The EU Framework Programme for Research and Innovation

HORIZON 2020

Activities and initiatives in advanced therapies

DG RTD

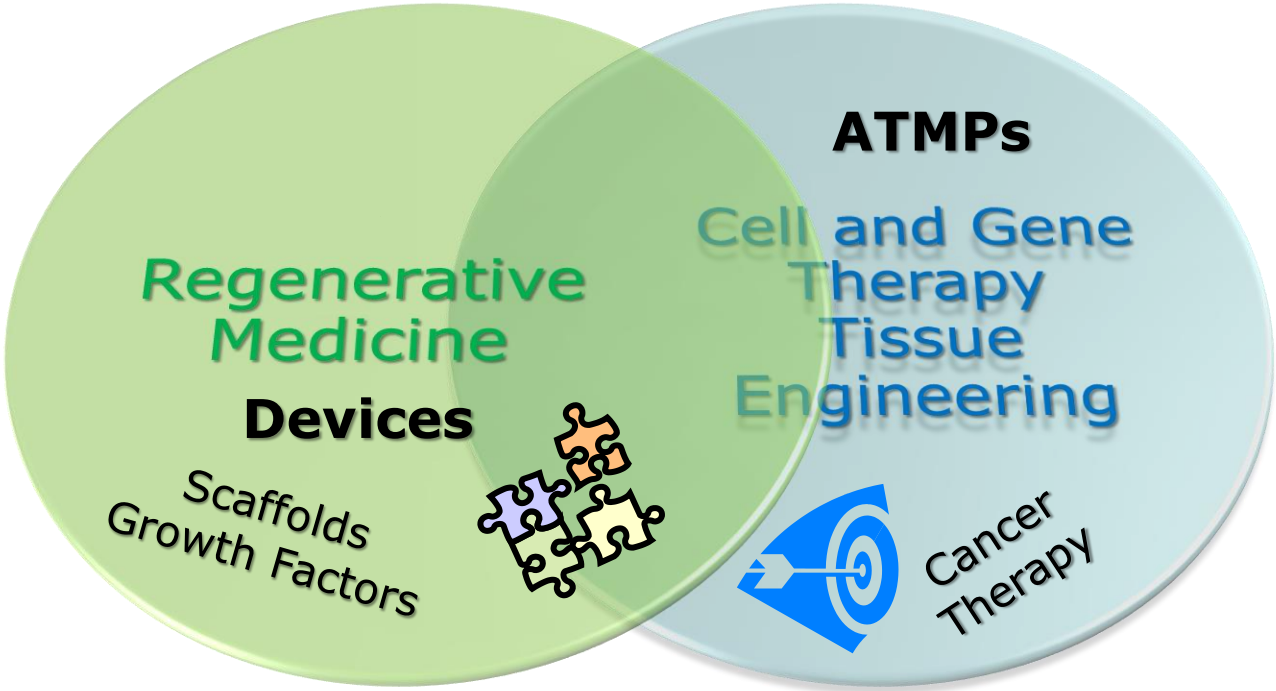
European Commission
Unit E5

Research and Innovation

European Commission

EU research on cell and gene therapy, regenerative medicine and ATMPs in Horizon 2020

New therapies overlapping fields



Research and Innovation

European Commission

Advanced Therapy Medicinal Products (ATMP)

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)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission,

Having regard to the Opinion of the European Economic and Social Committee (1),

been defined in Annex I to Directive 2001/83/EC, but a legal definition of tissue engineered products remains to be laid down. When products are based on viable cells or tissues, the pharmacological, immunological or metabolic action should be considered as the principal mode of action. It should also be clarified that products which do not meet the definition of a medicinal product, such as products made exclusively of non-viable materials which act primarily by physical means, cannot by definition be advanced therapy medicinal products.

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Advanced Therapy Medicinal Products (ATMP)

Means any of the following medicinal products for human use:

- a gene therapy medicinal product
- a somatic cell therapy medicinal product
- a tissue engineered product
- *combinations thereof*

Why is the EU supporting research on new therapies ?

- Offers hope for untreatable disease and quality of life, ageing population, etc.
- Reduces cost of expensive treatments (e.g. enzyme replacement therapy – storage disorder, or blood transfusion – thalassemia)
- Collaborative research across borders to:
  - ✓ Avoid duplication
  - ✓ Share facilities
  - ✓ Assemble multi-disciplinary team
  - ✓ Access to patient population
  - ✓ Obtain more robust results

EU-supported gene and cell therapy research: a long-lasting effort

FP6

- Stem cells
- ATMP Regulation
- 59 projects
- 266 million €

FP7

- Regenerative medicine term
- 53 projects
- 349 million €

So far in H2020

- 38 projects
- 223 million €
- 2 new calls: 2018 and 2019

Twenty Years of European Union Support to Gene Therapy and Gene Transfer

David Gancberg*

Health Directorate, Directorate-General for Research and Innovation, European Commission, Brussels, Belgium

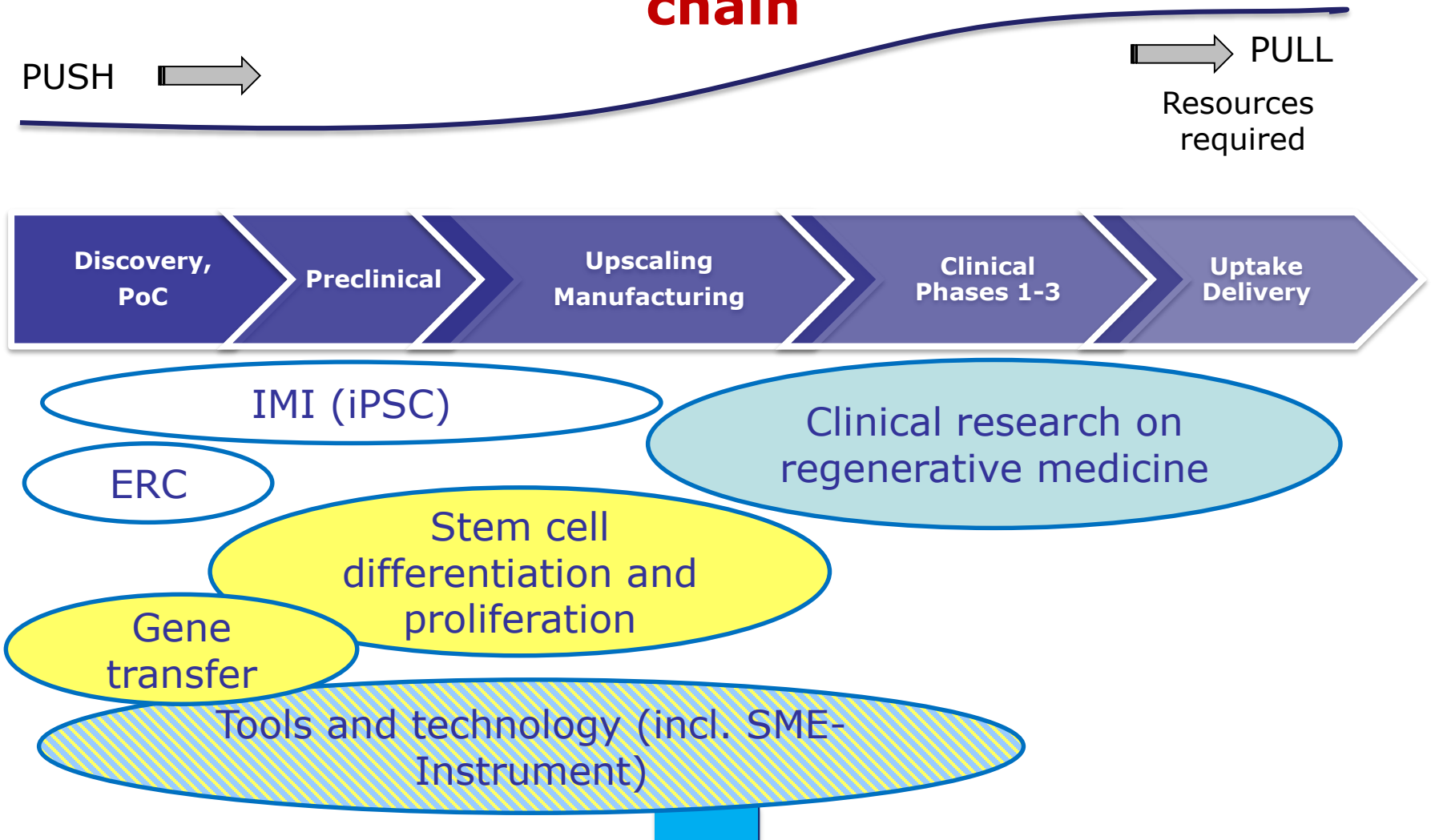
For 20 years and throughout its research programmes, the European Union has supported the entire innovation chain for gene transfer and gene therapy. The fruits of this investment are ripening as gene therapy products are reaching the European market and as clinical trials are demonstrating the safety of this approach to treat previously untreatable diseases.

Keywords: European Union, gene therapy, gene transfer, Framework Programme

NUCLEIC ACID TRANSFER can be used to treat many different disorders, including cardiovascular, neurodegenerative, infectious or rare diseases, and cancer. Twenty-five years ago, in Europe, a group of experts founded the European Working Group on Human Gene Therapy (EWGT), whose aim was to develop and coordinate clinical and scientific research in the field of gene transfer and therapy. Later on, the dimension of cell therapy was included in the remit of the group, leading to the

Already in 1994, the European Union (EU) supported the field of gene therapy with its Biomedical and Health research programme Biomed2 and its Biotechnology programme Biotech2 (1994–1998). In these programmes, more than 36 projects directly addressed the topic of gene transfer and/or gene therapy for various disorders, for a total amount of >€40 million. Of note, all but four investigated the development of new vectors or oligonucleotides and preclinical work. Of these four,

EU-support targeting the whole innovation chain



Horizon 2020 – Calls for proposals 2014-2017

Clinical research on regenerative medicine
(PHC 15 2014/2015 and SC1-PM-11-2016-2017)

- **Scope**:
  - ✓ Proposals should focus on regenerative medicine therapies which are ready for clinical (in-patient) research
  - ✓ Any justified disease or condition
  - ✓ Clinical work should represent a central part of the project
- **Expected impact**:
  - ✓ Obtain results of in-patient regenerative medicine research so that new therapies can be taken to the next level of testing, or be discarded

So far
18 Projects
€102
Million

Clinical research on regenerative medicine projects (2014-2016)

Project	Area/Condition	Approach/Technology	Phase
TREGeneration	GvHD (chronic)	Allogeneic Treg lymphocytes	I/II
RETHRIM	GvHD (acute)	Allogeneic bone marrow-derived MSC	III
SCIENCE	Ischemic heart disease	Allogeneic adipose-derived MSC	I/II
ADIPOA2	Osteoarthritis	Autologous adipose-derived MSC	IIb
SC0806	Spinal cord injury	Recombinant growth factor + device	I/II
ARISE	Heart valve	Allogeneic decellularized aortic valve	II
NISCI	Spinal cord injury	Antibodies against Nogo-A	II
BOOSTB4	Osteogenesis imperfecta	Allogeneic fetal-derived MSC	I/II
RESSTORE	Stroke	Allogeneic adipose-derived MSC	IIb
SEPCELL	Sepsis	Allogeneic adipose-derived MSC	I/II
TETRA	Trachea (severe airway disease)	Autologous MSC + decellularized trachea scaffold	II
BetaCellTherapy	Type-1 diabetes	Encapsulated hESC-derived progenitor cells	I, I/II
BIO-CHIP	Knee cartilage injury	Autologous nasal chondrocytes	II
RESPINE	Degenerative disc disease	Allogeneic bone marrow-derived MSC	IIb
ORTHOUNION	Long bone nonUNIONs	Autologous bone marrow-derived MSC + bioceramics	IIb
MUSIC	Stress Urinary Incontinence	Autologous muscle precursor cells + neuromuscular electromagnetic stimulation	I
PACE	Severe critical limb ischemia	Allogeneic placenta-derived stromal cells	III
REGENHEART	Refractory angina pectoris	Catheter-mediated intramyocardial AdenoVEGF-D	II

So far 15 Projects €91 Million

Other Cell and Gene Therapy research

Project	Area covered/Condition	Approach/Technology	Phase
SCIDNET	SCID	LV transduced autologous HSC	I/II, IIb
MYOCURE	Hereditary muscle disorders	AAV-based gene therapy	-
BATCure	Batten disease (storage disorder)	Includes gene therapy	-
HEMACURE	Hemophilia A	Ex vivo Factor VIII gene therapy	-
PRO-CF-MED	Cystic fibrosis	Oligonucleotide by inhalation	Ib, IIa, IIb
H2020MM04	Malignant mesothelioma	Autologous DC-based immunotherapy	II/III
PROCROP	Ovary and prostate cancer	Autologous DC-based immunotherapy	I/II
AML-VACCIN	Acute myeloid leukaemia	Dendritic cell vaccine therapy	IIb
EURE-CART	Cancer therapy	CAR T cell	I/II
CARAT	Cancer therapy	Automated CAR T cell production platform	-
AUTOSTEM	Cell therapy	Automated closed system MSC manufacturing	-
NEPHSTROM	Diabetic kidney disease	Allogenic bone marrow-derived MSC	Ib/IIa
TECHNOBEAT	Myocardial infarction	IPSC-based cardiac microtissue	-
INTENS	Short bowel syndrome	Autologous intestinal tissue engineering	-
Arrest Blindness	Corneal disorders	Tissue engineering	I/II

European Commission

10 Projects ~ €60 Million

2017 Results from Regenerative Medicine and Rare Disease calls

Project	Area covered/Condition	Approach/Technology	Phase
HIPGEN	**Hip Fractures**	Placenta-expanded adherent stromal cells	III
OSTEOproSPINE	**Lumbar back pain**	Scaffold + human bone morphogenetic protein 6	II
RESTORE	**Multiple sclerosis**	antigen-specific tolerance-inducing dendritic cells	I
SORAPRAZAN	**Stargardt disease**	Repurposing Soraprazan	II
MAXIBONE	**Maxillofacial bone surgery**	Autologous bone, MSC's and biomaterials	IIb
CureCN	**Crigler-Najjar Syndrome**	AAV-UGT1A1 mediated gene therapy in the liver	I/II
CARAMBA	**Multiple Myeloma**	SLAMF7- Sleeping beauty CAR T cells	I/IIa
RECOMB	**SCID (RAG-1 and 2)**	LV-transduced autologous HSC	I/II
UshTher	**Usher Syndrome type IB**	Dual AAV-MYO7A gene therapy in retina	I/II
TRACE	**Refractory viral infections (CMV, AdV, EBV) post- allo HSCT**	Allogeneic adoptive cell transfer	III

Horizon 2020 Regenerative medicine clinical research projects - Observations

- Majority are ATMPs, concentration on MSCs
- Wide range of conditions tackled such as heart, bone, spinal, eye diseases/defects or diabetes
- All clinical phases included, even phase III (3x)
- Remaining challenges are underestimated difficulties for obtaining cell manufacturing and clinical trial authorisations, and for recruiting patients
- However, many therapies most likely to be used via Hospital Exemption

Regenerative medicine: example of a successful project

EU project "ESPOIR"

Goal: To make human heart valve implants more tolerable in young children, avoiding follow-up surgery and allowing for largely normal lives

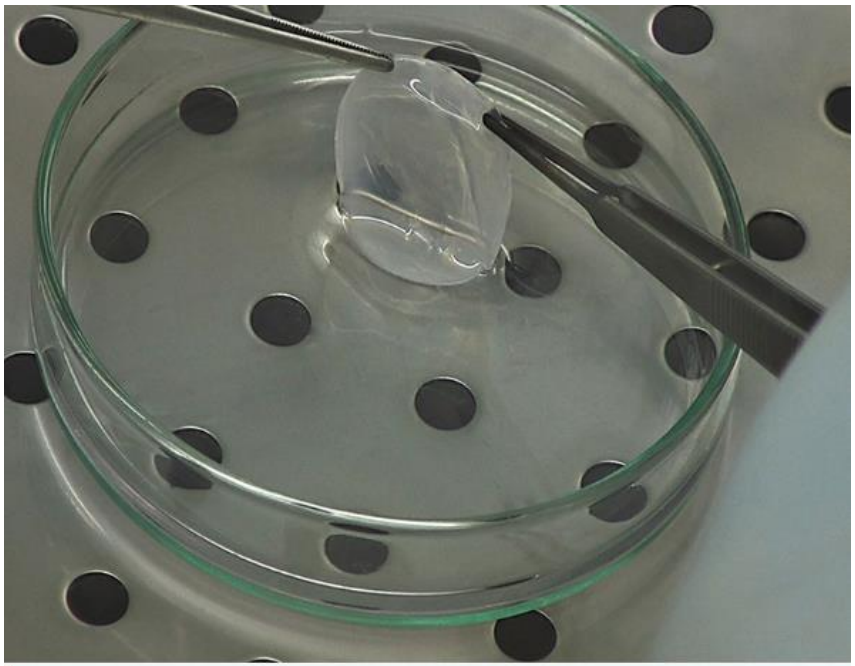
- 121 patients in 7 hospitals treated, with zero valve-related mortality
- The ESPOIR valve has been proven superior to other available valves
- Creation of the ESPOIR registry for long-term monitoring
- 99% of registered patients still have their ESPOIR valve working well
- Obtained regulatory and reimbursement approval for decellularised human heart valves in DE, CH, NL, IT, UK, BE

ESPOIR improved the health and quality of life of vulnerable patients and illustrates the impact of collaborative research across Europe

www.espoir-clinicaltrial.eu/

ATMPs: example of a successful precursor project

Tells the story: **www.optistem.org**



EUROPE APPROVES HOLOCLAR®, THE FIRST STEM CELL—BASED MEDICINAL PRODUCT

Date: 20/02/2015

EU funding has contributed to development of stem cell therapies that are now marketed

OptiStem brought together stem cell biologists and clinical experts from across Europe

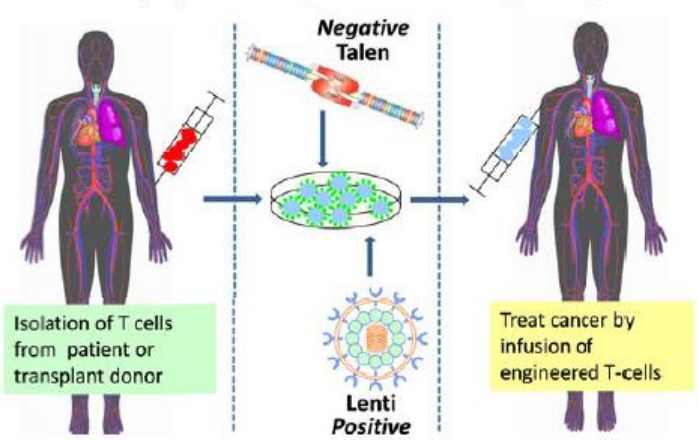
Amongst the partners were the founders of Holoclar, the first stem cell advanced therapy medicinal product (ATMP) for the treatment of vision loss

ATMPs: example of a successful project

ATECT
ADVANCED T-CELL ENGINEERED FOR CANCER THERAPY

SEVENTH FRAMEWORK PROGRAMME

- Two clinical trials (in adults) of anti-CD19 chimeric antigen receptor-modified (CAR) T-cell therapies using 'universal' CAR T cells
- UCART19 released for compassionate use resulted in molecular remission of B-ALL in two 18-month old infants



SCIENCE TRANSLATIONAL MEDICINE | REPORT

CANCER

Molecular remission of infant B-ALL after infusion of universal TALEN gene-edited CAR T cells

Waseem Qasim,[1,2]* Hong Zhan,[1] Sujith Samarasinghe,[2] Stuart Adams,[2] Persis Amrolia,[1,2] Sian Stafford,[1] Katie Butler,[1] Christine Rivat,[1] Gary Wright,[2] Kathy Somana,[2] Sara Ghorashian,[1] Danielle Pinner,[2] Gul Ahsan,[2] Kimberly Gilmour,[2] Giovanna Lucchini,[2] Sarah Inglott,[2] William Mifsud,[2] Robert Chiesa,[2] Karl S. Peggs,[3] Lucas Chan,[4] Farzin Farzeneh,[4] Adrian J. Thrasher,[1] Ajay Vora,[5] Martin Pule,[3] Paul Veys[1]

Autologous T cells engineered to express chimeric antigen receptor against the B cell antigen CD19 (CAR19) are achieving marked leukemic remissions in early-phase trials but can be difficult to manufacture, especially in infants or heavily treated patients. We generated universal CAR19 (UCART19) T cells by lentiviral transduction of non–human leukocyte antigen–matched donor cells and simultaneous transcription activator-like effector nuclease (TALEN)–mediated gene editing of T cell receptor α chain and CD52 gene loci. Two infants with relapsed refractory CD19+ B cell acute lymphoblastic leukemia received lymphodepleting chemotherapy and anti-CD52 serotherapy, followed by a single-dose infusion of UCART19 cells. Molecular remissions were achieved within 28 days in both infants, and UCART19 cells persisted until conditioning ahead of successful allogeneic stem cell transplantation. This bridge-to-transplantation strategy demonstrates the therapeutic potential of gene-editing technology.

CANCER IMMUNOTHERAPY

Baby's leukemia recedes after novel cell therapy

Gene editing used to create "off-the-shelf" T cells

Research and Innovation

What's in the pipeline ? (I)

- **2018: Innovation platforms for advanced therapies of the future**

  Scope: To create and exploit platforms around innovative concepts for advanced therapy development (and to overcome developmental bottlenecks)

  … could include studying basic biology of the potential therapy and investigating mode of action, proof-of-concept in animal models or first-in-man studies; safety, efficacy, characterization, refinement and manufacturing of the product could be considered

- **Impact**: Strengthen competitive position of advanced therapies research and development
- **Grant Agreements under preparation**

What's in the pipeline ? (II)

- **2019: Regenerative medicine: from new insights to new applications**

  Scope: To focus on innovative translational research to develop regenerative processes towards the ultimate clinical goal of addressing unmet clinical needs of large patient groups

  … may focus on any step(s) on the innovation chain, from early testing and characterization of regenerative mechanisms to preclinical research, proof of concept or first-in-man trial

- **Impact**: Potential new regenerative therapies to address unmet clinical needs of large patient groups identified

Thank you

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#EUHealthResearch

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