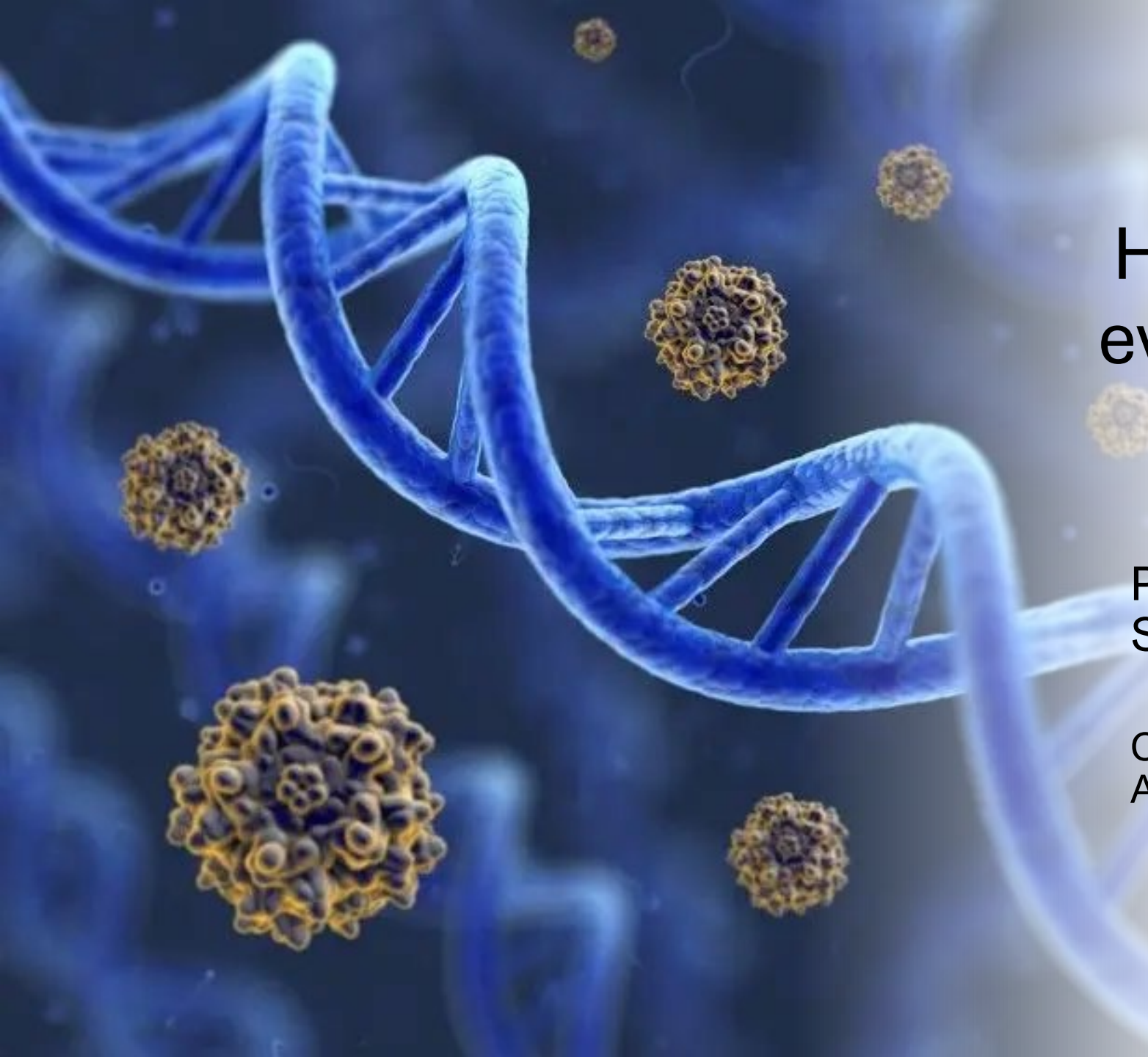


How have the ATMPs evolved over time?

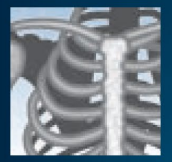
Paula Salmikangas, NDA / SSI Strategy

CAT Scientific Symposium on ATMPs, Amsterdam, 10th October, 2024

Businessweek July 1998

THE NEW ERA OF REGENERATIVE MEDICINE

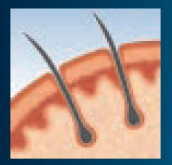
Dozens of biotech companies and university labs are developing ways to replace or regenerate failed body parts. Here are a few of the projects:



BONE

Bone-growth factors or stem cells are inserted into a porous material cut to a specific shape, creating new jaws or limbs. A product that creates shinbones is in clinical trials.

COMPANIES: Creative Biomolecules, Orquest, Sulzer Orthopedics Biologics, Genetics Institute, Osiris Therapeutics, Regeneron.



SKIN

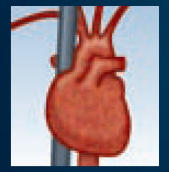
Organogenesis' Apligraf, a human-skin equivalent, is the first engineered body part to win FDA approval, initially for leg ulcers. Other skins are in the works for foot ulcers and burns.

COMPANIES: Organogenesis, Ad-vanced Tissue Sciences, Integra LifeSciences, LifeCell, Ortec International.

PANCREAS

Insulin-manufacturing cells are harvested from pigs, encapsulated in membranes, and injected into the abdomen. The method has been tested in animals and could be in human trials in two years.

COMPANIES: BioHybrid Technologies, Neocrin, Circe Biomedical

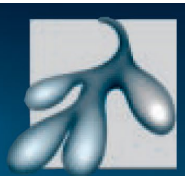


HEART VALVES, ARTERIES, AND VEINS

A 10-year initiative to build a heart has just started. Genetically engineered proteins have been successfully used to regrow blood vessels.

COMPANIES: Organogenesis, Advanced Tissue Sciences, Genetech, LifeCell, Reprogenesis.

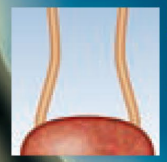
DATA: BUSINESS WEEK, DRUG & MARKET DEVELOPMENT REPORTS



SALIVA GLANDS

Proteins called aquaporins that allow cells to secrete water are used to recreate saliva glands damaged by disease or radiation. Glands are also being engineered to secrete healing drugs. The technique has proven successful in mice.

COMPANIES: None yet.



URINARY TRACT

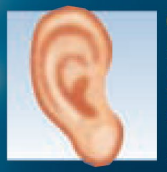
Cartilage cells are taken from the patient, packed into a tiny matrix, and injected into the weakened ureter, where they bulk up the tissue walls to prevent urinary backup and incontinence. The method is in late-phase clinical trials.

COMPANIES: Reprogenesis, Integra LifeSciences.

BLADDER

Doctors at Children's Hospital in Boston have grown bladders from skin cells and implanted them in sheep. They are about to try the same process on a patient

COMPANIES: Reprogenesis.



CARTILAGE

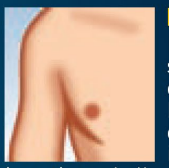
A product is already on the market that regrows knee cartilage. A chest has been grown for a boy and a human ear on a mouse.

COMPANIES: Genzyme Tissue, Biomatrix, Integra LifeSciences, Advanced Tissue Sciences, ReGen Biologics, Osiris Therapeutics

TEETH

Enamel matrix proteins are used to fill cavities. It works in dogs; human trials are a few years away.

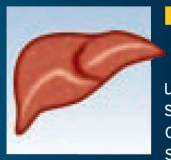
COMPANIES: Biora, Atrix Laboratories, Creative BioMolecules.



BREAST

In preclinical studies, several companies have been able to create a cosmetic nipple by inserting a ball of cartilage. Researchers are now trying to grow a whole cosmetic breast.

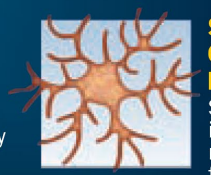
COMPANIES: Reprogenesis, Integra LifeSciences.



LIVER

A spongy membrane is built up and then seeded with liver cells. Organs the size of a dime have been grown, but a full-size liver could take 10 years due to its complexity.

COMPANIES: Advanced Tissue Sciences, Human Organ Sciences, Organogenesis.



SPINAL CORD NERVES

Scientists are investigating nerve-growth factors, injecting them at the site of damage to encourage regeneration or seeding them along biodegradable filaments and implanting them. Rats have been made to walk again.

COMPANIES: Acorda, Regeneron, CytoTherapeutics, Guilford Pharmaceuticals.

Early development of ATMPs

- Chondrocyte-containing products for treatment of cartilage defects as first licenced product containing living cells (Carticel, Genzyme US 1996)
- Tissue-engineered skin as the first approved combination product (Apligraf, US 1998)
- Autologous, cell-based products with simple expansion and formulation in clinical development also in the EU
- ChondroCelect first CBMP to gain a MA in EU (2009)
- Provenge first approved cancer immunotherapy product (US 2010, 2013 EU)
- appr. 50 Cell-based products on national markets in the EU (Hospital Exemption identified as a tool to bring these products under EU marketing authorization)

2009

Cancer Vaccines in Advanced Stage Clinical Trials

Category	Defined Antigen	Tumor Type	Company	Trade Name
Whole Cell	No	Prostate	Cell Genesys	GVAX™
HSP-96	No	Melanoma, Renal	Antigenics	Oncophage®
Dendritic Cell	PAP	Prostate	Dendreon	Sipuleucel-T (Provenge®)
Pox Vector (MVA)	5T4	Renal, Colon	Sanofi- Aventis	TroVax®
Conjugate	MUC 1	NSCLC	Merck KGaA	Stimuvax®
QS-21/CpG	MAGE-3	NSCLC	**GlaxoSmithKine**	MAGE-A3 ASCI

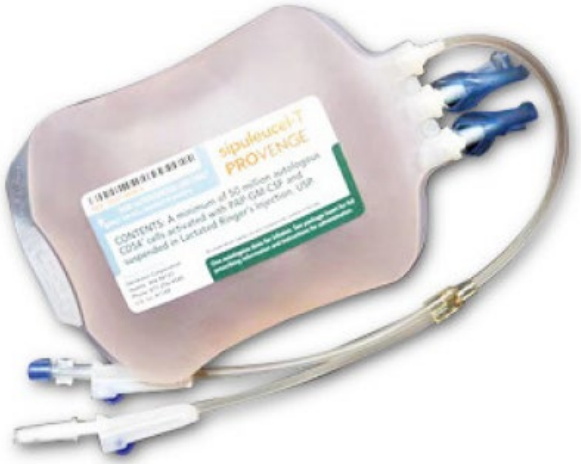
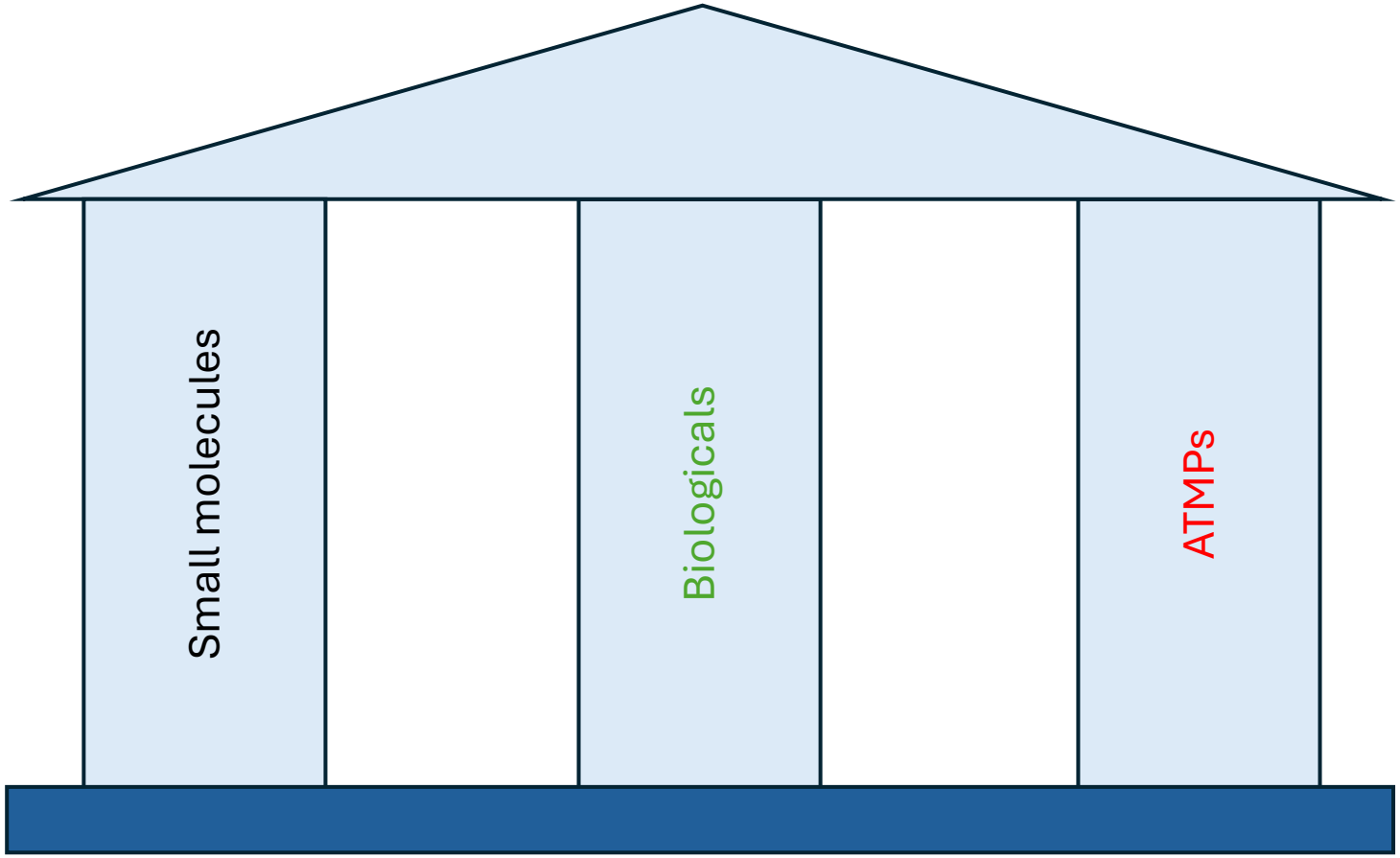


Table from www. cancerimmunity.org, 2008

Legal framework for ATMPs in 2009

- generated for oversight of products that were in national use and under development at that time!



- **Different production processes**: synthesis * recombinant protein production * cell culture and/or recombinant virus/nucleotide/plasmid production, manipulations
- **Different starting materials**: chemicals * production cells/MCB/plasmids * cells, viruses, plasmids, DNA/RNA, enzymes (nucleases)
- **Different expertise required for regulatory oversight**: chemistry * cell and molecular biology * cell and molecular biology, genetic modification of cells and viruses

2014

Marketing authorization applications / CAT 2009-2014 (May)

	2009	2010	2011	2012	2013	2014	Total	Approved
Submitted	3	1	2	3	2	1	**12**	**4**
GTMP	2	1				1	3	1
SCTMP				1			1	1
TEP	1		2	2	1		6	2
Variations	0	0	1	1	9	2	13	

Approved: **ChondroCelect** for cartilage repair (later withdrawn)
MACI for cartilage repair (later withdrawn)
Glybera for treatment of LPL deficiency (later withdrawn)
Provenge for treatment of advanced prostate cancer

Currently

- ✓ 4 ATMPs under evaluation
- ✓ 2 new starting Q3-4/2014

2024

US (38)

- Carticel (1997)
- Provenge (2010)
- Laviv, Fibrocell(2011)
- Hemacord(2011)
- Gintuit(2012)
- HPC, Cord Blood (2012)
- HPC, Cord Blood (2013)
- Ducord(2012)
- Allocord(2013)
- Imlygic(2015)
- Clevecord(2016)
- HPC, Cord Blood (2016)
- MACI (2016)
- Kymriah (2017)
- Luxturna(2017)
- Yescarta (2017)
- HPC, Cord Blood (2018)
- Zolgensma (2019)
- Tecartus (2020)
- Abecma (2021)
- Breyanzi (2021)
- Rethymic (2021)
- Stratagraft (2021)
- Carvykti (2022)
- Zynteglo (2022)
- Skysona (2022)
- Adstiladrin (2022)
- Hemgenix (2022)
- Elevidys (2023)
- Lantidra (2023)
- Omisirge (2023)
- Roctavian (2023)
- Vyjuvek (2023)
- Lyfgenia (2023)
- Amtagvi (2024)
- Beqvez (2024)
- Tecelra (2024)
- Lenmeldy (Libmeldy, 2024)

Canada (13)

- Prochymal (2014)
- Kymriah (2018)
- Yescarta (2019)
- Luxturna (2020)
- Zolgensma (2020)
- Abecma (2021)
- Tecartus (2021)
- Breyanzi (2022)
- Skysona (2022)
- Hemgenix (2023)
- Carvykti (2023)
- Beqvez (2023)
- Casgevy (2023)

EU (28)

- Chondrocelect(2009)
- MACI (2012)
- Glybera(2013)
- Provenge (2013)
- Holoclar(2015)
- Imlygic(2015)
- Strimvelis(2016)
- Zalmoxis(2016)
- Spherox(2017)
- Alofisel(2018)
- Kymriah (2018)
- Yescarta (2018)
- Luxturna (2018)
- Zynteglo (2019)
- Zolgensma (2020)
- Tecartus (2020)
- Libmeldy (2020)
- Abecma (2021)
- Skysona (2021)
- Breyanzi (2022)
- Carvykti (2022)
- Upstaza (2022)
- Roctavian (2022)
- Ebvallo (2022)
- Hemgenix (2023)
- Casgevy (2024)
- Altuvoct (2024)
- Durveqtix (2024)

Korea (20)

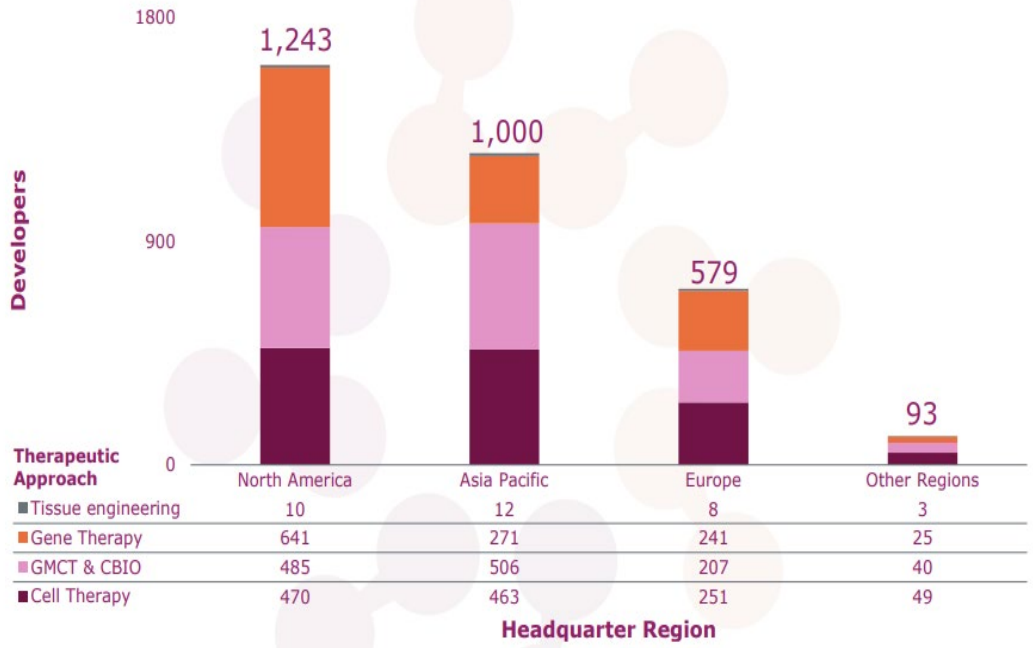
- Chondron(2001)
- Holoderm(2002)
- Kaloderm(2005)
- Keraheal(2006)
- Immuncell-LC (2007)
- RMS Ossron(2009)
- QueenCell (2010)
- CureSkin(2011)
- Hearticellgram-AMI (2011)
- Cartistem (2012)
- Cupistem (2012)
- CreaVax-RCC (2013)
- Neuronata-r (2014)
- KeraHeal-Allo (2015)
- Rosmir (2017)
- Invossa-K (2017)
- Cartilife (2019)
- Kymriah (2021)
- Zolgensma (2021)
- Luxturna (2021)

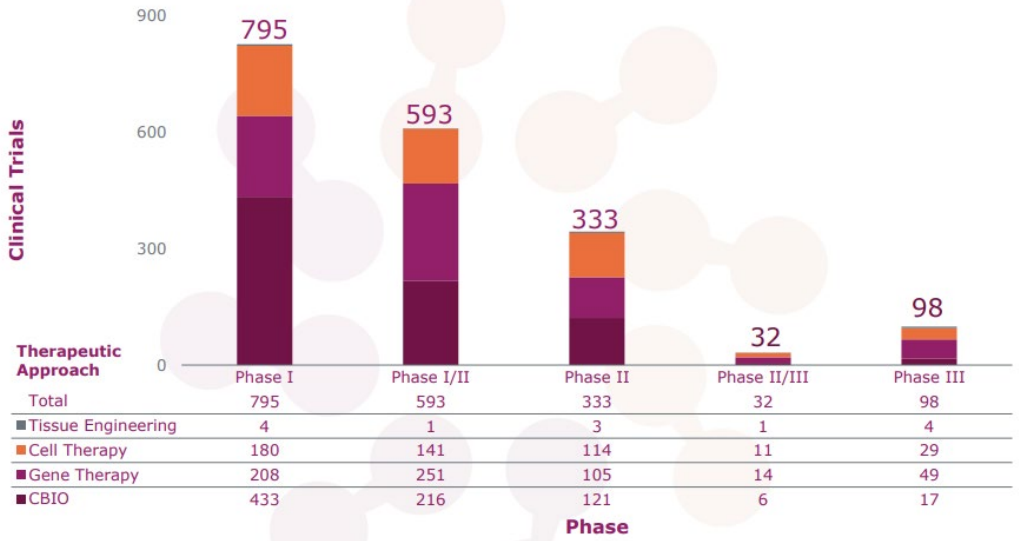
Japan (20+7)

- JACE (2007)
- JACC (2012)
- TEMCELL/Prochymal (2015)
- HeartSheet(2015)
- Stemirac, Stro1 (2018)
- Kymriah (2019)
- Collategene (2019)
- Zolgensma (2020)
- Nepic (2020)
- Yescarta (2021)
- Breyanzi (2021)
- Ocural (2021)
- Delytact /G47Δ (2021)
- Aloficel (2021)
- Abecma (2022)
- Sakracy (2022)
- Carvykti (2022)
- Vyznova (2023)
- Jacemin (2023)
- Luxturna (2023)
- JRM-001 (2016)
- CLS2702C/D (2017)
- iPS-der. neural precursor cells (2017)
- HLCM051 (Multistem, 2017)
- TBI-1301 (NY-ESO1, 2018)
- CLBS12 (CD34+ cells, 2018)
- SB623 (cell therapy, 2019)

Australia (10)

- Cartogen (2002)
- Imlygic (2016)
- T-OrthoACI (2017)
- Kymriah (2020)
- Luxturna (2020)
- Yescarta (2020)
- Tecartus (2021)
- Zolgensma (2021)
- Hemgenix (2022)
- Carvykti (2023)

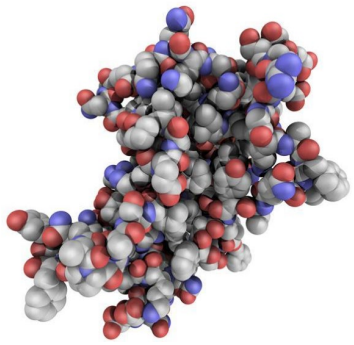


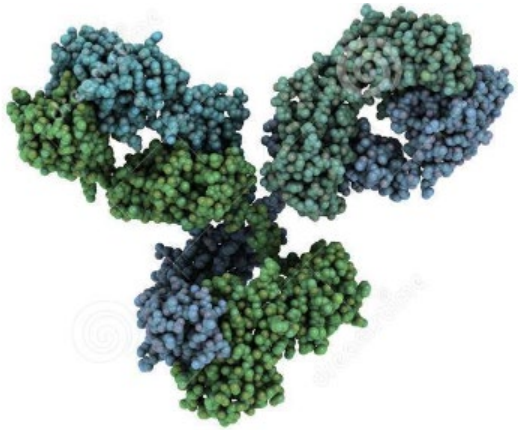


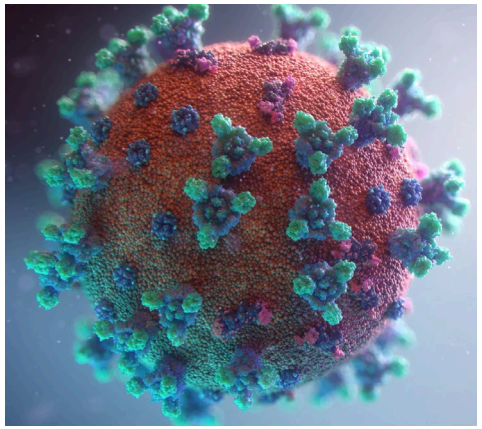
Alliance for Regenerative Medicine, Q2/2024 Sector data

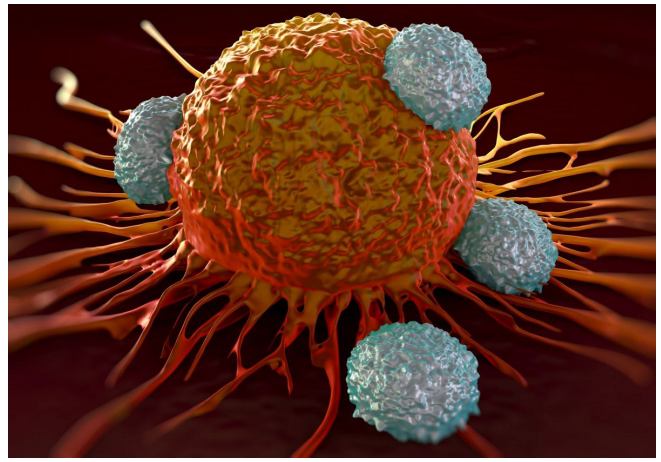
Small molecules vs. biological products vs. ATMPs

Relative molecular mass (Da)





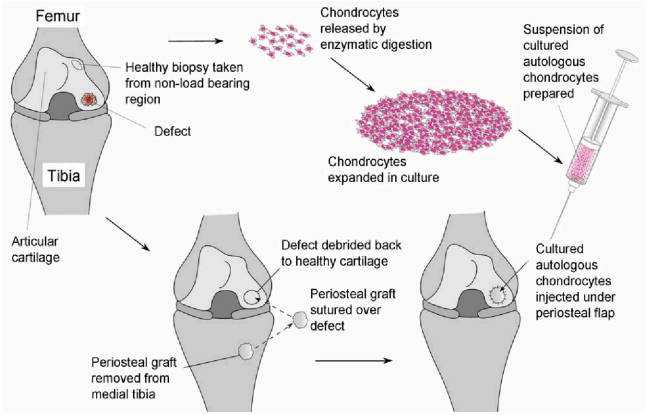




	Aspirin	**hGH**	**IgG**	**Adeno-associated virus**	**CAR-T cells**
	21 atoms/	~3000 atoms / ~20 KDa	~25 000 atoms / ~150 Kda	20 – 25 nm	~ 4,8 µm
Structure	simple	3D	4D	Complex	Highly complex
Risks	gen. toxicity	gen. toxicity tumourigenicity immunogenicity	gen. toxicity tumourigenicity immunogenicity	- tumourigenicity immunogenicity genotoxicity environmental risks long-term efficacy and safety?	- tumourigenicity immunogenicity genotoxicity environmental risks long-term efficacy and safety?

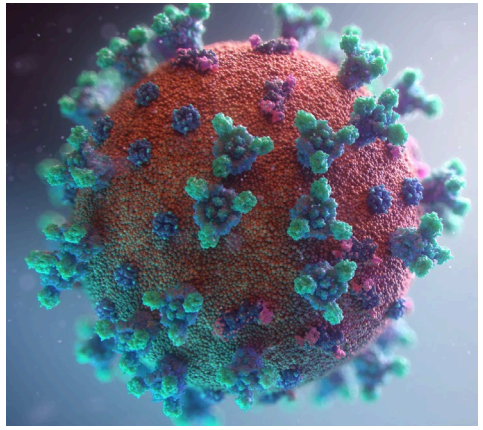
Level of control

Chondrocytes



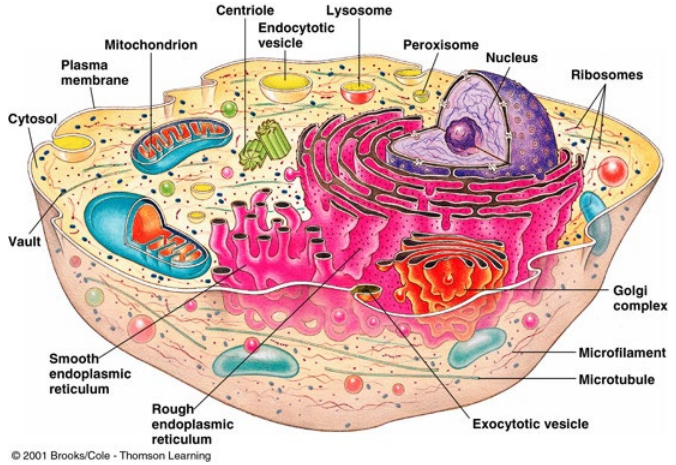
- General (appearance, pH,…)
- Identity (cell surface markers)
- Cell number and viability
- Purity (cell markers)
- Impurities / process-related (residuals)
- Microbiological purity
- Potency (in vitro cartilage formation)

AAV



- General (appearance, pH,…)
- Identity (genome sequencing)
- Structure (TEM, capsid, VPs)
- Viral particle number / titer
- Infectivity
- Capsid protein / genome ratio
- Viral impurities
- Impurities / product-related (rcAAV, empty capsids, aggregates)
- Impurities / process-related ((HCP, HC-DNA, process residuals)
- Residual plasmids
- Potency (transgene expression, functional assays)
- Integration analysis

Gene edited CAR T

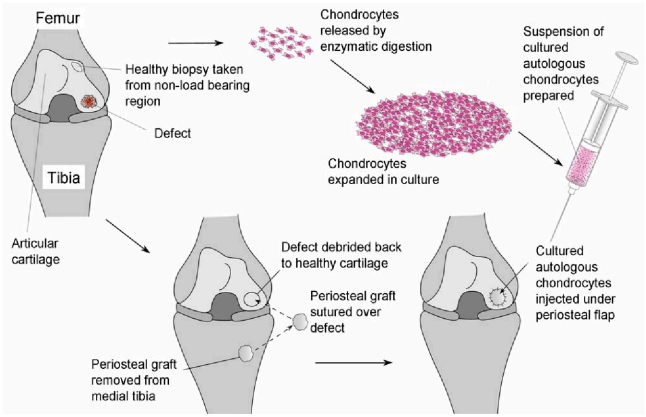


- General (appearance, pH,…)
- Identity (cell + modified genome)
- Cell number and viability
- Structure (cell surface markers)
- Virus copy number (if used), transduction efficiency
- Impurities / product-related (other cell types, non-modified cells, CAR- cells…)
- Impurities / process-related
- Potency (transgene expression, functional assays)
- Karyotyping, Integration analysis
- On-target / Off-target binding
- On-target / Off-target editing

Highly specific, complex analytical tools

Regulatory package

Chondrocytes



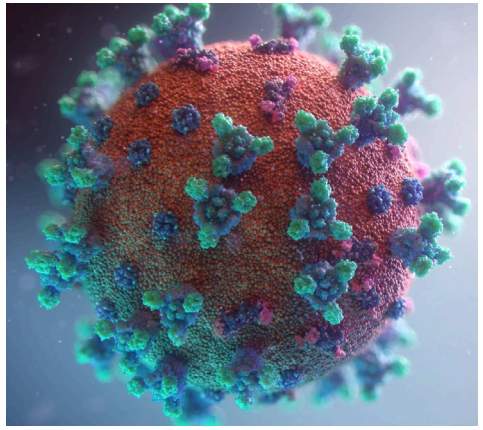
- Starting material:
  autologous cartilage biopsy

- Production process: cell expansion, harvest and formulation

- Active substance are the viable chondrocytes

- One Drug Substance / Drug substance part, usually continuous process, DS / DP not stored

AAV



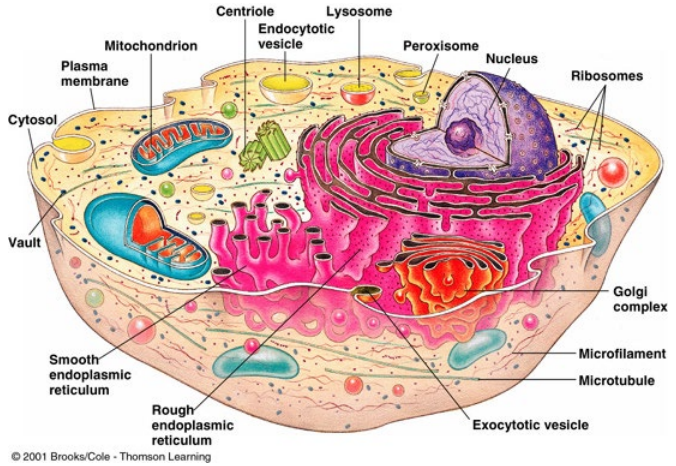
- Starting material:
  3 plasmids with genes for AAV packaging, transgene and helper functions + production cell line (e.g. HEK293 WCB)

- Production process: simultaneous transfection of all plasmids into the cells, incubation and harvest of the viral particles, purification and formulation

-active substance are the AAV particles

- One Drug Substance part and one Drug Product part, DS maybe released and stored

Gene edited CAR T



- Starting material:
T-cells, virus with 3 plasmids, guide-RNAs, Cas9 enzyme

-Production process: cell isolation, gene editing steps and virus transduction, cell washing and formulation

-active substance are the viable, genetically modified CAR+ T-cells

-Multiple starting material packages (= same content as for DS), one DS/DP, often DS not stored

- **Huge and complex data packages**

2024

Authorized

- *Ex vivo* gene therapy products using retro- or lentiviruses
- *In vivo* gene therapy using AAV-based GTMPs
- Genetically modified cells (CAR Ts)
- Product involving gene editing (Casgevy)

In clinical trials

- AAVs with modified capsids for repeat use
- Armored CAR Ts (4^{th} generation expressing cytokines), allogeneic CAR Ts
- Novel gene editing approaches (e.g. CRISPR/Cas9 with AAV6 instead of viral transduction for gene delivery)
- Combined use of ATMPs with other Biologicals

2030

- Currently more than 1,800 active and recruiting interventional gene and cell therapy trials globally
- By **2030** more than 60 US approvals of cell and gene therapy products are projected, with more than 500,000 patients anticipated to be treated with **gene therapies***
- Novel ATMPs and manufacturing technologies like gene editing are evolving with high speed; challenges often multidisciplinary requiring special expertise on cell and molecular biology, CMC, non-clinical and clinical issues, devices…

  → regulatory oversight requires multi-expert decision making, which was recognized already when Reg.1394/2007 was adopted

- US FDA has opened a super office for ATMPs, whereas draft EU Pharma Regulation is proposing to close the CAT???

  → does the revised draft EU legislation take into consideration the future prospects and the novel complex products currently in clinical development?

  → Should the EU regulatory capabilities be strengthened to meet the future challenges with complex ATMPs and to increase the support for industry?

*Drago et al. Mol Ther Methods Clin Dev. 2021; 21: 524–529


15
YEARS OF THE CAT
CONGRATULATIONS!!