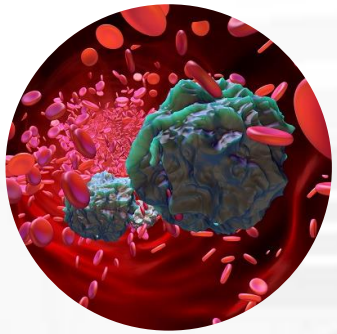
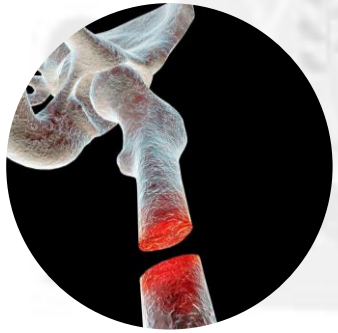
Unmet medical needs



Cancers

Genetic disorders

Tissue infarction

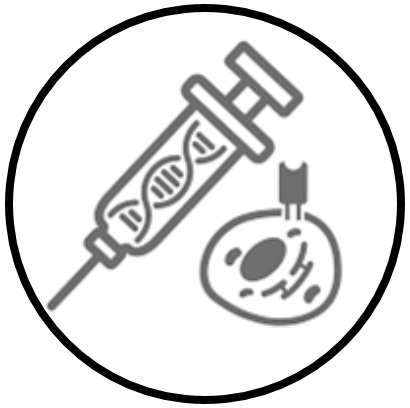


Critical size defects

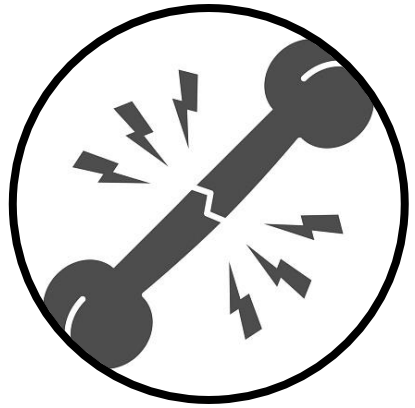
In the era of…

Advanced Therapy Medicinal Products (ATMPs)

Cell-based therapy



Gene-based therapy



Tissue-based therapy

Any cell or gene therapy product or tissue engineered product that has been substantially manipulated and/or performs a different function in the recipient than in the donor

WHO, Considerations in developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products, 2023

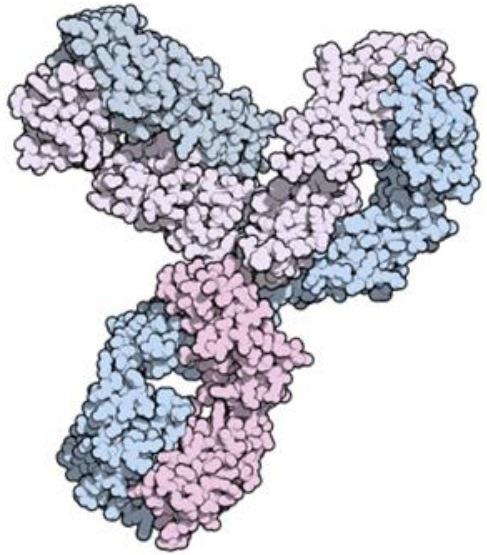
What makes ATMPs different?

Small molecule drugs

Aspirin (21 atoms)

- Well-known structure and conformation
- Predictable pharmacokinetics (PK) and pharmacodynamics (PD)
- Long history in medical uses, well-recognized production processes

Biologics



Pembrolizumab
(~20,000 atom, size ~14 nm)

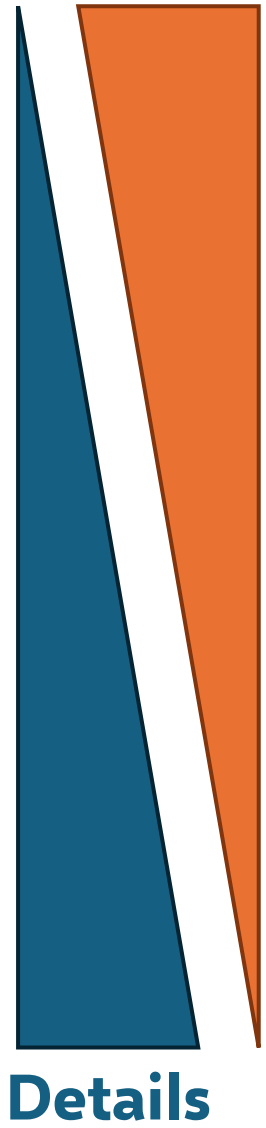
- Complicated structure and conformation, and susceptible to external conditions
- Recent but widely used in medicine, well documented in production process
- Predictable PK and PD

ATMPs

Circulating T cells
(5-7 μm)

- Highly complicated structure and highly susceptible to many external stimuli
- Viable cells can be expanded and differentiated
- Never followed the conventional PK/PD concepts
- Recognized as **Living drugs**

That's why we need a NEW control



Europe

Directive 2001/83/EC
(The community code relating to medicinal products for human use)
Regulation (EC) No. 726/2004
(Union procedures for the authorization and supervision of medicinal products for human use)

⇩

Commission Directive 2009/120/EC
(Medicinal products for human use as regards advanced therapy medicinal products)
Regulation (EC) No. 1394/2007
(Advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No. 726/2004)

⇩

Reflection paper on classification of advanced therapy medicinal products (EMA/CAT/600280/2010 rev.1)

⇨

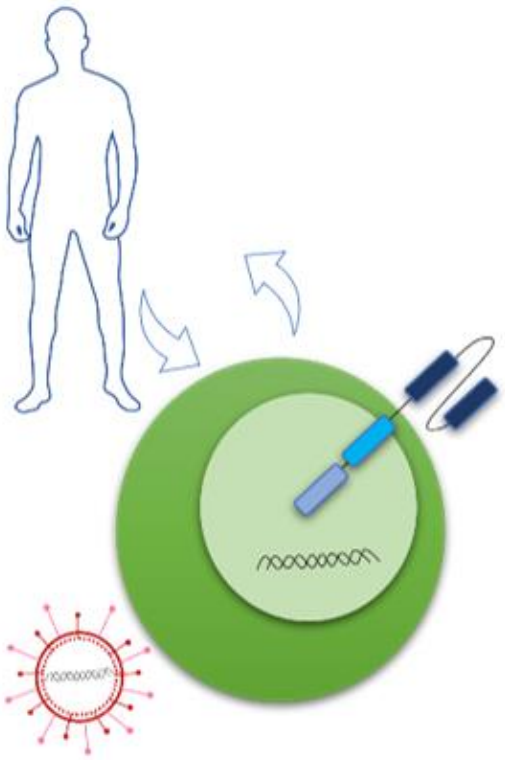
Thailand

พระราชบัญญัติยา พ.ศ.2510

⇩

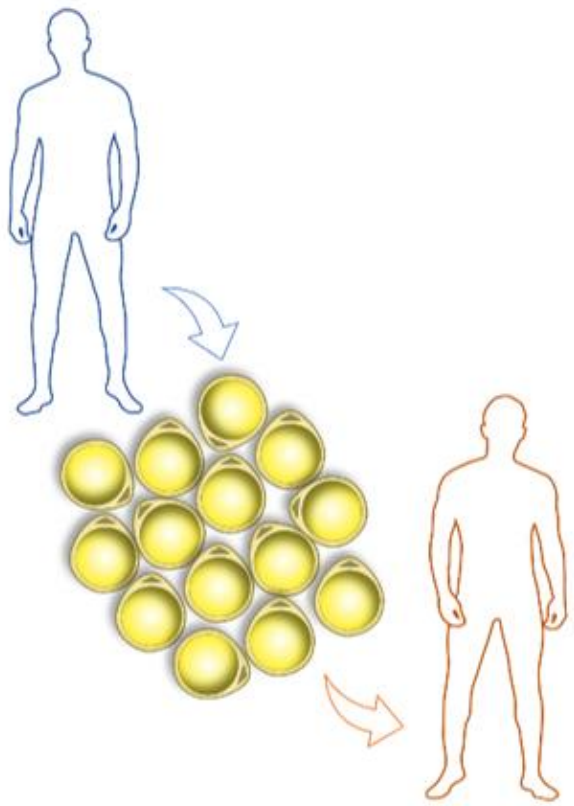
ประกาศสำนักงานคณะกรรมการอาหารและยา
เรื่อง แนวทางการจำแนกประเภทผลิตภัณฑ์การแพทย์ขั้นสูง

Classification of ATMPs



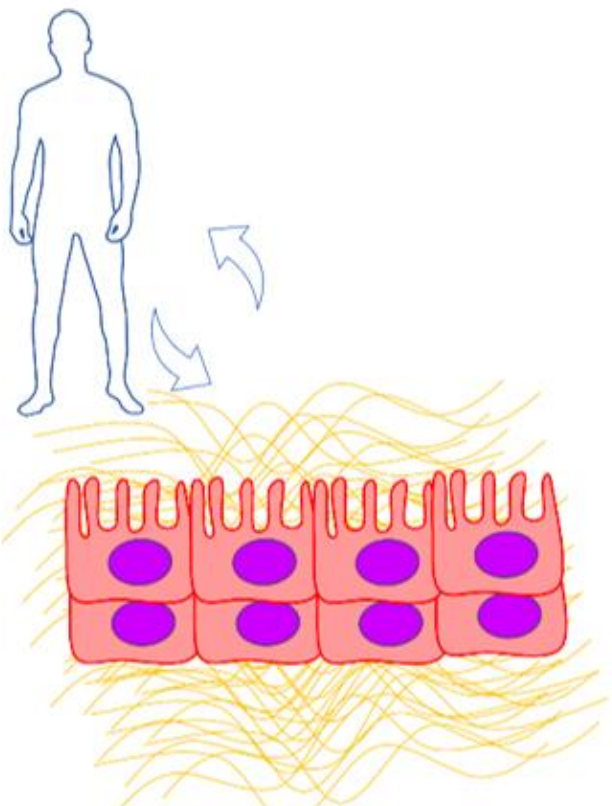
Gene Therapy Medicinal Product (GTMP)

E.g. genetically modified T cells



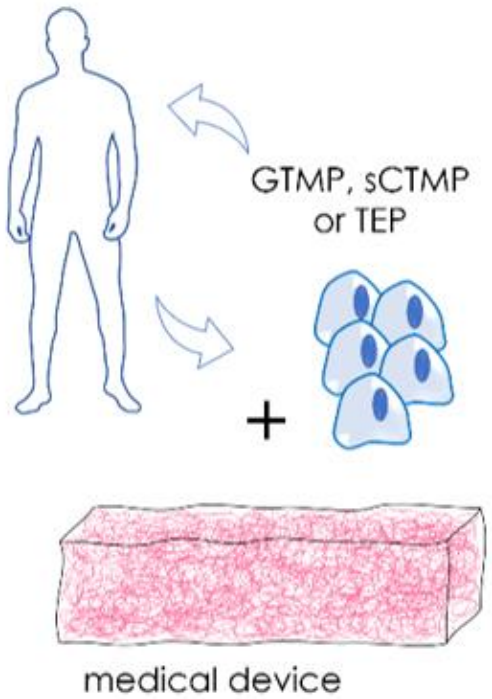
Somatic Cell Therapy Product (sCTMP)

E.g. *ex vivo* expanded adipose stem cells



Tissue-Engineered Product (TEP)

E.g. *ex vivo* expanded corneal epithelial cells attached to a fibrin support



Combined ATMP

E.g. porcine collagen scaffold seeded with autologous chondrocytes

Image courtesy of https://www.propharmagroup.com/

Is Blood Transfusion considered as an ATMP?

How EMA and WHO say?

Ref: Reflection paper on classification of advanced therapy medicinal products (EMA/CAT/600280/2010 rev.1) and WHO considerations on Regulatory convergence of Cell and Gene Therapy Products

Cell-based and gene therapy products (CGTPs)

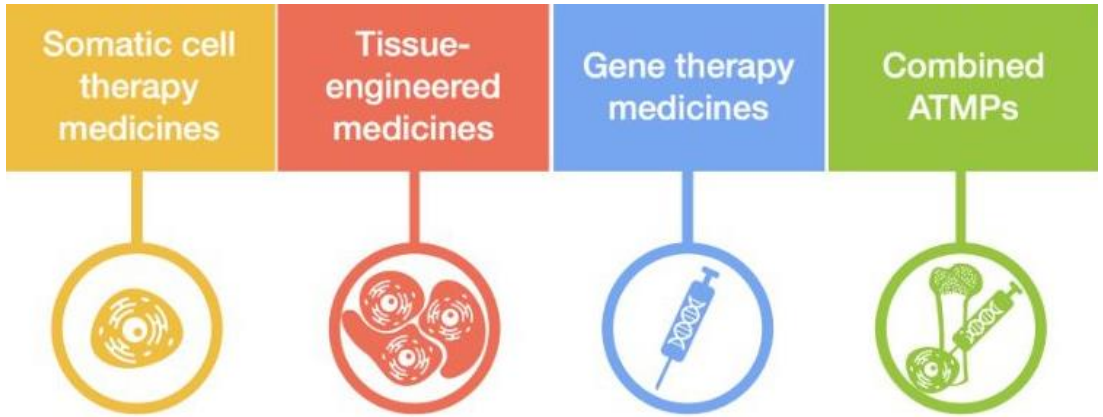
Substantial manipulation

or

Non-homologous use

Yes

Advanced Therapy Medicinal Products (ATMPs)



No

Human cells and tissues for medical use (HCTs)

- *Human cells for transfusion*
- *Human tissues for transplantation*

Substantial manipulation

The cells or tissue(s) have been manipulated during the manufacturing process so that their biological characteristics, physiological functions or structural properties have been modified to be relevant for their intended function.

Reflection paper on classification of advanced therapy medicinal products (EMA/CAT/600280/2010 rev.1)

การดัดแปลงอย่างมีนัยสำคัญ/การดัดแปลงมากกว่าการดัดแปลงเพียงเล็กน้อย (Substantial manipulation/more than minimal manipulation) หมายความว่า การดัดแปลงซึ่งส่งผลให้เกิดการเปลี่ยนแปลงลักษณะทางชีวภาพ (Biological) สรีรวิทยา (Physiological) หรือโครงสร้าง (Structure) ที่ส่งผลให้เซลล์หรือเนื้อเยื่อนั้นมีคุณสมบัติหรือกลไกการออกฤทธิ์ในการรักษาเปลี่ยนแปลงไปจากเซลล์หรือเนื้อเยื่อเดิม

ประกาศสำนักงานคณะกรรมการอาหารและยา เรื่อง แนวทางการจำแนกประเภทผลิตภัณฑ์การแพทย์ขั้นสูง

Cell and tissue manipulations considered minimal or non-substantial include:

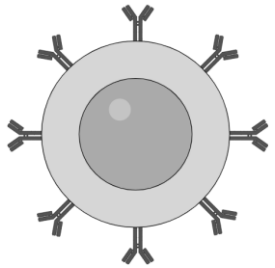
- Cutting, grinding, and shaping
- Centrifugation
- Soaking in antibiotic or antimicrobial solutions
- Sterilization and low-level irradiation
- Cell separation, concentration, or purification
- Filtering
- Lyophilization (freeze-drying)
- Freezing, Cryopreservation, Vitrification

Let's think!!!

Considering the following cell/tissue manipulations, would they be classified as substantial or minimal manipulation?

- Cell culture/expansion
- Isolation of keratinocytes from skin using enzymatic digestion

- Islet isolation from pancreas using enzymes



- Radio-labelling of leukocytes for diagnostic purposes

Referenced case scenario from Reflection paper on classification of advanced therapy medicinal products (EMA/CAT/600280/2010 rev.1)

Let's think!!!

Considering the following cell/tissue manipulations, would they be classified as substantial or minimal manipulation?

- Cell culture/expansion

  Substantial manipulation

  - Biological characteristics and structural properties could be modified during the cell proliferation
  - Repeated attachment and detachment cycles could lead to phenotypic changes especially on cell surface proteins

- Isolation of keratinocytes from skin using enzymatic digestion

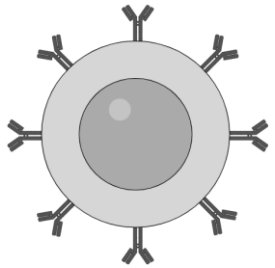
  Substantial manipulation

  - Enzymatic digestion destroys the tissue architecture and functional interaction of the cells, which cannot be regained

- Islet isolation from pancreas using enzymes

  Minimal manipulation

  - Scientific evidence proof that the original structural and functional characteristics are maintained



- Radio-labelling of leukocytes for diagnostic purposes

  Minimal manipulation

  - The manipulation does not alter the functional properties of the cells

Referenced case scenario from Reflection paper on classification of advanced therapy medicinal products (EMA/CAT/600280/2010 rev.1)

Non-homologous use

The same essential function (or homologous use) for a cell population means that the cells when removed from their original environment in the human body are used to maintain the original function(s) in the same anatomical or histological environment.

Reflection paper on classification of advanced therapy medicinal products (EMA/CAT/600280/2010 rev.1)

Non-homologous use หมายความว่า ผลิตภัณฑ์การแพทย์ขั้นสูงที่มีหน้าที่ หรือกลไกการทำงานในตัวผู้รับ (recipient) แตกต่างจากหน้าที่หรือกลไกการทำงานของเซลล์หรือเนื้อเยื่อเดิมจากตัวผู้ให้ (Donor)

ประกาศสำนักงานคณะกรรมการอาหารและยา เรื่อง แนวทางการจำแนกประเภทผลิตภัณฑ์การแพทย์ขั้นสูง

Let's think!!!

Considering the following cell/tissue applications, would they be classified as homologous or non-homologous use?

- Bone marrow cell transplantation in hematologic cancer patients
- Pancreatic Langerhans' islets transplantation

- Skin transplantation from one part of the body to another part
- Autologous bone marrow stem cell injection for myocardial infarction

Referenced case scenario from Reflection paper on classification of advanced therapy medicinal products (EMA/CAT/600280/2010 rev.1)

Let's think!!!

Considering the following cell/tissue applications, would they be classified as homologous or non-homologous use?

- Bone marrow cell transplantation in hematologic cancer patients

  Homologous use

  - Minimal manipulation
  - The original functions (hematopoietic or immune reconstitution) are maintained

- Pancreatic Langerhans' islets transplantation

  Homologous use

  - Minimal manipulation: No alteration on their biological characteristics
  - Use in the same essential functions in recipients

- Skin transplantation from one part of the body to another part

  Homologous use

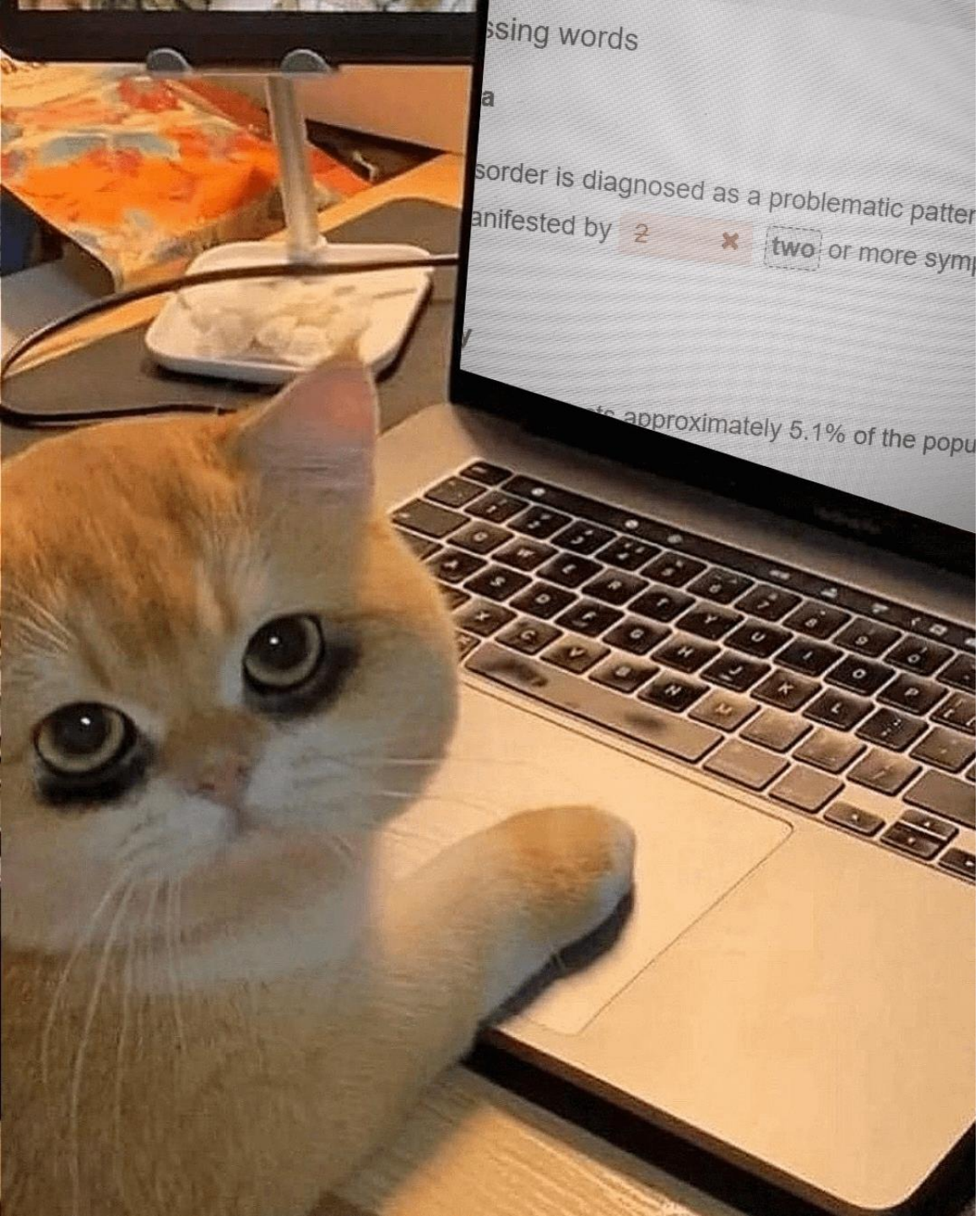
  - Minimal manipulation
  - Use in the same anatomical and histological environments in the recipients

- Autologous bone marrow stem cell injection for myocardial infarction

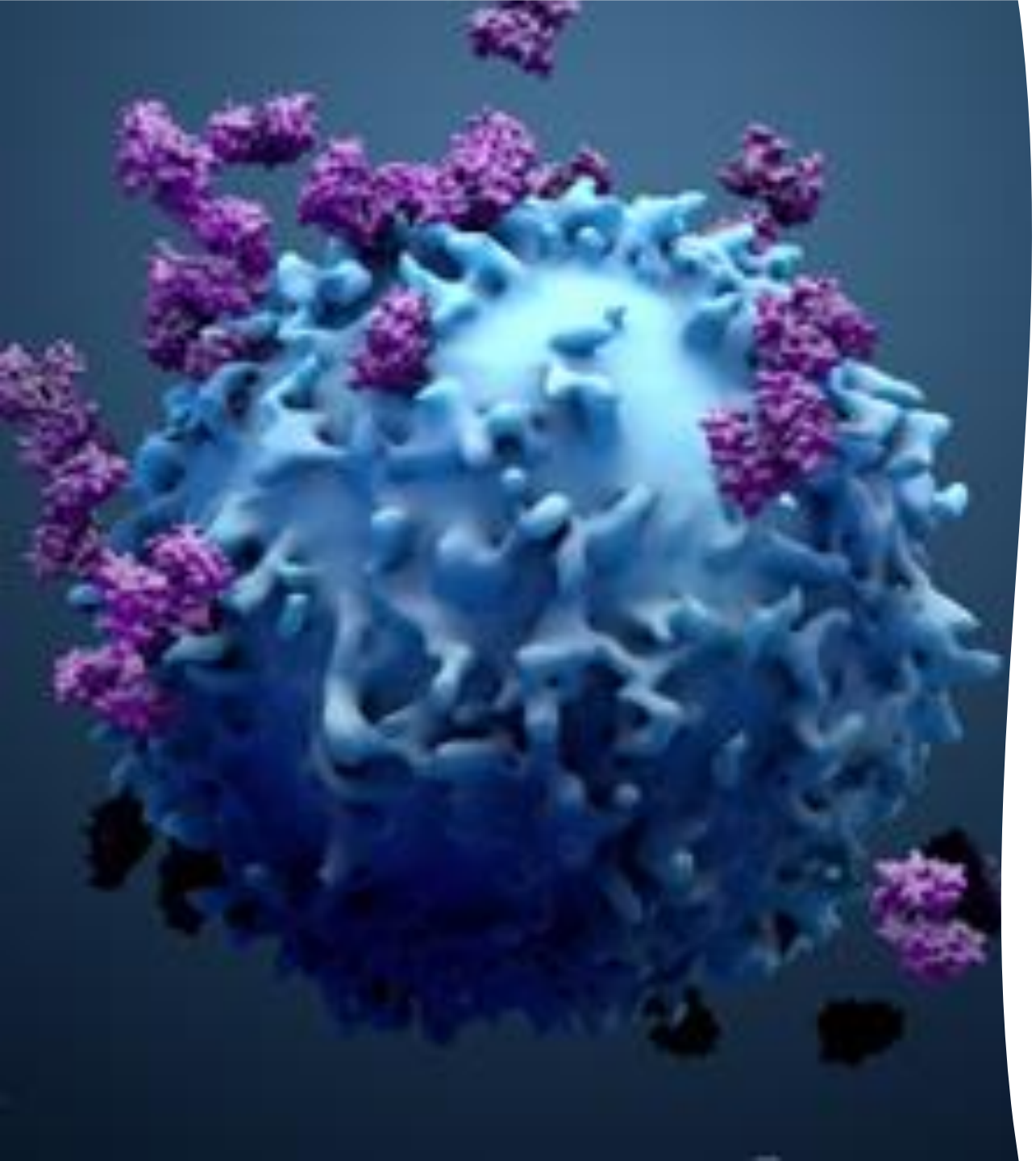
  Non-homologous use

  - Minimal manipulation, but
  - Use in the different essential functions (regeneration of myocardial cells) in the different anatomical environment

Referenced case scenario from Reflection paper on classification of advanced therapy medicinal products (EMA/CAT/600280/2010 rev.1)



Types of ATMPs: Definitions and Classifications



Somatic cell therapy medicinal products (sCTMPs)

- *(a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;*

- *(b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.*

Example: FDA-approved sCTMPs

AMTAGVI (lifileucel), Iovance Biotherapeutics, Inc.

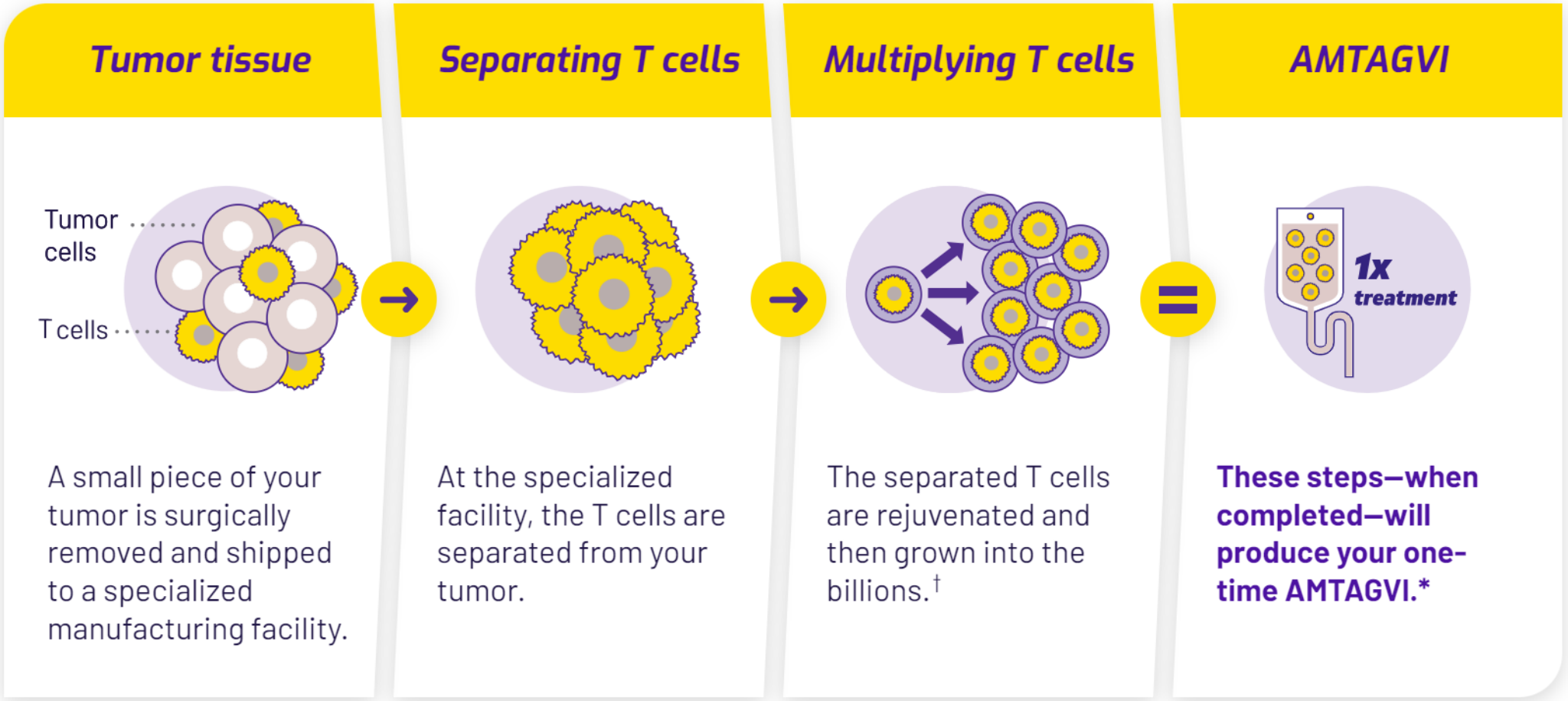
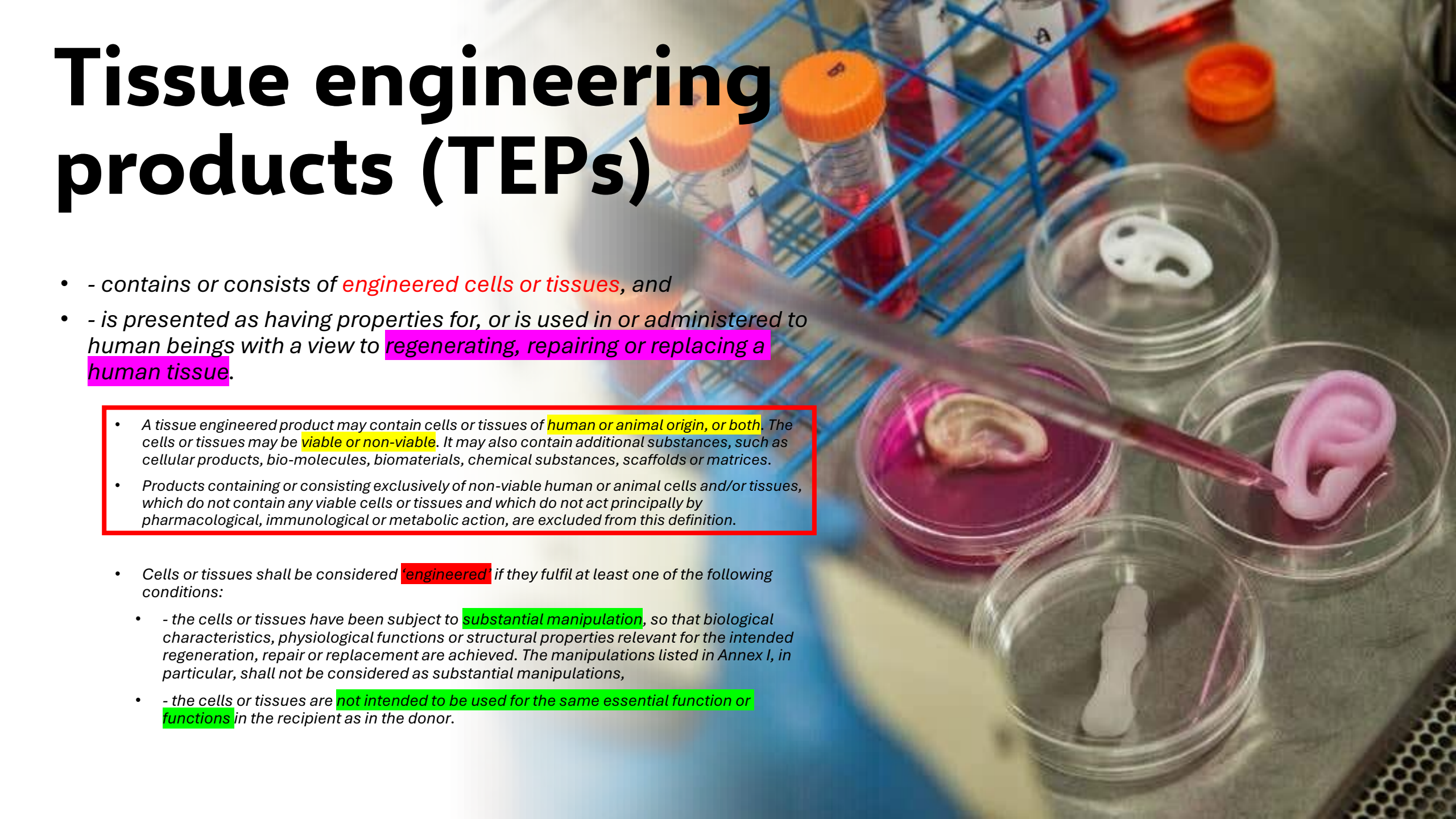


Image courtesy of IOVANCE Biotherapeutics, Inc.

Tissue engineering products (TEPs)



- *- contains or consists of engineered cells 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.*

  - *A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices.*
  - *Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, are excluded from this definition.*

  - *Cells or tissues shall be considered 'engineered' if they fulfil at least one of the following conditions:*
    - *- the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations,*
    - *- the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.*

Products containing or consisting of *animal cells or tissues* to be administered to humans will always be considered as ATMPs.

Genetically altered pig heart transplanted into a human for the second time

By Megan Molteni Sept. 22, 2023 Reprints

The University of Maryland team prepares the pig heart for transplant.

COURTESY UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE

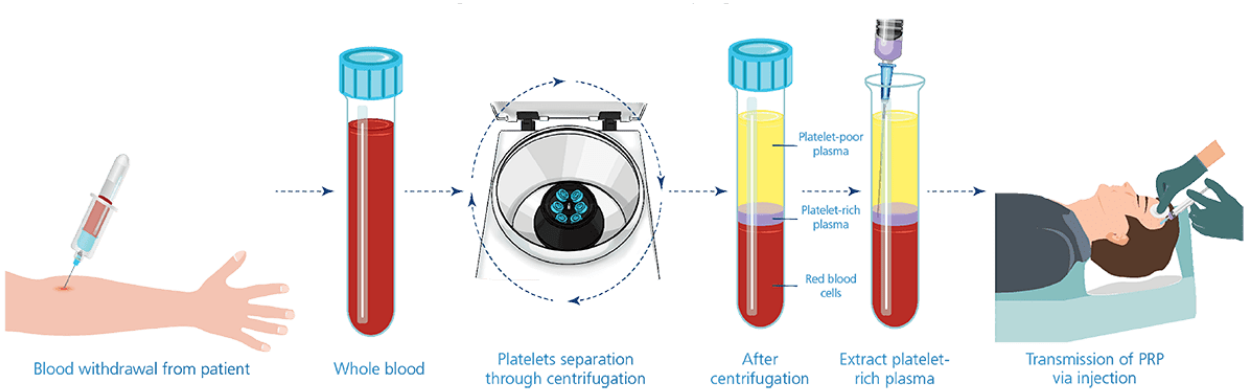
Let's think!!!

From the following hint:

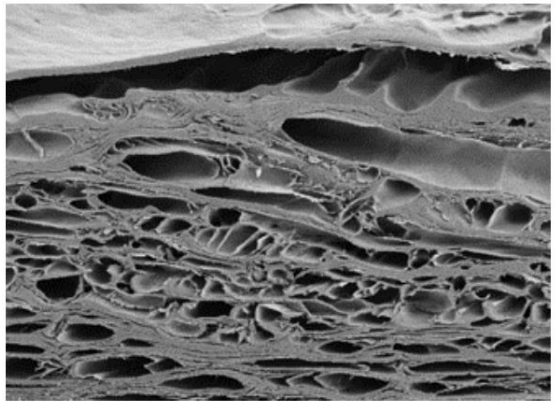
"Products containing or consisting exclusively of non-viable cells or tissues and which do NO act principally by pharmacological, immunological or metabolic action, will not be considered ATMPs."

Are the following products considered as ATMPs?:

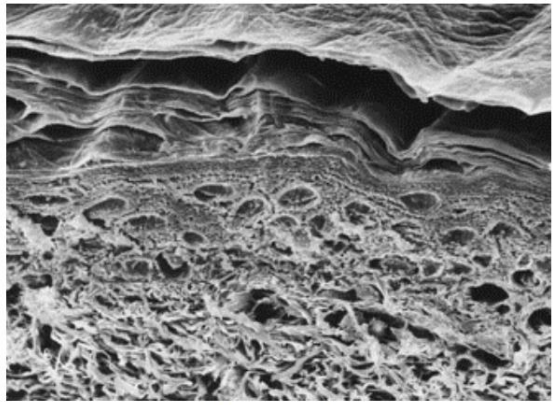
- Decellularized scaffolds
- Cornea/Amniotic membrane for transplantation
- Demineralized bone matrix (DBMs)
- Platelet rich plasma (PRPs)



Platelet rich plasma (PRP)



Fish skin



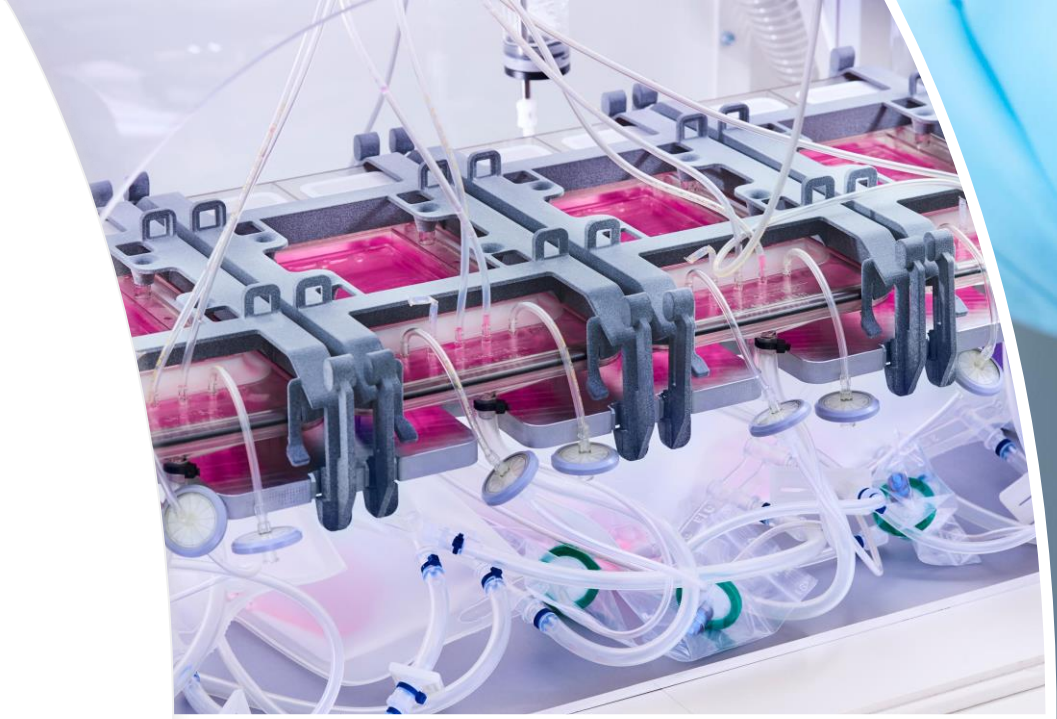
Human skin

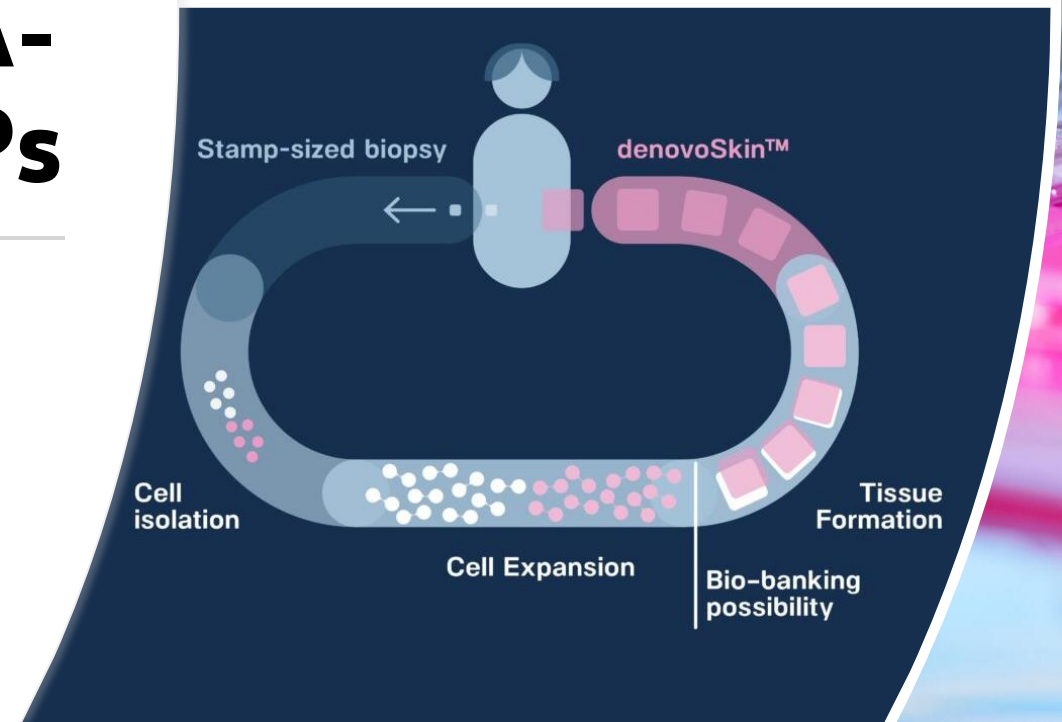
Decellularized scaffolds from fish skin for the treatment of skin wounds (Image courtesy of Keresis, Iceland)

Demineralized bone matrix (Image courtesy of MTF, USA)

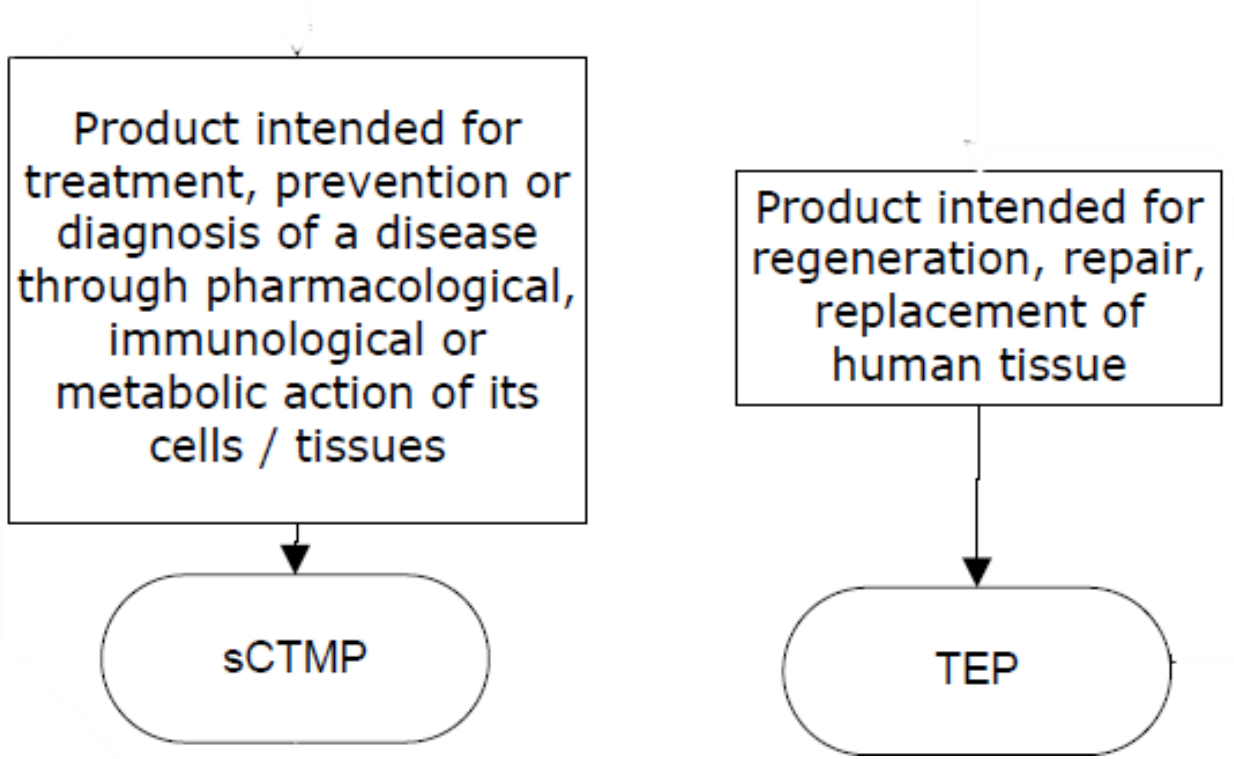
Example: FDA-approved TEPs

denovoSkin™, CUTISS AG, Switzerland

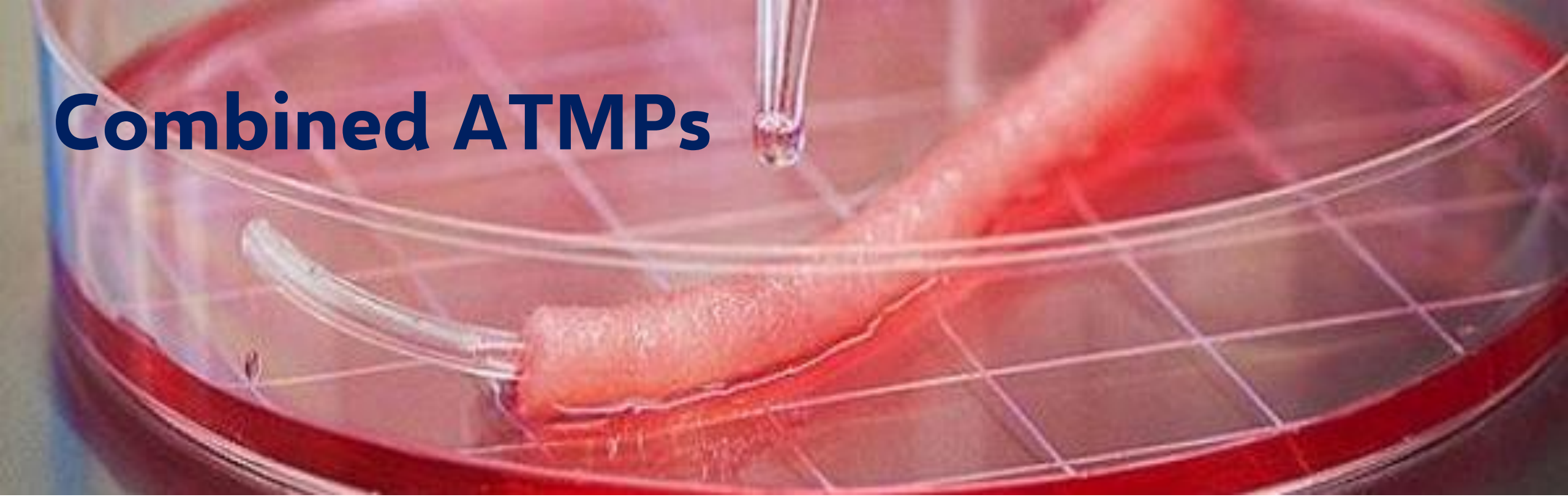




How to distinguish between sCTMPs and TEPs



Information on the claimed mode of action (MoA) is particularly important to ascertain whether the product is for treatment, prevention or diagnosis of a disease, and exerts its activity via a pharmacological, immunological or metabolic action, or whether the product is intended for regeneration, repair or replacement of cells/tissues. The possible MoA should be considered in relation to the intended indication.



Combined ATMPs

- it must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC, and

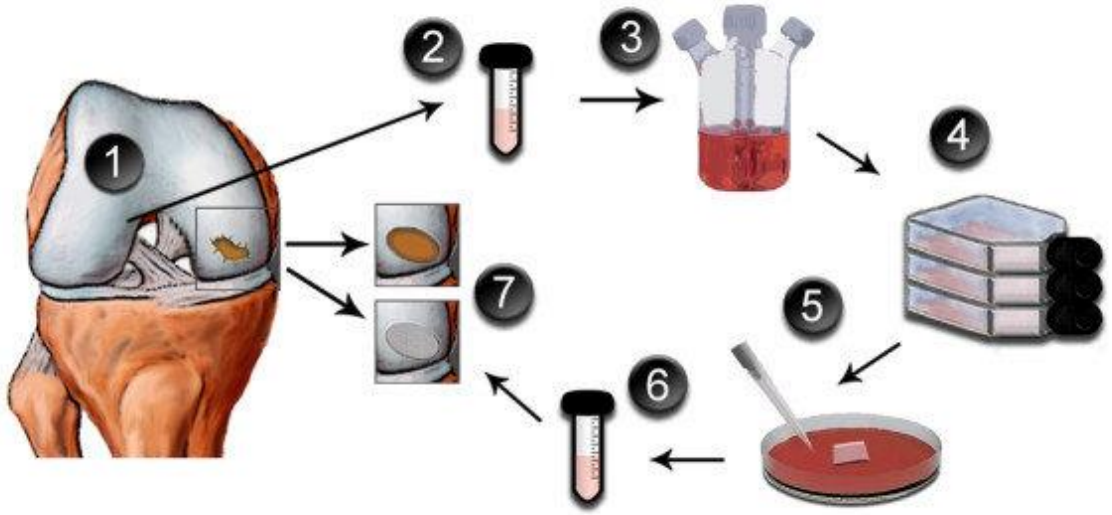
- its cellular or tissue part must contain viable cells or tissues, or

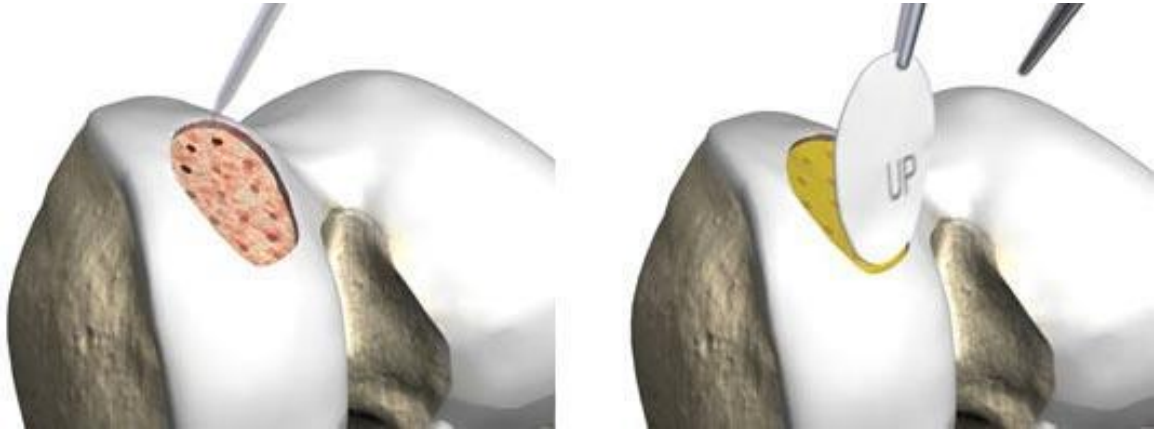
- its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.

The medical device should retain its intended purpose / mode of action in the combination to be considered as being "integral part" of the final product

Examples: Combined ATMPs

MACI (Autologous Cultured Chondrocytes on a Porcine Collagen Membrane), Vericel Corporation





*Jacobi, M., Villa, V., Magnussen, R.A. et al. MACI - a new era?. BMC Sports Sci Med Rehabil **3**, 10 (2011).*

The MACI procedure:

(1) Initial arthroscopy with evaluation of the injured cartilage and harvest of a full-thickness cartilage biopsy;

(2) the biopsy is sent in a sterile and cooled container to the cell culture laboratory;

(3) the cartilage is enzymatically digested;

(4) expansion of the chondrocytes in monolayer culture for about four weeks;

(5) the cells are seeded onto the scaffold a few days before implantation;

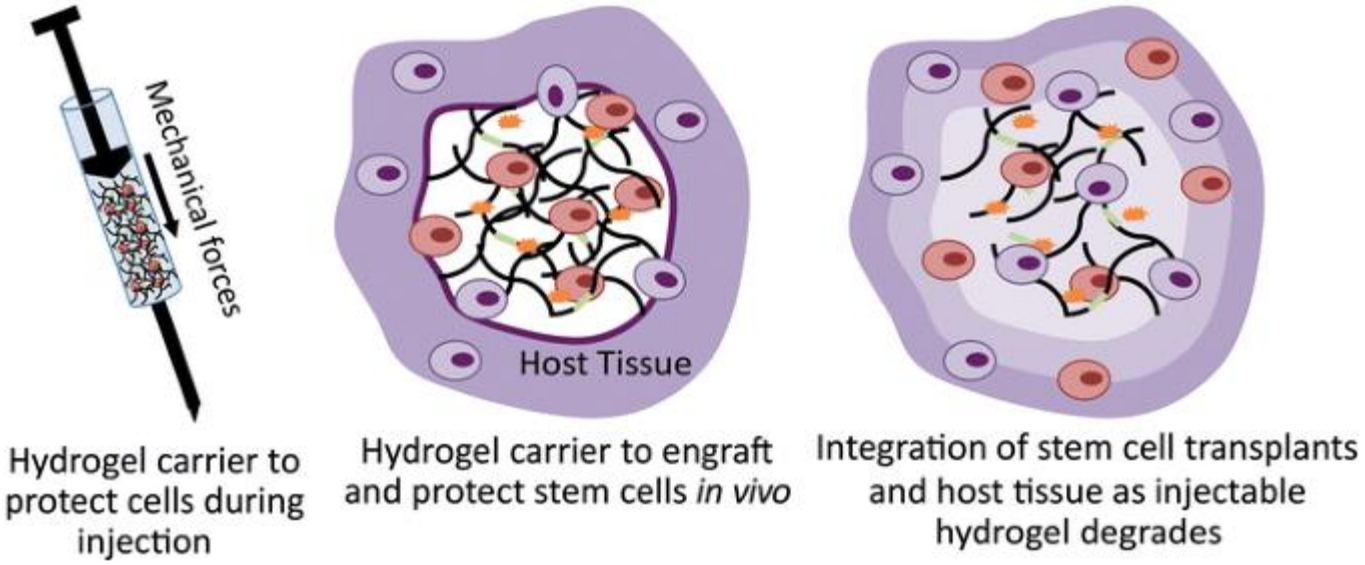
(6) the engineered implant is sent back to the surgeon in a sterile container;

(7) definitive surgery with debridement of the injured cartilage followed by implantation of the MACI-implant, which is trimmed to fit the defect size and glued with a thin layer of fibrin glue.

How can we determine if a medical device is considered an integral part?

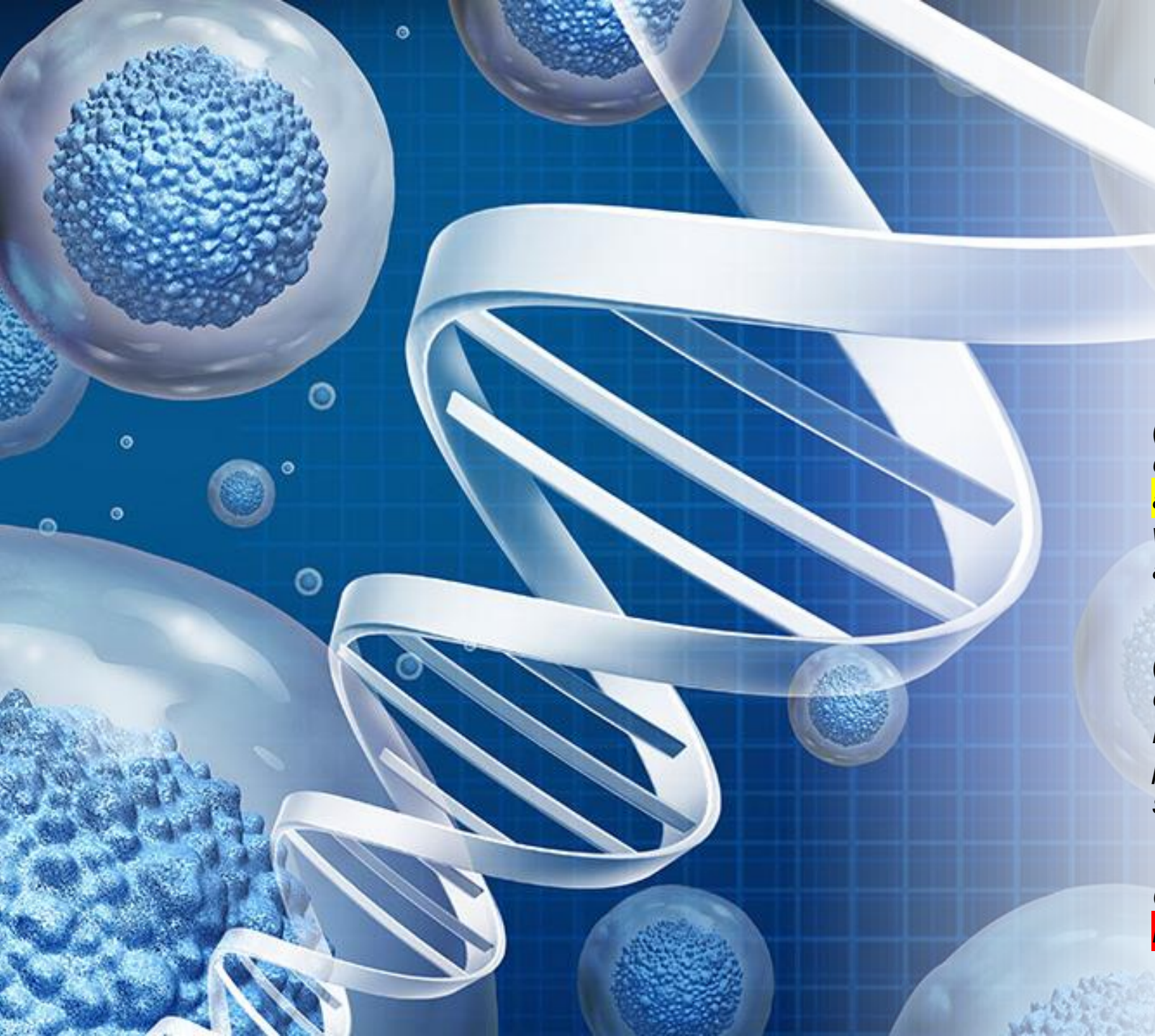
If the combined component (although CE marked) is not or no longer used as a medical device but should be considered as an "excipient" in the final formulation of the drug (and therefore not combined).

Example: Injectable gel matrix for cell transplantation



*Marquardt, L.M., Heilshorn, S.C. Design of Injectable Materials to Improve Stem Cell Transplantation. Curr Stem Cell Rep **2**, 207–220 (2016).*

- The gel matrix has the function to keep the cells around the administration site
- The manufacturing process uses the matrix in a different way than its intended use when considered as a medical device
- The matrix was not considered to be a medical device any more
- The CAT therefore classified the product as a sCTMP, not combined ATMP



Gene therapy medicinal products (GTMPs)

(a) 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;

(b) 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.

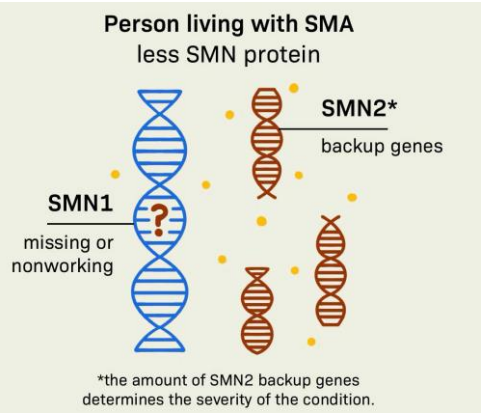
Gene therapy medicinal products shall not include vaccines against infectious diseases.

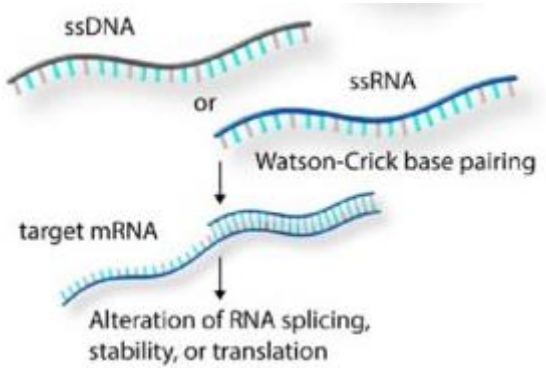
Roles of gene as therapeutics

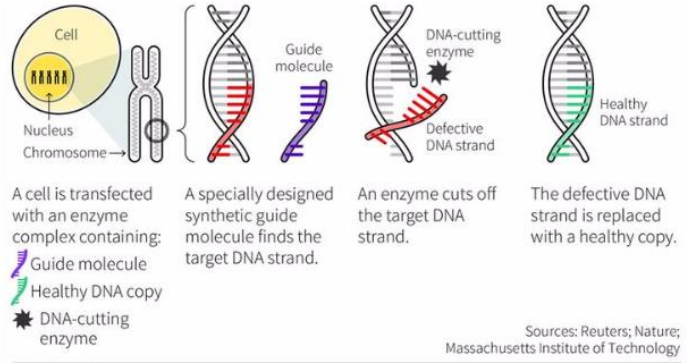
1. Expression: Target proteins are translated based on the input DNA or RNA

2. Silencing or Interference: Protein expression is suppressed, using short strand nucleotides (such as antisense oligonucleotides, or silencing RNA (siRNA)) to interfere the translation process.

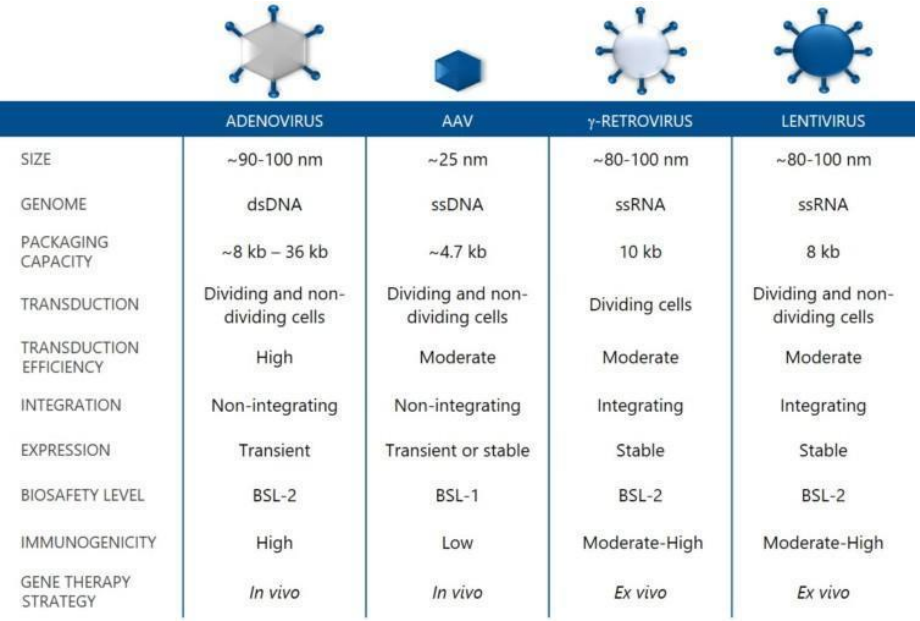
3. Editing: Host genome is permanently edited, either by an addition, deleting, or replacing (mainly perform using CRISPR/Cas technology)







Gene delivery systems



	ADENOVIRUS	AAV	γ-RETROVIRUS	LENTIVIRUS
SIZE	~90-100 nm	~25 nm	~80-100 nm	~80-100 nm
GENOME	dsDNA	ssDNA	ssRNA	ssRNA
PACKAGING CAPACITY	~8 kb – 36 kb	~4.7 kb	10 kb	8 kb
TRANSDUCTION	Dividing and non-dividing cells	Dividing and non-dividing cells	Dividing cells	Dividing and non-dividing cells
TRANSDUCTION EFFICIENCY	High	Moderate	Moderate	Moderate
INTEGRATION	Non-integrating	Non-integrating	Integrating	Integrating
EXPRESSION	Transient	Transient or stable	Stable	Stable
BIOSAFETY LEVEL	BSL-2	BSL-1	BSL-2	BSL-2
IMMUNOGENICITY	High	Low	Moderate-High	Moderate-High
GENE THERAPY STRATEGY	*In vivo*	*In vivo*	*Ex vivo*	*Ex vivo*

Gene therapeutic formulation

Viral vector

- High transduction efficiency
- Many products are currently in the market
- Long history in uses, lot more knowledge
- Immune reaction to virus components
- Insertion mutagenesis
- Limit size of transgenes

Non-viral vector

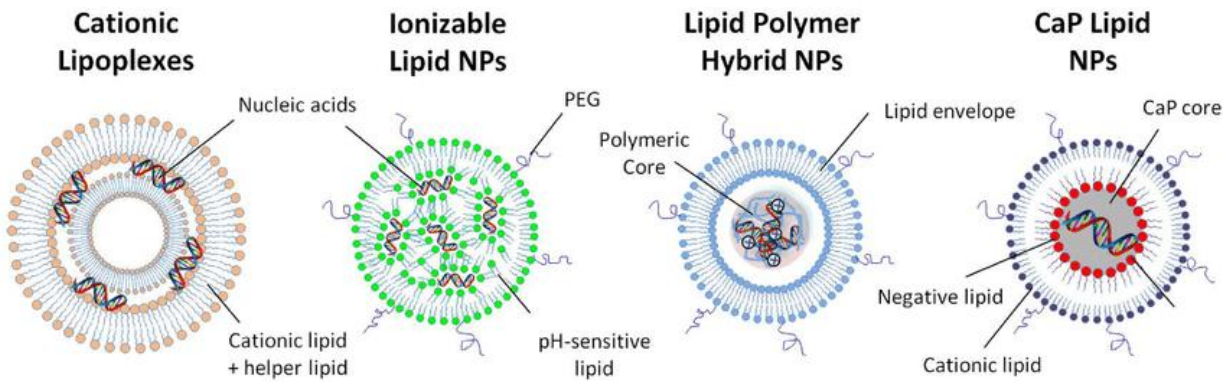
- Safer (Low immunogenicity, low risk of genetic insertion)
- Simple production at low cost
- Low transduction efficiency

Lipoplex

- E.g., Lipid nanoparticles, Liposomes
- Recently commercialized products

Polyplex

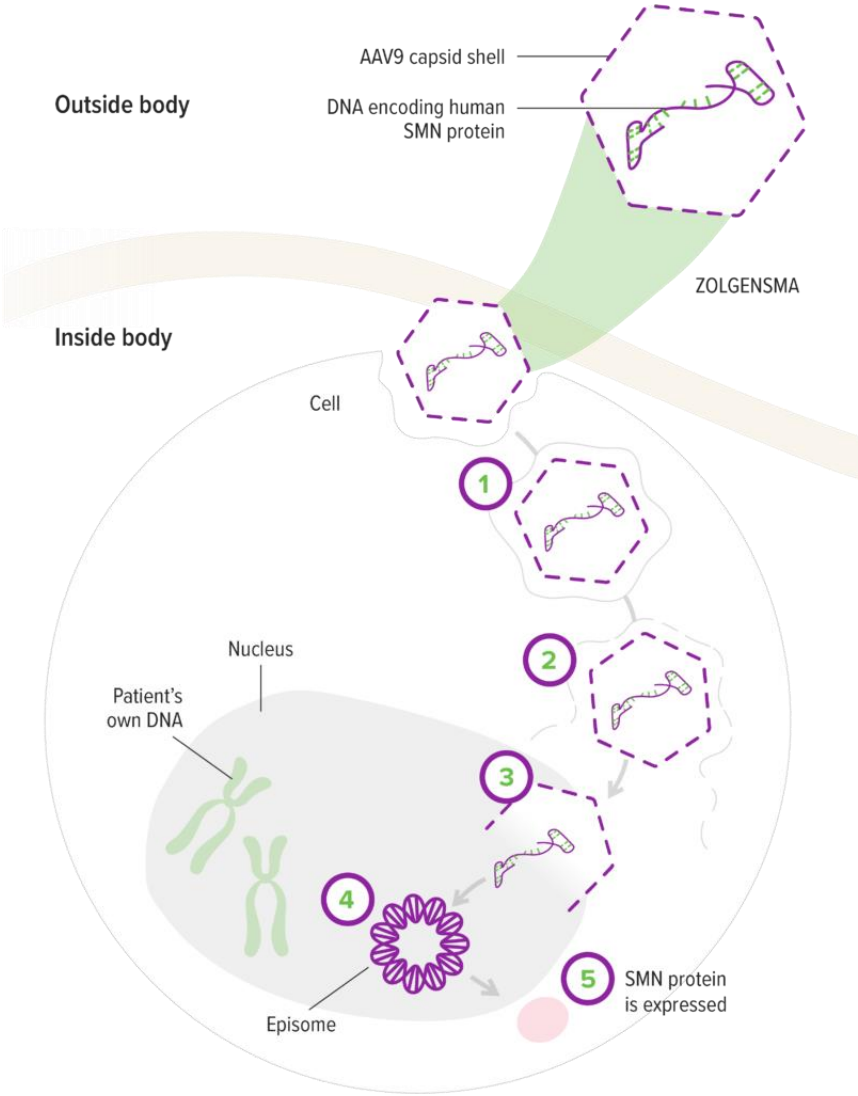
- E.g., Cationic polymers (e.g., PEI, PBAE)
- Less clinically advanced, mainly used in research



(a) 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;

The recombinant nucleic acids should be of biological origin independently from the origin of the vector system used (e.g., viral/bacterial vectors or micellar and liposomal formulations, etc.)

Example: *In vivo* gene therapy



ZOLGENSMA (onasemnogene abeparvovec-xioi), Novartis Gene Therapies, Inc.

Does not need to know that…

Prefix: Fantasy element to provide unique identification; to contribute to the distinct name.

Infix: Element to denote the type of viral vector such as:
-adeno- [adenovirus]
-cana- [canarypox virus]
-foli- [fowlpox virus]
-herpa- [herpes virus]
-lenti- [lentivirus]
-morbilli- [paramyxoviridae morbillivirus]
-parvo- [adeno-associated virus (parvovirdae dependovirus)]
-retro- [other retro viruses]
-vaci- [vaccinia virus]

onasemnogene abeparvovec-xioi

Ref: American Medical Association (AMA)

Infix: Element to denote the gene's mechanism of action (pharmacologic class) such as:
-ald- [adrenoleukodystrophy (ALD) protein]
-bermin- [vascular endothelial growth factor]
-cima- [cytosine deaminase]
-etid- [eczema-throbocytopenia-immunodeficiency syndrome]
-far- [interferon]
-kin- [interleukins]
-lip- [human lipoprotein lipase]
-naco- [coagulation factor IX]
-nermin- [tumor necrosis factor (TNF)]
-pap- [human papilloma virus]
-permin- [hepatocyte growth factor]
-reti- [retinal pigment]
-stim- [colony stimulating factor]
-tusu- [tumor suppression]
-beglo- [βA-t87Q-globin]
-cabta- [cell expressed antibody and T cell activation]
-ermin- [growth factor]
-fermin- [fibroblast growth factor]
-lim- [immunomodulator]
-mul- [multiple gene]
-nad- [NADH dehydrogenase]
-octoco- [coagulation factor VIII]
-papkino- [human papilloma virus and IL-2]
-repi- [REP-1 gene]
-semn- [SMN]
-tima- [thymidine kinase]

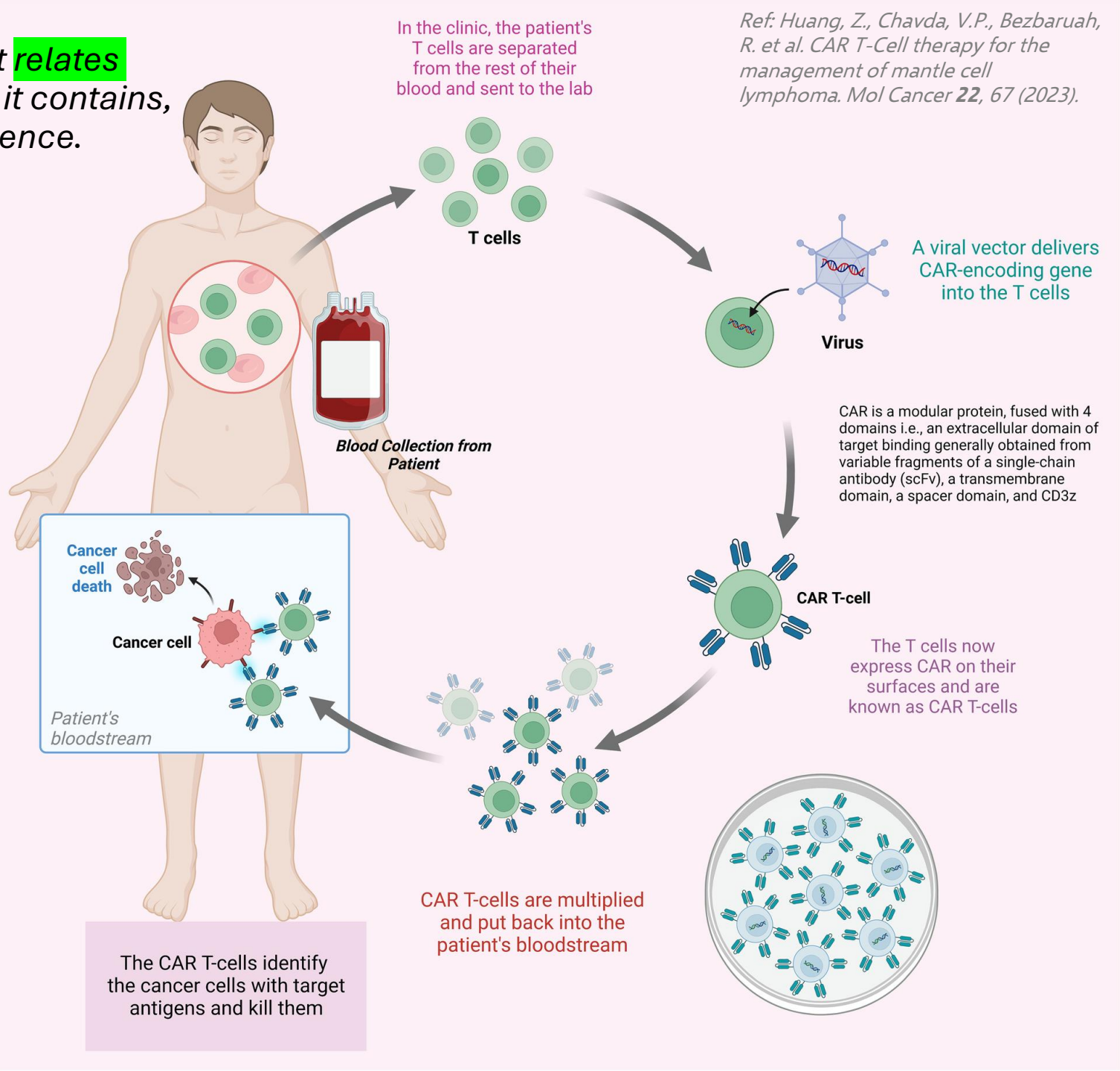
Stem: Element to identify type of vector
-vec [non-replicating viral vector]
-repvec [replicating viral vector]
-plasmid [plasmid vector]

(b) 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.

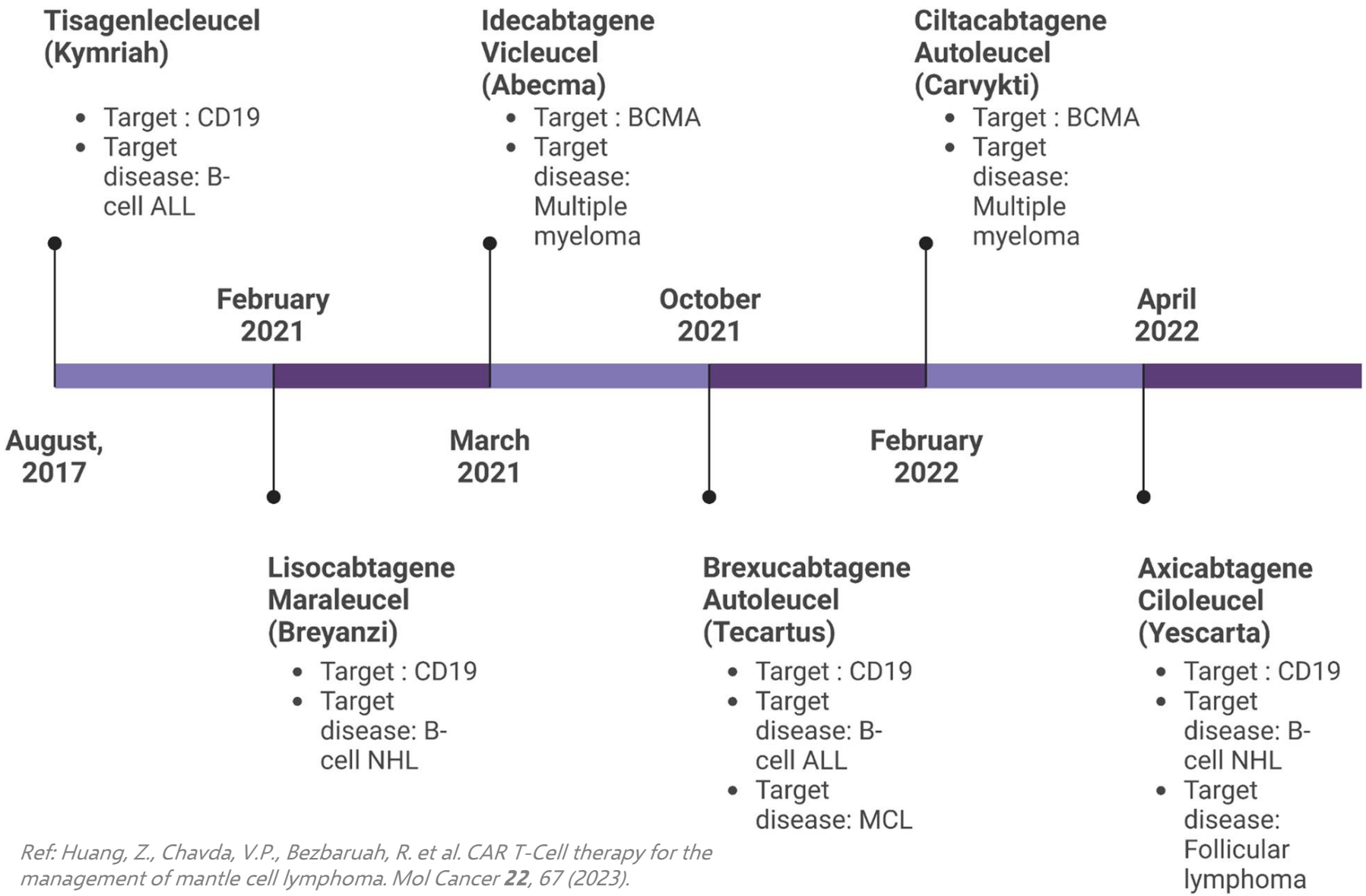
Genetic manipulation does not necessarily have to take place in the human body, since for example products consisting of genetically modified cells generated *ex-vivo* have also been classified as a gene therapy medicinal product.

Example:

Ex vivo CAR T cells



USFDA approved CAR T cell products

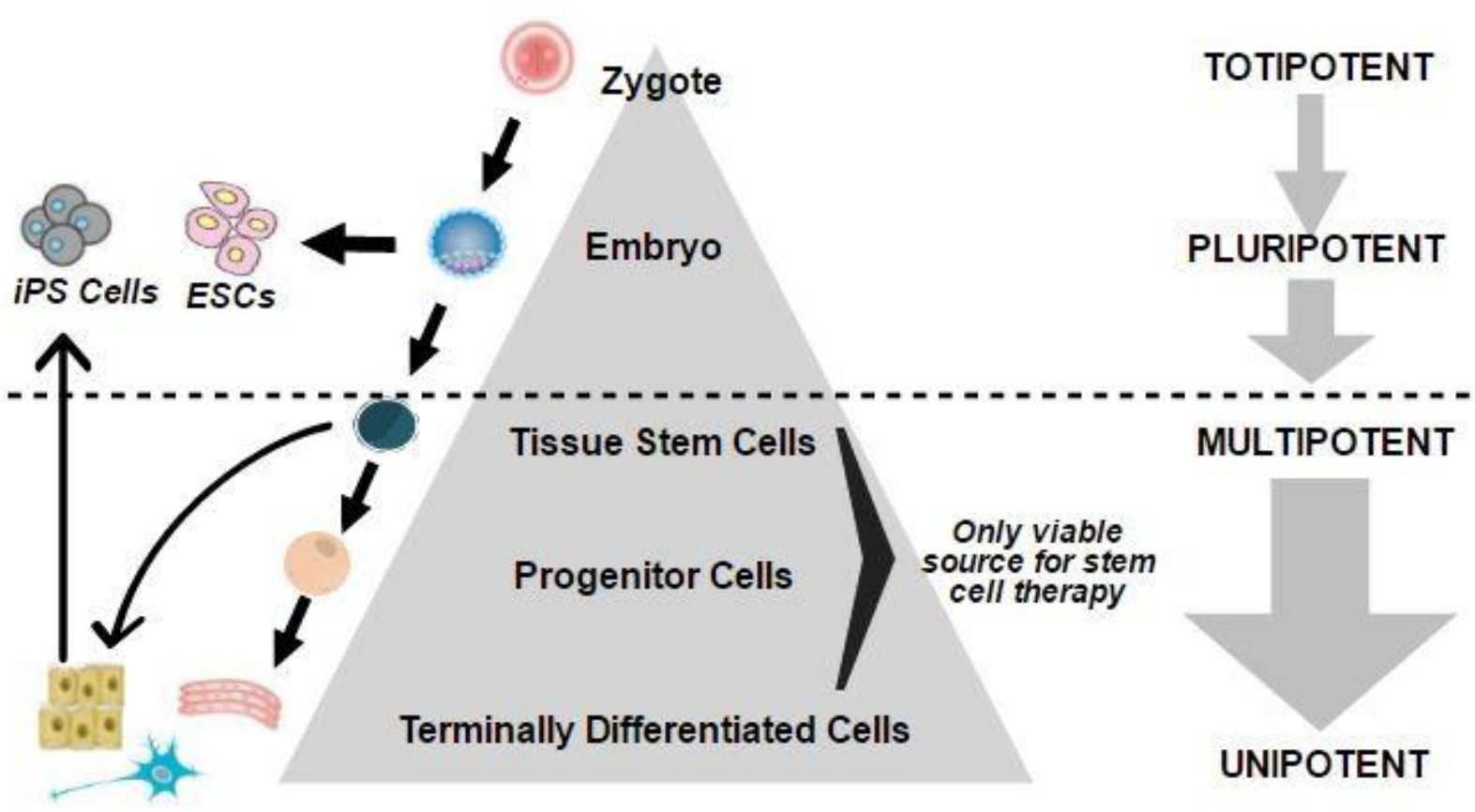


*Ref: Huang, Z., Chavda, V.P., Bezbaruah, R. et al. CAR T-Cell therapy for the management of mantle cell lymphoma. Mol Cancer **22**, 67 (2023).*

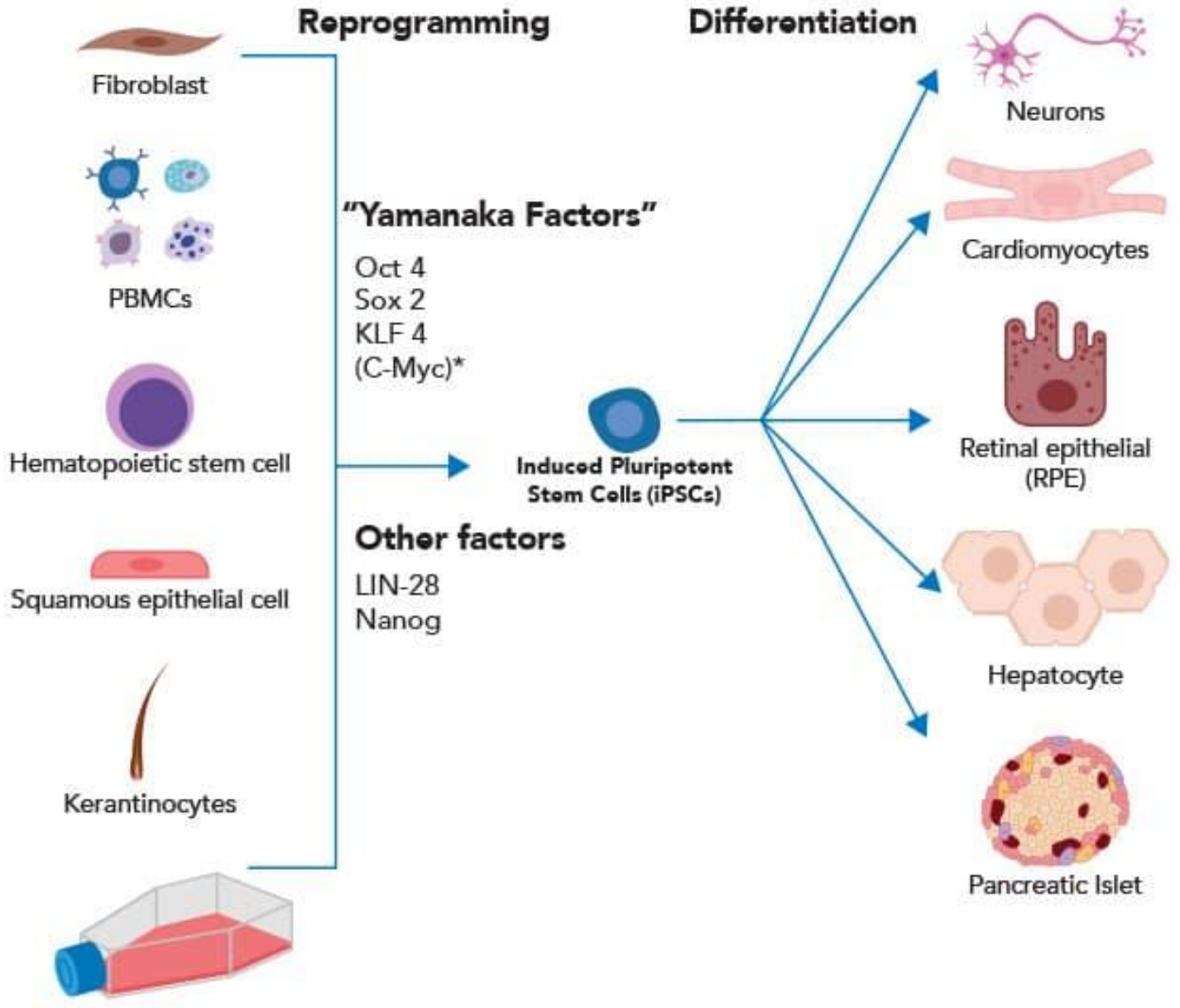
(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

The MoA and proposed indication, as claimed by the applicant are of essential to assess if there is a "direct" relationship between the therapeutic, prophylactic or diagnostic effect of the product and the delivered genetic sequence or the expressed product.

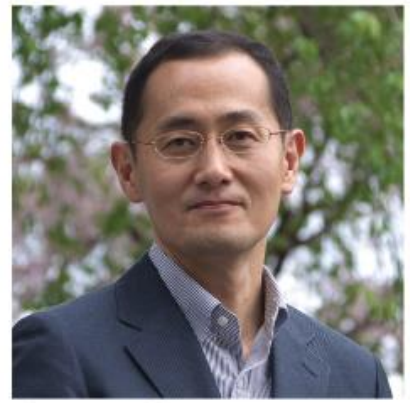
Do iPSCs qualify as GTMPs?



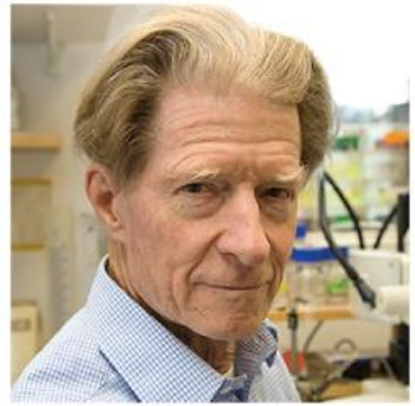
Stem cell reprogramming process



2012 Nobel Prize in Physiology or Medicine



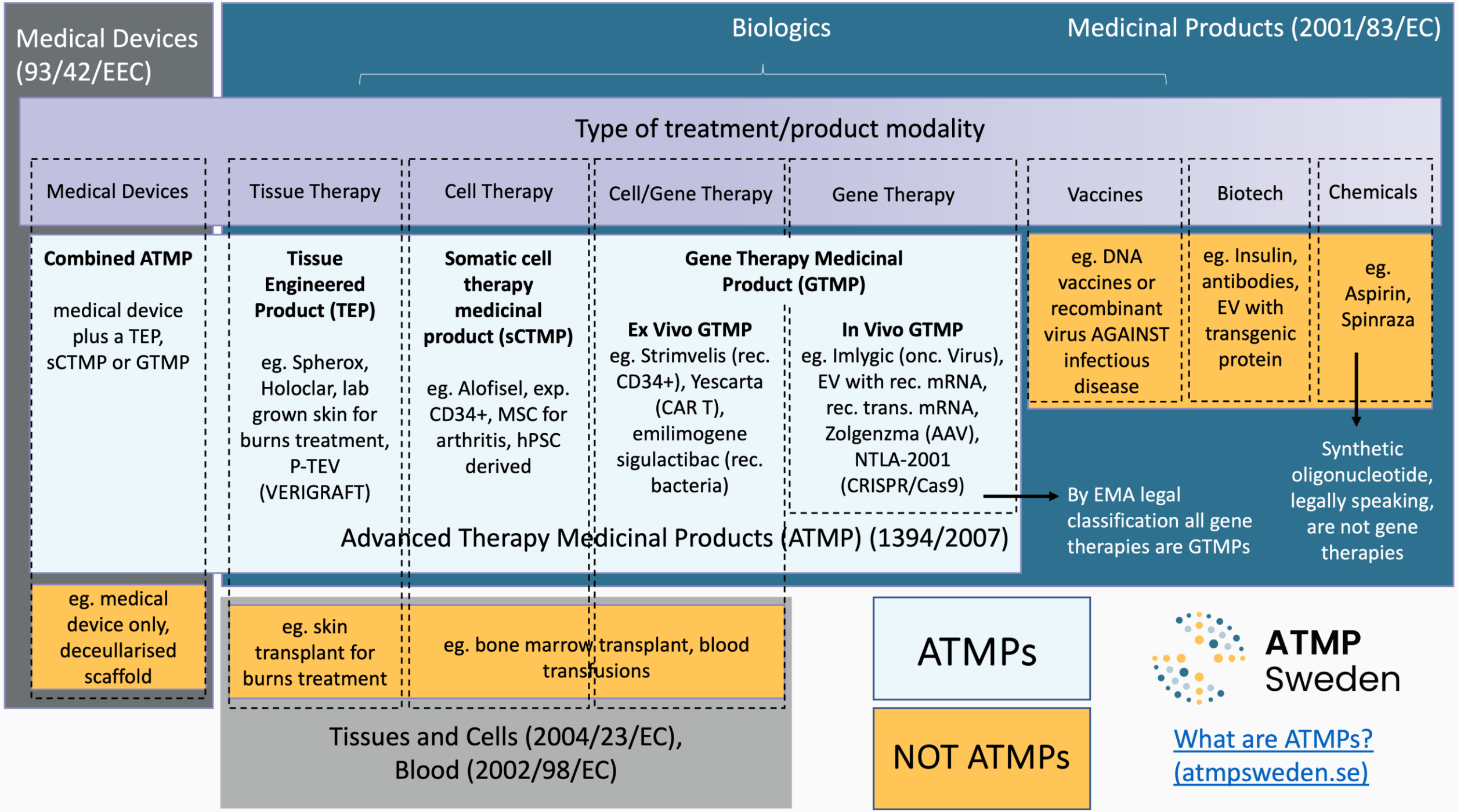
Shinya Yamanaka
University of Kyoto, Japan
Photo Credit:
Center for iPS cell Research and Application, Kyoto University

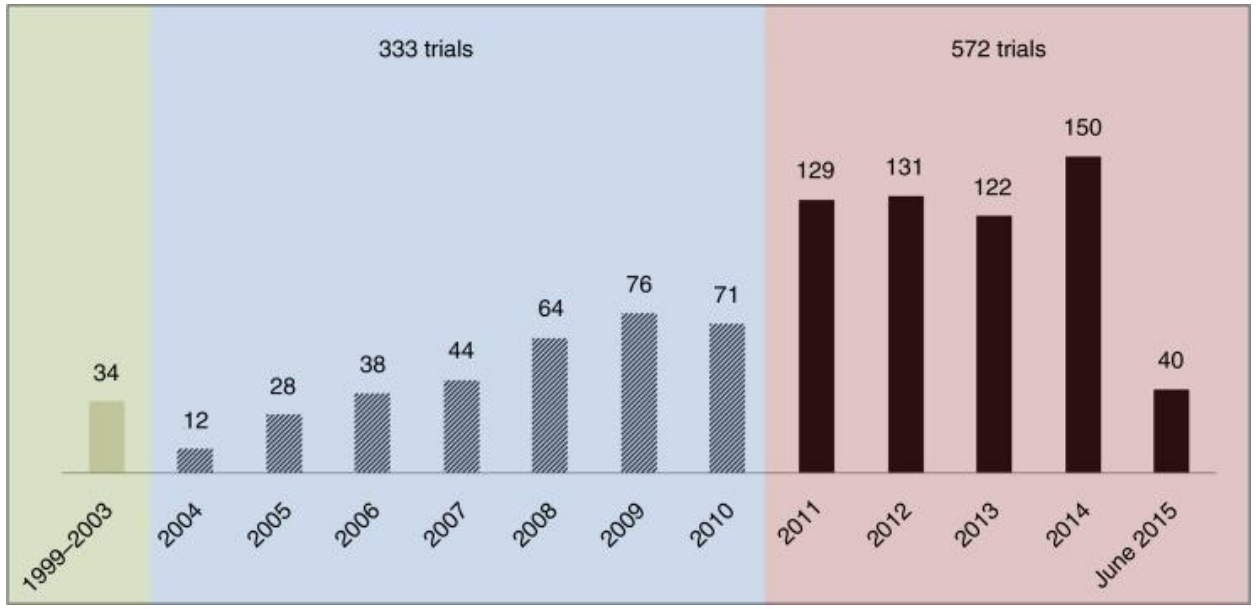


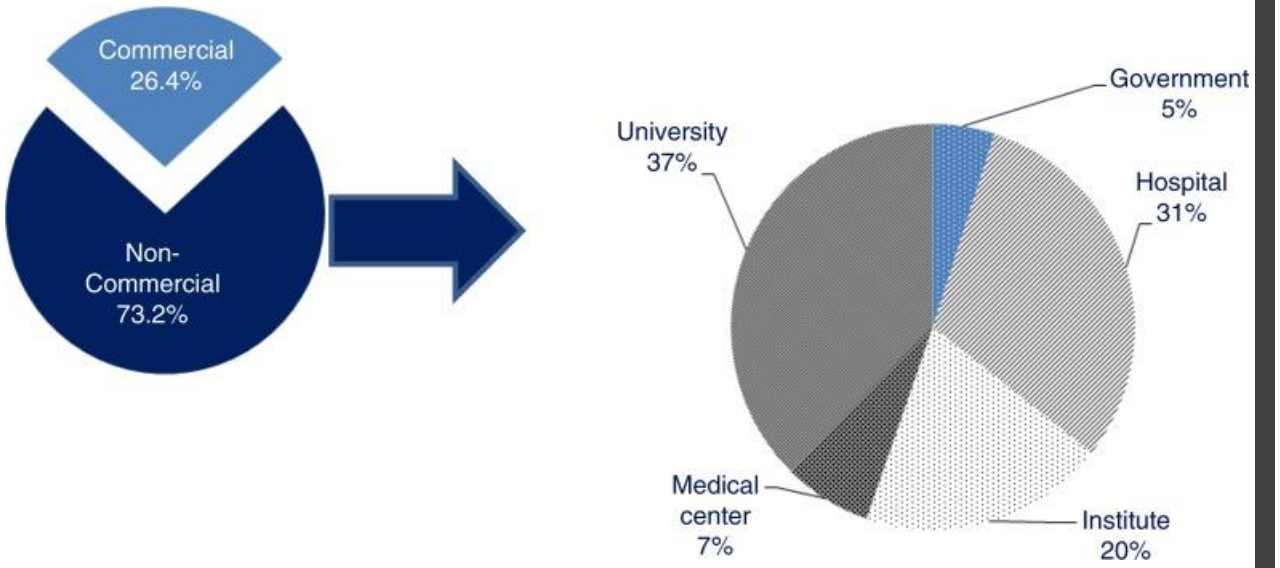
John B. Gurdon
Gurdon Institute in Cambridge, UK

- The recommendation on the classification as tissue engineering products considered that the primary role of the cells was the "regenerate/repair/replace" of the patients' tissues, while the genetic modification was limited to a secondary role of cellular reprogramming.
- the classification does not necessarily exempt from the relevant and applicable scientific requirements of GTMP

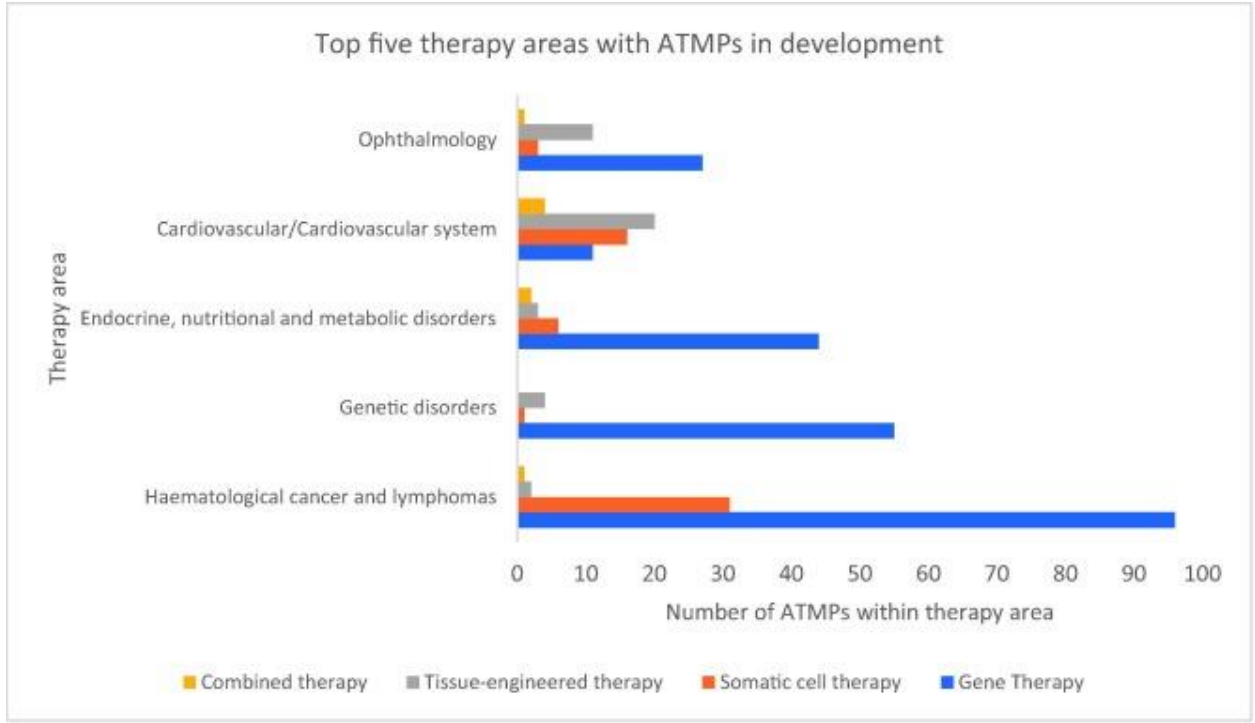
- The CAT classification examples in the reflection paper should not be understood as generic classifications for certain classes of ATMPs.
- Future applicants should apply caution when extrapolating the CAT classifications to their product and should consider applying for ATMP classification of their product.
- While the recommendation on classification provided by the Agency is not binding, the procedure can help developers to clarify the applicable regulatory framework.


Medical Devices (93/42/EEC)
Biologics
Medicinal Products (2001/83/EC)
Type of treatment/product modality
Medical Devices
Tissue Therapy
Cell Therapy
Cell/Gene Therapy
Gene Therapy
Vaccines
Biotech
Chemicals
Combined ATMP
medical device plus a TEP, sCTMP or GTMP
Tissue Engineered Product (TEP)
eg. Spherox, Holoclar, lab grown skin for burns treatment, P-TEV (VERIGRAFT)
Somatic cell therapy medicinal product (sCTMP)
eg. Alofisel, exp. CD34+, MSC for arthritis, hPSC derived
Gene Therapy Medicinal Product (GTMP)
Ex Vivo GTMP
eg. Strimvelis (rec. CD34+), Yescarta (CAR T), emilimogene sigulactibac (rec. bacteria)
In Vivo GTMP
eg. Imlygic (onc. Virus), EV with rec. mRNA, rec. trans. mRNA, Zolgenzma (AAV), NTLA-2001 (CRISPR/Cas9)
eg. DNA vaccines or recombinant virus AGAINST infectious disease
eg. Insulin, antibodies, EV with transgenic protein
eg. Aspirin, Spinraza
Synthetic oligonucleotide, legally speaking, are not gene therapies
By EMA legal classification all gene therapies are GTMPs
Advanced Therapy Medicinal Products (ATMP) (1394/2007)
eg. medical device only, deceullarised scaffold
eg. skin transplant for burns treatment
eg. bone marrow transplant, blood transfusions
Tissues and Cells (2004/23/EC), Blood (2002/98/EC)
ATMPs
NOT ATMPs
ATMP Sweden
What are ATMPs? (atmpsweden.se)



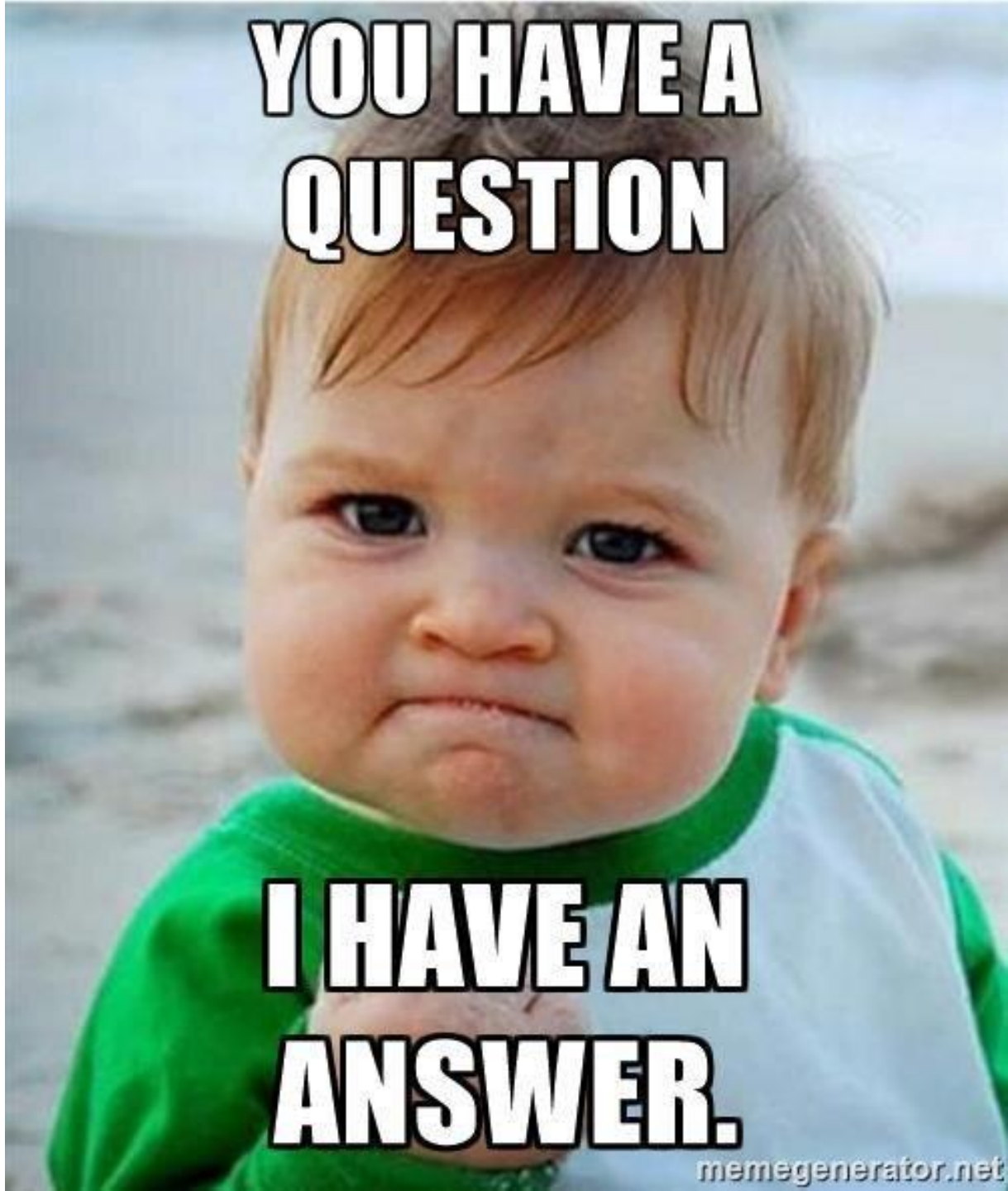


Wilkins GC, Lanyi K, Inskip A, Ogunbayo OJ, Brhlikova P, Craig D. A pipeline analysis of advanced therapy medicinal products. Drug Discov Today. 2023 May;28(5):103549.

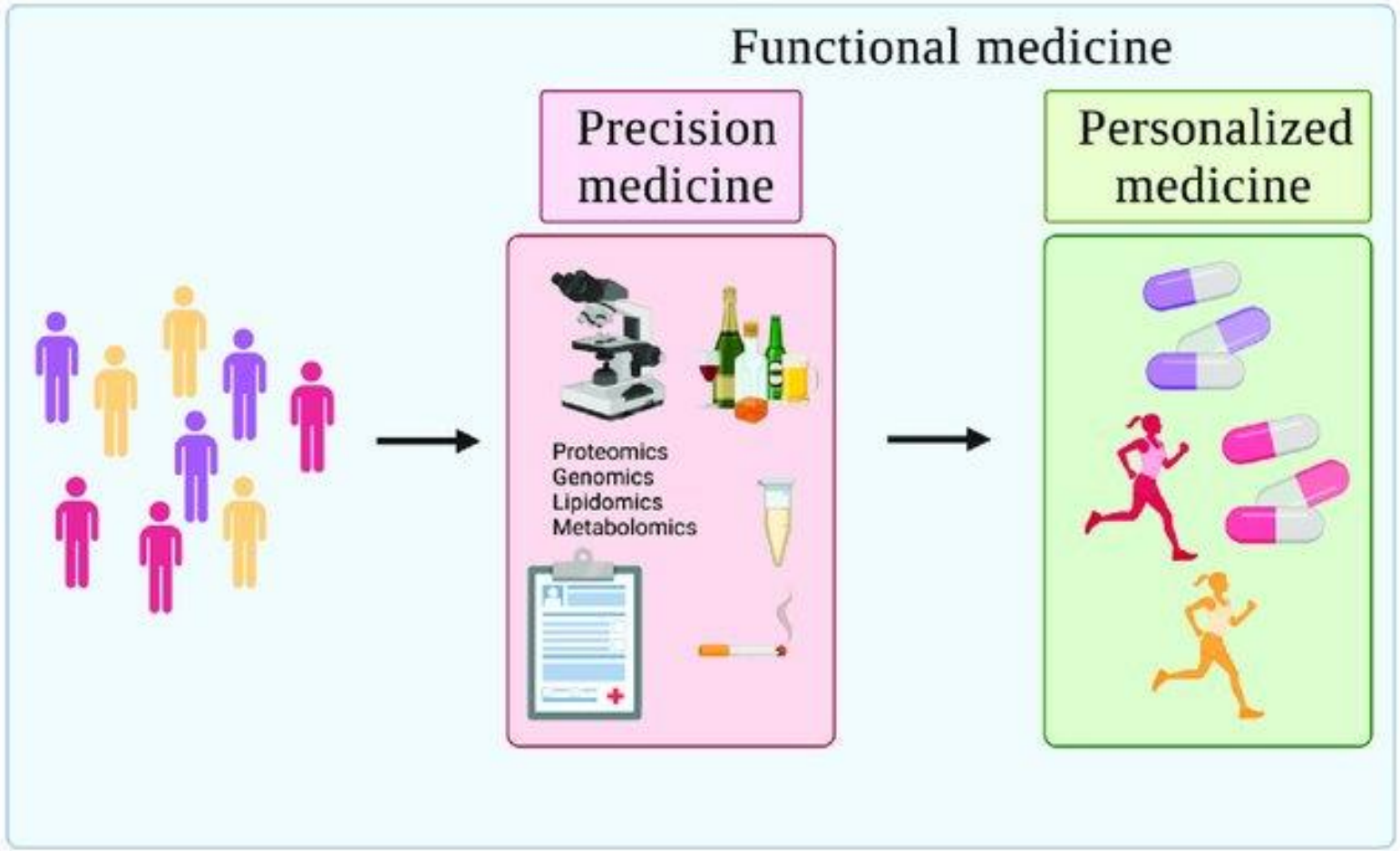


Current status of ATMP development

FAQs:
Are ATMPs a subtype of personalized medicine?



Personalized medicine vs Precision medicine



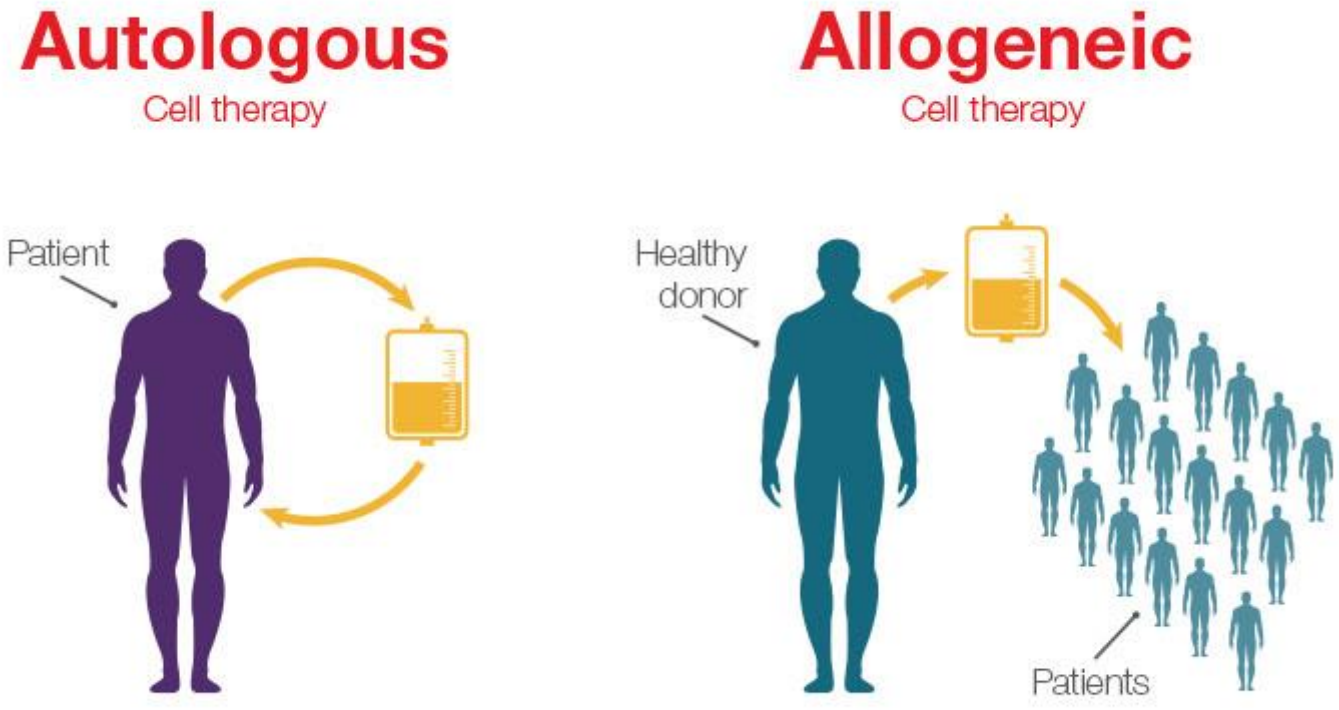
Precision medicine identifies differences in individuals, categorizing based on environmental, biological, and psychosocial factors.

Personalized medicine takes these differences and implements preventions/treatments tailored to the individual.

Carbonara, K.; MacNeil, A.J.; O'Leary, D.D.; Coorssen, J.R. Profit versus Quality: The Enigma of Scientific Wellness. J. Pers. Med. ***2022****, 12, 34.*

Why we wonder about that?

Autologous vs Allogenic transplantation



ATMPs are based on genes, cells, or tissues delivered to patients to provide a therapeutic benefit based on a specific target of interest. This is often referred to as personalized medicine by many. ATMPs include cells, engineered tissues, or the manipulation of the patient's genome. This is in contrast with traditional manufacturing processes for compounds that are synthetically derived (i.e., small molecule) or proteins or peptides expressed by cellular systems (i.e., large molecule biopharmaceuticals). - ISPE

Image courtesy of The International Society for Pharmaceutical Engineering (ISPE)

Contact:

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Department of Biochemistry and Microbiology, Faculty of Pharmaceutical Sciences, Chulalongkorn University

Email: Chavee.L@chula.ac.th

Relevant documents

- **สำนักงานคณะกรรมการอาหารและยา**

  ประกาศสำนักงานคณะกรรมการอาหารและยา เรื่อง แนวทางการจำแนกประเภทผลิตภัณฑ์การแพทย์ขั้นสูง

  https://drug.fda.moph.go.th/announcement-administration/176-fda-20230203-2
- **EMA**

  Commission Directive 2009/120/EC (Medicinal products for human use as regards advanced therapy medicinal products)

  https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009L0120

  Regulation (EC) No. 1394/2007 (Advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No. 726/2004)

  https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32007R1394

  Reflection paper on classification of advanced therapy medicinal products (EMA/CAT/600280/2010 rev.1)

  https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en.pdf-0

WHO

Considerations in developing a regulatory framework for human cells and tissues and for advanced therapy medicinal products

https://cdn.who.int/media/docs/default-source/biologicals/bs-documents-(ecbs)/post-ecbs-documentation/annex-3---hcts-atmps-regulatory-considerations---clean-for-posting---12-may-2023.pdf?sfvrsn=f4b86b89_1&download=true