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SÚKL

Advanced Therapy Medicinal Products (ATMP)

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Day 2 – 24. 2. 2021

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 825881

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Overview

- ATMP definition
- Legislation
- **Examples of ATMPs**
  - Gene Therapy (GT)
  - Somatic Cell Therapy (SCT)
  - Tissue Engineered Product (TEP)
- Committee for Advanced Therapies (CAT)
- Where to find information?
- Clinical Trials with ATMPs: statistics
- List of ATMPs with Marketing Authorisation

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ATMP Definition

- gene therapy medicinal product (as defined in Part IV of Annex I to Directive 2001/83/EC)
- somatic cell therapy medicinal product (as defined in Part IV of Annex I to Directive 2001/83/EC)
- tissue engineered product (Regulation (EC) No 1394/2007)

EU legislation

- Directive 2001/83/EC
- Regulation (EC) No 726/2004
- Regulation (EC) No 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004
- *EMA guidelines (not legally binding)*
- *Hospital Exemption – depending on national legislation of MS*

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ATMP classification criteria

- Is definition of medicinal product fulfilled?
- Does it consist or contain cells or tissues?
- Are those cells /tissues substantially manipulated?
- Are those cells /tissues used in the same essential function as in donor („homologous use“)?

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Somatic cell therapy

SCT

- pharmacological, immunological or metabolic action
- substantially manipulated **OR** not homologous use
- List of substantial manipulations – Annex I of Reg. 1394/2007
- GT › TEP › SCT (in case the product fulfills more categories)

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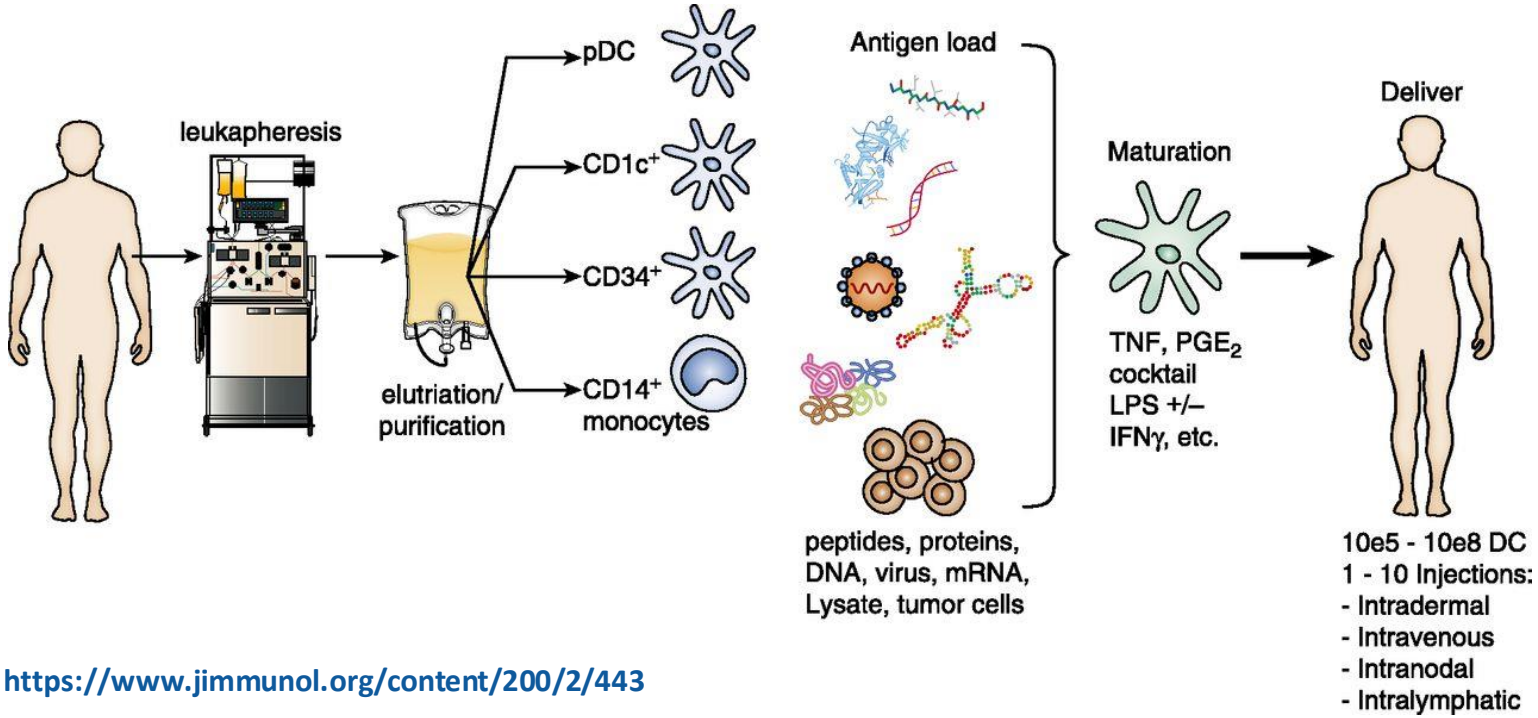
Non-substantial manipulations

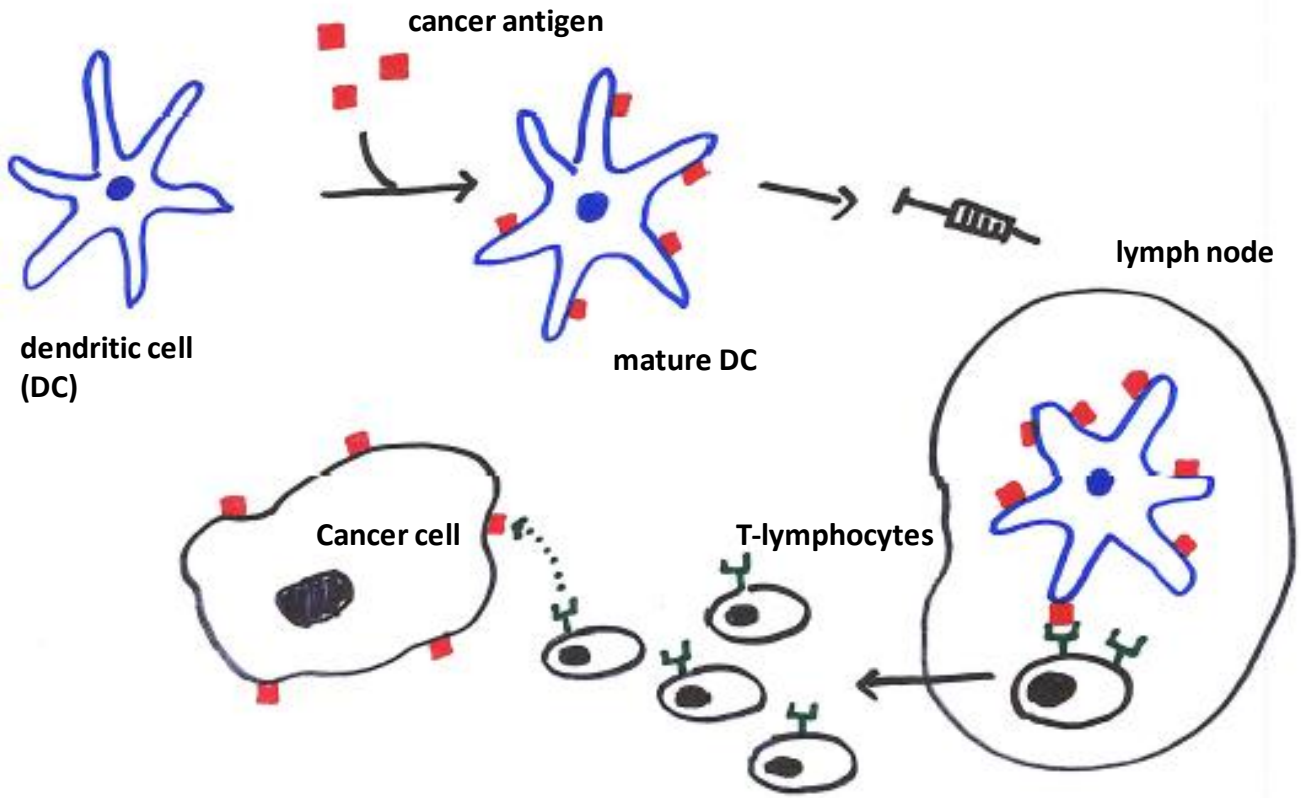
- cutting
- grinding
- shaping
- centrifugation
- soaking in antibiotic or antimicrobial solutions
- sterilization
- irradiation
- cell separation, concentration or purification
- filtering
- lyophilization
- freezing
- cryopreservation
- vitrification

SCT Example

- **Anti-cancer immunotherapy** (cell based)
- Co-cultivation of APC (antigen presenting cells) with tumour antigen
- Formerly approved Provenge (Sipuleucel-T in USA)

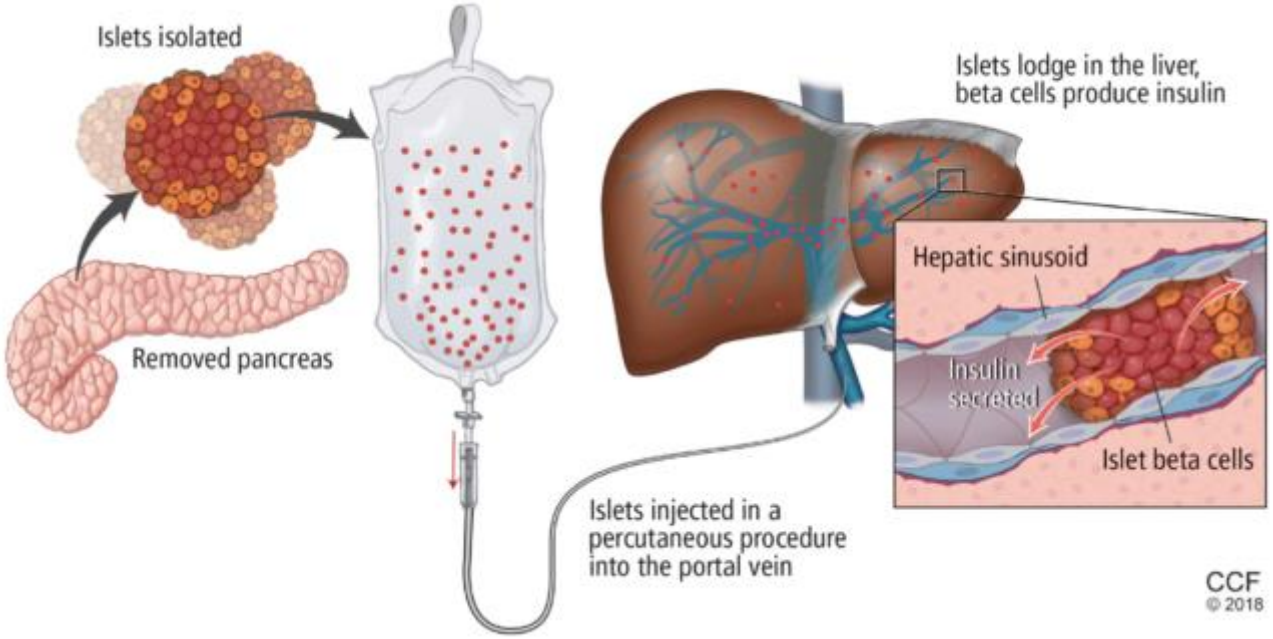


https://www.jimmunol.org/content/200/2/443


cancer antigen
dendritic cell
(DC)
mature DC
lymph node
Cancer cell
T-lymphocytes

Not SCT
Example

- Transplant of Islets of Langerhans
- Not substantial manipulation, used for the same essential function



https://consultqd.clevelandclinic.org/beta-cell-therapies-for-type-1-diabetes-transplanting-islet-cells-and-bionics/

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Tissue Engineered Product

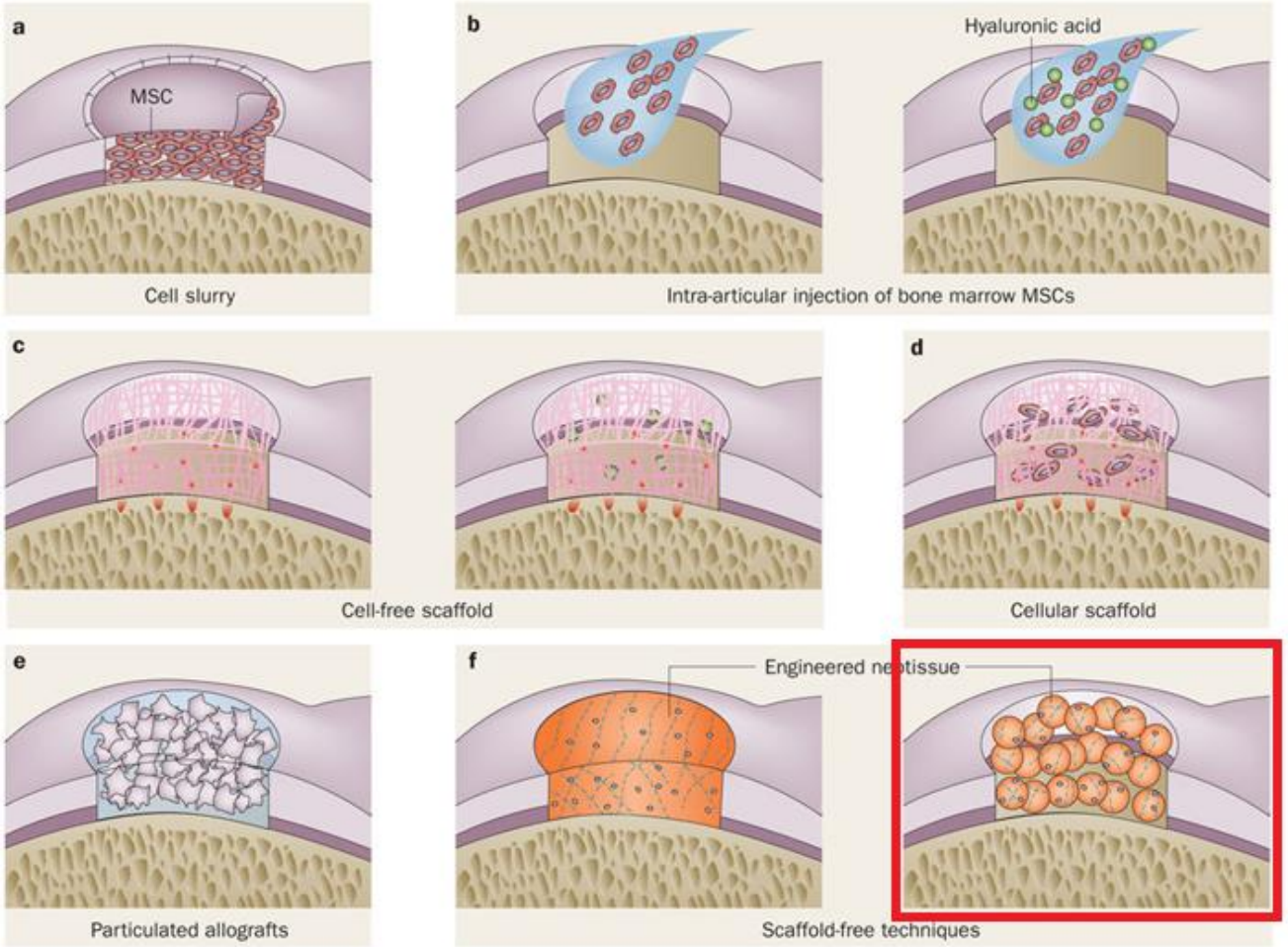
TEP

- contains or consists of engineered cells (substantially manipulated or non-homologous use) or tissues,
- AND is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue
- Engineered cells = substantially manipulated OR non-homologous use

TEP Example

Subheader

- **Spherox**
- spheroids (spherical aggregates) of chondrocytes, cells found in healthy cartilage, that have been prepared from the patient's own tissues
- when the spheroids are implanted into the patient's cartilage, they attach to the area of the defect and produce new tissue, thereby repairing the defects in the knee.
- EU approval: 10. 7. 2017



http://www.nature.com/nrrheum/journal/v11/n1/full/nrrheum.2014.157.html?message-global=remove&foxtrotcallback=true

Not TEP

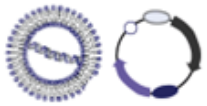
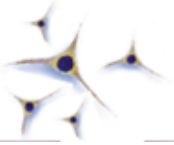
Example

- Autologous collagen derived from human adipose tissue (decellularized)
- Does not contain cells

Gene Therapy

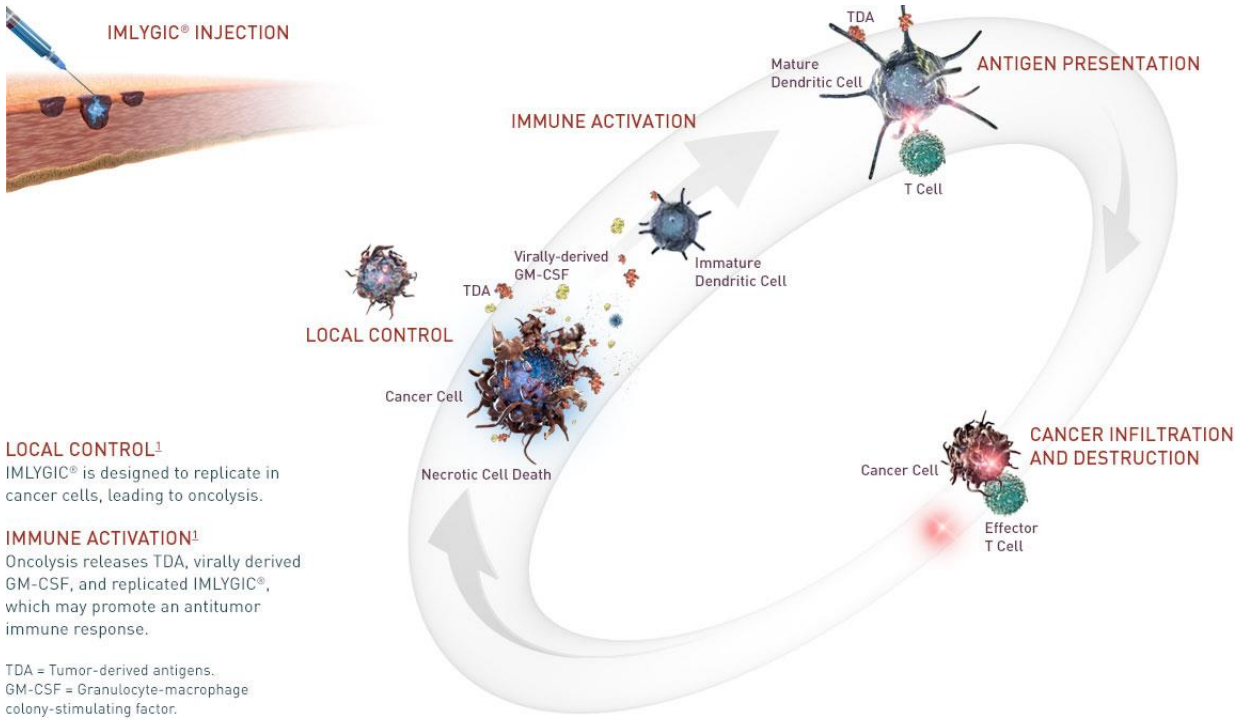
GT

- it contains an active substance which contains or consists of a **recombinant** nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence
- its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.
- Gene therapy medicinal products **shall not include vaccines against infectious diseases**.

Type of drug substances in GTMPs (recombinant)	Examples
(a) recombinant nucleic acid sequence(s) 	- oligonucleotides (of biological origin) - plasmid DNA → naked or formulated with synthetic delivery systems such as lipids, polymers and/or peptide ligands
(b) genetically modified virus(es)	- replication-deficient - replication-competent - conditionally replication-competent → e.g. retrovirus, adenovirus, adeno-associated virus, herpes simplex, vaccinia virus
(c) genetically modified microorganism(s)	- *Mycobacterium bovis* (BCG), *Shigella, Clostridia* → genetically modified e.g. by plasmids
(d) genetically modified cells 	- autologous, allogeneic, xenogeneic - primary cells or stable cell lines → genetically modified by one of the products described above

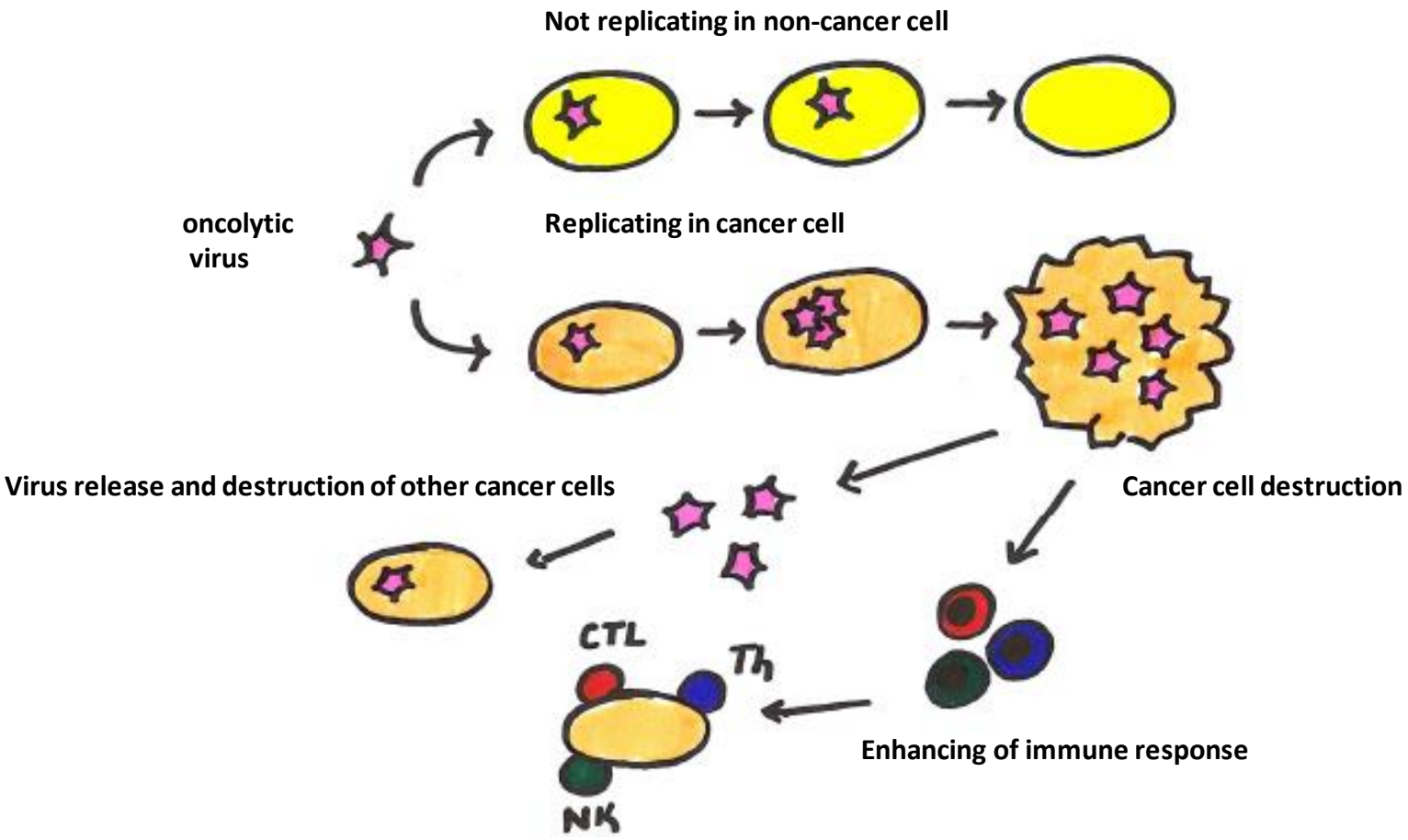
GT Example

- **Imlygic**
- attenuated herpes simplex virus type-1 (HSV-1) derived by functional deletion of 2 genes (ICP34.5 and ICP47) and insertion of coding sequence for human granulocyte macrophage colony-stimulating factor (GM-CSF)
- indicated for the treatment of adults with unresectable melanoma that is regionally or
- EU Approval Date: 16. 12. 2015

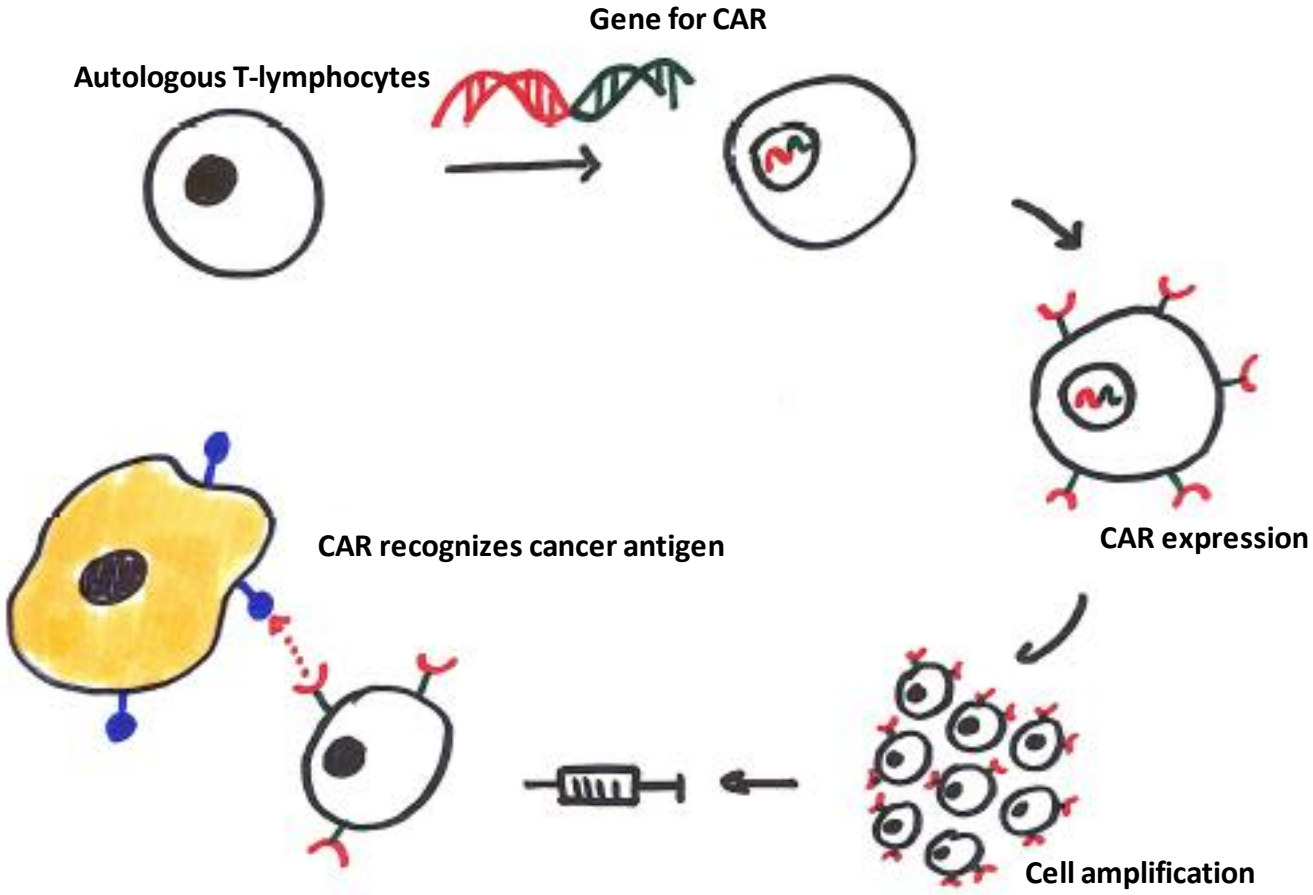


http://www.imlygic.com/mechanism-of-action

Oncolytic immunotherapy



CAR – Chimeric Antigen Receptor



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Not GT

Example

- Adenoviral vector derived from ChAd3 expressing NS region of HCV
- Intended for treatment of HCV and HCV induced hepatocelluar carcinoma
- Classified as vaccine, therefore cannot be considered GT

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Combined advanced therapy medicinal product

- it must incorporate, as an integral part of the product, one or more medical devices or one or more active implantable medical devices within the meaning

AND

- its cellular or tissue part must contain viable cells or tissues

OR

- its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered

Combined ATMP

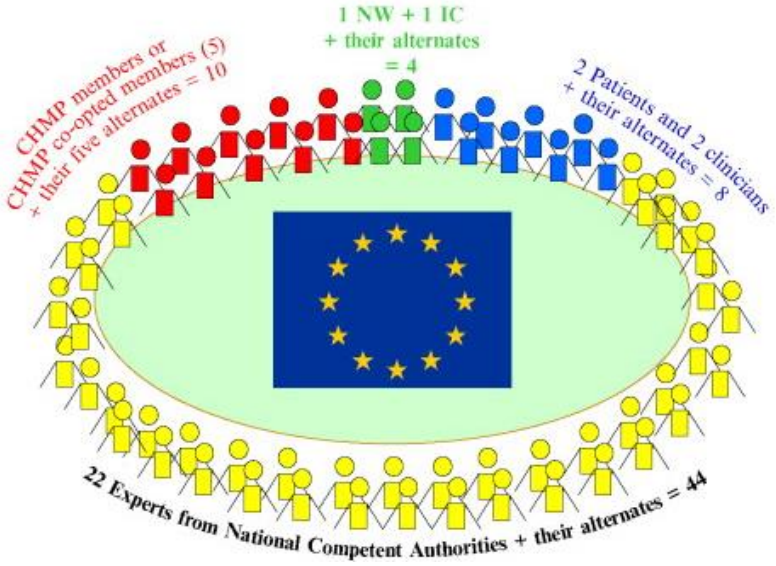
Example

- Adipose Tissue derived MSC combined with beta-tricalcium phosphate
- Treatment of bone defects
- Expanded cells + Medical Device (tricalcium phosphate is integral part of ATMP)

Committee for Advanced Therapies

CAT

- Created based on 1394/2007/EC
- 33 members (+ chair): 27 (22 + 5) members (representatives of Member States) + 2 (Norway, Iceland) + 2 representatives of patient organisations a 2 representatives of clinicians; + their alternates
- Monthly plenary meetings
- CAT Rules of procedure EMA/CAT/EMA/454446/2008



CAT Responsibilities

- draft opinion on each ATMP application submitted to EMA
- opinion on any scientific matter relating to ATMPs
- certifying quality and non-clinical data for small and medium-sized enterprises developing ATMPs
- participates in providing scientific recommendations on the classification of ATMPs
- contributes to scientific advice, in cooperation with the Scientific Advice Working Party (SAWP)
- takes part in any procedure delivering advice on the conduct of efficacy follow-up, pharmacovigilance or risk-management systems for ATMPs
- advises the CHMP on any medicinal product that may require expertise in ATMPs for the evaluation of its quality, safety or efficacy
- assists scientifically in developing any documents relating to the objectives of the Regulation on ATMPs
- provides scientific expertise and advice for any Community initiative related to the development of innovative medicines and therapies that requires expertise on ATMPs;
- supports the work programmes of the CHMP working parties

Where to find information?

- http://www.ema.europa.eu
- Human Regulatory → Overview→ Advanced Therapies
- Committees → CAT
- Links to guidelines
- Scientific Reccomendations on Classification
- …

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Human regulatory

Overview | Research and development | Marketing authorisation | Post-authorisation | Herbal products

- Adaptive pathways
- Advanced therapies
  - Advanced therapy development
  - Scientific guidelines
- Clinical trials
- Compassionate use
- Compliance
- Data on medicines (ISO IDMP standards)
- Ethical use of animals
- Innovation in medicines
- Medicines for older people
- Orphan designation
- Paediatric medicines
- Pharmacovigilance
- PRIME: priority medicines
- Quality by design
- Scientific advice and protocol assistance

Advanced therapies: research and development

Share

The European Medicines Agency (EMA) provides guidance and support to companies researching, developing and manufacturing advanced therapy medicinal products (ATMPs). This includes scientific and regulatory guidance, compliance standards as well as incentives for companies developing ATMPs.

In this section

- Advanced therapy development
- Scientific guidelines

Related content

- Advanced therapies: overview
- Advanced therapies: marketing authorisation
- Advanced therapies: post-authorisation
- Scientific advice and protocol assistance
- Scientific guidelines
- Supporting SMEs

External links

- European Commission: Advanced therapies - Major developments

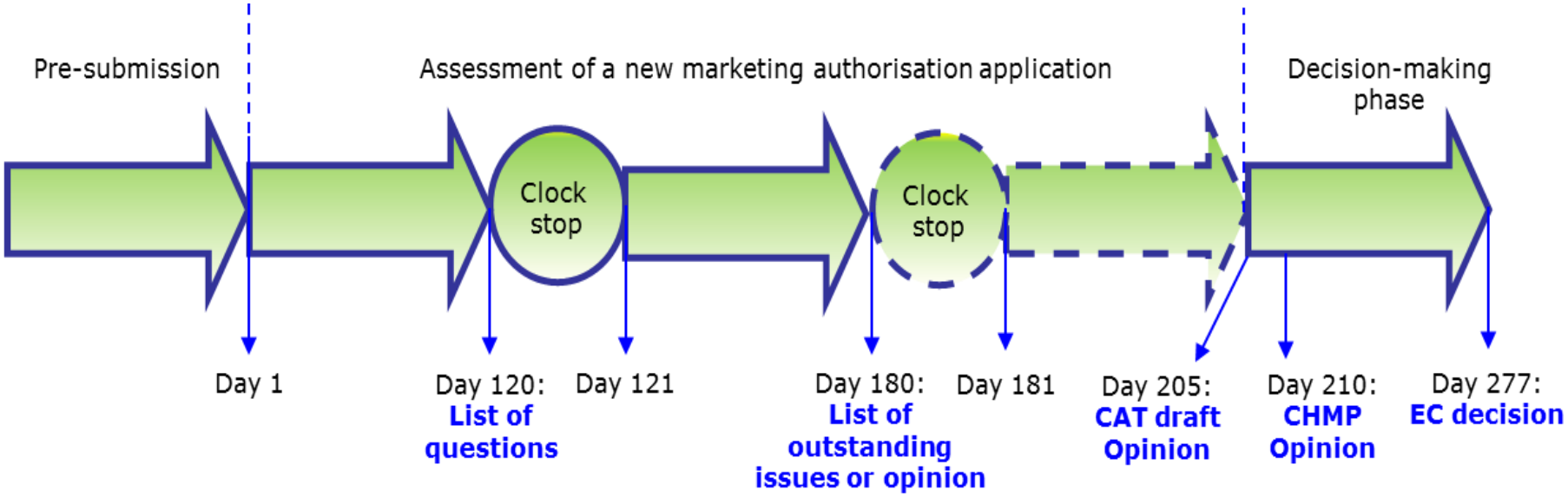
Contact point

advancedtherapies@ema.europa.eu

- The **overarching guideline** for human cell- based medicinal products is the guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006)
- Reflection paper on **stem cell-based medicinal products** (EMA/CAT/571134/2009)
- Reflection paper on in-vitro cultured **chondrocyte** containing products for cartilage repair of the knee (EMA/CAT/CPWP/568181/2009)
- Guideline on **xenogeneic cell-based medicinal products** (EMEA/CHMP/CPWP/83508/2009)
- Guideline on potency testing of **cell based immunotherapy medicinal** products for the treatment of cancer (CHMP/BWP/271475/06)
- Reflection paper **on clinical aspects related to tissue engineered products** (EMA/CAT/573420/2009)
- Guideline on **safety and efficacy follow-up and risk management** of advanced therapy medicinal products (EMEA/149995/2008)
- The **overarching guideline** for human gene therapy medicinal products is the Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (CHMP/GTWP/671639/2008)
- **Questions and answers** on gene therapy (EMA/CAT/80183/2014)
- Guideline on scientific requirements for the **environmental risk assessment** of gene therapy medicinal products (CHMP/GTWP/125491/06)
- Reflection paper on **design modifications** of gene therapy medicinal products **during development** (EMA/CAT/GTWP/44236/2009)
- Reflection paper on quality, non-clinical and clinical issues relating specifically to recombinat adeno-associated viral **vectors** (CHMP/GTWP/587488/07)
- ICH Considerations - **Oncolytic Viruses** (EMEA/CHMP/ICH/607698/2008)
- Guideline on quality, non-clinical and clinical aspects of medicinal products containing **genetically modified cells** (CAT/CHMP/GTWP/671639/2008)
- Guideline on the non-clinical studies required **before first clinical use** of gene therapy medicinal products (EMEA/CHMP/GTWP/125459/2006)
- Guideline on non-clinical testing for **inadvertent germline transmission** of the gene transfer vectors (EMEA/273974/2005)
- Reflection paper on management of clinical risks deriving from **insertional mutagenesis** (CAT/190186/2012)
- Guideline on **follow-up of patients** administered with gene therapy medicinal products (EMEA/CHMP/GTWP/60436/2007)
- Guideline on **safety and efficacy follow-up and risk management** of advanced therapy medicinal products (EMEA/149995/2008)

Authorisation of ATMPs

- Obligatory Centralised Marketing Authorisation (EMA opinion and EC decision)
- Standard procedure, or conditional MA or MA under exceptional circumstances
- *Hospital Exemption*

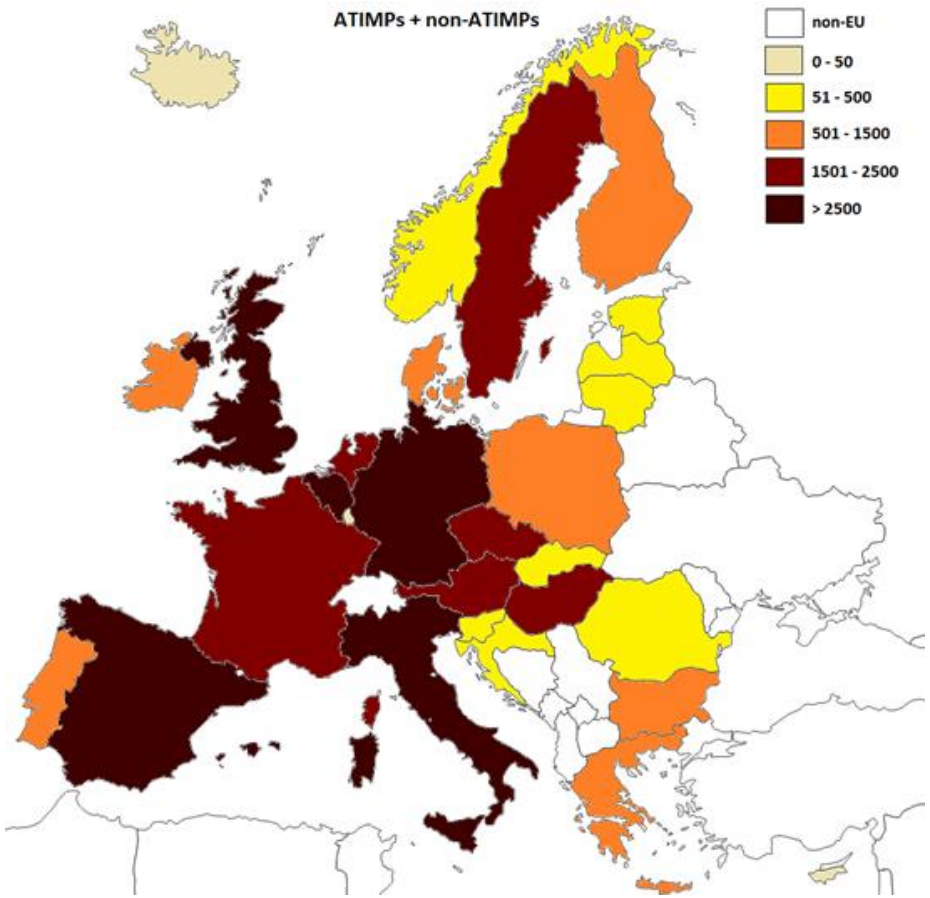


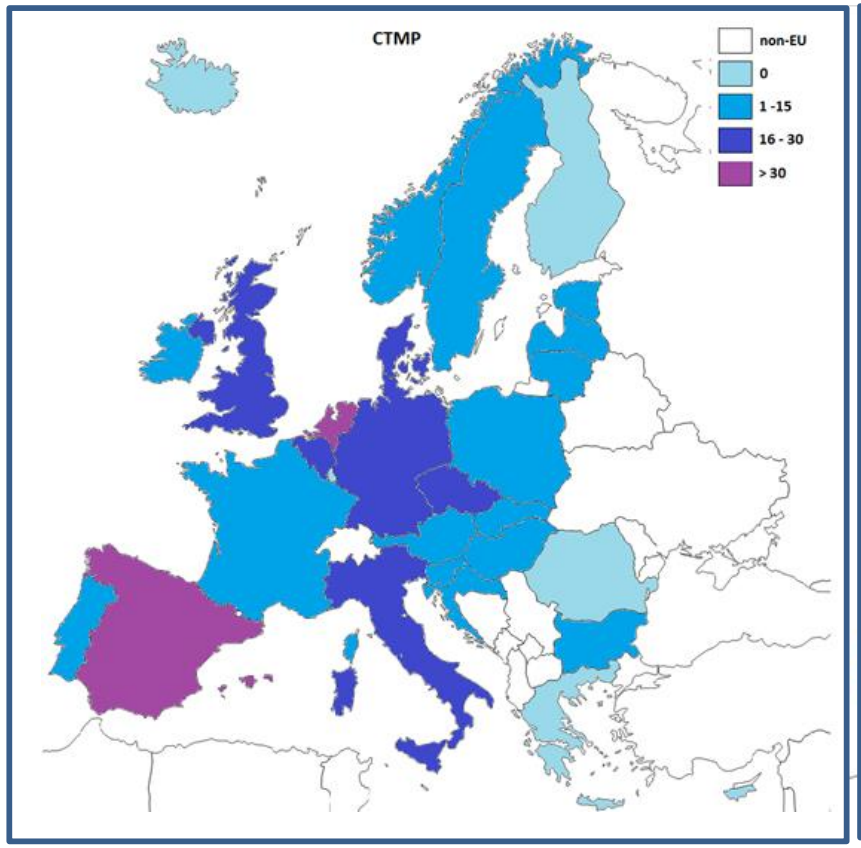
Clinical Trials with ATMPs

Statistics

- Hum Gene Ther Clin Dev. 2017 Sep;28(3):126-135

Clinical Development and Commercialization of Advanced Therapy Medicinal Products in the European Union: How Are the Product Pipeline and Regulatory Framework Evolving?

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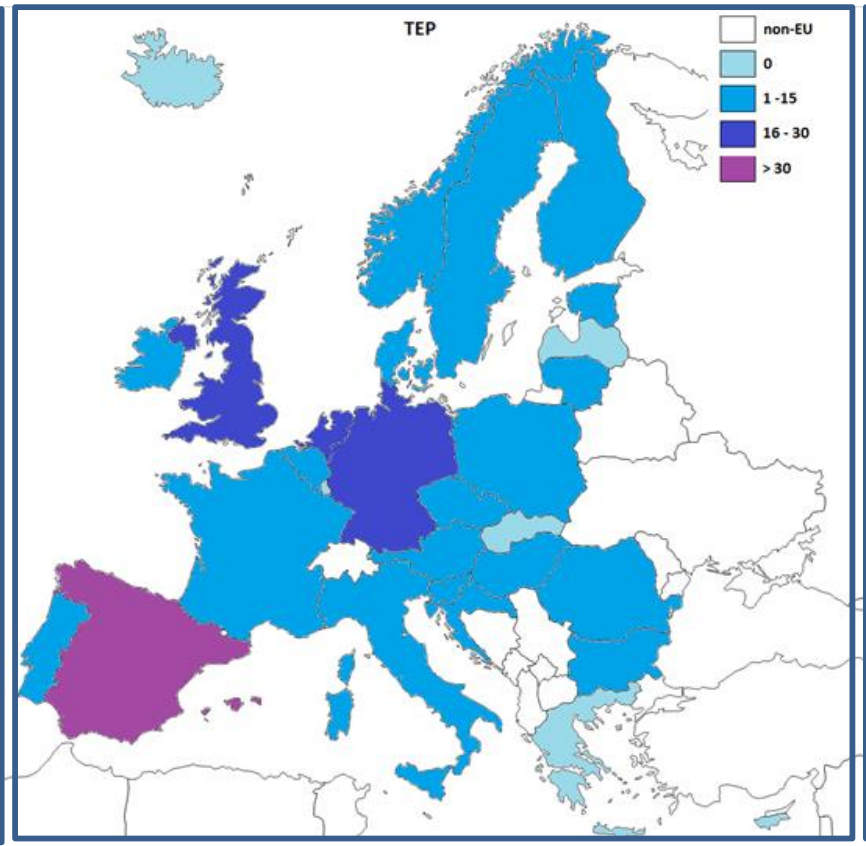
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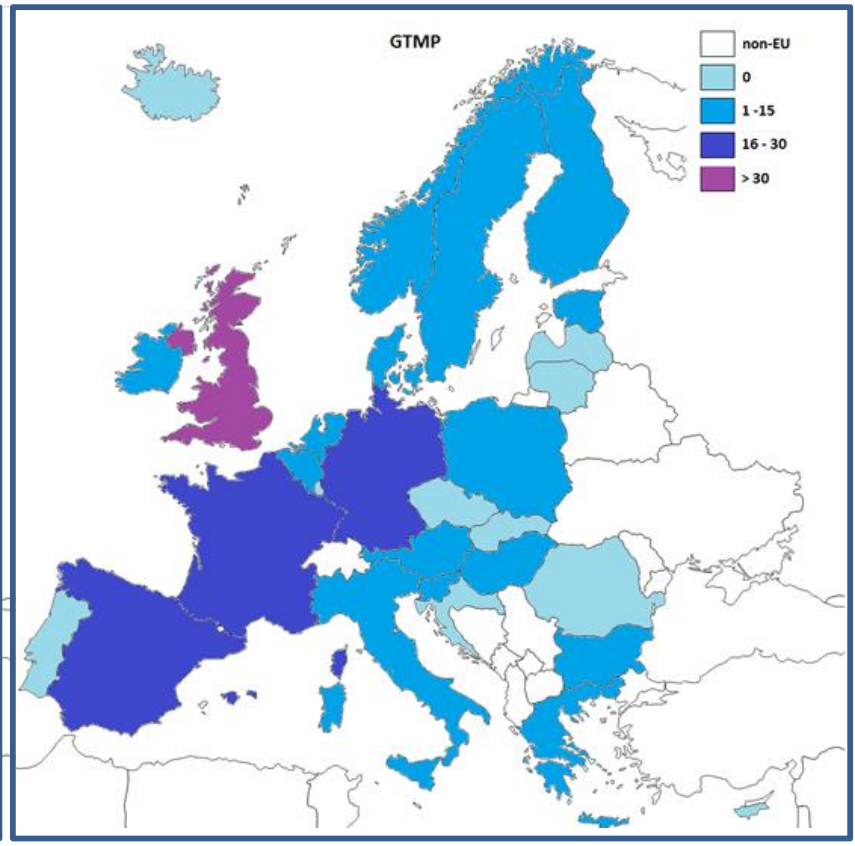
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List of ATMPs with Marketing Authorisation
TI and SCT

TI

Holoclar (17. 2. 2015): *Ex vivo* expanded autologous human corneal epithelial cells containing stem cells. Treatment of adult patients with moderate to severe limbal stem cell deficiency due to physical or chemical ocular burns.

Spherox (10. 7.2017): Spheroids of human autologous matrix-associated chondrocytes for implantation suspended in isotonic sodium chloride solution. Repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee.

SCT

Alofisel (23. 3. 2018): Darvadstrocel is an expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue (expanded adipose stem cells - eASC). Alofisel is indicated for the treatment of complex perianal fistulas in adult patients with nonactive/mildly active luminal Crohn's disease.

List of ATMPs with Marketing Authorisation

GT

GT

Imlygic (16. 12. 2015): Talimogene laherparepvec is an attenuated herpes simplex virus type-1 (HSV-1) derived by functional deletion of 2 genes (ICP34.5 and ICP47) and insertion of coding sequence for human granulocyte macrophage colony-stimulating factor (GM-CSF). Imlygic is indicated for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic with no bone, brain, lung or other visceral disease.

Luxturna (22.11.2018): Voretigene neparvovec is a gene transfer vector that employs an adeno-associated viral vector serotype 2 (AAV2) capsid as a delivery vehicle for the human retinal pigment epithelium 65 kDa protein (hRPE65) cDNA to the retina. Luxturna is indicated for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells.

Zolgensma (18. 5. 2020): Onasemnogene abeparvovec is a gene therapy medicinal product that expresses the human survival motor neuron (SMN) protein. It is a non replicating recombinant adeno associated virus serotype 9 (AAV9) based vector containing the cDNA of the human SMN gene under the control of the cytomegalovirus enhancer/chicken-β-actin-hybrid promoter. Zolgensma is indicated for the treatment of: patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.

Strimvelis (26. 5. 2016): An autologous $CD34_+$ enriched cell fraction that contains $CD34_+$ cells transduced with retroviral vector that encodes for the human adenosine deaminase (ADA) cDNA sequence from human haematopoietic stem/progenitor ($CD34_+$) cells. Strimvelis is indicated for the treatment of patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available.

Yescarta (23. 8. 2018): (axicabtagene ciloleucel) is a CD19-directed genetically modified autologous T cell (CAR-T) immunotherapy. Indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

Kymriah (23. 8. 2018) is an immunocellular therapy containing tisagenlecleucel, autologous T cells genetically modified *ex vivo* using a lentiviral vector encoding an anti-CD19 chimeric antigen receptor (CAR). Kymriah is indicated for the treatment of: Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse. Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

Zynteglo (29. 5. 2019): A genetically modified autologous $CD34_+$ cell enriched population that contains haematopoietic stem cells (HSC) transduced with lentiviral vector (LVV) encoding the $\beta_{A\text{-}T87Q}$-globin gene. Zynteglo is indicated for the treatment of patients 12 years and older with transfusion-dependent β-thalassaemia (TDT) who do not have a β_0/β_0 genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available.

Acknowledgement

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 825881