IdiSNA
INSTITUTO DE INVESTIGACIÓN SANITARIA DE NAVARRA

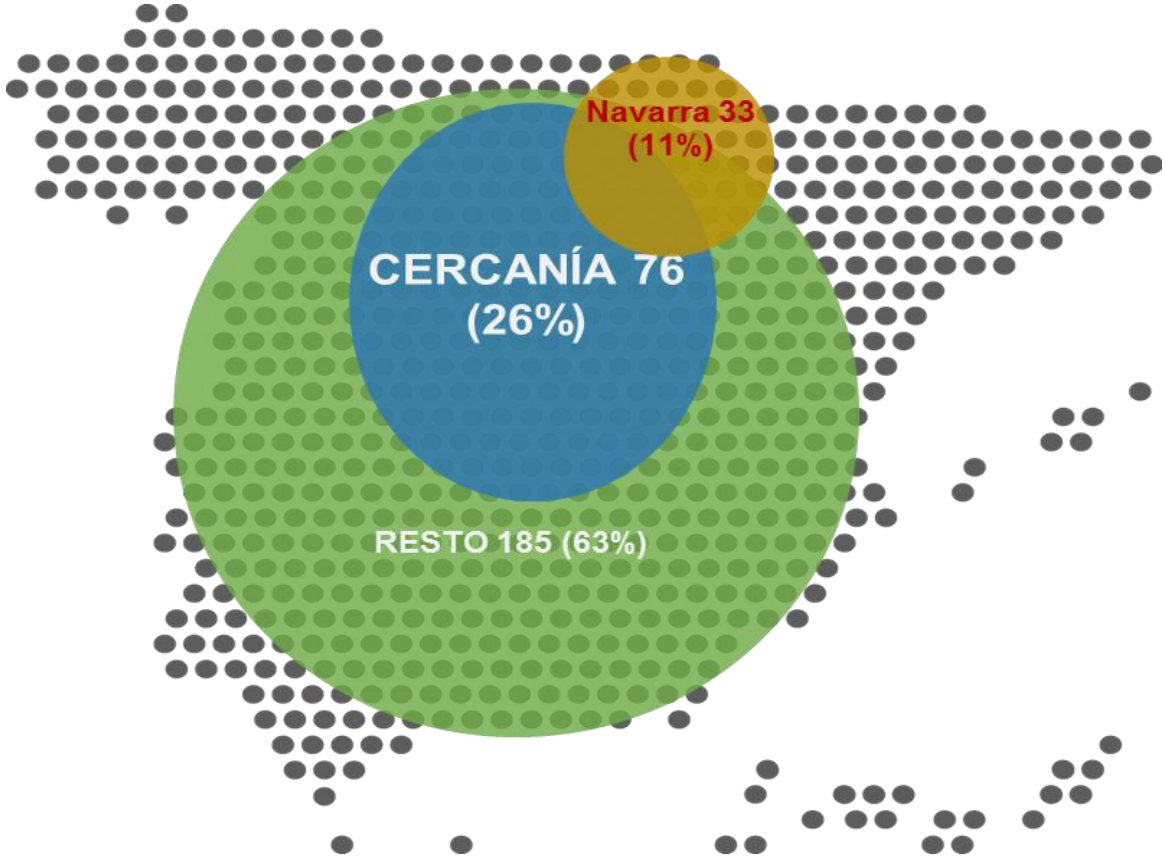
Clínica Universidad de Navarra

Investigación clínica en fases tempranas:

Terapias Avanzadas

Un hospital privado y vinculado al Sistema Nacional de Salud

Distribución geográfica de los pacientes CUN



PACIENTES RECLUTADOS

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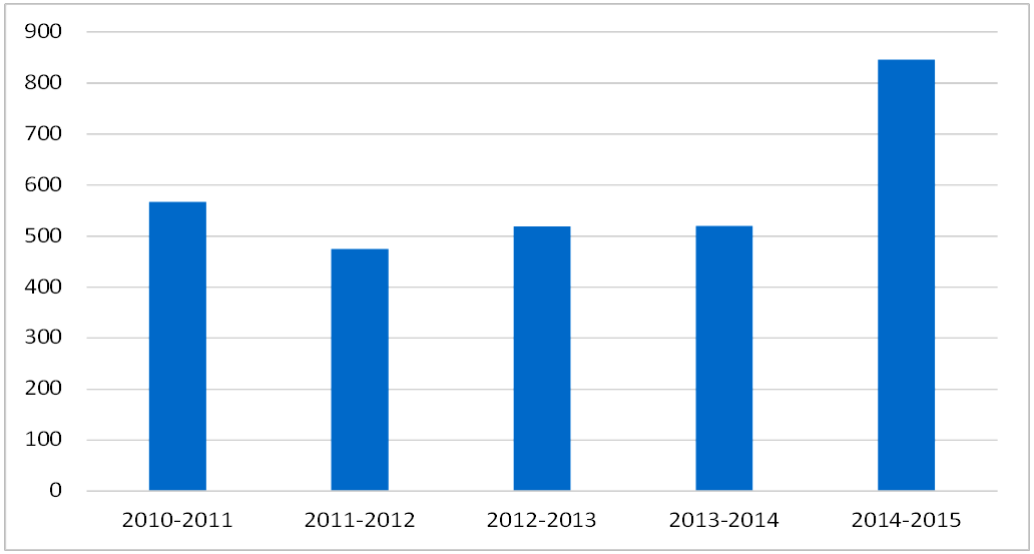

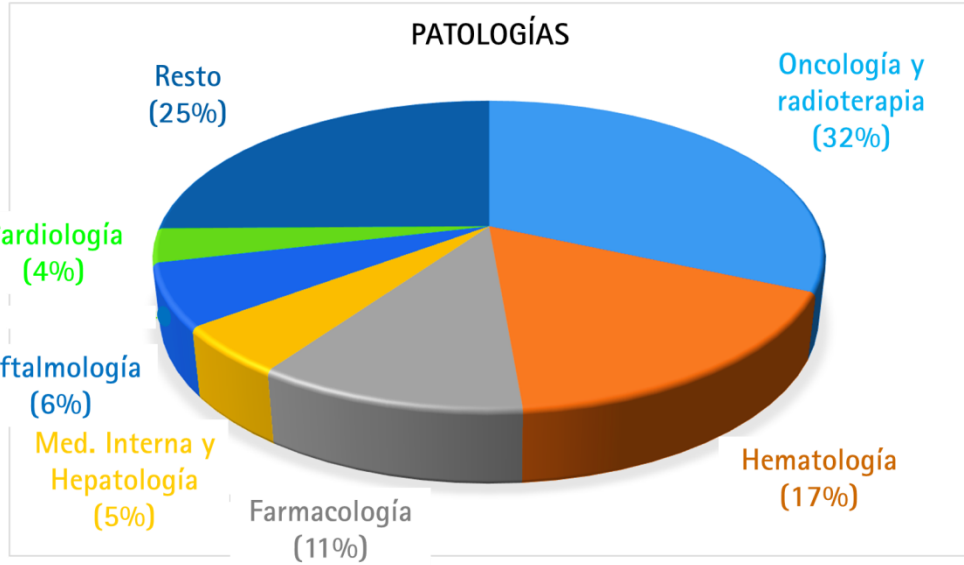

DATOS 2014-2015	TOTAL ACTIVIDAD ESTUDIOS CLÍNICOS					
	Iniciados	Activos	Pacientes	Dptos	Investigadores	Facturación
Estudios Observac y EPA	30	104	307	22	41	47.122
Ensayos Clínicos Propios	2	23	77	14	17	165.354
Ensayos Voluntarios sanos	8	13	157	2	1	327.015
Ensayos con Promotor externo	55	208	305	35	90	2.590.906

PACIENTES POR TIPO DE ENSAYO

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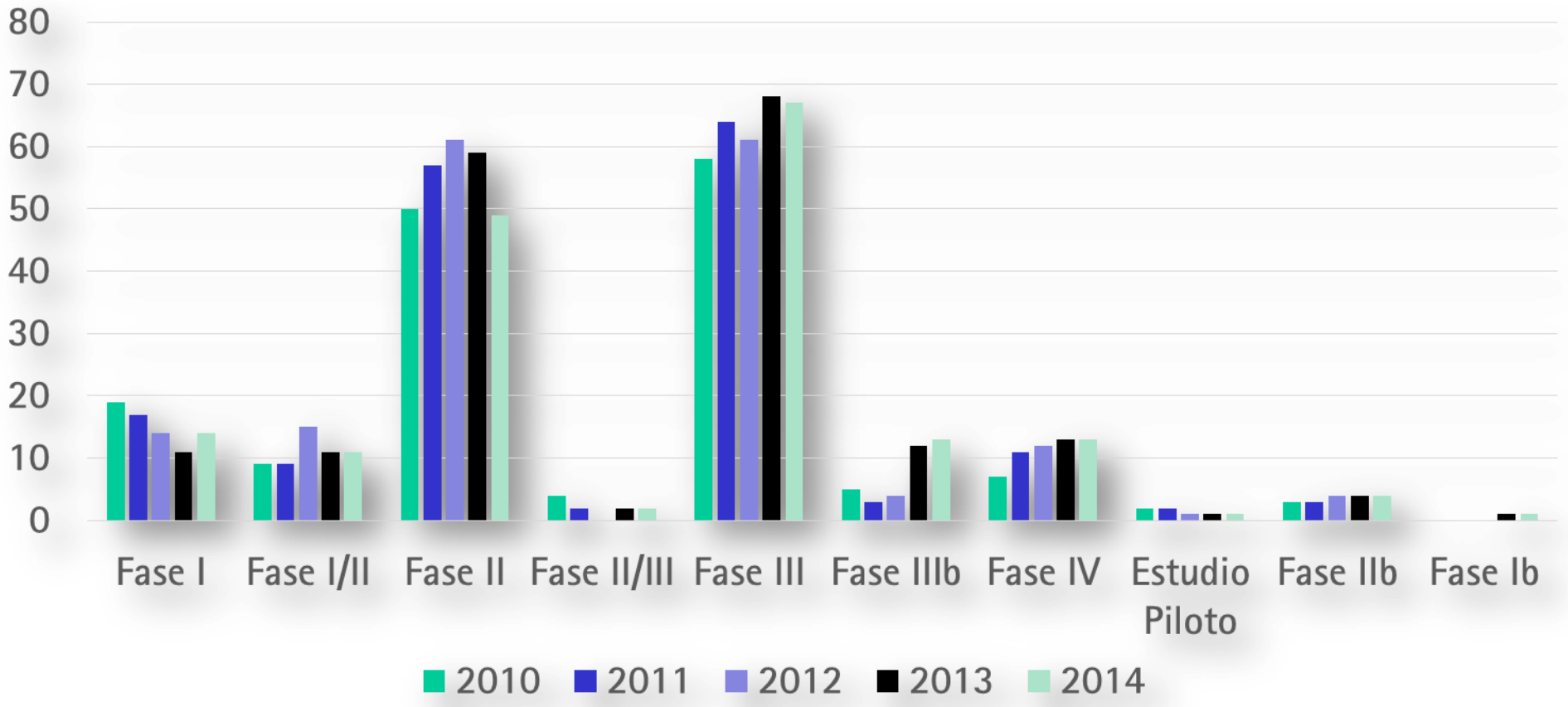

Ensayos clínicos: promoción CUN

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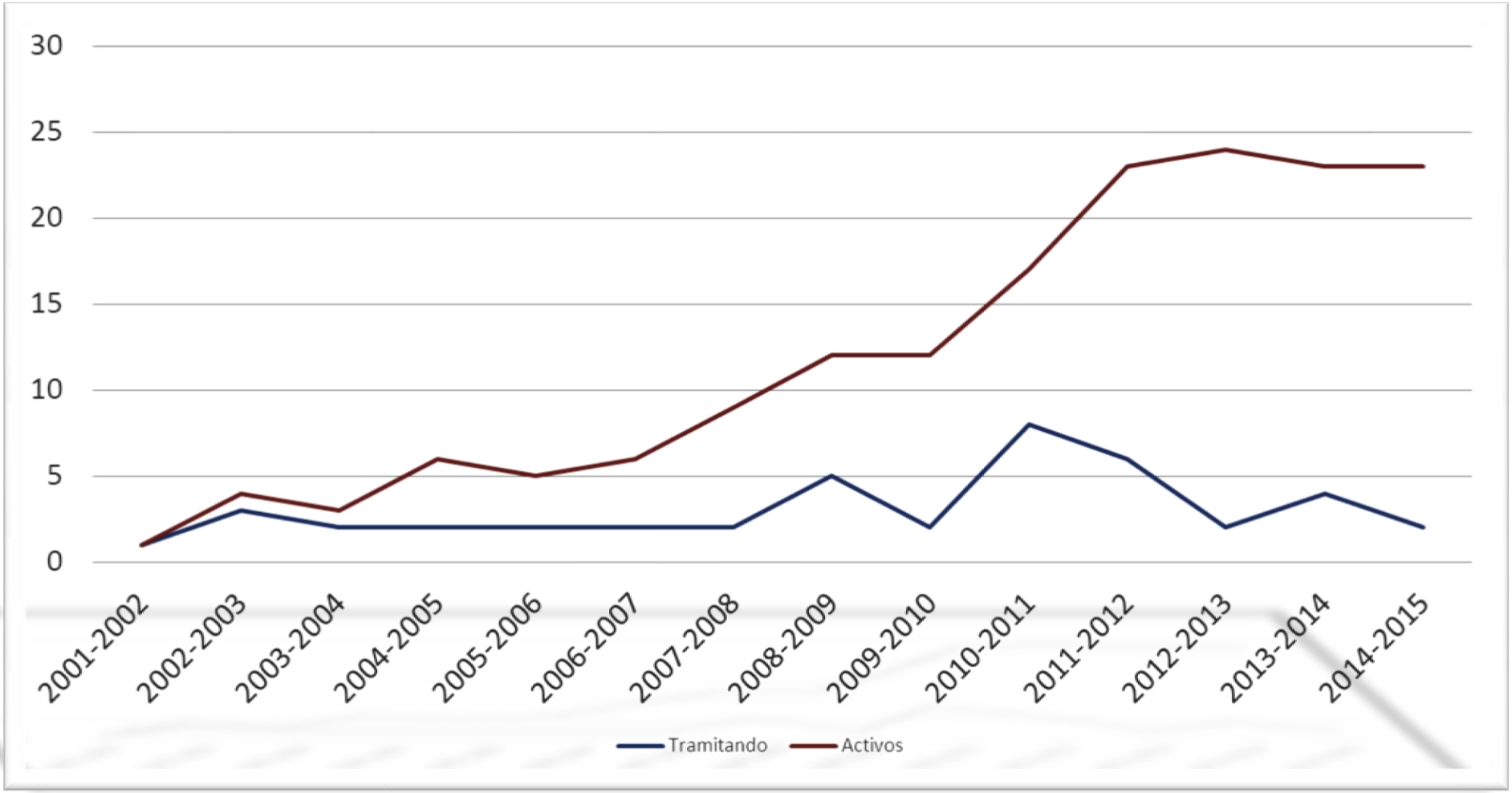


Modelo de Investigación traslacional en la Clínica Universidad de Navarra

Clínica Universidad de Navarra

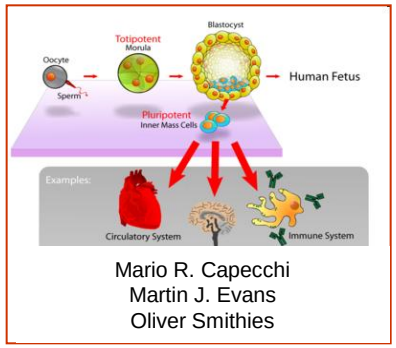
- Multidisciplinar, innovadora y dinámica
- Basada en el establecimiento de colaboraciones y estructuras permanentes
- Fondos públicos competitivos
- Partiendo de un investigación básica con un objetivo eminentemente clínico

CAMPUS BIOMÉDICO

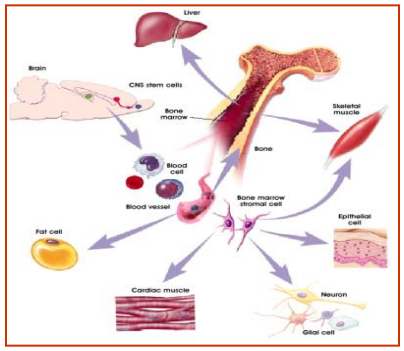
Clínica Universidad de Navarra

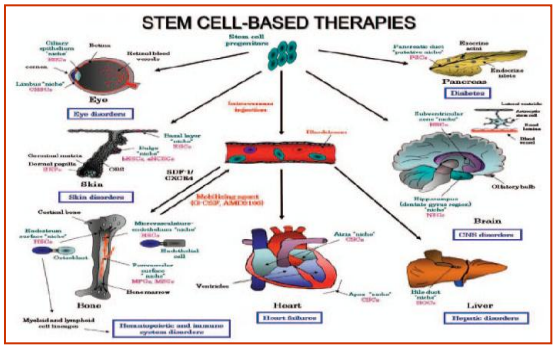
CELL THERAPY

Clínica Universidad de Navarra



Mario R. Capecchi
Martin J. Evans
Oliver Smithies





1954
Stem Cell Transplant

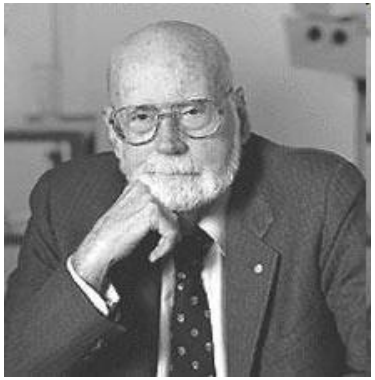
1981
Mouse ESC

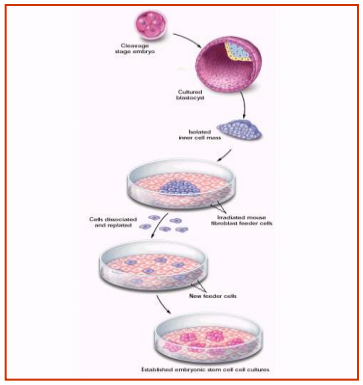
1998
Human ESC

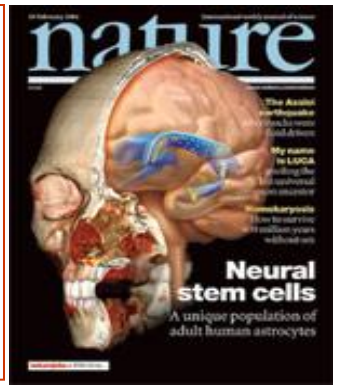
2001-2006
Adult SC Plasticity

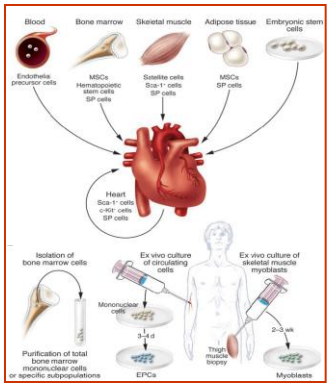
2000-
Cell Therapy Clinical Trials

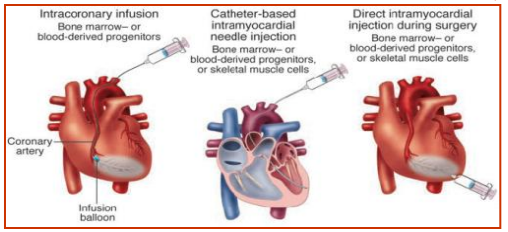
2006-07
Mice/Human iPS











Cell Therapy

INNOVATION

Cell-Based Therapeutics: The Next Pillar of Medicine

Michael A. Fischbach,[1, 2*] Jeffrey A. Bluestone,[3] Wendell A. Lim[1,4,5*]

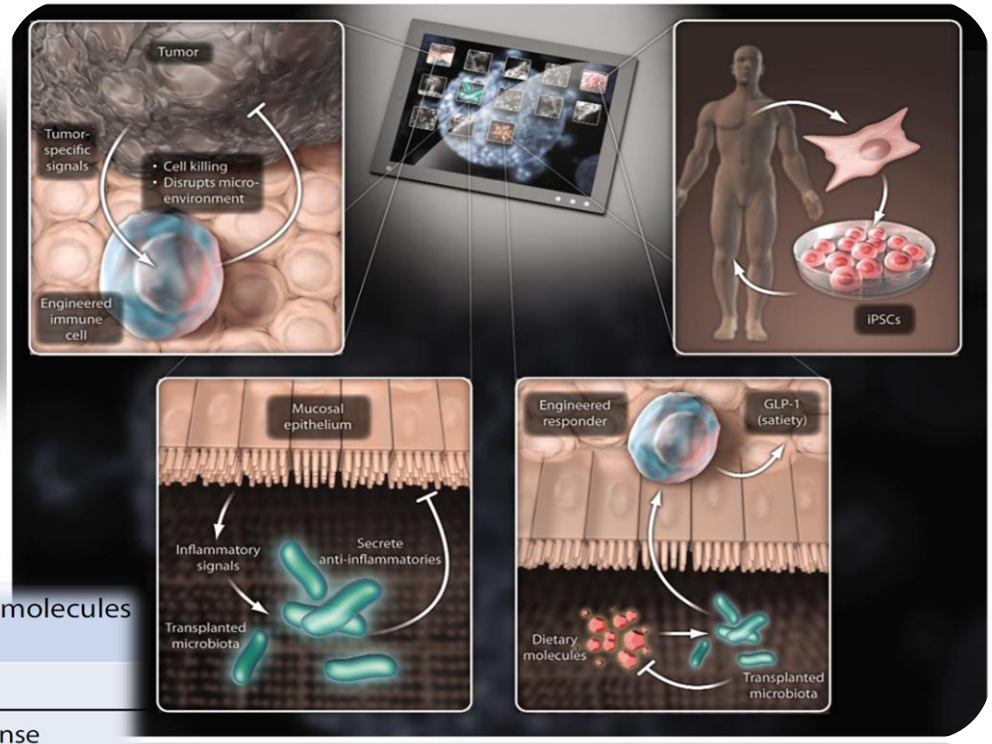


Table 1. Therapy's cast of characters. Cell-based therapeutics are compared to small molecules and biologics.

Comparisons	Small molecules and Biologics	Cells
Selectivity	Molecular recognition	Complex sensing and response systems
Distribution	Diffusion and transport Controlled PK/PD	Directed cell migration
Dose	Controlled at time of administration	Cell decision-making: • Proliferation/activation/death • Closed-loop autoregulation
Therapeutic niche	Conditions for which distribution and duration of action do not need fine control	Conditions that require precise dynamic control over distribution, level, and duration of action

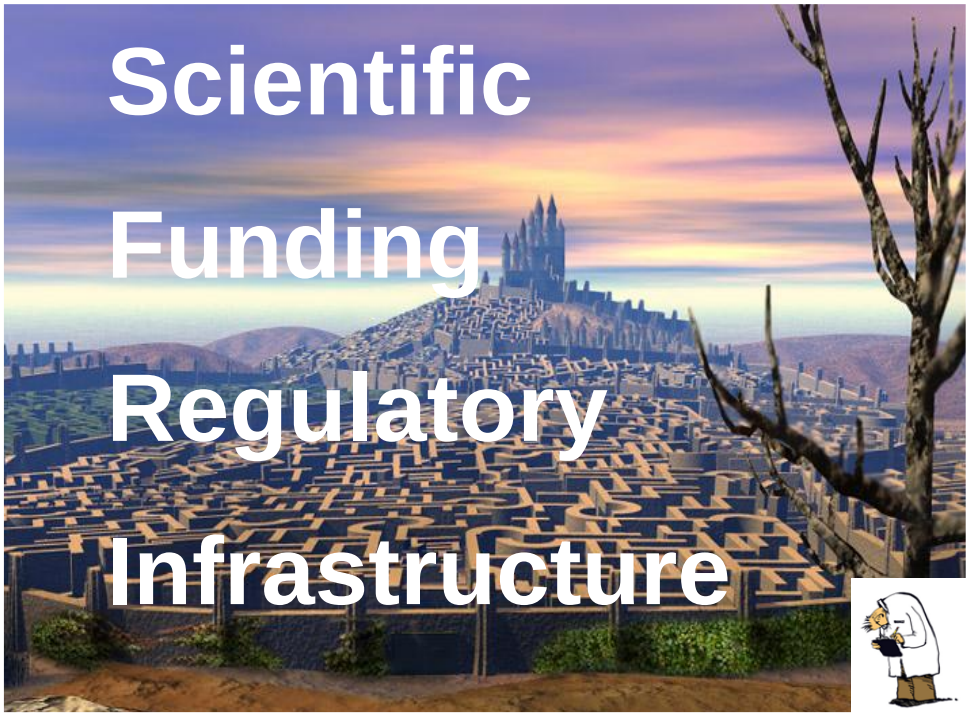
Sci Transl Med. 2013; 5:179

Open Questions

- Can stem cells regenerate the tissues and are we able to apply these knowledge to human diseases
- How do stem cells work: MoA
- If SC are “drugs” what are the doses, schedule, route….
- Allogeneic versus autologous
- Combine products: tissue engineering and gene therapy

- Business models….commercialization
- Prescribing physicians

Cell Therapy: Valley of Death



Translational medicine is the integrated application of innovative pharmacology tools, biomarkers, clinical methods, clinical technologies and study designs to improve disease understanding, confidence in human drug targets and increase confidence in drug candidates, understand the therapeutic index in humans, enhance cost-effective decision making in exploratory development and increase phase II success

(Littman et al. Clin Sci. 2007; 112:217-27)

Productos de Terapias Avanzadas

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07/2007	**CEREPRO**	***AdV-HSVtk***. Withdrawn by the applicant
12/2008	**ADVEXIN**	***AdV-p53***. Withdrawn by the applicant
07/2009	**CHONDROCELECT**	***Autologous chondrocytes***
07/2012	**GLYBERA**	***AAV-LPL***
01/2013	**HYALOGRAFT C AUTOGRAFT**	***Autologous chondrocytes***. Withdrawn by the applicant
03/2013	**ORANERA**	***Autologous oral mucosal epithelial cells***. Withdrawn by the applicant
04/2013	**MACI**	***Matrix-induced autologous chondrocyte implantation.*** Now suspended
06/2013	**PROVENGE**	***Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (sipuleucel-T).*** Company declared bankruptcy

ÁREA DE TERAPIA CELULAR

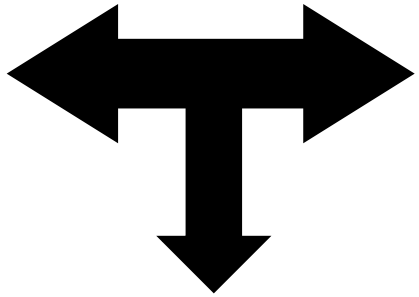
Clínica Universidad de Navarra

Desarrollo de nuevas estrategias terapéuticas basadas en terapia celular e ingeniería de tejidos

Programa de Investigación Básica

Identificar, aislar y estudiar nuevas fuentes de células madre

Definir el potencial de las células madre y la ingeniería de tejidos en el tratamiento de distintas enfermedades



Investigación Clínica (Laboratorio GMP)

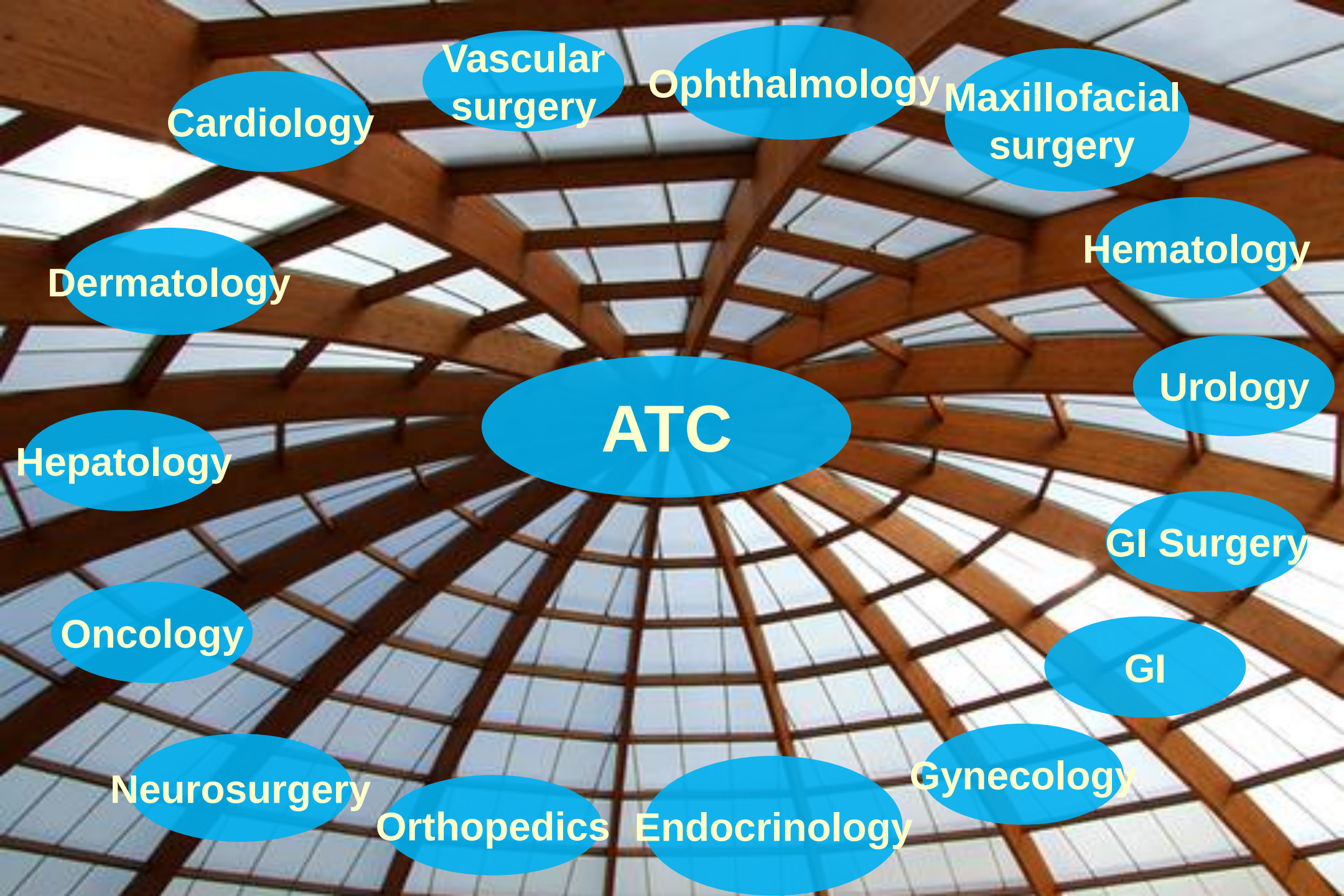
Traslación de los desarrollos preclínicos

Desarrollo del conocimiento en el tratamiento de distintas enfermedades

Empleo de terapias avanzadas

Colaboraciones Multidisciplinares

CUN: Departamentos Clínicos
UNAV (Galénica)
CEIT

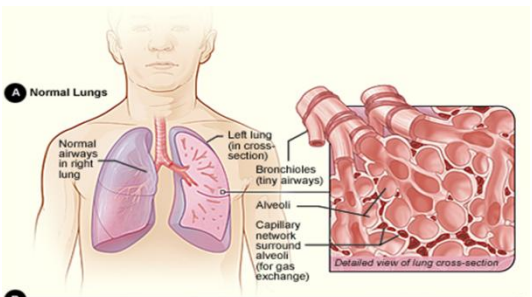

Vascular surgery
Ophthalmology
Maxillofacial surgery
Cardiology
Hematology
Dermatology
Urology
ATC
Hepatology
GI Surgery
Oncology
GI
Gynecology
Neurosurgery
Orthopedics
Endocrinology

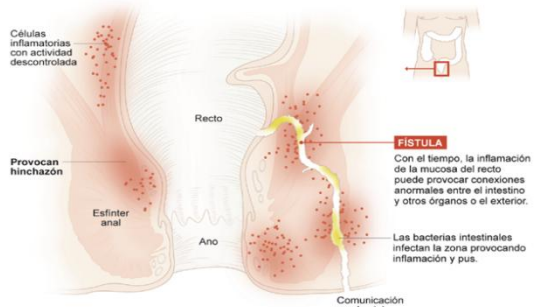
Restricciones o aclaraciones relacionadas con el ámbito de estas operaciones de fabricación / *Any restrictions or clarifying remarks related to the scope of this manufacturing operations*

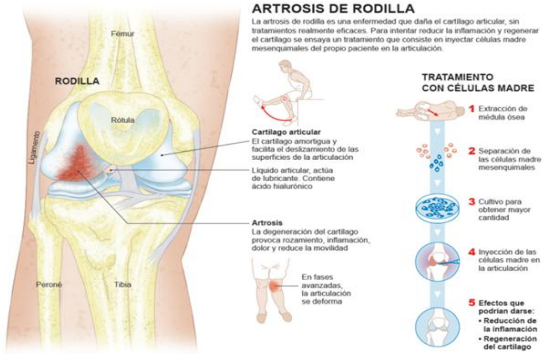
1. **Mioblastos** troncales adultos autólogos de músculo esquelético expandidos.
2. **Células Mesenquimales** troncales adultas autólogas de **médula ósea** expandidas.
3. Células Mesenquimales troncales adultas alogénicas de médula ósea expandidas.
4. **Células Mesenquimales** troncales adultas autólogas de **tejido adiposo** expandidas.
5. Células Mesenquimales troncales adultas alogénicas de tejido adiposo expandidas.
6. **Células dendríticas** diferenciadas adultas autólogas de sangre periférica no expandidas derivadas de monocitos y **pulsadas con lisado tumoral** autólogo.
7. **Células CD133+** troncales_adultas autólogas seleccionadas de médula ósea no expandidas.
8. **Melanocitos** diferenciados adultos autólogos de piel expandidos.
9. **Células limbares** troncales adultas autólogas de limbo esclerocorneal expandidas.
10. Células limbares troncales adultas alogénicas de limbo esclerocorneal expandidas.
11. Linfocitos diferenciados adultos infiltrantes de tumor autólogos expandidos (**TIL**).
12. Células linfoides diferenciadas adultas autólogas de sangre periférica expandidas estimuladas por citoquinas (**LAK**).
13. Células endoteliales troncales adultas autólogas de médula ósea expandidas (**EPC**).
14. **Células mononucleares** adultas autólogas de **médula ósea** no expandidas.
15. **Células dendríticas** diferenciadas adultas autólogas de sangre periférica no expandidas derivadas de monocitos y **transducidas con adenovirus**.
16. Colirio de **extracto de membrana amniótica**.

Clinical Trials of ATMP (CUN)

Clínica Universidad de Navarra







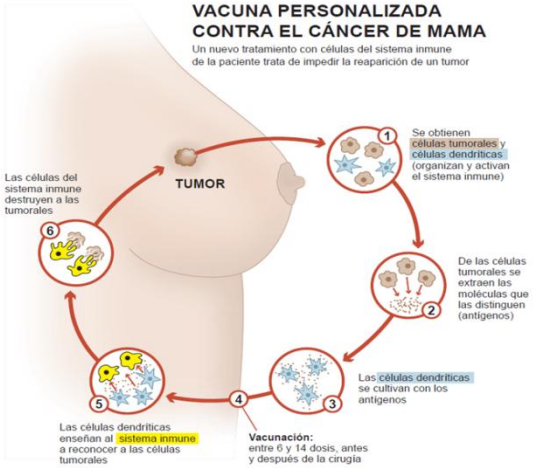
Trial Code	EudraCT	Status	Number Pt Included
Mio/Reg/perc	2006-000679-14	Completed	36
CD-2007-01	2006-005238-19	Completed	29
CD133/isquemia	2008-000693-20	Cancelled	2
DEND/GM	2009-009879-35	Completed	31
CSM/CROH	2009-009880-71	Completed	14
CMM-EM	2009-016442-74	Completed	10
EPC/CIRR	2009-014278-16	Completed	20
CD-2009-01	2008-007795-23	Recruiting	10/36
DEND/CM	2009-017402-36	Completed	18
LEA/VIT	2009-017757-36	Completed	30
LFNK	2009-017829-19	Completed	30
CMM/ART	2009-017624-72	Completed	30
CMM/DM1	2009-017228-24	Cancelled	-
CSM-EICH-2010	2010-020947-11	Completed	20
CD-AdNS3	2010-024043-32	Completed	10
FISPAC-2011	2012-001178-28	Recruiting	25/80
CDCC/2010	2010-024118-73	Recruiting	8/30
CMM-PRGF-ART	2011-006036-23	Recruiting	8
CMM-Fibrosis	2011-006240-75	Recruiting	6

PLoS One. 2014; 9:e113936.

BBMT. 2014; 20:1580-5

Clinical Trials of ATMP (CUN)

Clínica Universidad de Navarra



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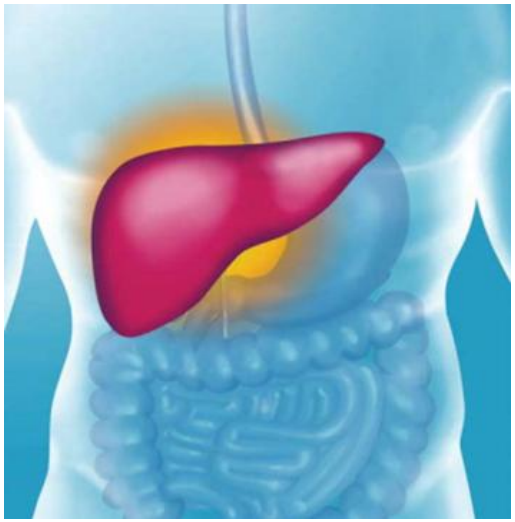
J Immunol. 2011; 187:6130-42

W J Clin Oncol. 2012; 3:142-9

Clinical Trials of ATMP (CUN)

Clínica Universidad de Navarra



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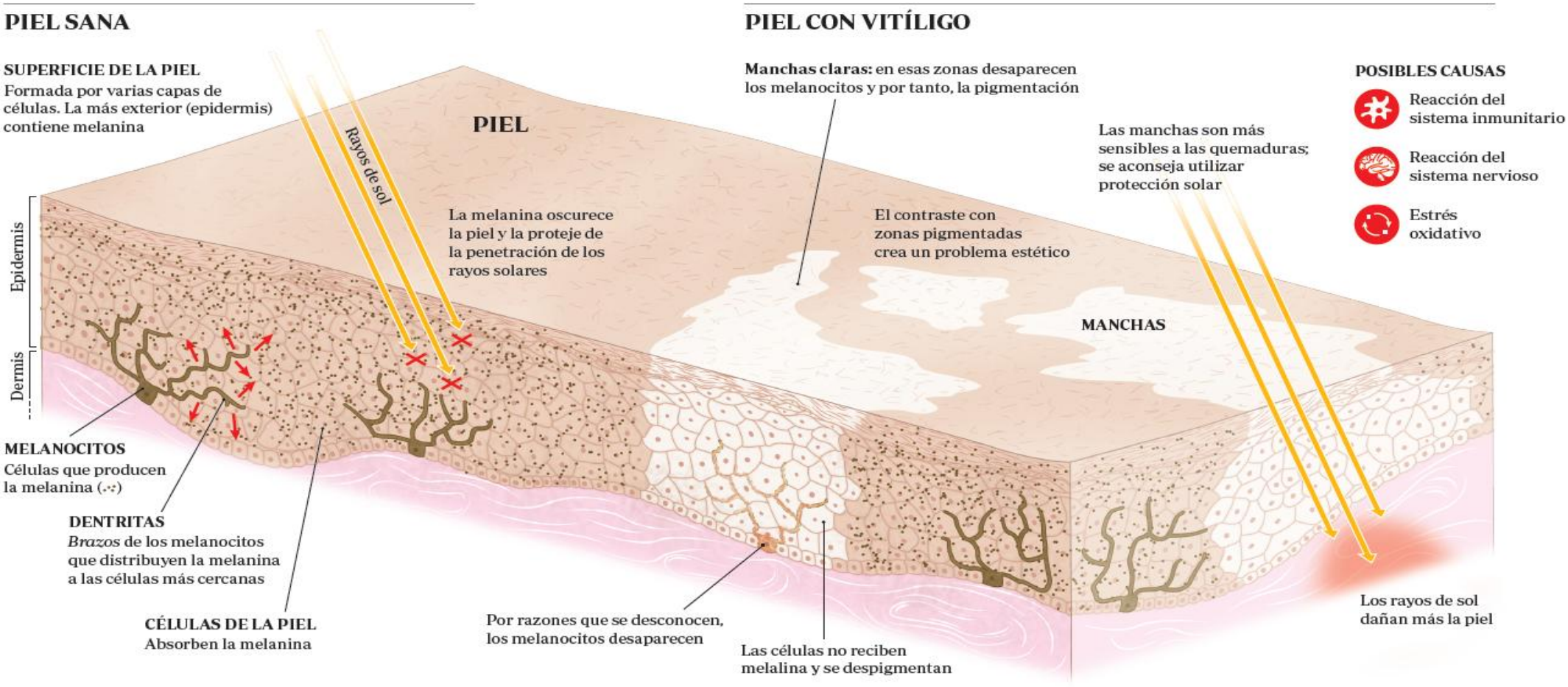
JAMA Dermatol. 2015

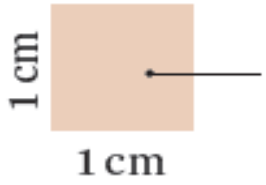
VITÍLIGO

Clínica Universidad de Navarra



1 PIEL SANA

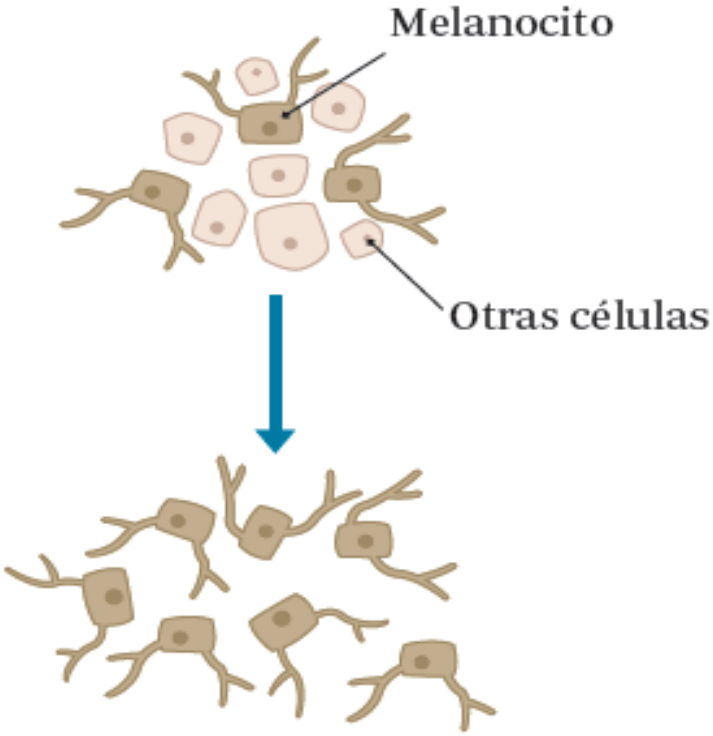
Se extrae una porción de epidermis sana de la zona lumbar del paciente



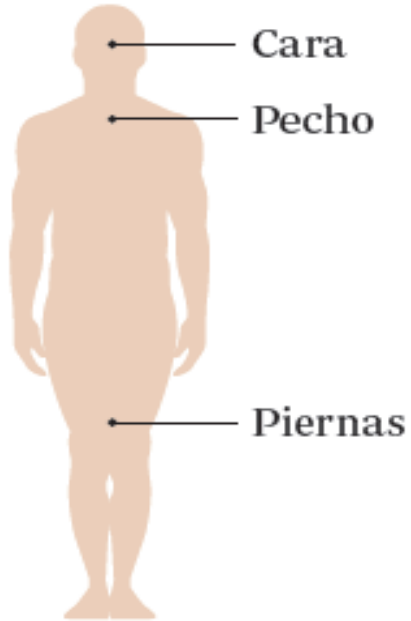
Con una muestra de **1 cm²** se puede regenerar un área de **22 x 22 cm**

2 CULTIVO

En unas condiciones que hacen que solo se multipliquen los melanocitos



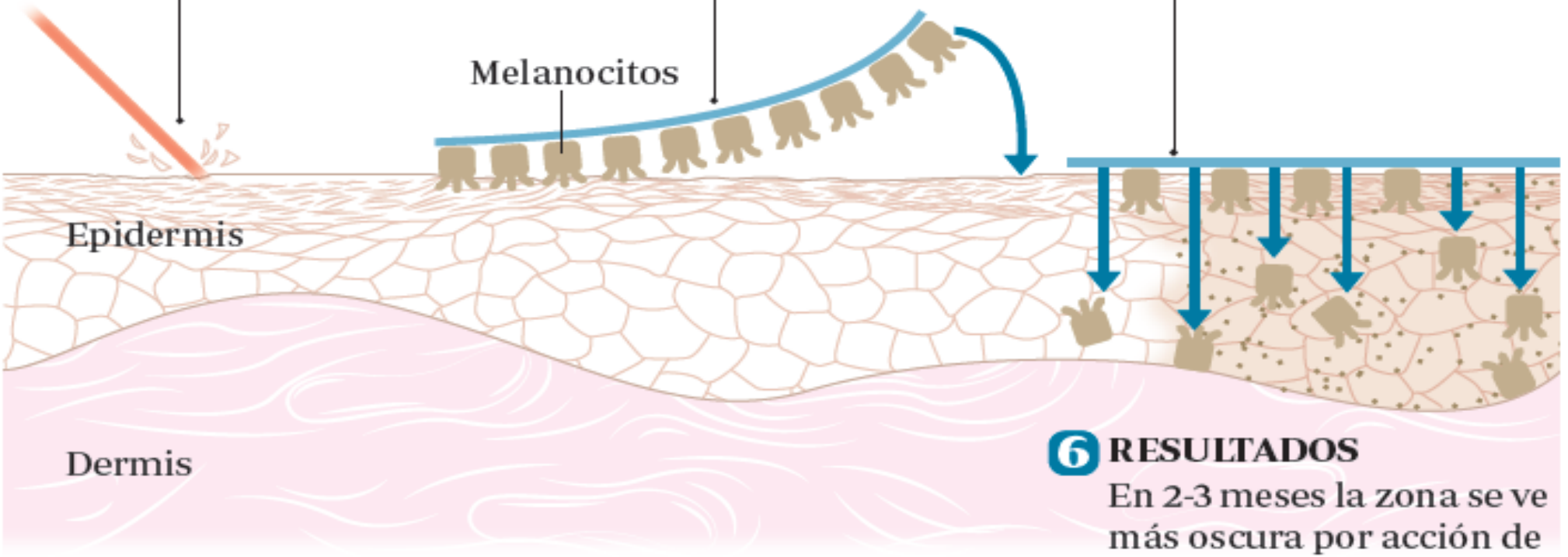
Tratamiento: zonas visibles



3 DERMOABRASIÓN O LÁSER CO_2
Se eliminan la capa de células epidérmicas de la zona a tratar

4 APLICACIÓN
Se cubre con una membrana que contiene los melanocitos

5 TRANSFERENCIA
Los melanocitos pasan a la piel, donde producirán melanina con normalidad



6 RESULTADOS
En 2-3 meses la zona se ve más oscura por acción de la melanina

Tissue Engineering for Vitiligo

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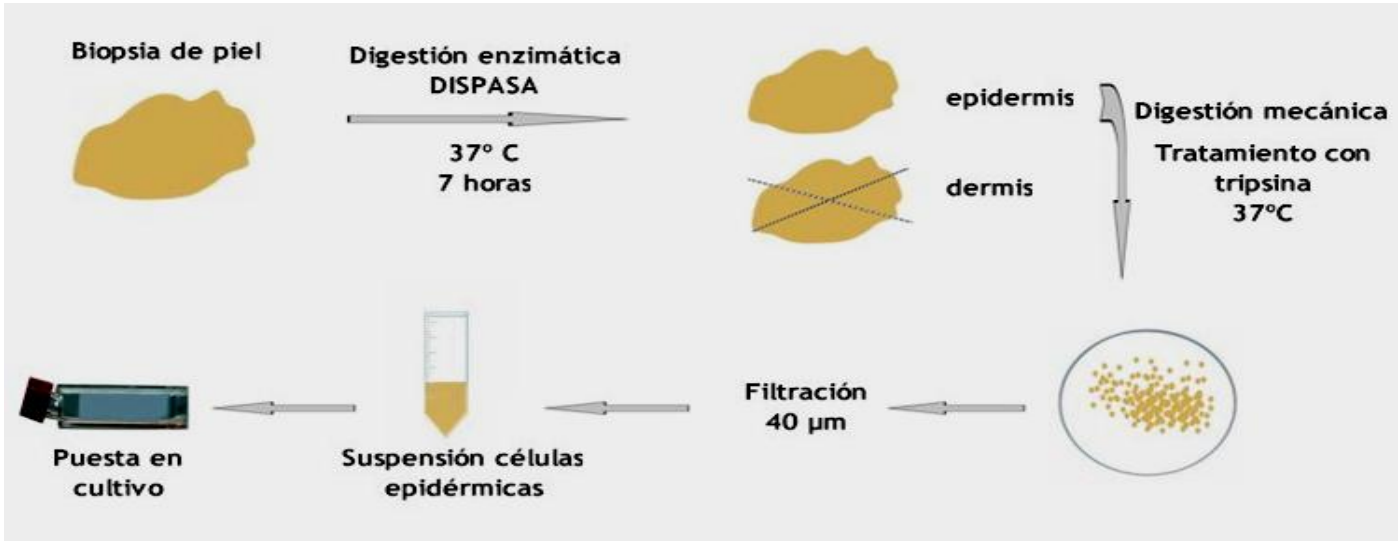
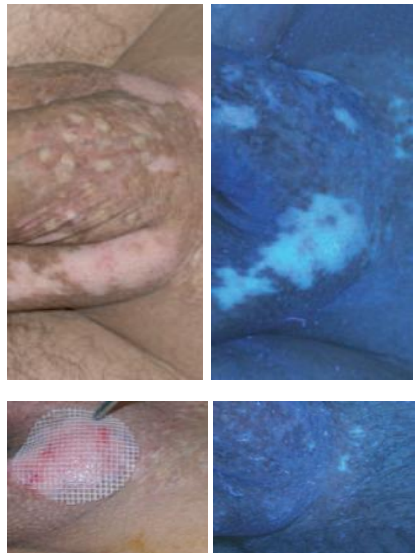
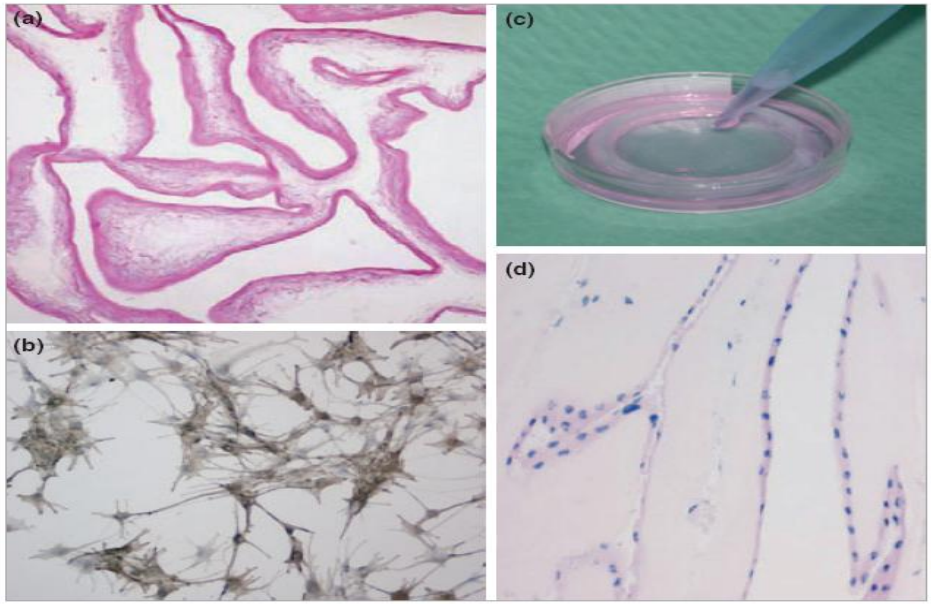
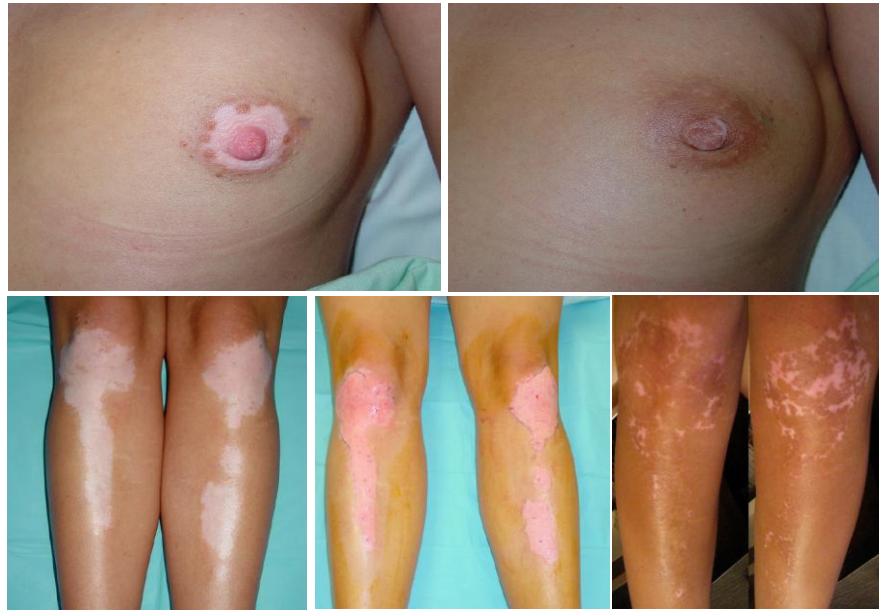




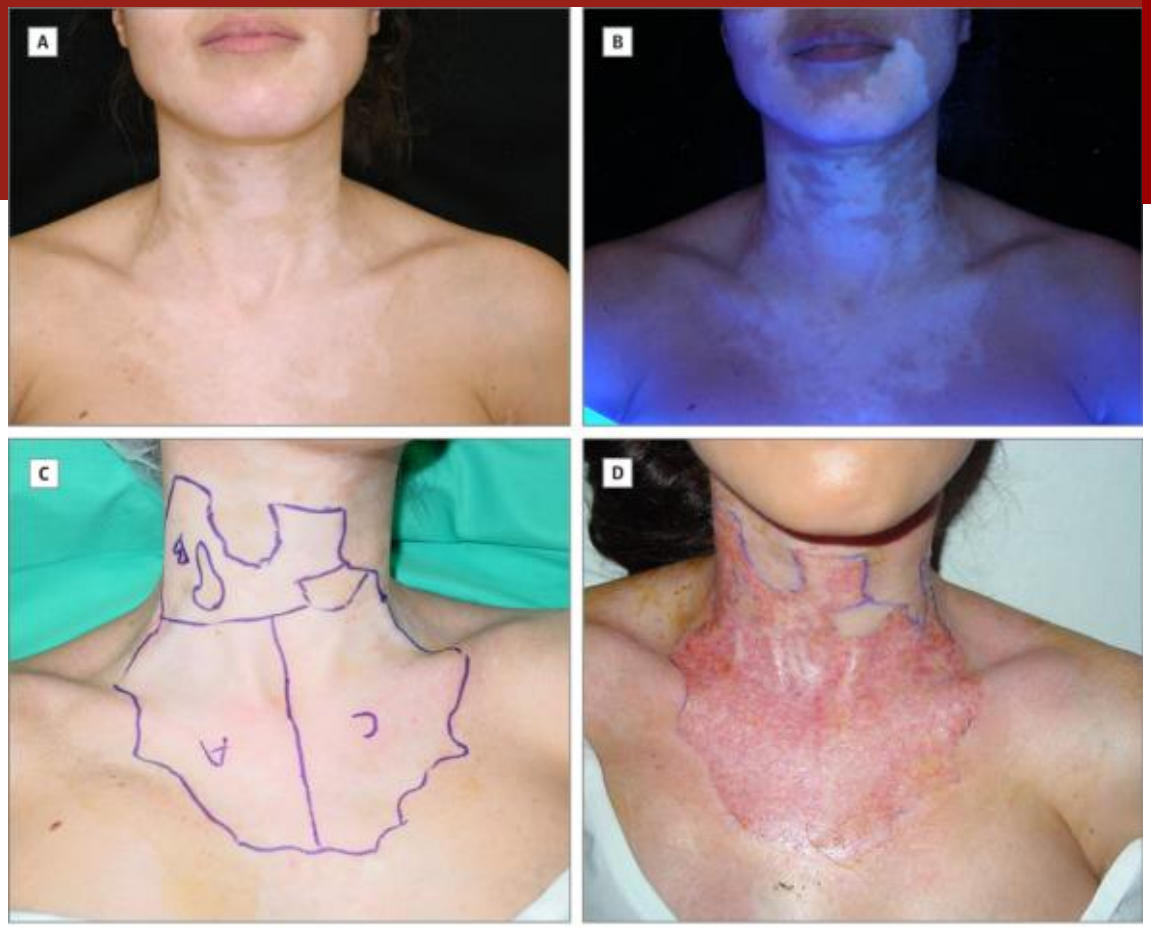




Redondo et al. (2008) Br J Dermatol.; 158:1168-71

Redondo et al. (2011) Dermatol Res Pract. 2011:532139

Ensayo clínico fase II controlado intraindividualmente para evaluar la eficacia del trasplante de melanocitos autólogos sobre un soporte de membrana amniótica en el tratamiento del vitíligo estable



A. A woman in her 30s with vitiligo on the neck and trunk.

B. The Wood light examination clearly reveals sites of vitiligo.

C. Three areas were randomized to receive:

•amniotic membrane–cultured epidermal cell grafting (area A)

•cultured epidermal cell suspension (area B)

•or placebo (area C).

The randomization process was designed and executed by a distance centralized randomization service formed by staff with no clinical involvement in the trial. A computer-generated, permuted, block-randomization scheme was used to allocate interventions. Patients, data analysts, and physicians involved in the recruitment, as well as those delivering the intervention or measuring outcomes, were blinded to allocation.

D. The achromic epidermis was removed using carbon dioxide laser, with a similar clinical appearance 96 hours later.

Table. Effects of the Experimental Intervention on Pigmentation

	Repigmentation at Follow-up, Percentage Points						Patients' Perception of Improvement at Follow-up, Score[a]					
	3 mo (n = 23)			6 mo (n = 19)			3 mo (n = 24)			6 mo (n = 18)		
Intervention	Mean (SD)	Median (25th-75th Percentile)	*P* Value	Mean (SD)	Median (25th-75th Percentile)	*P* Value	Mean (SD)	Median (25th-75th Percentile)	*P* Value	Mean (SD)	Median (25th-75th Percentile)	*P* Value
Control	23.5 (32.7)	5 (0-40)	.08	27.9 (34.5)	10 (5-50)	.81	1.5 (1.1)	2 (1-2)	.27	1.5 (1.2)	1 (0.75-2.25)	.33
CES	37.8 (37.8)	20 (5-80)		43.4 (38.3)	25 (10-85)		1.9 (1.7)	2 (1-3)		2.3 (1.1)	2.5 (1-3)	
AM-CEG	30.2 (35.7)	10 (0-70)		38.9 (38.7)	20 (0-80)		1.9 (1.4)	2 (1-3)		2.0 (1.5)	1.5 (1-3.3)	

Abbreviations: AM-CEG, amniotic membrane–cultured epidermal cell grafting; CES, cultured epidermal cell suspension.

[a] The patients' perception of pigmentation improvement in each of the 3 intraindividual randomized areas was evaluated at the 3- and 6-month visits using an 11-point self-reported repigmentation scale (from 0 [no changes since treatment started] to −5 [vitiligo worsened intensely since treatment started and incapacitated the patient for everyday activities] or 5 [vitiligo disappeared since treatment started]).

Redondo et al. (2015) JAMA Dermatol. 151(8):897-9

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