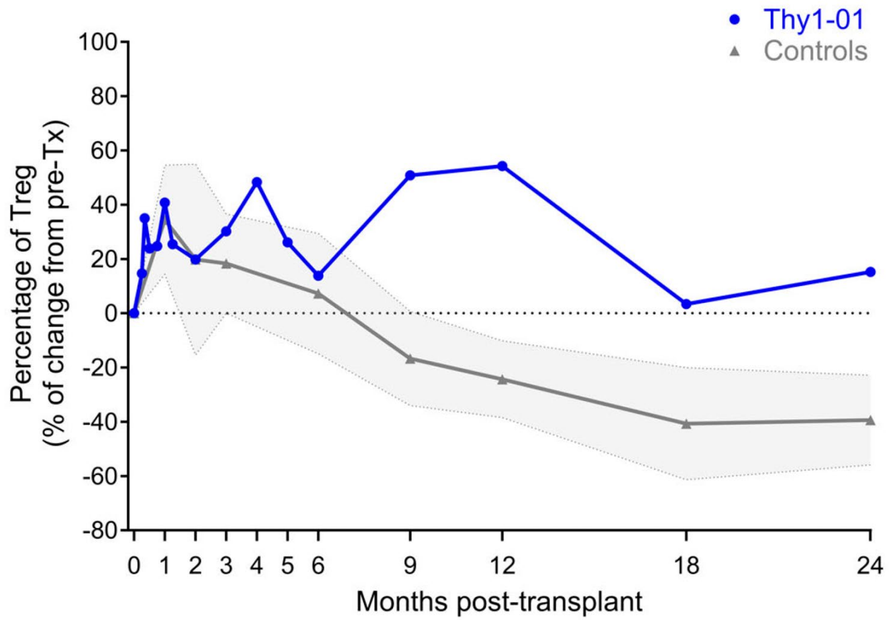


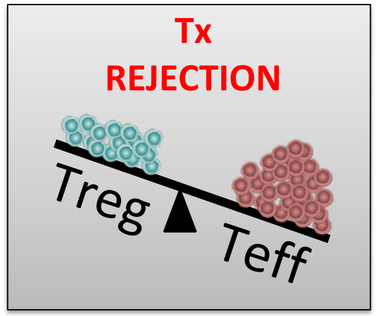
2014	2017	2019	2021	2023
Research	Pre-clinic	EECC Phase I	EECC Phase II	
600k €	700k €	2 M €	1,6 M €	

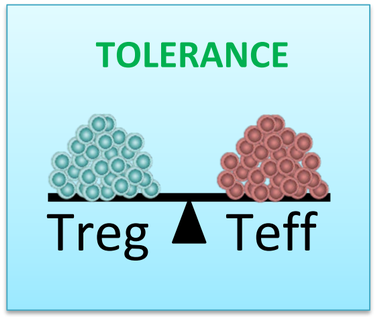
FAMILIA ALONSO FUNDACIÓN

A Pioneering Clinical Trial with thyTreg in Heart Transplant Infants

Patient 1 (6 months ♀)







JEM Journal of Experimental Medicine

BRIEF DEFINITIVE REPORT

First-in-human therapy with Treg produced from thymic tissue (thyTreg) in a heart transplant infant

Esther Bernaldo-de-Quirós[1], Manuela Camino[2], Marta Martínez-Bonet[1], Juan Miguel Gil-Jaurena[3], Nuria Gil[2], Diana Hernández-Flórez[1], Maria Eugenia Fernández-Santos[4], Laura Butragueño[5], I. Esmé Dijke[6,7,8], Megan K. Levings[7,9], Lori J. West[7,8,10], Marjorie Pion[1], and Rafael Correa-Rocha[1,7]

Bernaldo de Quirós et al.
Journal of Experimental Medicine. 2023 Vol. 220 No. 12
doi.org/10.1084/jem.20231045

EL PAÍS

Madrid

COMUNIDAD DE MADRID · AYUNTAMIENTO DE MADRID · CERCANÍAS · METRO · EMT · MADRID CENTRAL · ÚLTIMAS NOTICIAS

TRASPLANTES >

Irene, la primera bebé trasplantada del mundo en recibir un tratamiento celular producido a partir de un órgano que hasta ahora se desechaba

Un equipo del Gregorio Marañón ha creado una terapia con células T reguladoras extraídas del timo, entre el esternón y el corazón, que hasta ahora se retiraba durante la cirugía para reemplazar el corazón, y que podrían ser la solución al rechazo en los trasplantes

Results to date:

* **No complications attributed to thyTreg administration**.
* **No suspicion of graft rejection episodes** ⍰ Good cardiac function.
* **No nosocomial or opportunistic infections,** relatively frequent in the postoperative period.

✓ **Feasibility and safety**

✓ **Repopulation of Treg cells** (preliminary results)

Our experience as an example of existing challenges

The Pathway from the Bench to the Patient …

Laboratorio de Inmuno-Regulación
Instituto de Investigación Sanitaria Gregorio Marañón

Treg Research

GMP Protocol thyTreg

AEMPS authorise thyTreg

Allogenic "off-the-self & ready-to-use" thyTreg

Spin-off THYTECH

PHARMA INDUSTRY

2014 2017 2019 2021 2023

Research | Pre-clinical | CT Phase I | CT Phase II | CT Allo Phase I/II | CT Phase III | Approb. EMA/FDA | PATIENT

thyTreg discovery

1st patient treated worlwide

7 patients treated / 1st patient completed trial

Our experience as an example of existing challenges

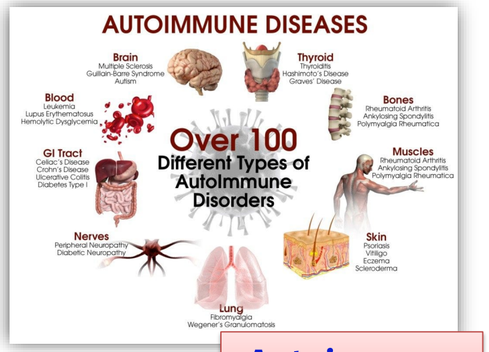
thyTreg. An innovative therapy to induce immune tolerance …

First-in-Class Regulatory T Cells

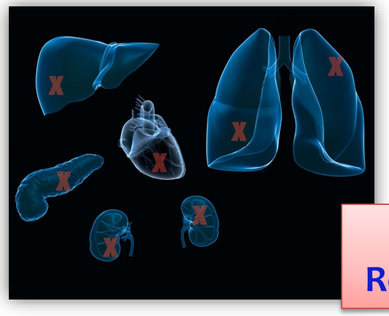
- Sourced from thymus discarded during pediatric heart surgery
- Abundant source of high quality, proprietary thyTreg™ cells
- Naturally hypoimmunogenic, for allogeneic use
- GMP protocol in place and suppling clinical trials
- First-in-human autologous investigator-initiated trial (IIT) confirming safety and showing positive outcomes in pediatric heart transplantation
- First-in-human allogeneic IIT open for enrollment in immune hyperactivation

ThyTreg BIOBANK

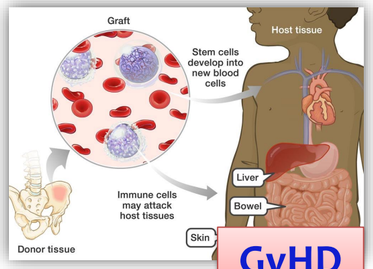
Off-the-self
Ready-to-use



Autoimmune diseases



Graft Rejection



GvHD

Challenges to transfer ATMPs based in SoHO to the Patient

Challenges we are facing…

- Scientists must become entrepreneurs have we got the skills? or we must transfer the control to professional CEO and board members?
- SoHO Supply Can I have access to thymical tissue to produce thyTreg therapeutical doses?
- Ethical aspects even if we use a discarded tissue, donors and institution can be compensated?
- Regulatory aspects Which criteria will be used to provide thymus to competitor companies ? How will be regulated the access in different countries depending of donors/recipients availability?
- Transfer to the patient Hospital exemption could facilitate the access to our therapy?
- Sustainability The price of the final product will be affordable for the National Health Systems?

Promote and facilitate, but establishing a new cooperative and sustainable model to guarantee the accessibility

GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD

ONT
ORGANIZACIÓN NACIONAL DE TRASPLANTES

EU23
SPANISH PRESIDENCY
COUNCIL OF THE EUROPEAN UNION

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GOBIERNO DE ESPAÑA
MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES

Instituto de Salud Carlos III

FAMILIA ALONSO
FUNDACIÓN

MARIE CURIE ACTIONS
European Commission
Horizon 2020
European Union funding for Research & Innovation

CUMBRE DE TRASPLANTES DE SANTANDER

SANTANDER TRANSPLANT SUMMIT