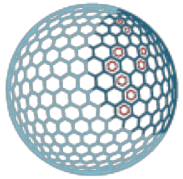

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agencia española de medicamentos y productos sanitarios

EU Innovation Network

London, November 16, 2018

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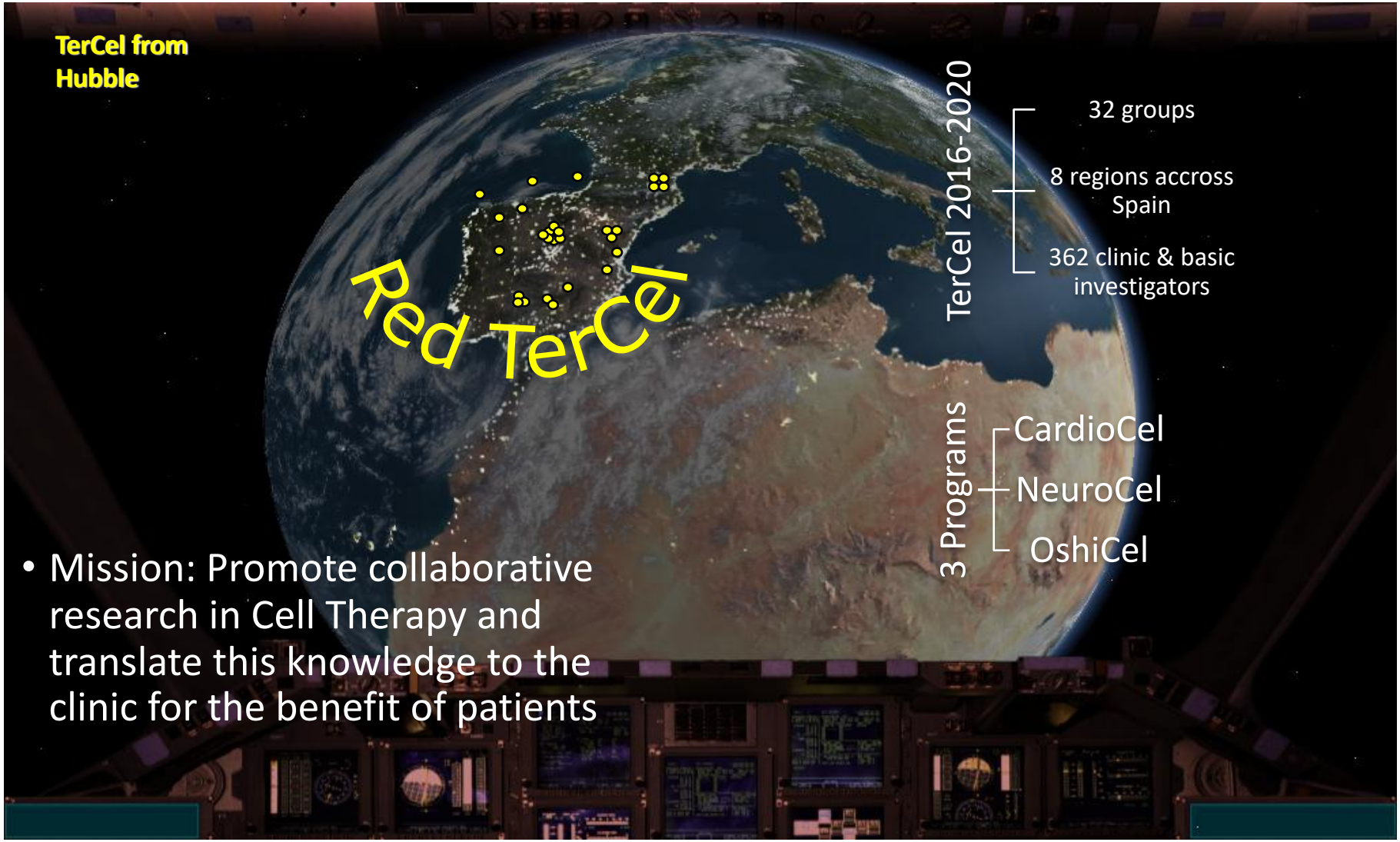
isciii

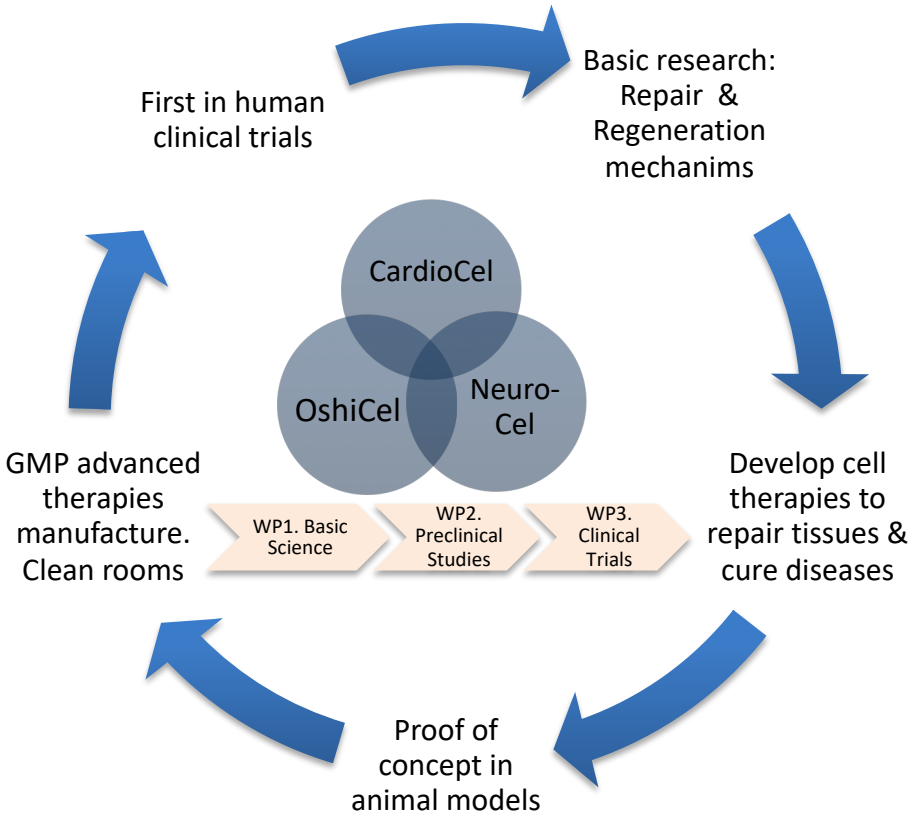
MINISTERIO
DE ECONOMÍA, INDUSTRIA
Y COMPETITIVIDAD

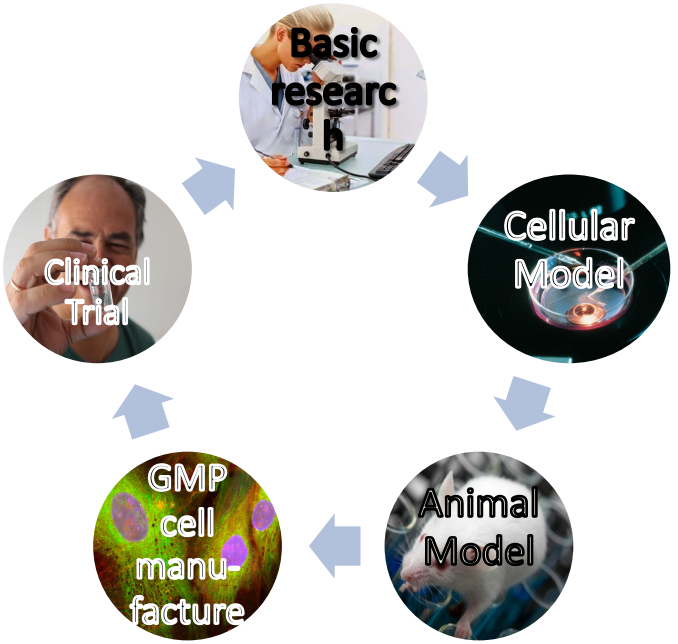
Instituto
de Salud
Carlos III



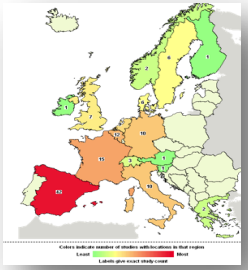
- Mission: Promote collaborative research in Cell Therapy and translate this knowledge to the clinic for the benefit of patients

Scientific Strategy





Clinical Trials

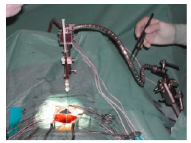


Region Name	Number of Studies
World [map]	428
Europe	106
Austria	1 [studies]
Belgium	12 [studies]
Denmark	6 [studies]
Finland	1 [studies]
France	16 [studies]
Germany	10 [studies]
Greece	2 [studies]
Ireland	1 [studies]
Italy	10 [studies]
Netherlands	9 [studies]
Norway	2 [studies]
Slovenia	1 [studies]
Spain	42 [studies]
Sweden	6 [studies]
Switzerland	3 [studies]
United Kingdom	7 [studies]

- Phase I-II

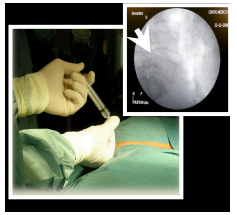
STEM CELLS

2012 Mar 13. ***Neurotrophic Bone Marrow Cellular Nests Prevent Spinal Motoneuron Degeneration in ALS Patients: A Safety Study***



TRANSPLANTATION

2016 Sept 21. ***Intervertebral disc repair by allogeneic mesenchymal bone marrow cells: a randomized controlled trial.***

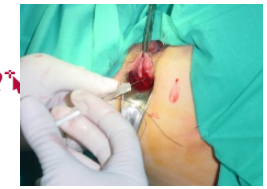


- Phase III

THE LANCET

Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial

*Julián Panés, Damián García-Olmo, Gert Van Assche, Jean Frederic Colombel, Walter Reinisch, Daniel C Baumgart, Axel Dignass, Maria Nachury, Marc Ferrante, Lili Kazemi-Shirazi, Jean C Grimaud, Fernando de la Portilla, Eran Goldin, Marie Paule Richard, Anne Leselbaum, Silvio Danese, for the ADMIRE CD Study Group Collaborators**

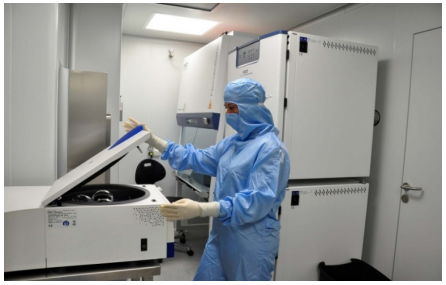


L 262/22 ES Diario Oficial de la Unión Europea 14.10.2003

DIRECTIVA 2003/94/CE DE LA COMISIÓN
de 8 de octubre de 2003
por la que se establecen los principios y directrices de las prácticas correctas de fabricación de los medicamentos de uso humano y de los medicamentos en investigación de uso humano
(Texto pertinente a efectos del EEE)

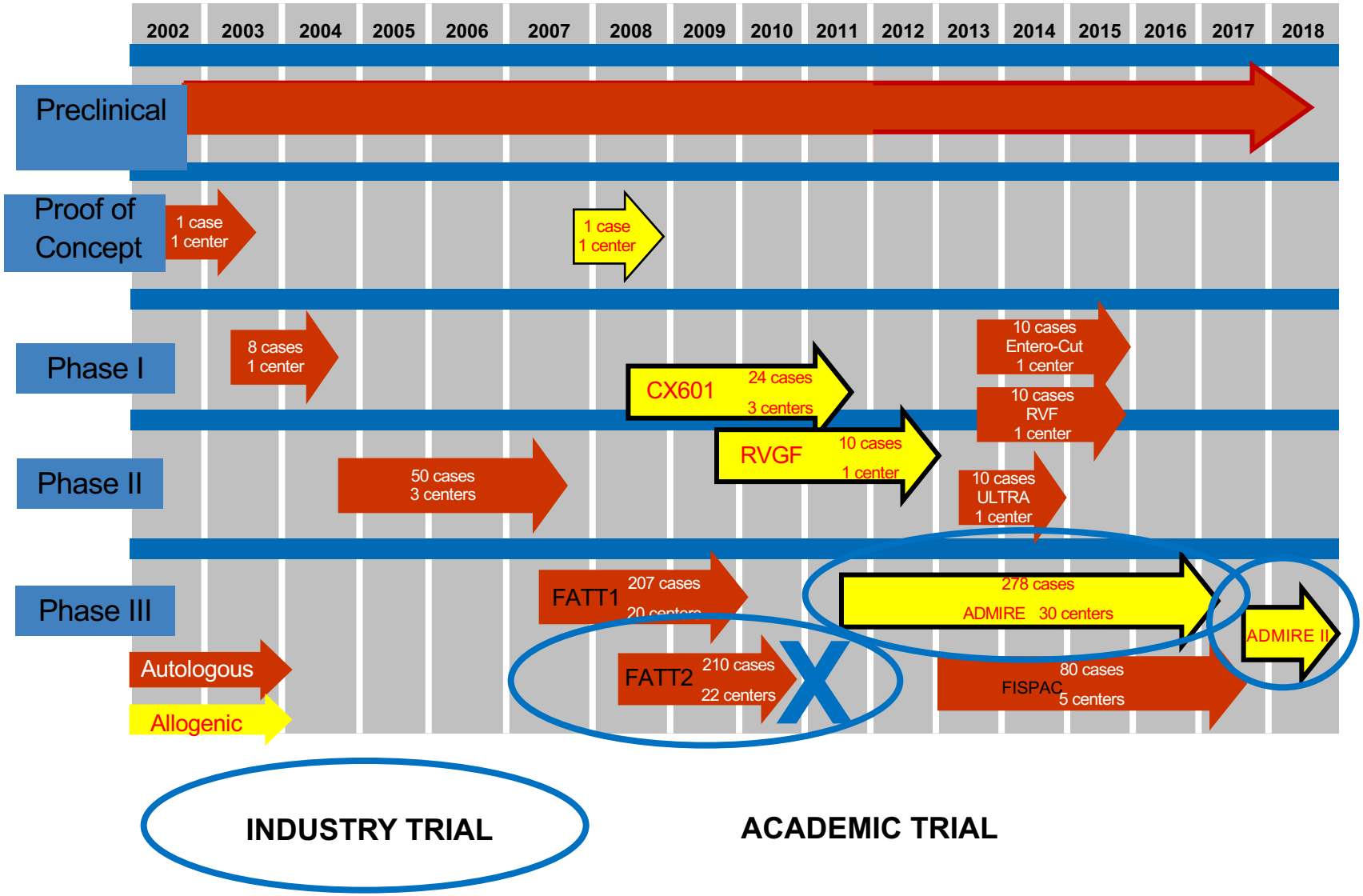
Spain RD 2183/2004 and 1301/2006 transposition of the European Directive

TerCel: GMP CELL MANUFACTURING FACILITIES: 8 certified "clean rooms"

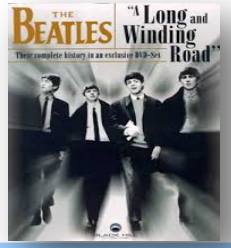


Clinical Trials

ASC Clinical Development in fistula



Academic Clinical Trials



Critical vision from the principal investigators:

- Low quality control during the study
- Low implication of CRO
- Low implication of participants
- Worse patients selection..

May be academy is not the best place for advanced trials?

Lack of translational research

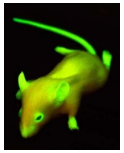
… nevertheless we can translate to industry trials from early studies!

What can we do:

- Excellent safety profile
  - Dose increase. Repeated doses
- Cell mortality
  - Improving methods of delivery
- Soft effects:
  - Cell product improvements (next generation of cells)
    - Improve effect: cell ingeniering
    - Improve traffic: fucosilation
- Design robust clinical trials
  - CRO implication from the beginning
  - Patient selection
  - IP education and implication

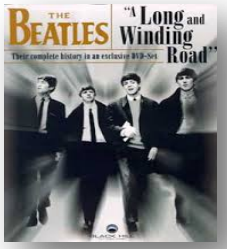
The biggest challenges of carrying out academic clinical studies

- Preclinical Studies: To prepare the dossier for the Registry of research medication
  - Preclinical models have limitations: NOT easy to get “Proof of concept”.
  - More efforts in good science. Reference centers for ensuring data quality?



  Finantial support. New models. Lost in translation

- Clinical Studies: prepare the dossier for the Registry of research medication
  - Phase I-II: PK & PD. Reference centers for particular diseases / therapies?
  - Phase III studies: New designs? Public CRO with special expertise in ATM?
    - Efficacy parameters. Biomarkers, surrogate data. New designs?
    - Coordination of multicenter clinical trials. Limited budgets. Public CRO @ low cost?
    - Administrative problems (CRO, data quality): Limited budgets. Public CRO @ low cost?
    - Raw materials homogeneity: cell of origin. Autologous vs Allogeneic. EU guideliness
    - GMP quality Cell product manufacture scalation. Transport, trazability EU certified sites?
      - Take into account new ATMP (viral vectos, nanotechnology, microvesicles, exosomes, ingeneering)
      - Academic GMP sites: implications in registry and comercialization of ATMP



  New models to enhance quicker translation. More coordination, eficiency and safety. Increase collaboration with private sector? Public-private model?

Need for training of regulatory guidelines and processes

- **YES, Training in regulatory science in ATMPs is an ”unmeet” need**
  - ATMP is a totally new area of knowledge with continuous and very rapid advances and quite a few scientific areas of uncertainty
  - Regulation of ATMP is also new and requires dynamic changes according to knowledge. There is also variable interpretation among countries.
  - Institutions (hospitals) need experts with formal training in regulatory science
  - Clinical investigators need some training, but also support from specialized personnel of national or EU platforms that aid the academic trials in ATM

Training available in your country on regulatory science

- There is no formal training in Spain. Few workshops, conferences in meetings
- There is learning materials on the web page of the Spanish Medicines Agency
- Some regional initiatives like the IATA in Andalucia, and the Advancecat in Catalonia to help local investigators in ATMP basic and clinical research
- TerCel ask AEMPS experts to participate in clinical and technical meetings

Experiences on dealing with national regulatory authorities (scientific advice, clinical trial applications, GCP inspections, etc.)

- Excellent collaboration with the Spanish Medicines Agency (AEMPS)
  - Regular meetings with AEMPS representatives to discuss common problems and areas of interest.
  - We have been learning together a new scientific field and the way to implement the rules to get new ATMP of good quality, safety and efficacious for our patients.
  - We have been asked our opinion in the transposition of the European rules to the national legislation. It has been a coordinated effort
  - They have been comprehensive and flexible towards the needs of the patients, the National Health system, and the public hospital limitations.

- Scientific advice: always available, rapid and good
- Clinical trial applications: advice available, rapid and good
- GCP inspections: rigorous, but flexible and friendly

Spanish strategy on ATMP

- Public Grants to promote academic clinical trials (ISCIII)
- Public Grants to generate GMP facilities
- From 2006-2011
- New call for grants on ATMP in 2017
- Specific programs for ATMPs. Looking for collaboration among centers.
- Advanced Phase II-III, multicentric clinical trials
- TerCel achieved grants to launch clinical trials in:
  - Arthritis (Artrocell)
  - Critical limb ischemia (NOMA, no more amputations)
  - Cardiac ischemia
  - ALS
  - Academic CAR-T cells