Challenges with cell based medicines in the EU

Margarida Menezes Ferreira
margaridamenezesferreira@gmail.com

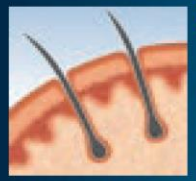
THE NEW ERA OF REGENERATIVE MEDICINE

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

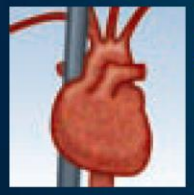
Organogenesis' Apligraf, a human-skin equivalent, is the first engineered body part to win FDA approval, initially for leg ulcers. Other skins are in the works for foot ulcers and burns.

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.

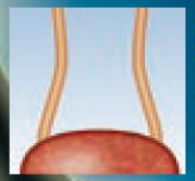
COMPANIES: Organogenesis, Advanced Tissue Sciences, Genetech, LifeCell, Reprogenesis.

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

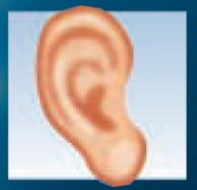
Cartilage cells are taken from the patient, packed into a tiny matrix, and injected into the weakened ureter, where they bulk up the tissue walls to prevent urinary backup and incontinence. The method is in late-phase clinical trials.

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

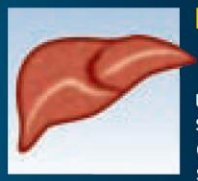
Enamel matrix proteins are used to fill cavities. It works in dogs; human trials are a few years away.

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.

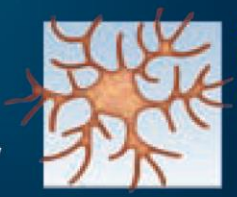
COMPANIES: Reprogenesis, Integra LifeSciences.



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 in-vestigating 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.

Businessweek July 1998

Cell Based Medicinal Products

(Annex I of Directive 2001/83/CE – Directive 2009/120/EC)

Somatic cell therapy medicinal product

cells or tissues 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, and

- used with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

Tissue engineered product

contains or consists of engineered cells or tissues; = **subject to substantial manipulation**, so that their original biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement, are altered. / heterologous use / combined products

–used with a view to, regenerating, repairing or replacing a human tissue;

Genetically modified cell gene therapy – GENE THERAPY

cells modified with recombinant nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es).

Directive 2009/120/EC revising 2001/83/EC – legal framework

- **Risk based approach to construct the dossier**
- **Cells as starting materials collected and donor tested according to Directives 2004/23/EC and2006/17/EC**
- Traceability of all raw, starting materials and active substance
- TSE minimization and viral safety of active substance considering all raw and starting materials
  - Scaffolds, cells, vectors, bank to produce vector = starting materials
  - bioactive molecules and cell medium not part of AS = raw materials
- **Characterisation include identity, purity, viability, potency, kariology, tumourigenicity, genetic stability**
- Genetically modified cells = gene therapy + cell therapy requirements
- Preclinical studies with homologous models
- Biocompatibility of matrix, scafold, cells, excipients, substances in final product
- **Risk management plan include long term follow-up of safety and efficacy**

Human cells = starting materials

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUN

of 13 November 2007

on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

Article 3

Donation, procurement and testing

Where an advanced therapy medicinal product contains human cells or tissues, the donation, procurement and testing of those cells or tissues shall be made in accordance with Directive 2004/23/EC.

L 102/48 EN Official Journal of the European Union 7.4.2004

DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 31 March 2004

on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

COMMISSION DIRECTIVE 2006/17/EC

of 8 February 2006

implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells

Supervision of tissues and cell collection procurement + donor testing

by EU transplantation authority

Manufacturer using cells imported and exported from and into the EU have to ensure compliance with the procurement and testing as defined in Directives 2004/23/EC and 2016/17/EC

Viable human cells not possible in **Medical Devices –** Regulation 2017/745, Art 1. 6.
Human cells not possible in **Cosmetics** - Regulation 1223/2009 Annex 2 substances Prohibited (416)

GMP for ATMP

- GMP mandatory for all products entering clinical trials
- GMP or equivalent quality system for Hospital Exemption
- Many trials from academic / hospital investigators

- **Specific GMP framework for ATMP**
- **GMP guide for ATIMP and ATMP**

- Other quality systems in use in tissue banks acceptable for non-manipulated cell preparations for heterologous use

Guideline on quality, non-clinical and clinical requirements for **investigational advanced therapy medicinal products** in clinical trials EMA/CAT/852602/2018 – CONSULTATION CLOSED

For **CBIMP** the following aspects should be considered as applicable:
– A clear definition of a production batch from cell sourcing to labelling of final container should be provided (i.e. size, information on intermediate cell-banking, number of cell passages/cell population doublings, pooling strategies, batch numbering system).

– a description of the manipulation steps after sourcing. This should include a description of any selection/separation equipment used. – The type of manipulation(s) required for cell processing shall be described.

– Manufacture of combined medicinal products consisting of cells and matrices/devices/scaffolds require additional consideration regarding cell-matrix/scaffold interactions and associated quality issues. Attention should be given to biodegradable materials, which may effect environmental changes (e.g. raising pH) for the cells during the manufacture.

– Information on procedures used to transport material during the manufacturing process of the product, including transportation and storage conditions and holding times, should be provided.

– Microbiological process control and quality evaluation of all cell preparations and should be thoroughly described and justified.

REMARKS ON CELL QUALTY ISSUES throughout development

- **Complexity requires product definition and a target profile**
- **The product is as good as the quality of the starting and raw materials**
- **The manufacturing process to be characterised, progressively qualified and validated at the commercial scale**
- **The analytical methods matter - qualified later validated**
- **Potency assays are essential for consistency, stability, comparability**
- **Any manipulation and changes in cell may have an impact on cell characteristics, fate, persistence, engraftment and overall efficacy**
- **Comparability should be measurable**
- **Combined / genetically modified cells - added complexity – consider the cell component *per se* and as part of the whole product**

- Salmikangas P, Menezes- Ferreira M, Reischl I et al. Manufacturing, characterization and control of cell-based medicinal products: challenging paradigms toward commercial use. ***Regen. Med.*** (2015) 10(1), 65–78

Market Authorisation Applications CAT 2009-2020

APPROVED AND LATER WITHDRAWN:

ChondroCelect - for cartilage repair, 2009 *(withdrawn 06/2016)

MACI - for cartilage repair, 2012 *(closure of EU manufacturing site 09/2014)

Provenge - advanced prostate cancer, 2013 *(withdrawn 05/2015)

Glybera - LPL deficiency, 2013 ..... withdrawn 10/2017

APPROVED :

Holoclar - limbal stem cell deficiency, 2015

Imlygic - advanced melanoma, 2015

Strimvelis - ADA-SCID, 2016

Zalmoxis - high-risk haematological malignancies (adjunctive to HSCT), 2016

Spherox - for cartilage repair < 10 cm^2, 2017

Alofisel - complex anal fistulas in Crohn's disease, 2018

Kymriah - children + adult <25yo ALL and adult DLBCL, 08/2018

Yescarta - adult DLBCL and PMBCL, 08/2018

Luxturna - children and adult retinal dystrophy biallelic RPE65 mutations, 09/2018

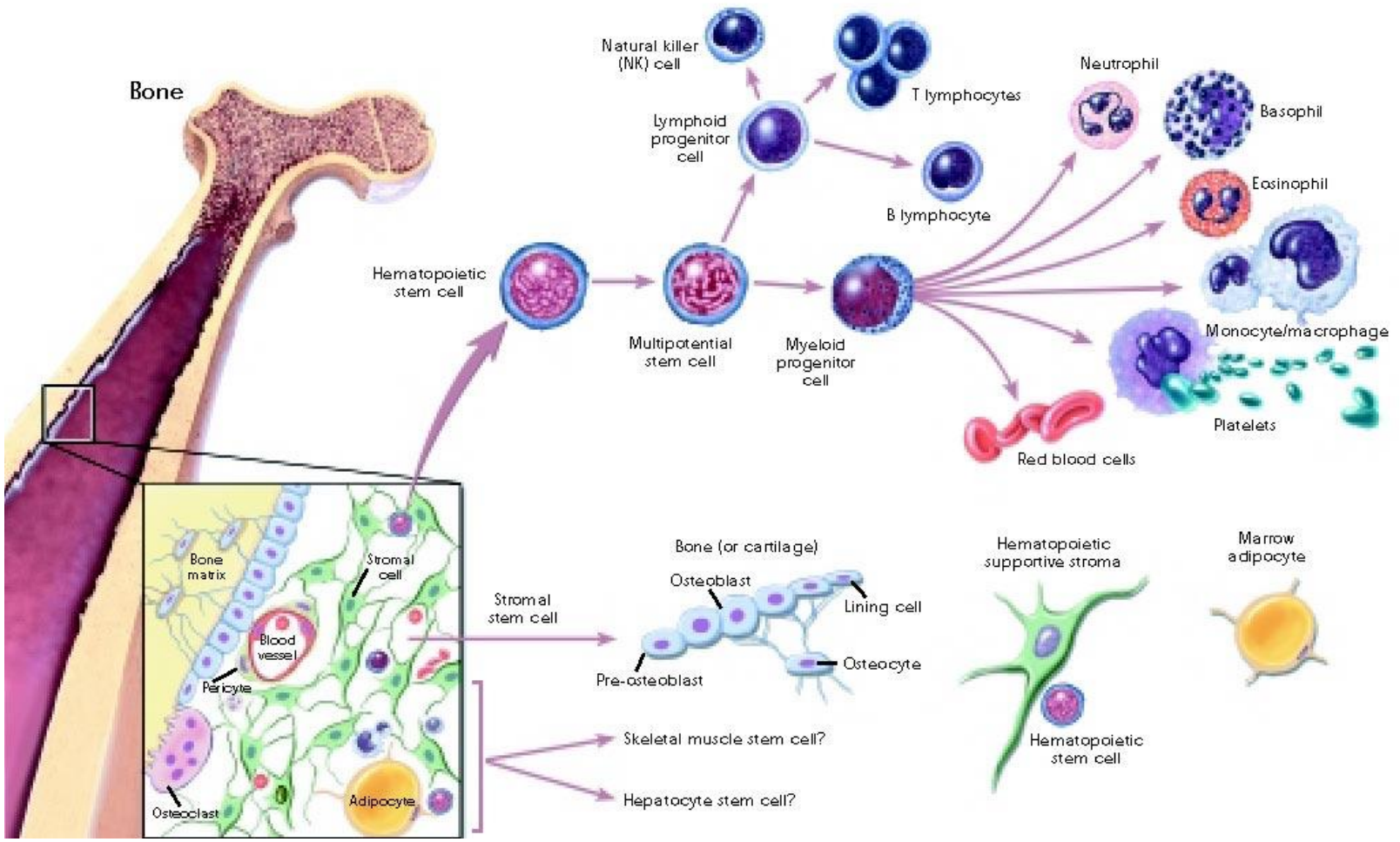
Zynteglo – β Thalassemia - non β0/β0, 03/2019

Zolgensma – spinal muscular atrophy (SMA) / bi-allelic mutation in the SMN1 gene, 03/2020

Examples of potential **risk factors** for CBMP

- Origin of cells (autologous vs allogeneic)
- Ability to proliferate and differentiate
- Ability to initiate an immune response (as target or effector)
- Level of cell manipulation (in vitro / ex vivo expansion/activation, genetic manipulation)
- manufacturing process including biologically active reagents
- Mode of administration (ex vivo perfusion, local, systemic)
- Duration of exposure (short to permanent)
- ...

Regenerative medicine – stem / stromal cells



http://stemcells.nih.gov/StaticResources/images/figure2_lg.jpg

[Intervention Review]

Stem cell treatment for acute myocardial infarction

David M Clifford[2], Sheila A Fisher[3], Susan J Brunskill[3], Carolyn Doree[3], Anthony Mathur[4], Suzanne Watt[5], Enca Martin-Rendon[1]

[1]Stem Cell Research Department, NHS Blood and Transplant, Oxford, UK. [2]Stem Cell Research Lab, Nuffield Department of Clinical Laboratory Sciences, University of Oxford, Oxford, UK. [3]Systematic Review Initiative, NHS Blood and Transplant, Oxford, UK. [4]Department of Clinical Pharmacology, William Harvey Research Institute, London, UK. [5]Stem Cell and Immunotherapy, NHS Blood and Transplant, Oxford, UK

Editorial group: Cochrane Heart Group.

Review content assessed as up-to-date: 23 July 2011.

Main results

Thirty-three RCTs (1765 participants) were eligible for inclusion. Stem/progenitor cell treatment was not associated with statistically significant changes in the incidence of mortality (RR 0.70, 95% CI 0.40 to 1.21) or morbidity (the latter measured by re-infarction, hospital re-admission, restenosis and target vessel revascularisation) A considerably high degree of heterogeneity has been observed among the included trials. In short-term follow up, stem cell treatment was observed to improve left ventricular ejection fraction (LVEF)

Authors' conclusions

Despite the high degree of heterogeneity observed, the results of this systematic review suggest that moderate improvement in global heart function is significant and sustained long-term. However, because mortality rates after successful revascularization of the culprit arteries are very low, larger number of participants would be required to assess the full clinical effect of this treatment. Standardisation of methodology, cell dosing and cell product formulation, timing of cell transplantation and patient selection may also be required in order to reduce the substantial heterogeneity observed among the included studies.

Cell product definition
Can conclusions be drawn from experience?

- Cardiomyocytes progenitor ? Endothelial progenitor ? Both ?
- Progenitor cells vs cardiomyocytes – differentiation stage ?
- Autologous vs allogeneic- Immunoregulatory properties ?
- Different Sources of progenitor cells – different clinical outcome?
- - Bone marrow – " gold standard" ?
- - Adipocytes – Peripheral blood – cord blood – placenta ?
- - Characterisation beyond ISCT ?

European Journal of Heart Failure (2016) **18**, 133–141
doi:10.1002/ejhf.422

REVIEW

Cell-based therapies for cardiac repair: a meeting report on scientific observations and European regulatory viewpoints

Martina Schüssler-Lenz[1,2†*], Claire Beuneu[1,3†], Margarida Menezes-Ferreira[1,4†], Veronika Jekerle[5†], Jozef Bartunek[6], Steven Chamuleau[7], Patrick Celis[1,5], Pieter Doevendans[1,8], Maura O'Donovan[1,9], Jonathan Hill[10], Marit Hystad[1,11], Stefan Jovinge[12], Ján Kyselovič[1,13], Metoda Lipnik-Stangelj[1,14], Romaldas Maciulaitis[1,15], Krishna Prasad[16,17], Anthony Samuel[1,18], Olli Tenhunen[1,19], Torsten Tonn[20], Giuseppe Rosano[17,21], Andreas Zeiher[22], and Paula Salmikangas[1,19†]

Table 1. Summary of criteria to identify MSC

1	Adherence to plastic in standard culture conditions		
2	Phenotype	Positive (≥ 95% +)	Negative (≤ 2% +)
		CD105	CD45
		CD73	CD34
		CD90	CD14 or CD11b
			CD79α or CD19
			HLA-DR
3	*In vitro* differentiation: osteoblasts, adipocytes, chondroblasts (demonstrated by staining of *in vitro* cell culture)		

Q&A minimally manipulated cells = cardiac repair

Risk Risk factor / Quality	Tumour formation	Unwanted tissue formation	Unwanted immunogenicity	Disease transmission[3]	Treatment failure Lack of efficacy	Toxicity Safety issues
Cell starting material	Autologous cells, not substantially manipulated, are expected to represent no risk for tumourigenicity		Autologous cells are not expected to trigger immune reactions	For autologous product disease transmission to the recipient is not an issue	Quality and consistency of cells has to be ensured; harmonized procedures for procurement, handling, transport. Acceptance criteria for volume and cell numbers	In principle autologous cells are not expected to be associated with toxicity, but altered environment for cells has to be considered
Aspects of the manufacturing process and level of cell manipulation	Autologous cells, not substantially manipulated, are expected to represent no risk for tumourigenicity				The process should not introduce additional variability; the consistency needs to be ensured. Conditions for manipulation/handling before final product administration (including transport) need to be defined.	Safety of the product could be affected by the potential process-related impurities and microbiological contamination
Cell population, heterogeneity & differentiation potential	Autologous cells, not substantially manipulated, are expected to represent no risk for tumourigenicity		Autologous cells are not expected to trigger immune reactions	For autologous product disease transmission to the recipient is not an issue;	Quality and consistency of cells/mixture has to be ensured and monitored; Though the manufacturing is very limited, the cell selection process has to be validated	In principle autologous cells are not expected to be associated with toxicity, but altered environment for cells has to be considered
Structural / functional integrity					Potency assay needs to be established; functional & viability markers	

Q&A for minimally manipulated – EMA July 2017

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/07/WC500230417.pdf

Expansion / modification
– variable complexity / risk evaluation / ipc

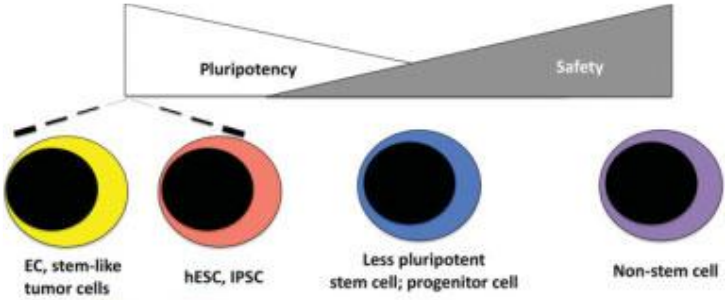
- **Always considered substantial manipulation**
- **Biological raw materials – Ph.Eur. text**
- **Culture conditions - Development studies provide relevant information on conditions for cell growth**
- **In-process controls – pH, temperature, oxigen, time, critical atributes, safety**
- **Extensive process characterisation to support target phenotypic and genotypic profile**
- **Population doubling time based on exponential growth phase + passage number - cumulative population doublings** – *dedifferentiation* – *senescence* – *apoptosis* – *genetic stability*

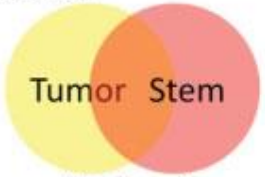
Alofisel
expanded adipose stem cells - eASC

- Darvadstrocel
- Expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue
- 5 million cells/mL suspension for injection
- Authorised: 23 March 2018
- **Approved indication**: treatment of complex perianal fistulas in adult patients
- Marketing Authorisation Holder: Takeda Pharma A/S
  - original MAH: Tigenix

- EPAR: https://www.ema.europa.eu/en/medicines/human/EPAR/alofisel

Tumorigenicity – as quality control





Venn diagram of gene expression overlap between stem and tumor cells

EMBRYONIC STEM CELLS/INDUCED PLURIPOTENT STEM CELLS

Deconstructing Stem Cell Tumorigenicity: A Roadmap to Safe Regenerative Medicine

PAUL S. KNOEPFLER[a,b]

STEM CELLS 2009;27:1050–1056

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Reflection·paper·on·stem·cell-based·medicinal·products¶
16·March·2010¶

2.5.4. Tumourigenicity and genomic stability

Undifferentiated and proliferative / pluripotent cells namely iPSCs and hESCs have a relatively high potential risk of tumour formation, which should be carefully addressed during product development. The presence of proliferative and pluripotent cells tolerated in the final product should be limited and justified. Therefore it is essential that stem cell preparations undergoing extensive *in vitro* manipulation such as prolonged cell culture, as well as those derived from hESCs or iPSCs are evaluated for both their tumourigenicity and chromosomal stability before their initial clinical use.

Cytogenetic analysis, telomerase activity, proliferative capacity and senescence could be of relevance.

Risk of Tumourigenicity – Alofisel (eASC)

QUALITY LEVEL

- Genetic stability of AS – release specification

(QUALITY) NON-CLINICAL LEVEL in vitro - eASC expansion process studied beyond clinical population doublings

- negligible telomerase activity
- low c-myc expression with no increase in telomerase activity or c-myc expression during the process of expansion
- eASC preparations showed no anchorage-independent growth in the soft-agar test.
- normal male or female diploid karyotypes

NON-CLINICAL LEVEL in vivo -

– human cells in animal model no tumour formation observed

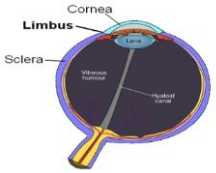
CLINICAL LEVEL

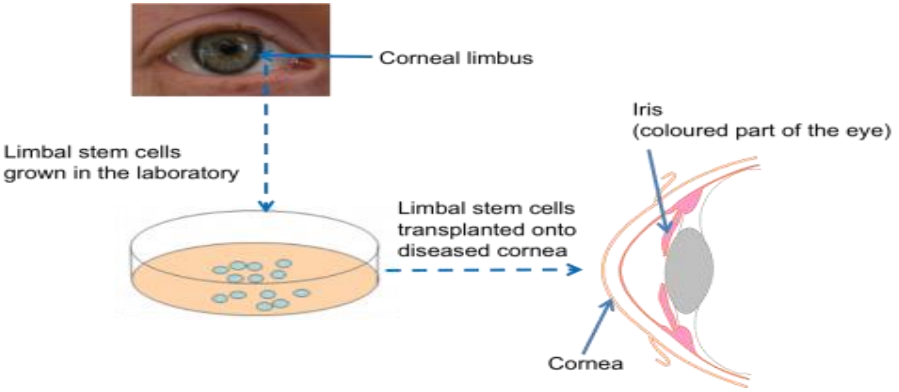
- Ectopic tissue formation and tumourigenicity included in the RMP to be followed up to 5 yrs with the agreed PASS

5th ATMP authorised in the EU – March 2015

HOLOCLAR

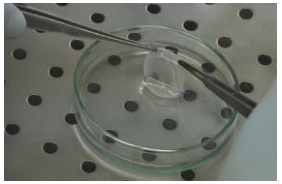
HOLOSTEM TERAPIE AVANZATE





transparent circular sheet of 300,000 to 1,200,000 viable autologous human corneal epithelial cells (79,000-316,000 cells/cm2)

expanded in cell culture and including on average 3.5% (0.4% to 10%) limbal stem cells in addition to stem cell-derived transient amplifying and terminally differentiated cells.



Questions

potency, feeder cell safety, risk mitigation for safety (shelve life 36h), stability, container closure transport stability.

Release based on macroscopic and microscopic appearance and results of intermediate control testing.

Tumorigenicity at non-clinical (cells + 3T3 J2 feeder cells)
– Karyotype, soft agar, growth factor dependent

CELL & GENE THERAPY INSIGHTS

NAVIGATING THE GLOBAL REGULATORY LANDSCAPE

SPOTLIGHT

REVIEW

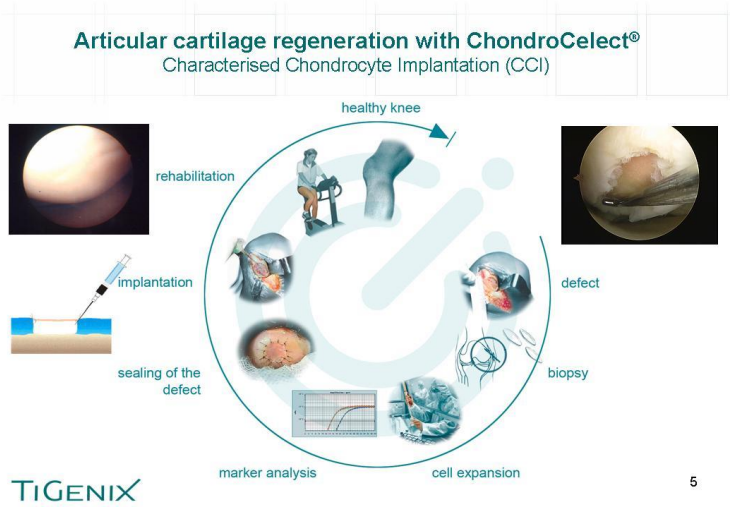
Regulatory viewpoints on the development of advanced stem cell–based medicinal products in light of the first EU-approved stem cell product

Egbert Flory, Paolo Gasparini, Veronika Jekerle, Tiina Palomäki, Patrick Celis, Tomáš Boráň, James W McBlane, John Joseph Borg, Jan Kyselovic, Metoda Lipnik-Stangelj, Toivo Maimets, Margarida Menezes-Ferreira, Guido Pante, Stefanie Prilla, Una Riekstina, Christian K Schneider, Asterios Tsiftsoglou and Paula Salmikangas

Chondrocytes

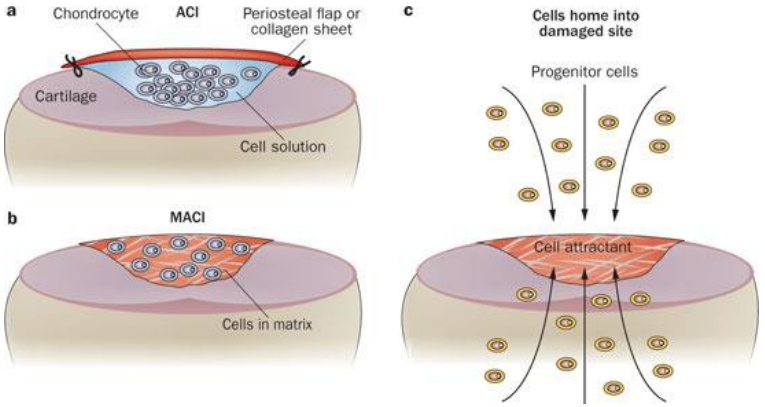
ChondroCelect ®- 1st generation = cell supension - < 5 cm2

2009 - withdrawn



MACI ®- 2nd generation = cell in matrix - 3- 20 cm2

2012 - withdrawn



Spherox®- 2nd generation = cell spheres - < 10 cm2

2017

London, 08 April 2010
EMA/CAT/CPWP/568181/2009
Committee For Advanced Therapies (CAT)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Reflection paper on *in-vitro* cultured chondrocyte containing products for cartilage repair of the knee

Final

Adoption by CAT	16 April 2010

http://www.biotechnologie.de/bio/generator/

CONSIDERATIONS ON QUALITY DATA –
Starting material - biopsy
Manufacturing process – dedifferentiation – fibroblast like / contamination
Potency – hyaline cartilage formation
Biocompatibility with all materials in contact with the cells

CONSIDERATIONS ON NON-CLINICAL DATA
In vitro and small species (rodents / rabbits) for initial proof-of-concept ECFA (ectopic cartilage forming)
Large species (goat, horse, sheep) for pivotal study - to validate MRI
Safety end-points on POC studies

CONSIDERATIONS ON CLINICAL DATA
Pharmacology – Macroscopic, histological, MRI assessment ok for pharmacodynamic
Exploratory trials - Dose reflecting cell engraftment (minimum nº of cells/cm2
Confirmatory trials – primary and secondary end-point s - (eg KOOS)
Trial design and clinical safety

KYMRIAH – EPAR = YESCARTA EPAR

Availability of tocilizumab and site qualification

To minimise the risks associated with the treatment of KYMRIAH, the MAH must ensure that hospitals and their associated centres that dispense KYMRIAH are specially qualified in accordance with the agreed control distribution program.

The MAH must ensure on-site, immediate access to 4 doses of tocilizumab for each patient as CRS management medication prior to treating patients.

KYMRIAH will only be supplied to hospitals and associated centres that are qualified and only if the healthcare professionals involved in the treatment of a patient have completed the educational program.

The availability of tocilizumab at all hospitals and associated centres must be ensured by the MAH until an authorised treatment for CRS is available in the EU.

- Automated manufacturing
- Bed side / descentralised manufacturing
- Exceptional OOS administration

Guidelines on GMP for ATMPs - Section 17
Automated manufacturing

- CE mark not sufficient
- Qualification DQ / IQ /OQ / PQ as ATMP-GMP
- Training / maintenance
- Aseptic process – integrity + cleaning validation
- Closed system in controlled area grade D
  - except single very short procedure at operating theatre clinically justified
- Process validation reduced if used as recommended by the device manufacturer
- Start / stop / critical points defined and controlled
- Batch release - certified by QP
  - except QP release for decentralised manufacturing as defined

Guidelines on GMP for ATMPs - Section 11.3.3.

- **Batch release process in cases of decentralised manufacturing**

A "central site", which should be established in the EU, should be identified. The central site is responsible for the oversight of the decentralised sites.

To this end, the **central site assumes**, as a minimum, the following tasks:

(i) ensuring that those involved in the batch certification and release process are adequately qualified and trained for their tasks, and

(ii) performing audits to confirm that the batch certification and release process (as descripted in SOP) is complied with.

Guidelines on GMP for ATMPs - Section 11.5

- **Administration of out of specification products**

Questions and answers on the use of out-of-specification batches of authorised cell/tissue-based advanced therapy medicinal products

https://www.ema.europa.eu/en/documents/other/questions-answers-use-out-specification-batches-authorised-cell-tissue-based-advanced-therapy_en.pdf

In exceptional circumstances only
the administration of a cell/tissue-based ATMP that does not comply with the specifications set out in the marketing authorisation may be considered to avoid an immediate significant hazard to the patient.

The MAH/manufacturer/importer should immediately inform the treating physician and to conduct an evaluation of risks
– Physician confirms the need
– Patients may be informed but they are not part of the decision

The MAH/manufacturer/importer should inform EMA within 48h after administration that a oos batch was used

Pharmacovigilance reporting obligations or specific additional obligations to follow-up patients treated with the ATMP (e.g. registry) continue to apply in respect of OOS batches

Common issues with CBMP

PRODUCT DEFINITION – COMPOSITION / MODE OF ACTION /POTENCY

CELL PROCUREMENT AND DONOR TESTING -

CELL EXPANSION – POPULATION DOUBLINGS / GENETIC STABILITY / DEDIFFERENTIATION

CHANGES IN DONOR / PROCESS – COMPARABILITY

SHORT SHELF LIFE AND STAGGERED RELEASE

LOGISTICS / TRANSPORT / ACCEPTANCE CRITERIA

PREPARATION / RECONSTITUTION /RELEASE AT BEDSIDE


Thank you!