Investigación y Traslación en Terapia Génica para el Tratamiento de Enfermedades Monogénicas y Patologías Inflamatorias

Grupo de Terapias Avanzadas

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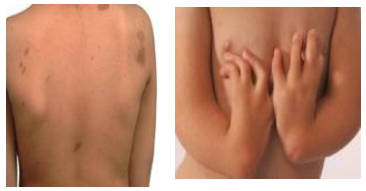
OBJETIVOS

- Desarrollo de **Medicamentos Innovadores de terapia génica** y celular (Designación de Orphan Drugs y Patentes)
- Nuevos **Ensayos Clínicos** con Medicamentos de Terapias Avanzadas
- **Registro** de nuevas terapias para patologías de mal pronóstico

Patologías Diana

- **EERR**
  - **Anemia de Fanconi**
  - **Deficiencia de Adhesión Leucocitaria**
  - **Piruvatoquinasa Eritrocitaria**
  - Anemia de Blackfan Diamond
  - Síndrome de Glanzmann
- **Enf Inflamatorias**
  - **Enfermedad de Injerto contra el Huésped**
- **Cáncer**
  - **CARs no virales para Leucemia Linfocítica**

Biología y Clínica en Anemia de Fanconi

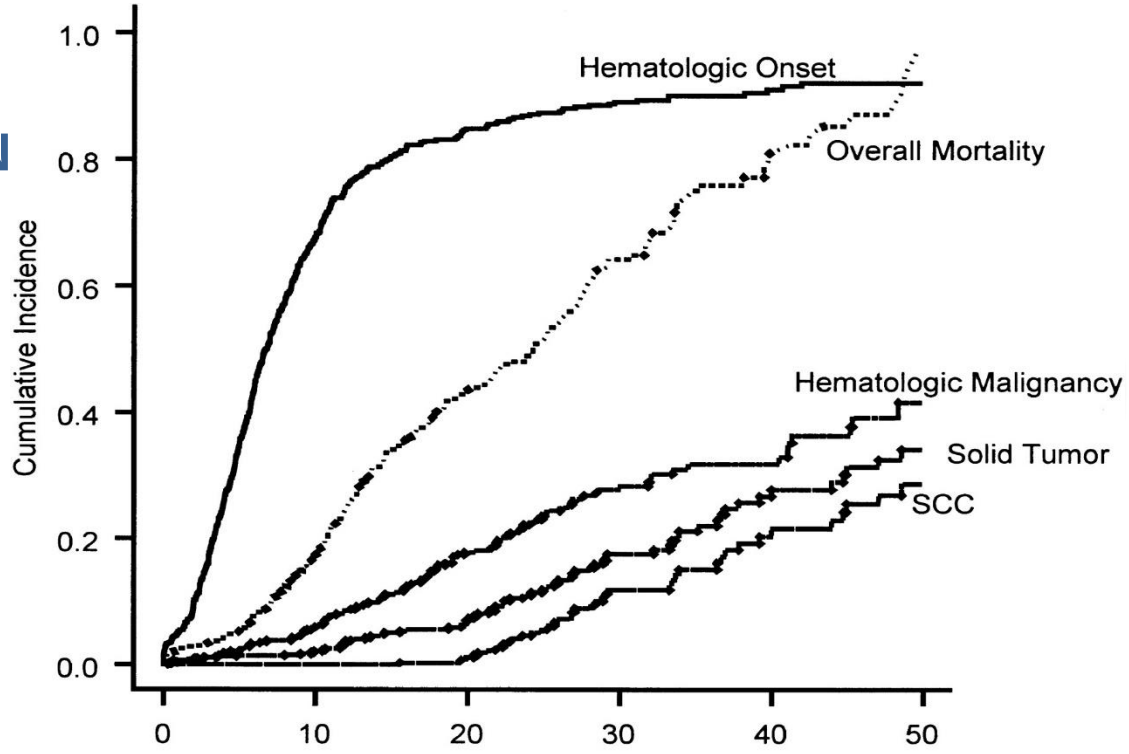


- **Enfermedad hereditaria**
- **Enfermedad Rara 1-3 casos por millón**

- **Mutaciones en genes de reparación del ADN**
  - 22 genes descritos (***FANCA*** - *FANCW*)
  - Reparación defectiva de entrecruzamientos en el ADN
  - Inestabilidad genética y muerte celular
- **Anomalías congénitas**

- **Predisposición al cáncer**
  - Leucemias
  - Tumores sólidos

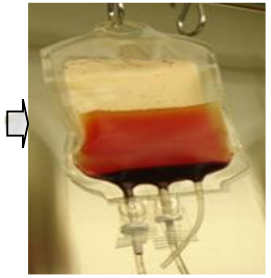
- **<u>Fallo de Médula ósea</u>**



Kutler et al, Blood 101:1249, 2003

Esquema de las Etapas del Ensayo Clínico

1. Movilización y purificación de las CMHs: 2-3 x (G-CSF+Plerixafor)

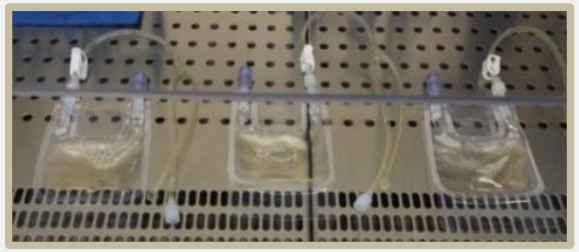


2. ± Criopreservación

5. Infusión
(No acondicionamiento)

CliniStem

PGK-*FANCA*.Wpre* LV



4. Transducción (24h)

Puesta en Marcha de la Sala Blanca CliniStem:

Producción de Células Modificadas Genéticamente para uso Clínico

The Engraftment of Corrected Cells confers HSPC and T-Cell Phenotypic Correction

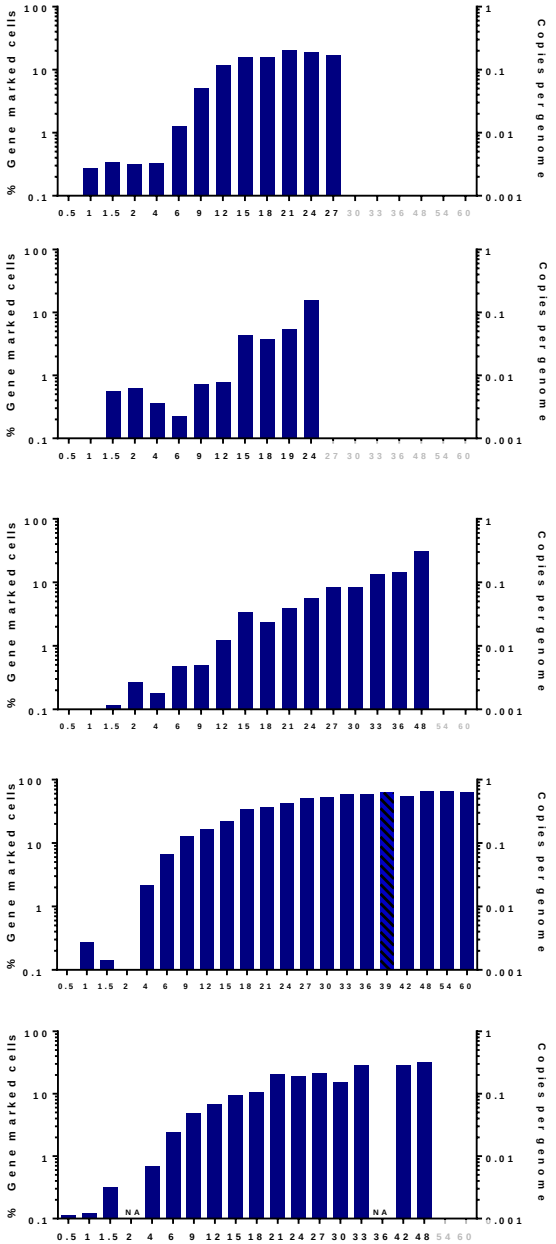
02013 (Cryo)
(135,000 cCD34⁺/Kg)

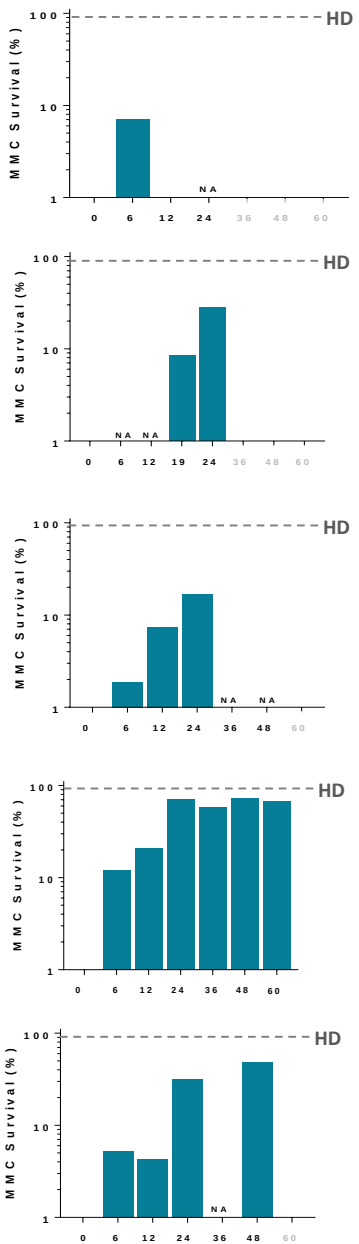
02008 (Fresh)
(157,000 cCD34⁺/Kg)

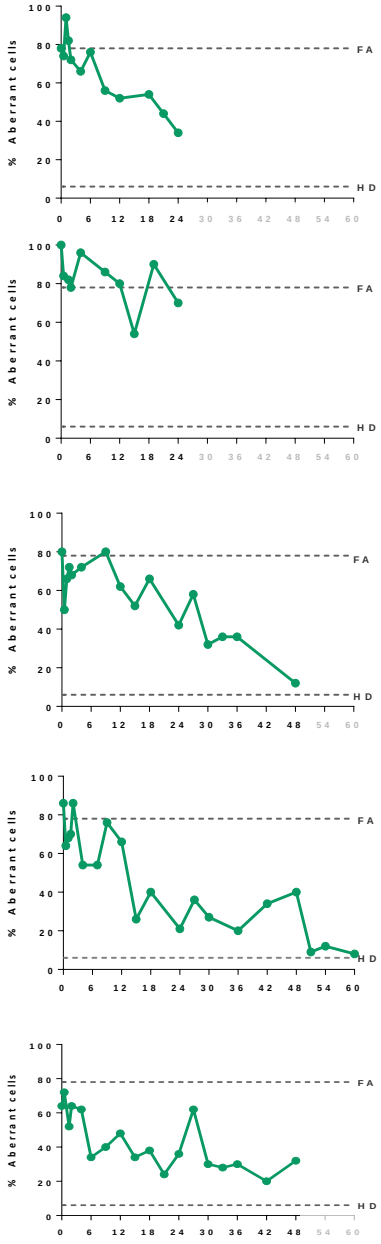
02004 (Cryo)
(163,000 cCD34⁺/Kg)

02002 (Cryo)
(246,000 cCD34⁺/Kg)

02006 (Fresh)
(410,000 cCD34⁺/Kg)

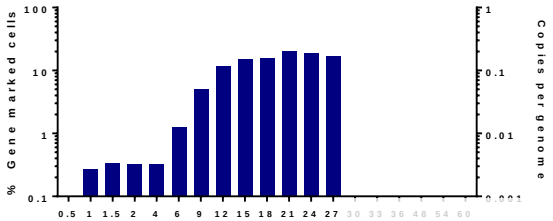


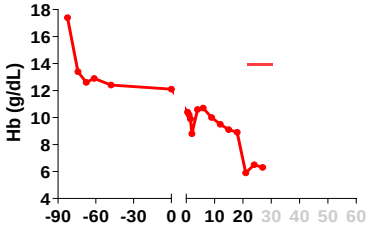


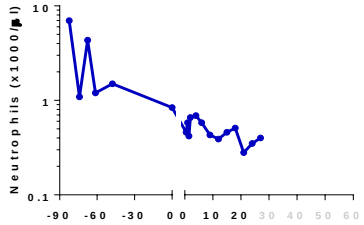


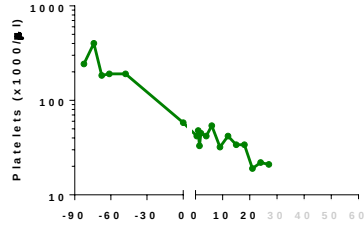
Engraftment in Early Stages of the Disease Results in Long-term Stabilization/Reversion of BMF

02013 (Cryo)
(135,000 cCD34⁺/Kg)

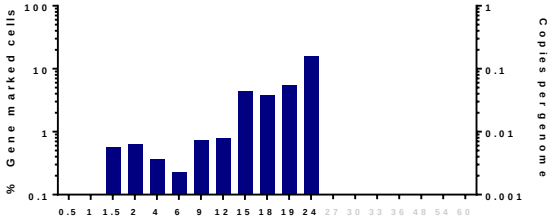


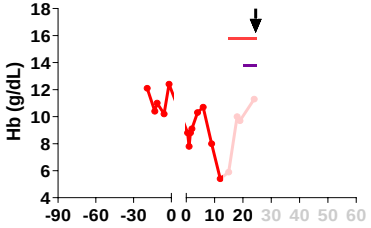


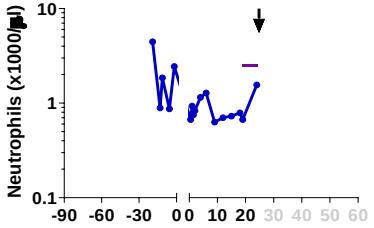


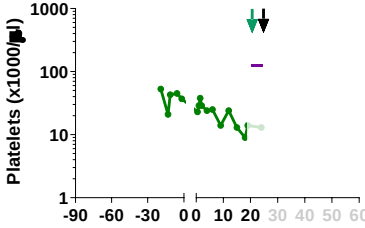


02008 (Fresh)
(157,000 cCD34⁺/Kg)

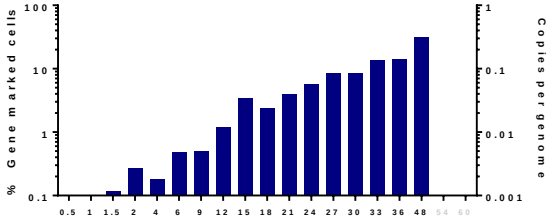


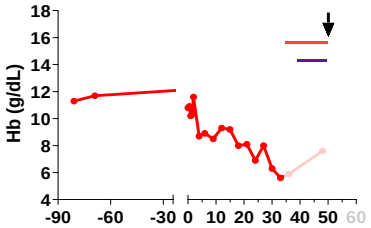


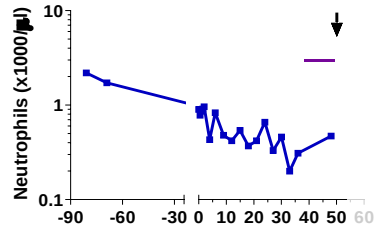


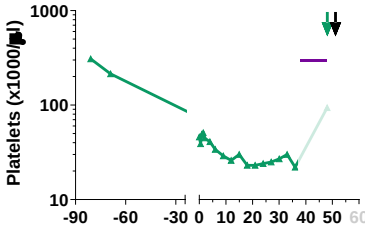


02004 (Cryo)
(163,000 cCD34⁺/Kg)

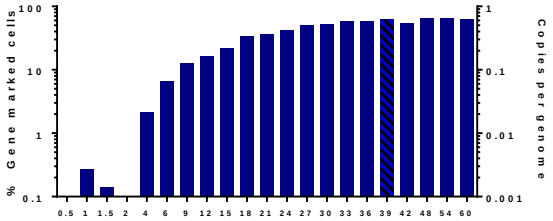


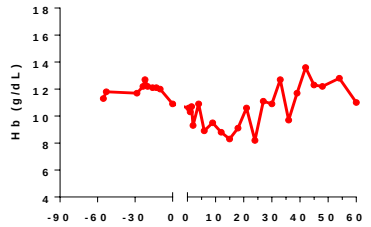


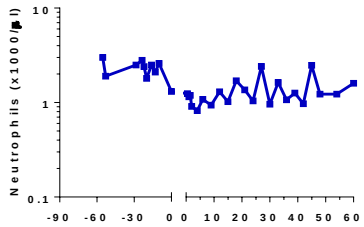


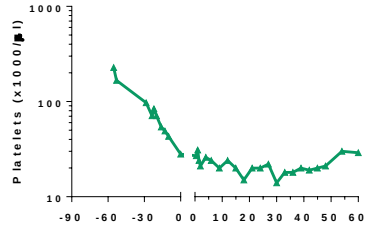


02002 (Cryo)
(246,000 cCD34⁺/Kg)

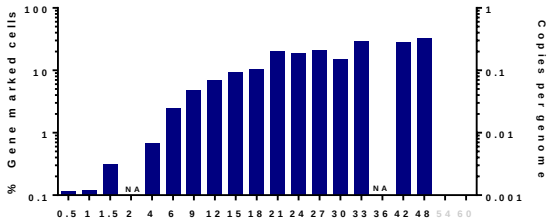


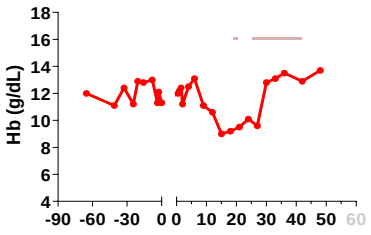


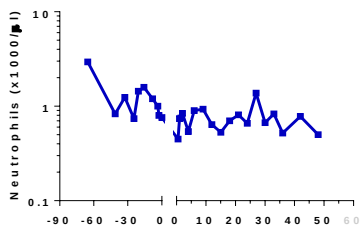


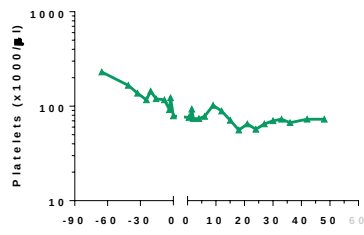


02006 (Fresh)
(410,000 cCD34⁺/Kg)









Months post-gene therapy

Months post-gene therapy

Months post-gene therapy

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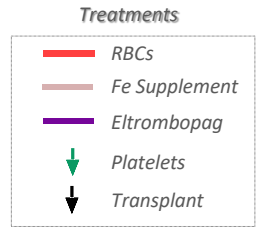

Preliminary Conclusions

- **First evidence of engraftment and repopulation advantage of multipotent HSCs in the absence of conditioning**
- **Slow, though progressive stabilization of BMF in patients infused with the highest doses of corrected CD34⁺ cells, mimicking the response observed in mosaic patients**

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https://doi.org/10.1038/s41591-019-0550-z
nature medicine

Successful engraftment of gene-corrected hematopoietic stem cells in non-conditioned patients with Fanconi anemia

Paula Río[1,2,3], Susana Navarro[1,2,3], Wei Wang[4,5], Rebeca Sánchez-Domínguez[1,2,3], Roser M. Pujol[2,6,7,8], José C. Segovia[1,2,3], Massimo Bogliolo[2,6,7,8], Eva Merino[2,9], Ning Wu[4], Rocío Salgado[10], María L. Lamana[1,2,3], Rosa M. Yañez[1,2,3], José A. Casado[1,2,3], Yari Giménez[1,2,3], Francisco J. Román-Rodríguez[1,2,3], Lara Álvarez[1,2,3], Omaira Alberquilla[1,2,3], Anna Raimbault[11,12], Guillermo Guenechea[1,2,3], M. Luz Lozano[1,2,3], Laura Cerrato[1,2,3], Miriam Hernando[1,2,3], Eva Gálvez[2,9], Raquel Hladun[13,14], Irina Giralt[14], Jordi Barquinero[14], Anne Galy[15], Nagore García de Andoín[16], Ricardo López[17], Albert Catalá[2,18], Jonathan D. Schwartz[19], Jordi Surrallés[2,6,7,8], Jean Soulier[11,12], Manfred Schmidt[4,5], Cristina Díaz de Heredia[13,14], Julián Sevilla[2,9] and Juan A. Bueren[1,2,3]*

A. Czechowicz
(Abstract # 697)

Stanford Children's Health | Lucile Packard Children's Hospital Stanford

FANCOLEN II (Phase-II Program)

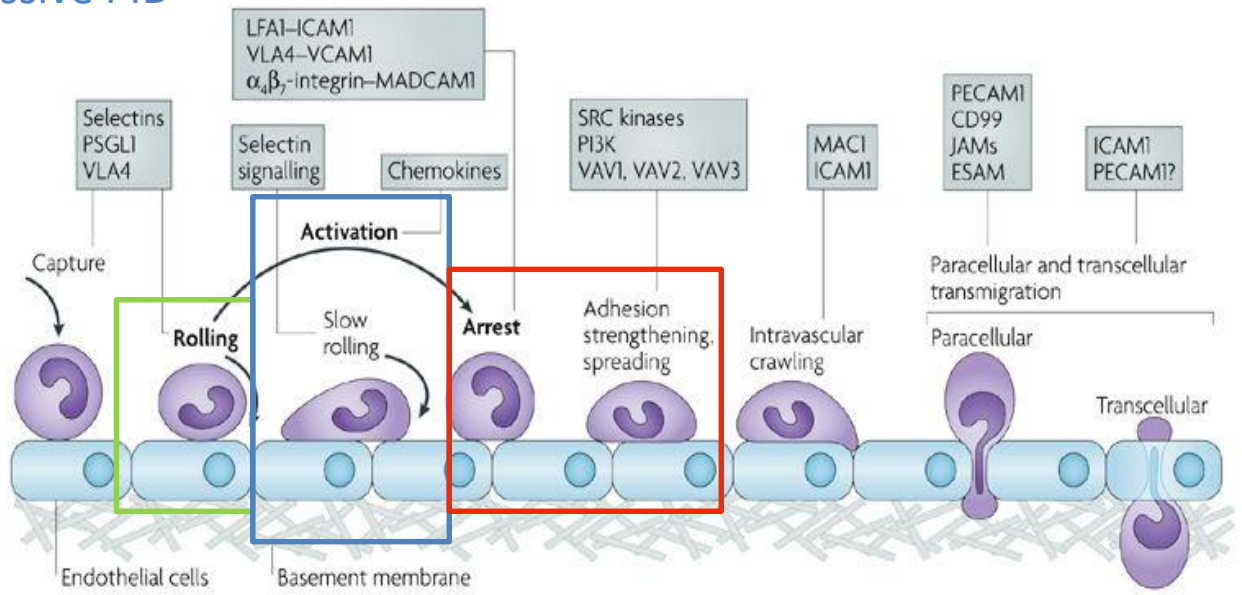
Sponsor

rocket pharma

- **Enrollment of patients with limited BMF: 9 patients**
- **Higher cell doses: Median cell dose 540,000 $CD34^+$ cells/kg ($2.5x10^5$ - $4.1x10^6$; CFC VCNs > 0.5)**
- **Outcomes consistent with patients 02002 and 02006 (FANCOLEN-I):**
  - For 2 of 3 patients with at F-U longer than 12 m, PB and BM VCNs > 0.1 (with concomitant increases in BM MMC-resistance).
  - For 3 of 4 additional patients with F-U longer than 6 months, PB VCNs were at least 0.05

Leukocyte Adhesion Deficiency

Autosomal Recessive PID



Edith van de Vijver et al. Blood Cells Mol Dis. 2012

	LAD-III	LAD-II	LAD-I
Gene	FERMT3	*SLC35C1*	***ITGB2 (21q22.3)***
Protein	kindlin-3	FucT1	**CD18**
Functional consequence	inside-out signaling β integrins	fucosylation	**Absence/ decreased β2**
Cascade point	Activation	Rolling	**Tight adhesion**
Patients	< 1 / 1 000 000	< 1 / 1 000 000	**1-9 / 1 000 000**

LAD-I Phenotype

Moderate:

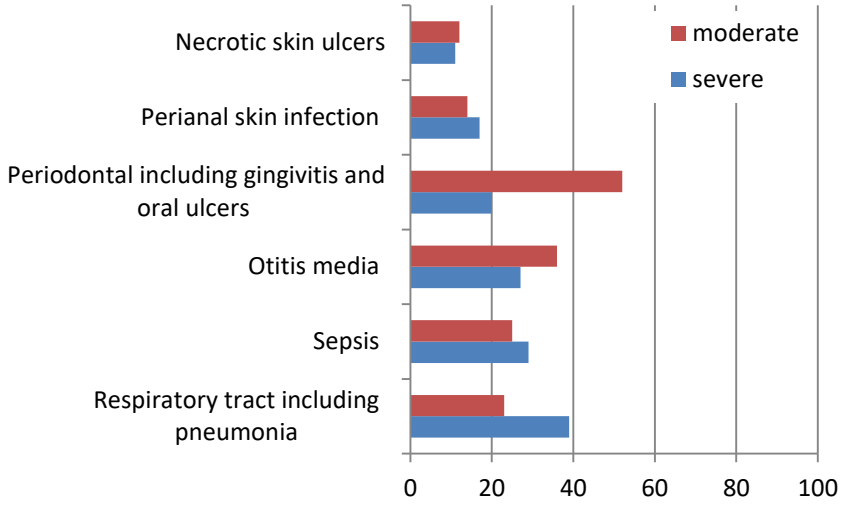
2 – 30% $CD18^+$ neutrophils

75% of patients die before 40 years old

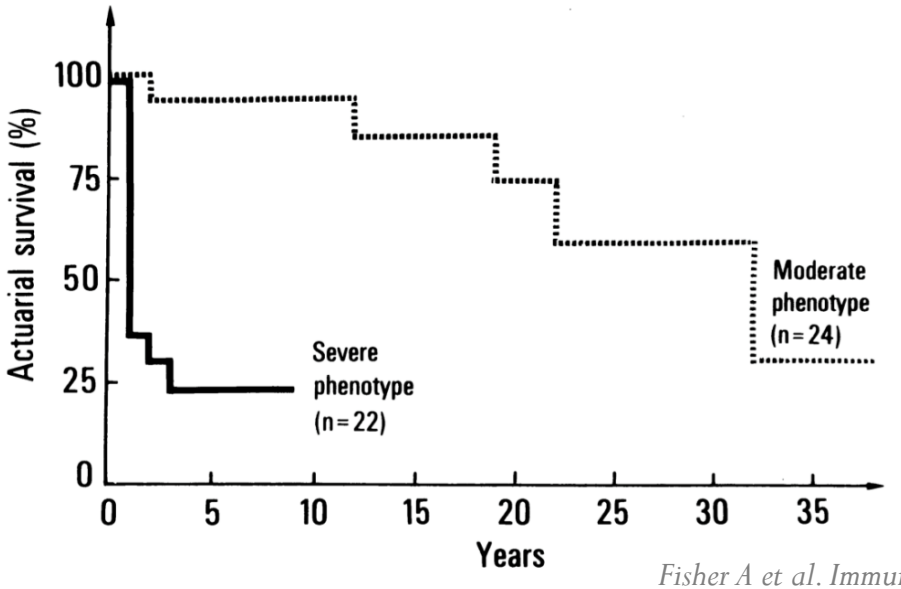
Severe:

< 2% $CD18^+$ neutrophils

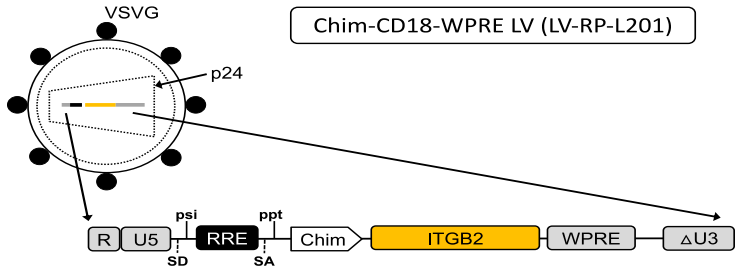
75% of patients die before 2 years old



Almarza et al, JACI in practice . 2018



Fisher A et al. Immunodefic Rev. 1988



León-Rico et al, Human Gene Ther . 2016

RP-L201 Clinical Trial and Outcome Measures

Trial Design – Non-Randomized Global Phase 1/2 Study

Phase	N (Planned)	N (Treated)
1	2	2
2	7	5

Primary Outcomes

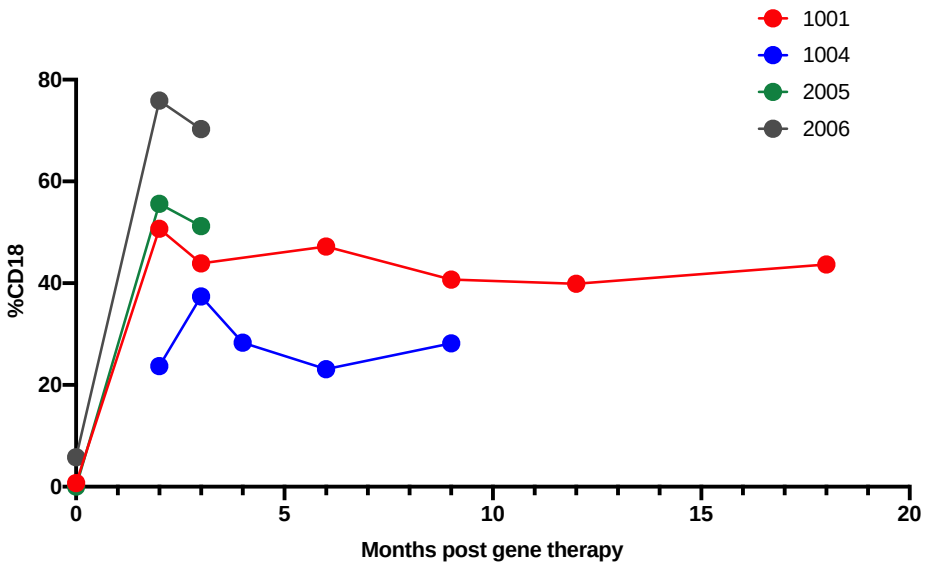
- **Phase 1:**
  - Safety & preliminary efficacy
- **Phase 2:**
  - Survival: proportion of patients alive at age 2 and at least 1-year post infusion (& not requiring alloHSCT)
  - Safety

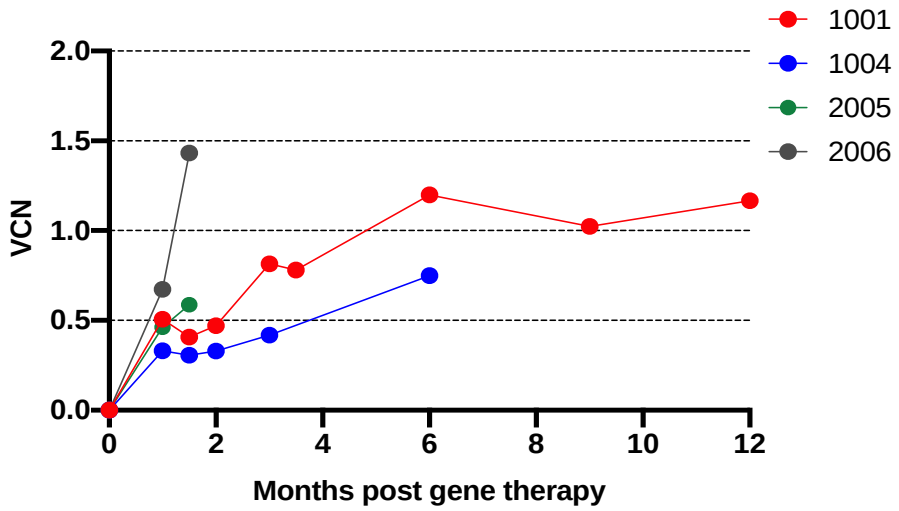
Secondary Outcomes

- % of pts w/neutrophil CD18 expression at least 10% of normal
- % of pts w/neutrophil VCN of at least 0.1 copies/cell at 6m post-rx
- Incidence and severity of infections
- Improvement/normalization of neutrophilia
- Resolution (partial or complete) of underlying skin rash or periodontal abnormalities

RP-L201 Clinical Trial and Outcome Measures

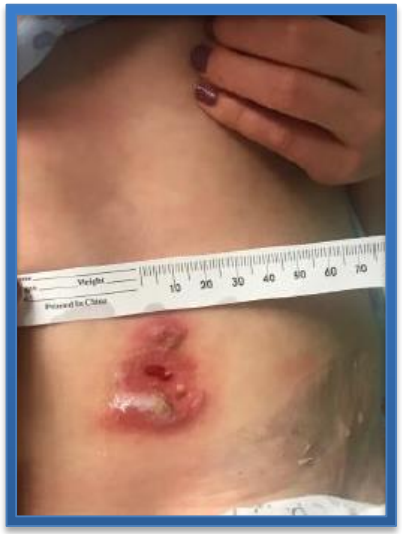
Patient	Gender	Age at enrollment	Drug Product VCN	CD34+ Cell Dose
L201-003-1001	F	9 yrs.	3.8	4.2 x 10^6 cells/kg
L201-003-1004	F	3 yrs.	2.5	2.8 x 10^6 cells/kg
L201-003-2005	F	2 yrs.	1.8	6.5 x 10^6 cells/kg
L201-003-2006	M	7 mo.	2.9	4.3 x 10^6 cells/kg



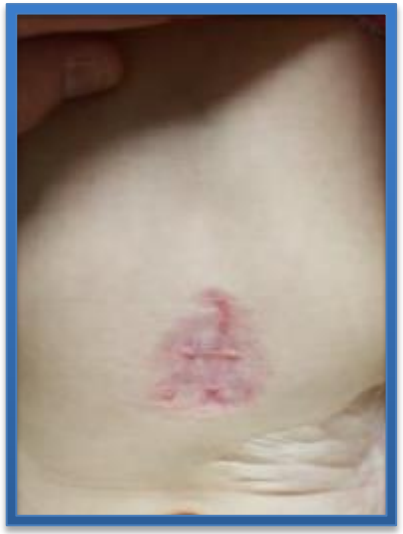


RP-L201: Visible Improvements Post-Treatment

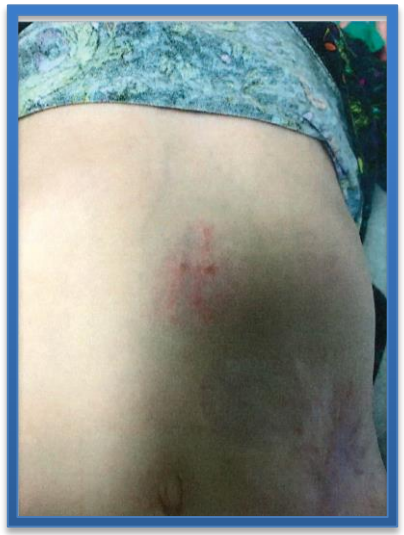
Spontaneous Abdominal Lesion



Baseline (Pre-Treatment)



3M



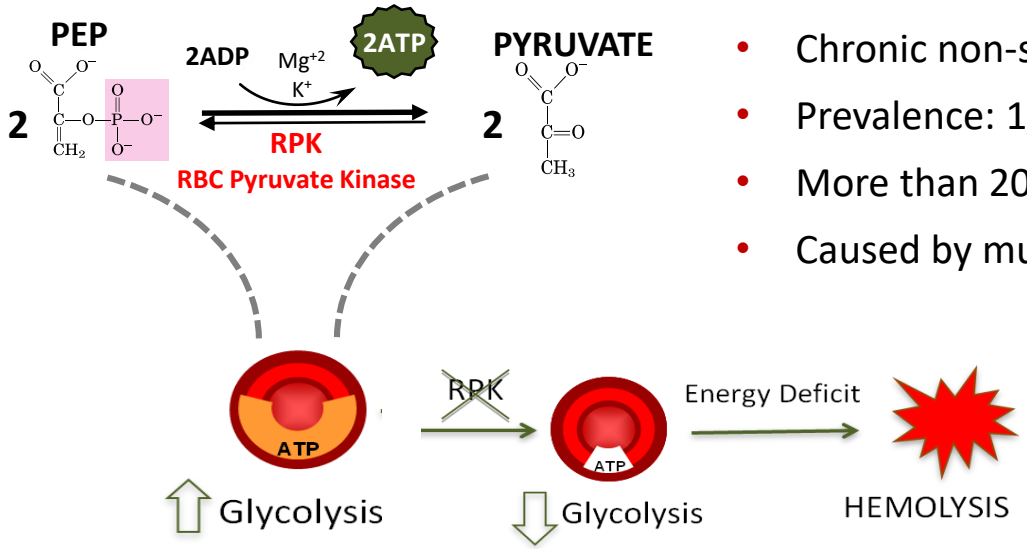
6M

UCLA Mattel Children's Hospital Data Sep 2020
LAD has received CIRM Funding

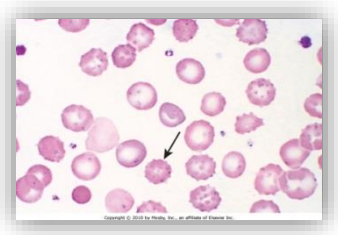
Preliminary Conclusions

- **Seven severe LAD-I patients** have been successfully treated with RP-L201 with at least 3 months of follow-up.
- **Safety profile of RP-L201 appears favorable**. No drug product-related SAEs.
- **Efficacy evident in 7 of 7 patients**, including 2 patients with ≥ 12 months of follow-up:
  - Durable CD18 expression and Vector Copy Numbers in PB cells
  - Resolution of pre-existing skin lesions
  - No infections/hospitalizations after hematopoietic reconstitution

Pyruvate Kinase Deficiency



- Autosomal recessive disorder
- Chronic non-spherocytic hemolytic anemia (CNSHA)
- Prevalence: 1/2x10^4 in Caucasian population (8,000 cases in EU and USA)
- More than 200 mutations described
- Caused by mutations in the *PKLR* gene



Clinical Signs
RPK activity <25%

- Anemia
- Reticulocytosis
- Hyperbilirubinemia
- Splenomegaly
- Iron overload

Treatment

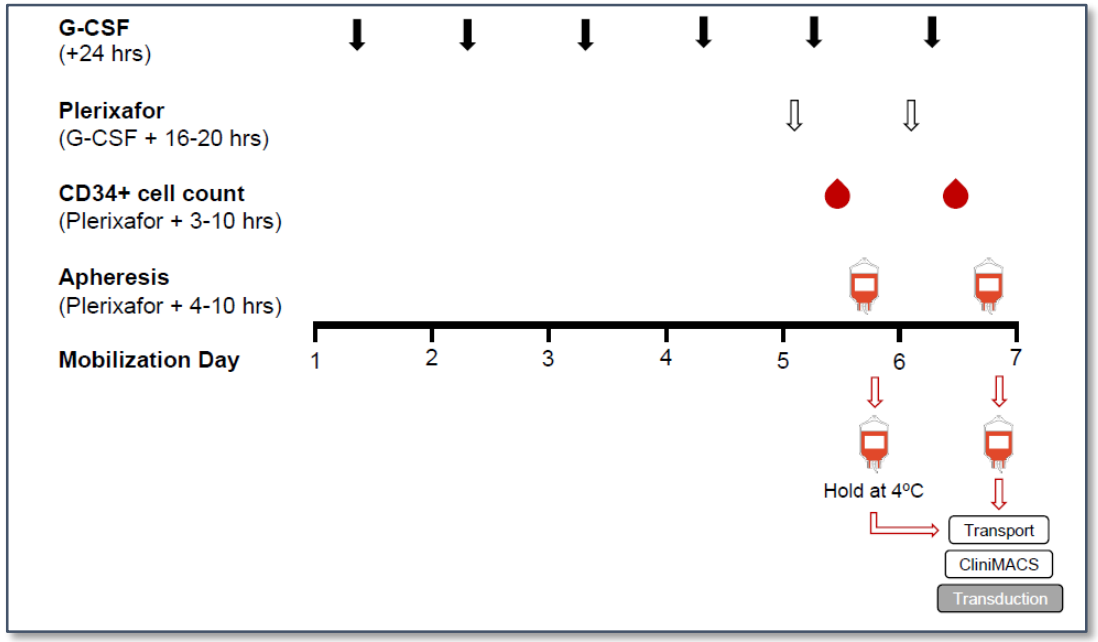
PKD: significant unmet medical need

Palliative
- Periodic transfusions
- Iron chelation
- Splenectomy

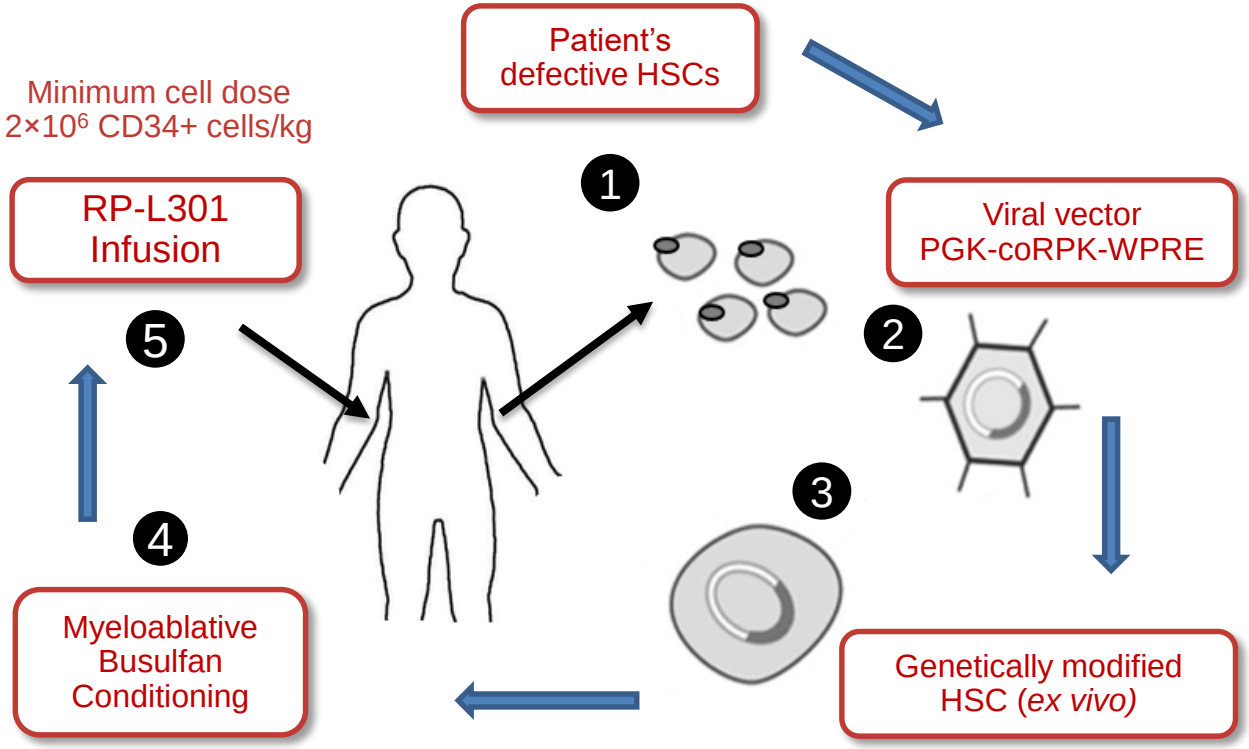
Curative
- Allogeneic BM transplant: performed in selected cases
- **Gene Therapy**

Study Design

CD34+ cell mobilization protocol with G-CSF and plerixafor



Product manufacture and treatment:

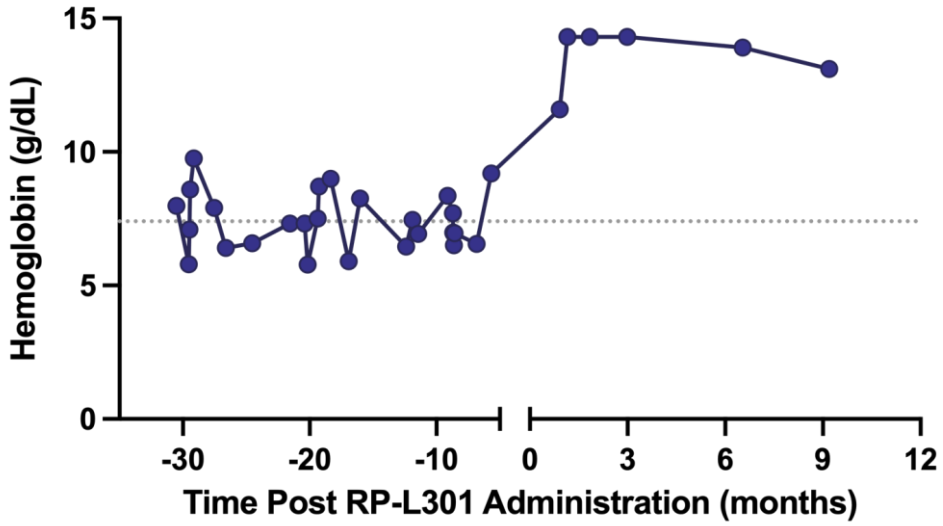


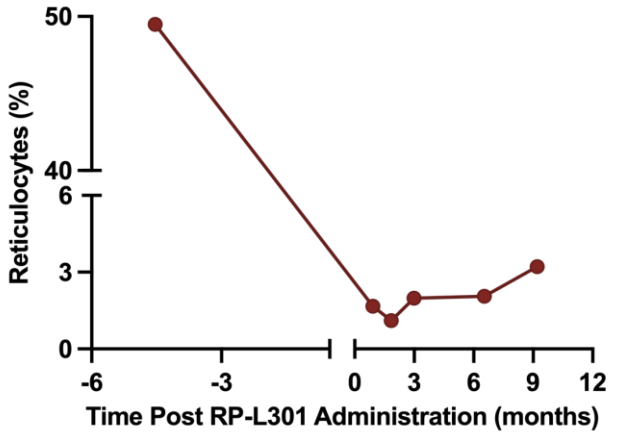
Global Phase 1 PKD Gene Therapy Study - Clinical Trial Sites

Adults		Pediatrics
	**EU: Madrid**	
Hospital Universitario Fundación Jiménez Díaz		Hospital Infantil Universitario Niño Jesús
	**US: California**	
Stanford University Hospital		Stanford University Hospital

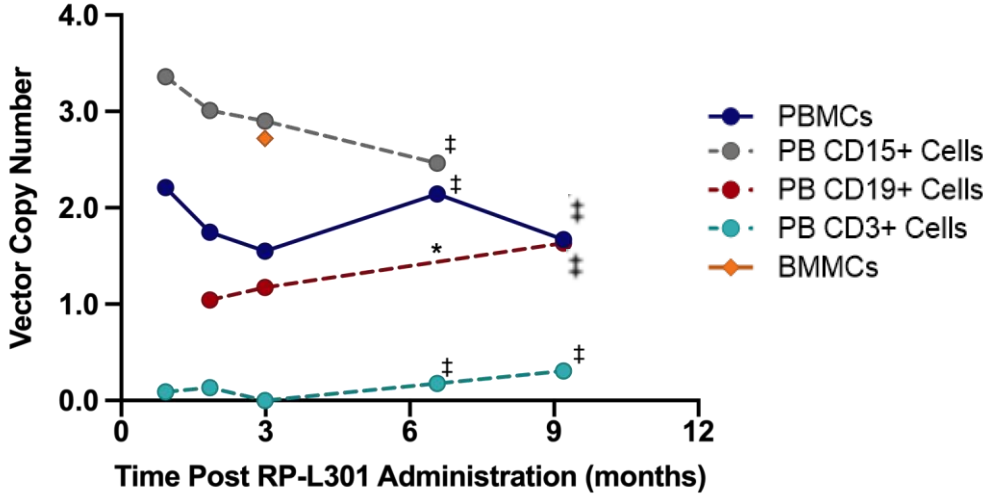
RP-L301-0119
NCT#04105166

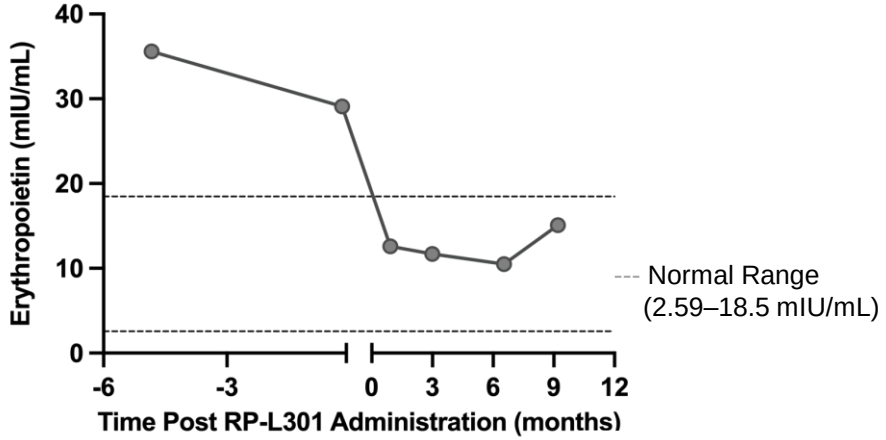
Preliminary Efficacy Results: L301-006-1001





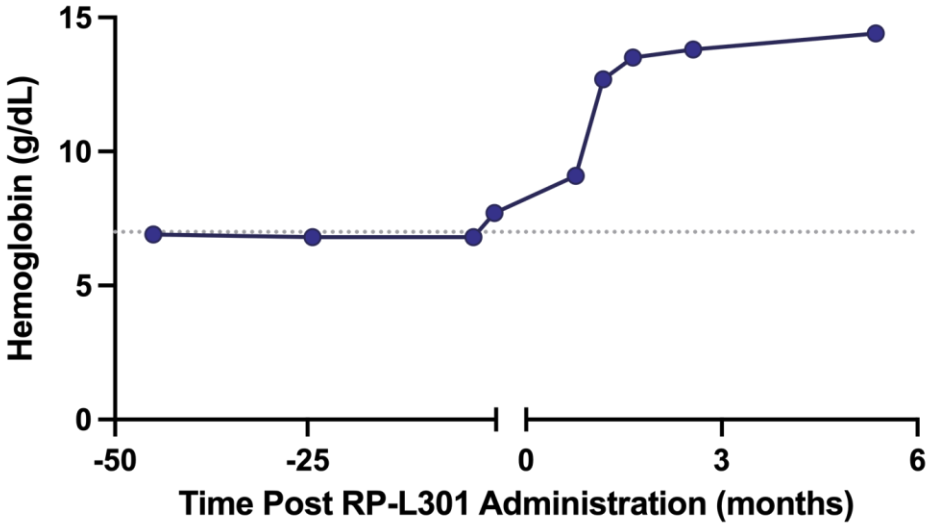
Sustained reduction in reticulocytes

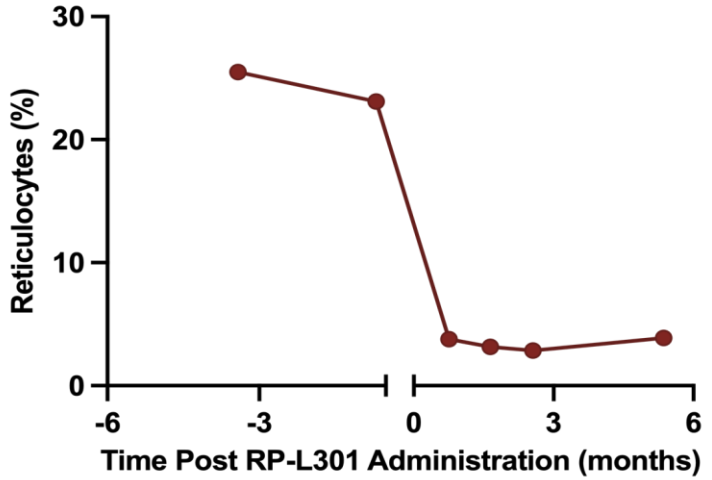


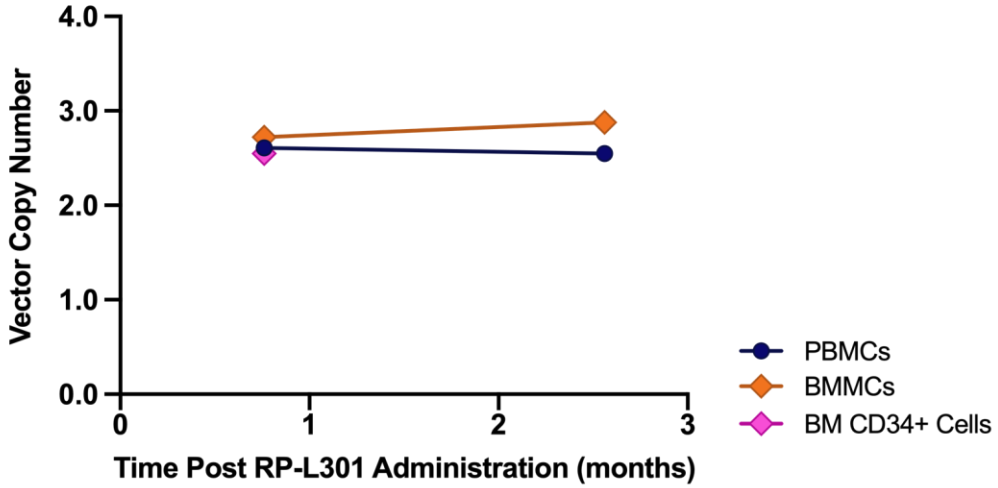


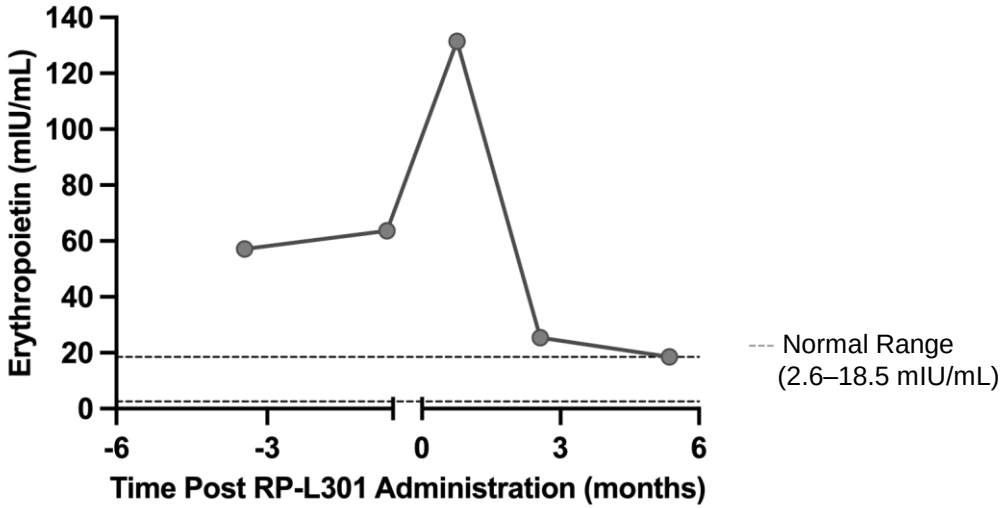
Continued erythropoietin normalization

Preliminary Efficacy Results: L301-001-1002





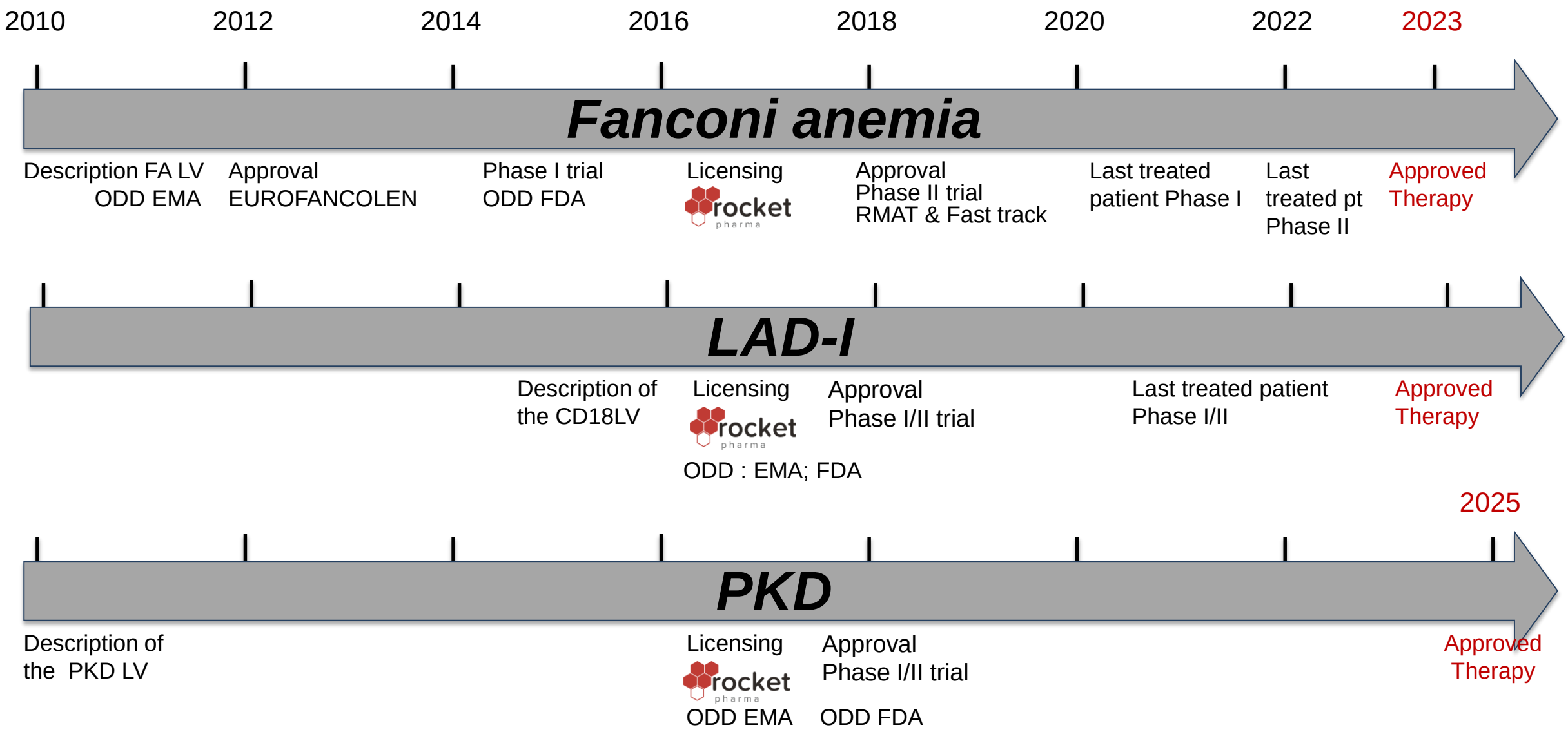




Preliminary Conclusions

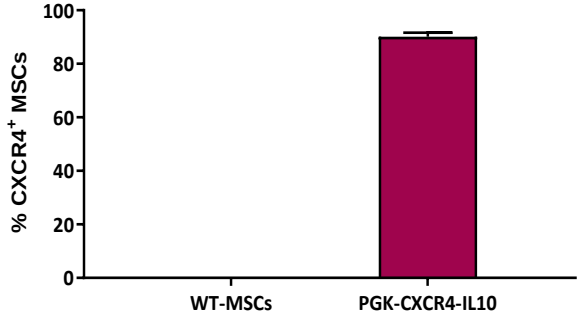
- **Safety profile of RP-L301 appears favorable**
  - Infusion well tolerated in (N=2); no IP-related serious adverse events (SAEs) at 9- and 6-months post- infusion in adult patients
  - Hematopoietic reconstitution in less than 2 weeks
  - Patients discharged from hospital within 1 month following RP-L301 infusion
- **Preliminary efficacy evident**
  - Both patients have **normalized hemoglobin, improved hemolysis markers, and no red blood cell transfusion requirements** post-engraftment
  - **No hospitalizations** post-hospital discharge
  - Clinical improvement is associated with evidence of engraftment as measured by PB and BM VCN

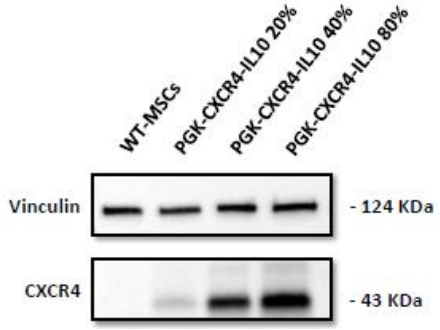
Ensayos Clínicos en Marcha



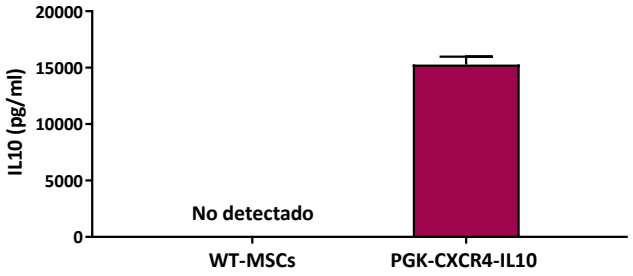
A New Generation of MSCs transduced with Lentiviral Vectors with Enhanced Anti-inflammatory Effects

Expression CXCR4

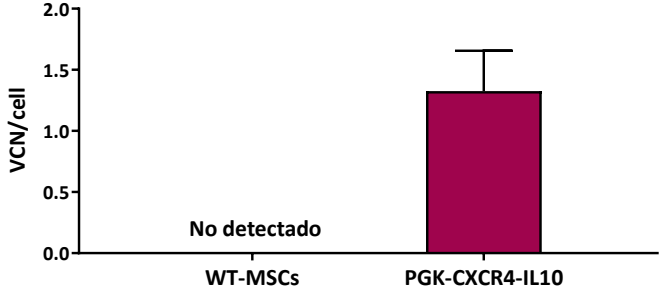




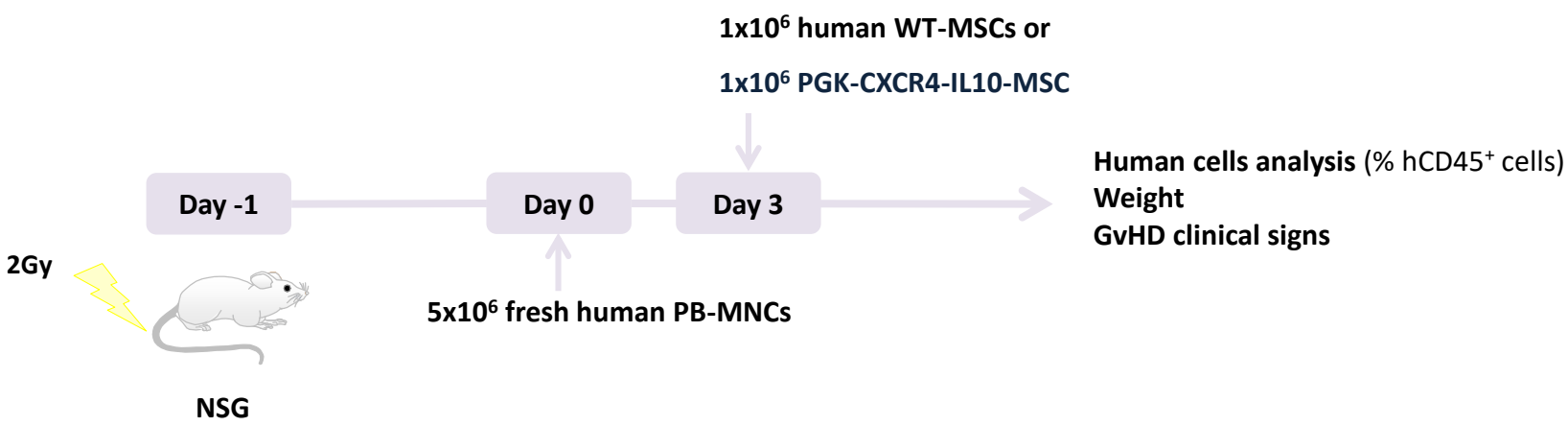
Secretion IL10

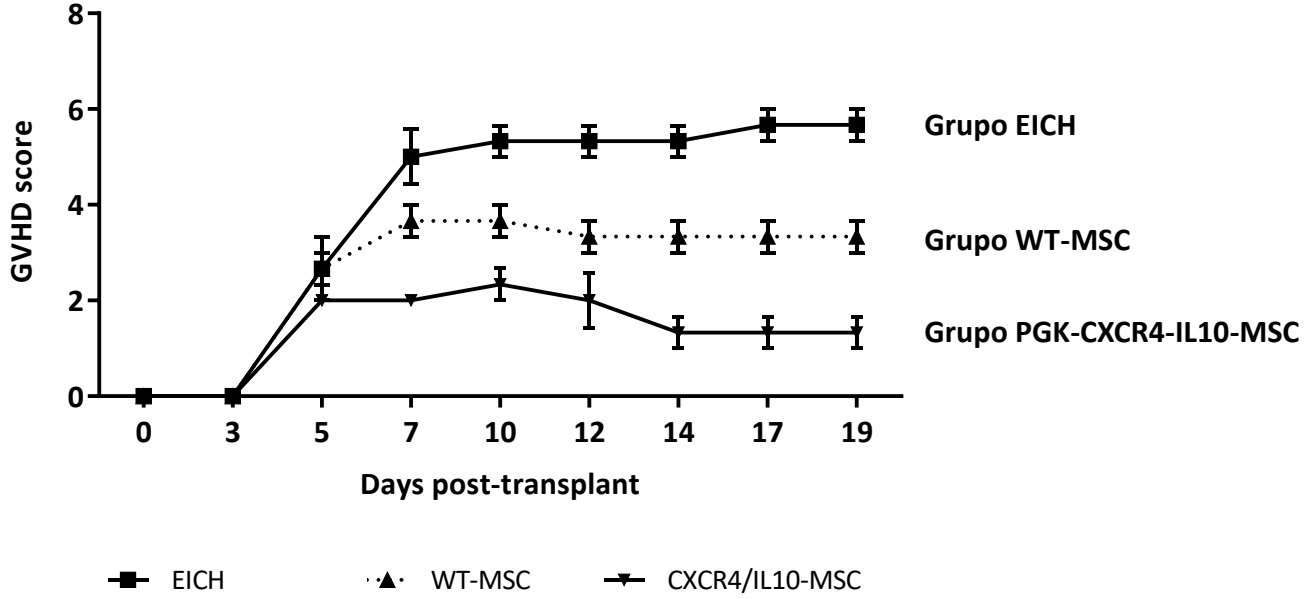


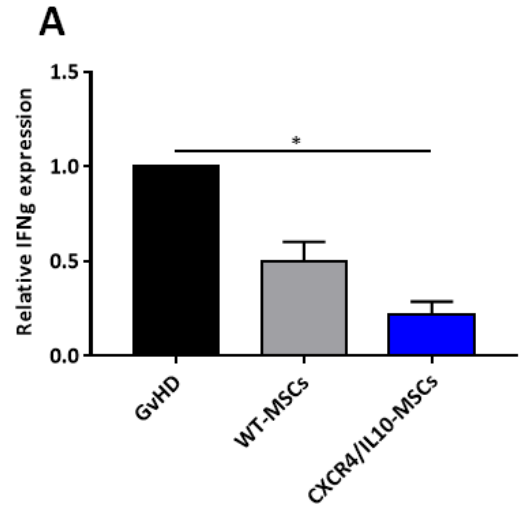
VCN/Cell

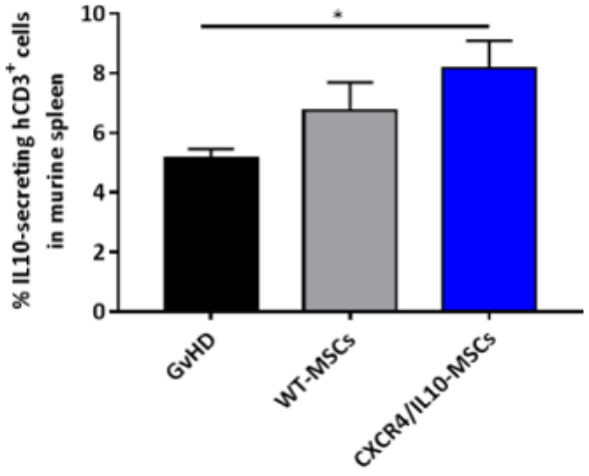


Enhanced anti-GVHD Effect of CXCR4/IL10-MSCs









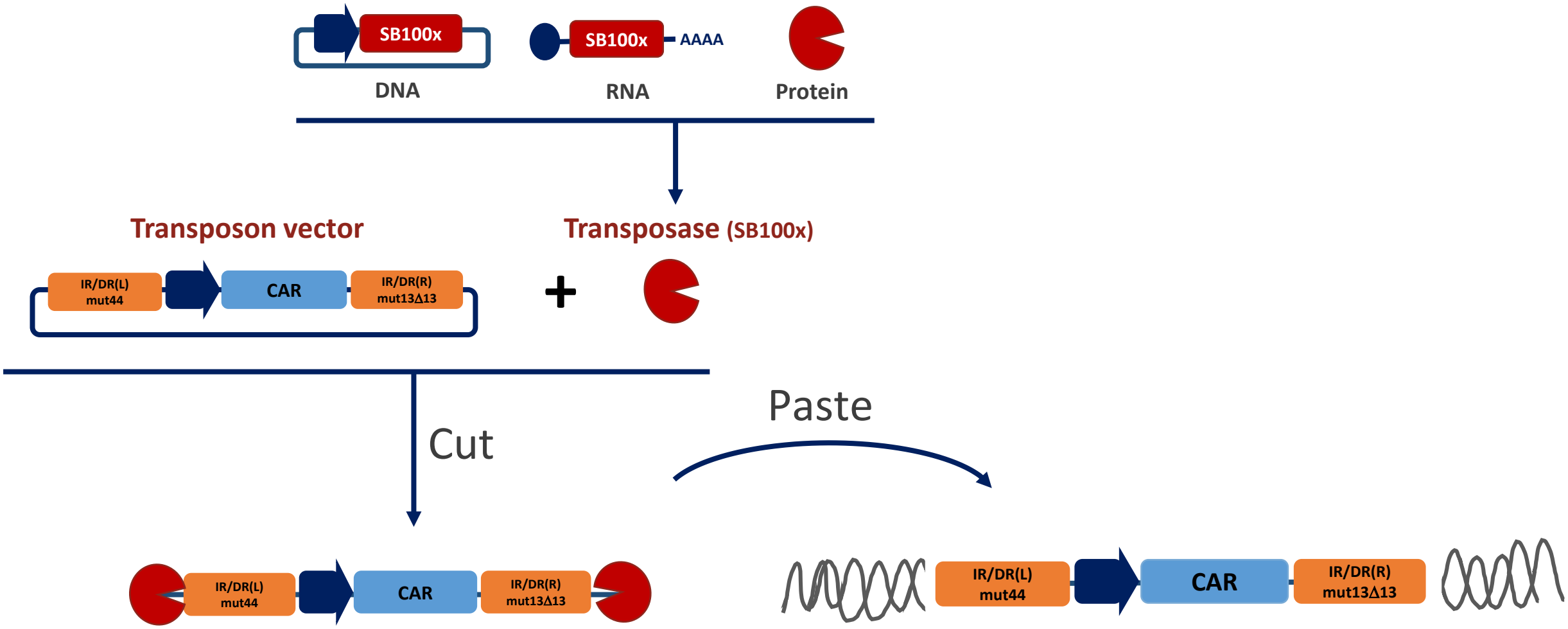
Europäisches Patentamt
European Patent Office
Office européen des brevets

Acknowledgement of receipt

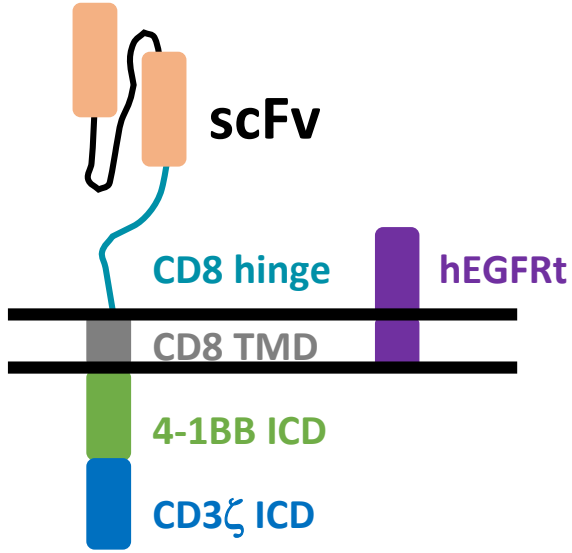
We hereby acknowledge receipt of your request for the processing of an international application according to the Patent Cooperation Treaty as follows:

Submission number	10167918
PCT application number	PCT/EP2021/074612
Date of receipt	07 September 2021
Receiving Office	European Patent Office, The Hague
Your reference	906 555
Applicant	Fundación Instituto de Investigación Sanitaria Fundación Jiménez Díaz (FIIS-FJD)
Number of applicants	3
Country	ES
Title	MESENCHYMAL STEM CELLS CO-EXPRESSING CXCR4 AND IL-10 AND USES THEREOF

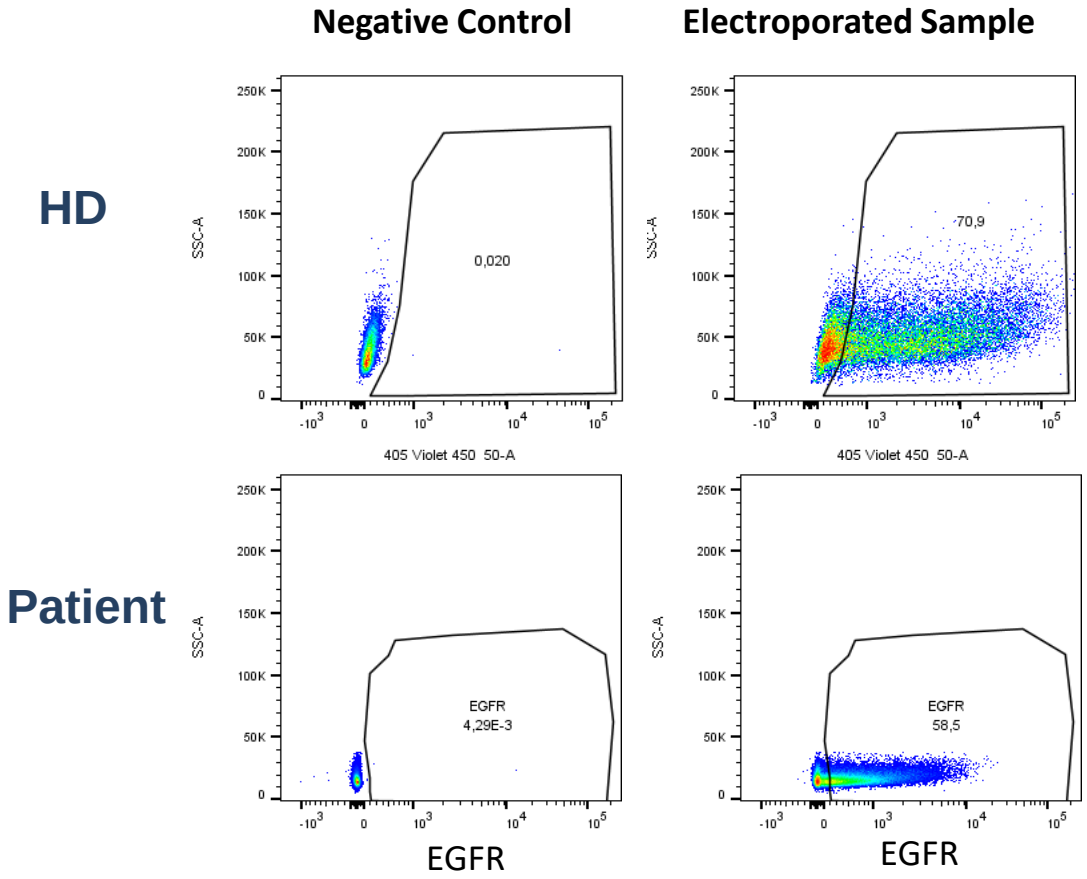
Non-viral CAR T cells

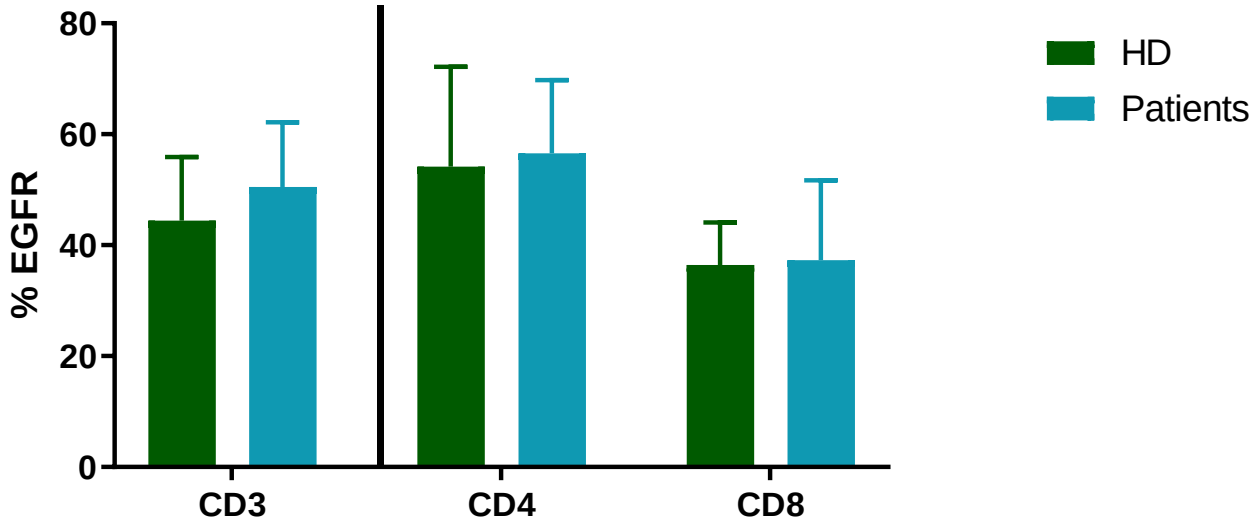


Design and Manufacturing of TranspoCART19

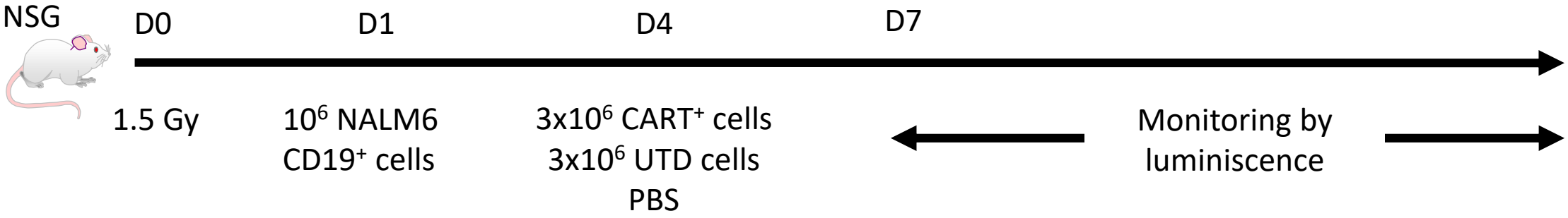


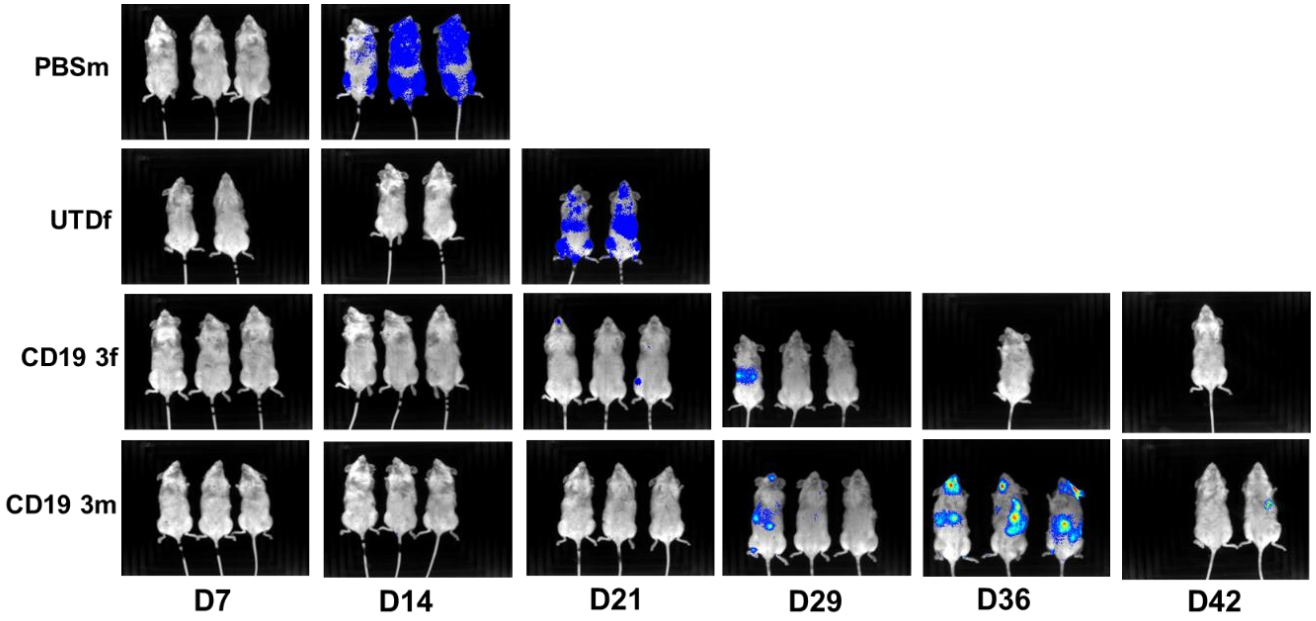
Efficient transposition in PB T Cells from HD and ALL-Patients

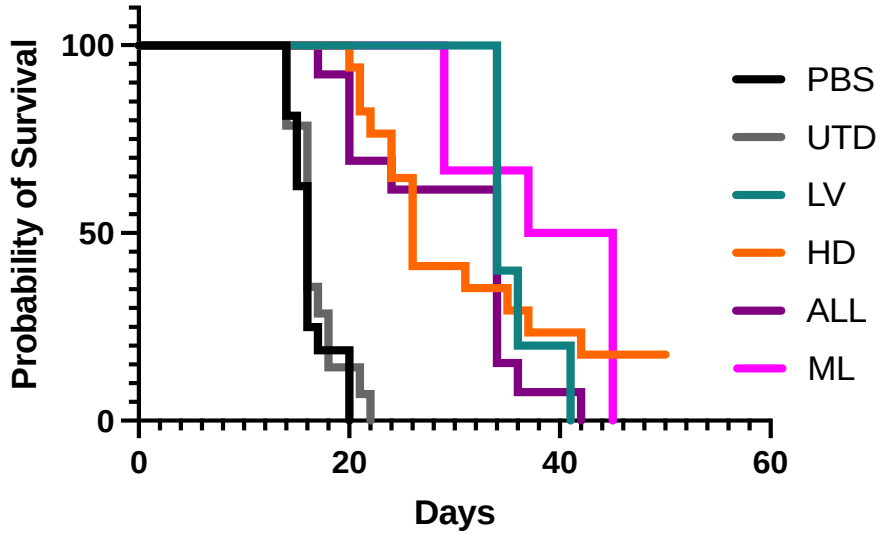




Efficient In vivo Cytotoxicity of Transpo-CART19







Clinical trial

Multicenter, first-in-human, phase I/II clinical trial with transposon-based CD19-specific CART cells in patients with $CD19^+$ R/R ALL

Pre-pandemic times…..

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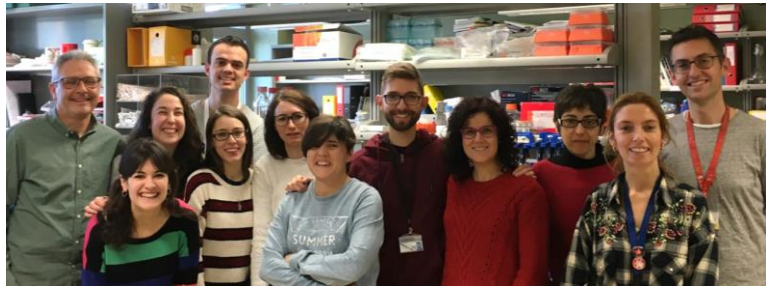

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TranspoCART partners

- Instituto de Investigación Biomédica de Salamanca (IBSAL)
- Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT)
- Clínica Universidad de Navarra (CUN)
- Instituto Murciano de Investigación Biosanitaria (IMIB)
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rocket pharma

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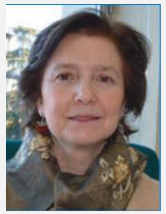

COLABORACIÓN

- ***Oferta:***

Traslación para el desarrollo de Medicamentos Innovadores propios con potencial de convertirse en nuevos Medicamentos de Terapias Avanzadas

- ***Demanda:***

Ayuda en el diseño de EECC competitivos con Medicamentos de Terapias Avanzadas