

ATMP

Tübingen 15th July 2019

Udo Schwuléra, Ph.D.

Curriculum vitae

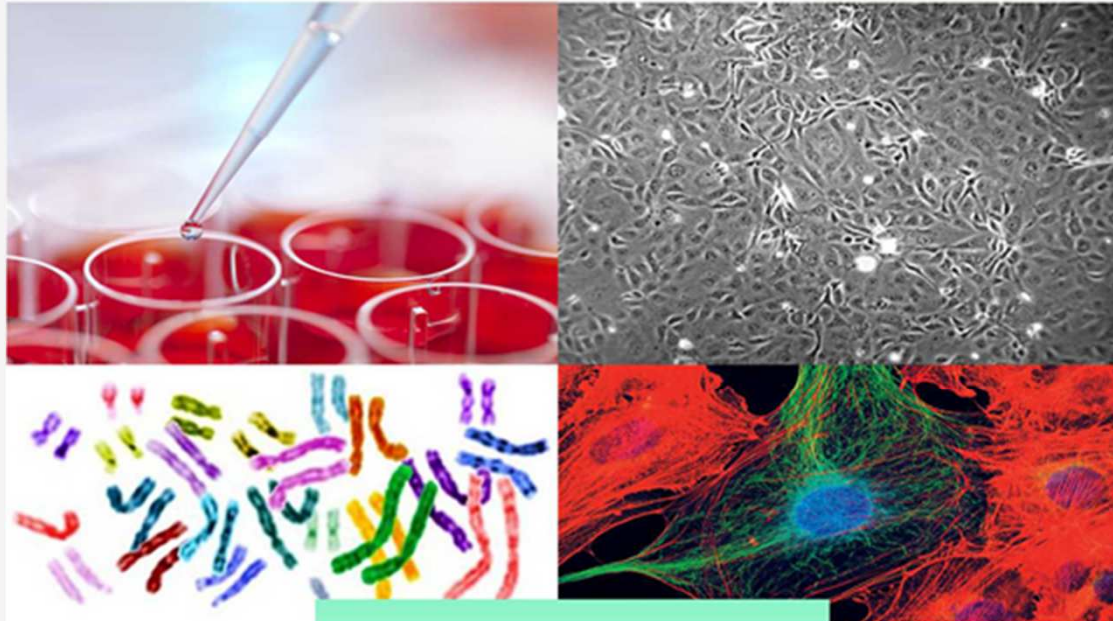


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<i>Study</i>	Study of Biology with Focus on Microbiology and Biochemistry and Promotion at J.W. Goethe University, Frankfurt a./M.
<i>Curriculum Vitae</i>	• 20 Years in Pharmaceutical Industry • Head of Production in Stem Cell Laboratory • Head of Production in University Pharmacy • QC- Manager Umbilical Cord Blood Bank • Head of Quality Control of Apheresis Station • Cleanroom Expert • GMP-Consultant • Qualified Person at several Companies
<i>GemLog mbH</i>	Foundation of GemLog mbH in 2001 Managing Director

Advanced Therapy Medicinal Products

ATMP

**New Diagnose
of disease**



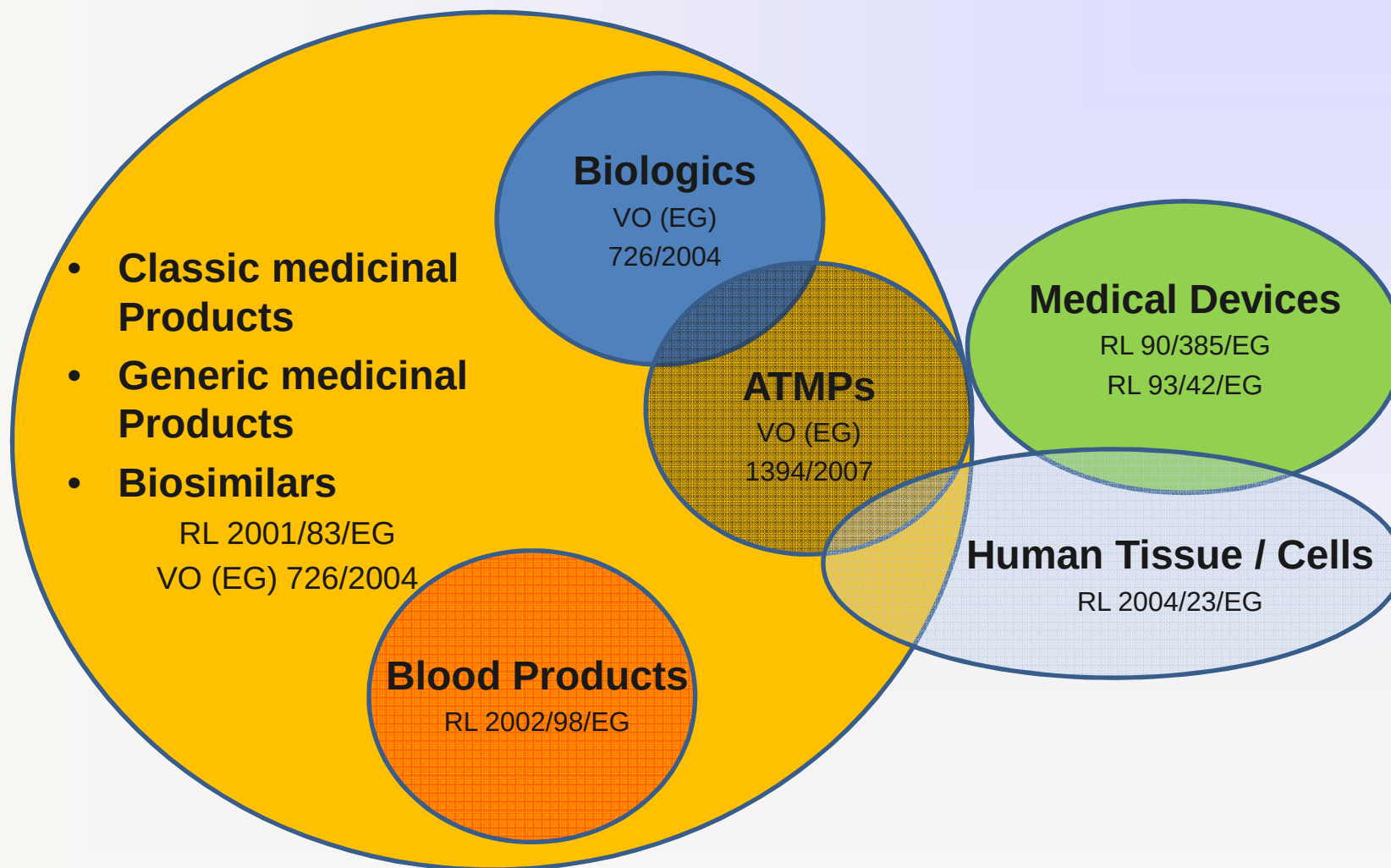
**Tissue
Engineering**

**Gene
Therapy**

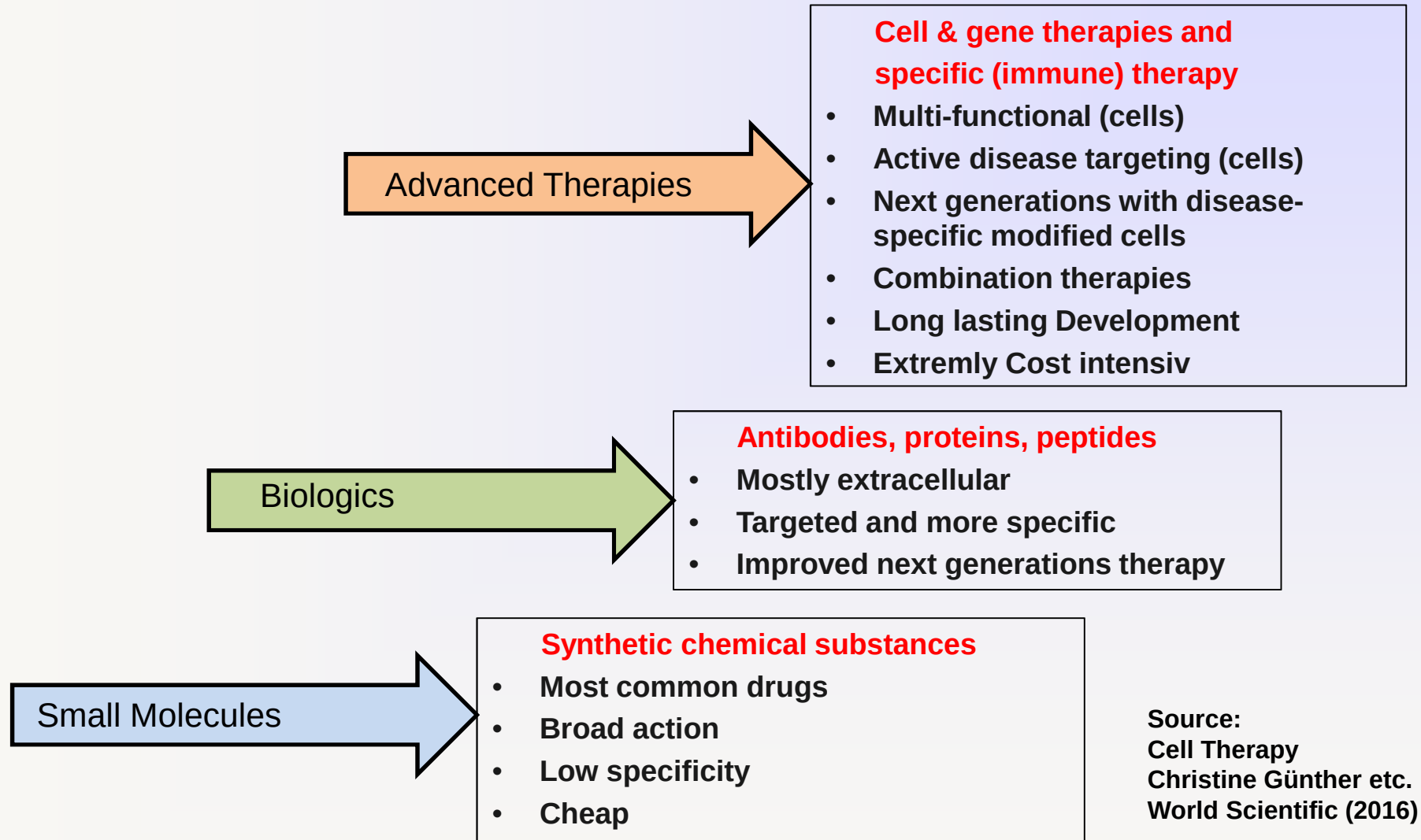
**Somatic
Cell
Therapy**

Areas of ATMPs

Overview of Medicinal Products



Overview Medicinal Products



“There are no old roads to new directions”

(Boston Consulting Group)

Aim of Medicinal Drug Laws



- ☐ **Increase security in the supply of medicinal products and medicinal devices to the public in respect of:**
 - ☐ **Quality**
 - ☐ **Efficacy**
 - ☐ **Safety**

(Preambles German Drug Law)

Legal Basis

EU-Directive → Member State Regulation and national laws



- **Commision Directive (EC) 2001/83:** Somatic Cell Therapy, Gene Therapy and diagnosis of disease
- **Commision Directive (EC) 1394/2007:** ATMP and Tissue engineered products
- **Commision Directive (EC) 2009/120:** Combination Products
- **Commision Directive (EC) 93/42:** Medical Device Directive
- **Commision Directive (EC) 2004/23:** Tissue Directive
- **Commision Directive (EC) 2006/17:** Tissue Directive
- **Commision Directive (EC) 2006/86:** Tissue Directive
- **Commision Directive (EC) Reg 726/2004:** Centralised Procedure for Medicinal Products
- **Commision Directive (EC) 90/385/EEC:** Active implantable medical devices

New Regulations

- **Centralized marketing authorization procedure**
- **New Committee for Advanced Therapies (CAT)**
- **Technical requirements adapted to the particular characteristics of these products**
- **Special incentives for small and medium-sized enterprises**

Advanced Therapies - Definition



Article 2

Definitions

1. In addition to the definitions laid down in Article 1 of Directive 2001/S3/EC and in Article 3, points (a) to (1) and (o) to (q) of Directive 2004/23/EC, the following definitions shall apply for the purposes of this Regulation:

(a) Advanced therapy medicinal products means any of the following medicinal products for human use:

- a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,
- a somatic cell therapy medicinal product as defined in Part V of Annex I to Directive 2001/83/EC,
- a tissue engineered product as defined in point (b)

10.12.2007 EN Official Journal of the European Union L 324/121	
REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance)	
THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,	been defined in Annex I to Directive 2001/83/EC, but a legal definition of tissue engineered products remains to be laid down. When products are based on viable cells or tissues, the pharmacological, immunological or metabolic action should be considered as the principal mode of action. It should also be clarified that products which do not meet the definition of a medicinal product, such as products made exclusively of non-viable materials which act primarily by physical means, cannot by definition be advanced therapy medicinal products.
Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,	
Having regard to the proposal from the Commission,	
Having regard to the Opinion of the European Economic and Social Committee ⁽¹⁾ ,	
After consulting the Committee of the Regions,	(4) According to Directive 2001/83/EC and the Medical Device Directives the basis for deciding which regulatory regime is applicable to combinations of medicinal products and medical devices is the principal mode of action of the combination product. However, the complexity of combined advanced therapy medicinal products containing viable cells or tissues requires a specific approach. For these products, whatever the role of the medical device, the pharmacological, immunological or metabolic action of these cells or tissues should be considered to be the principal mode of action of the combination product. Such combination products should always be regulated under this Regulation.
Acting in accordance with the procedure laid down in Article 251 of the Treaty ⁽²⁾ ,	
Whereas:	
(1) New scientific progress in cellular and molecular biotechnology has led to the development of advanced therapies, such as gene therapy, somatic cell therapy, and tissue engineering. This nascent field of biomedicine offers new opportunities for the treatment of diseases and dysfunctions of the human body.	(5) Because of the novelty, complexity and technical specificity of advanced therapy medicinal products, specially tai-

Advanced Therapies Principles



2.

Where a product contains viable cells or tissues, the pharmaceutical, immunological or metabolic action of those cells or tissues shall be considered as the principal mode of action of the product.

3.

An advanced therapy medicinal product containing both autologous (from the patient himself) and allogeneic (coming from another human being) cells or tissues shall be considered to be for allogeneic use. Use of xenogenetic cells possible.

4.

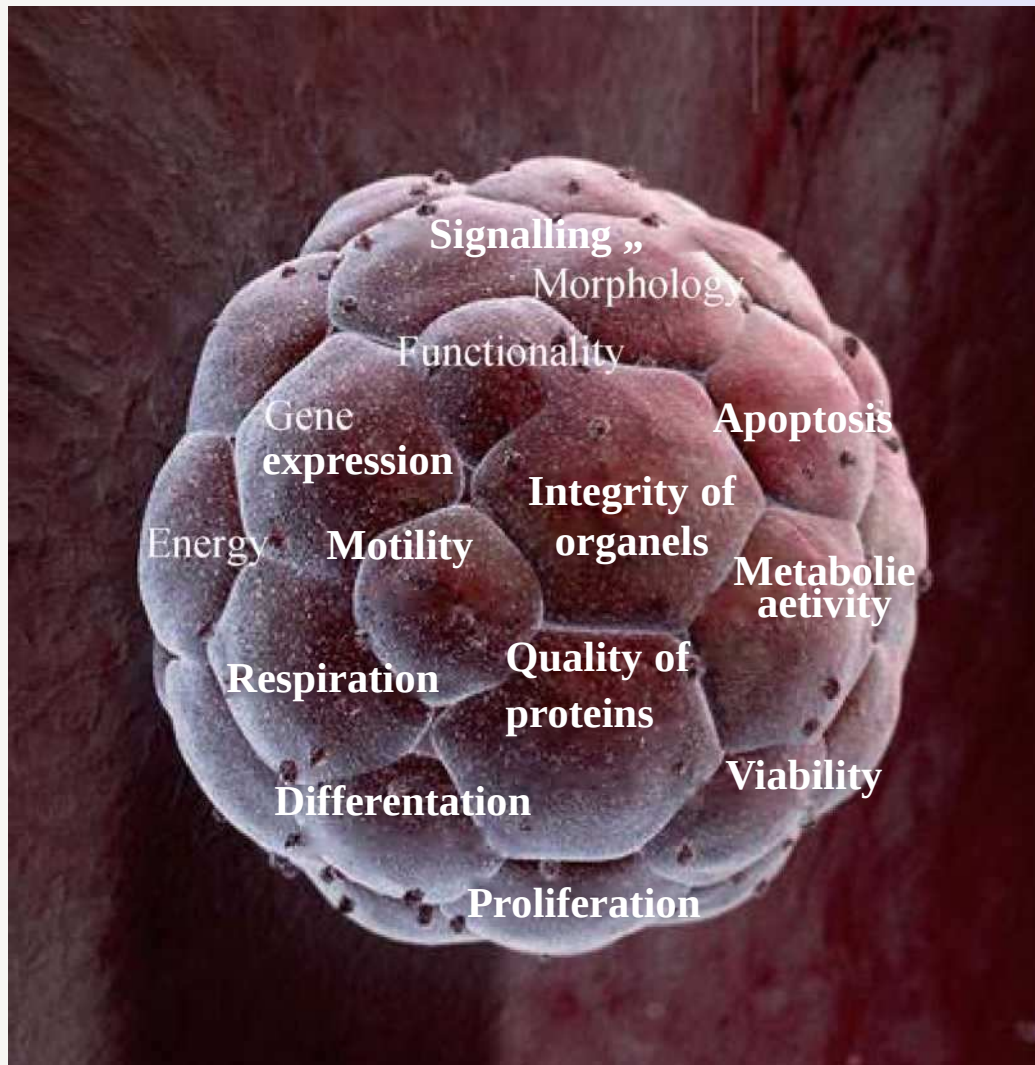
A product which may fall within the definition of a tissue engineered product and within the definition of a somatic cell therapy medicinal product shall be considered as a tissue engineered product.

5. A product which may fall within the definition of:

- a somatic cell therapy medicinal product or a tissue engineered product, and**
- a gene therapy medicinal product,**

shall be considered as a gene therapy medicinal product.

Critical parameters of cells?



- Manufacturing aspects & quality control
- Species specificities on molecular and tissue level
- Biodistribution/engraftment
- Mode of action
- Dosing

(Source: Paula Salmikangas 2010)

Innovative Therapies (i.e. Cell Therapies)



- **New class of therapeutics**
- **Limited or no prior experience**
- **Longer development cycles**
- **Higher capital intensity**
- **Convincing required! (does not fit with classic Pharma-Business)**

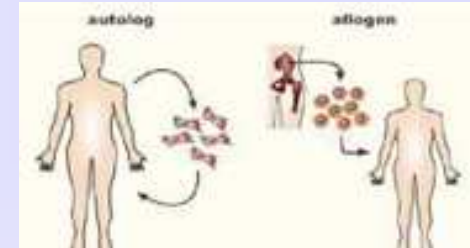
Examples of Advanced therapy medicinal products



- **Gene therapy medicinal products**
- **Somatic cell therapy medicinal products**
- **Specific Immunotherapy**
- **Tissue engineered products**
- **Regenerative Medicine**
- **Combined Advanced Therapy Medicinal Products**
(f.i. Medicinal Product and Medicinal Device)
- **Transplantation of Langerhans Pankreas Cells**
- **Stem Cell Transplantation**

Further Problems of ATMP s

Material



- Parenteralia
- Living cells: no sterilization step possible, aseptic manufacture
- Allogeneic, autologous and xenogeneic products
- Cryoconserved or „fresh“ products
- Genetically modified and non-modified products



Time



Challenge concerning Transport und Logistics: Stability of Cells

Short Stability of Living Cells:

- Traffic jam
- Human failure
- Eyjafjalla
(not expected events)
- Problems with customs
- No X-rays
- Temperature control



Hospital Exemption

Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on:

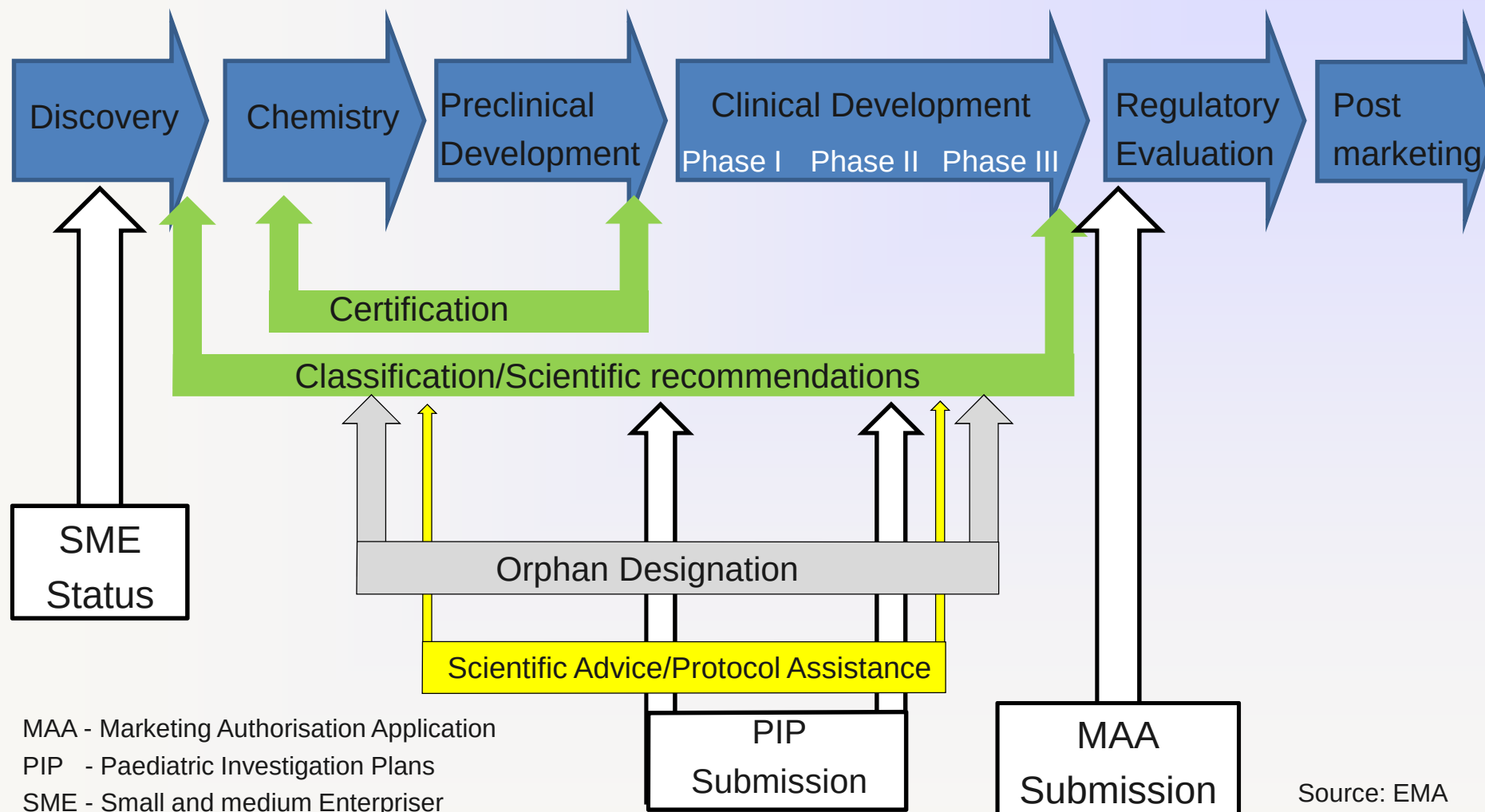
- **A non-routine basis**
- **Manufactured at Point of Care**
- **According to specific descriptions**
- **Not substantial manipulated**
- **And used within the same Member State**
- **In a hospitals or University Center**
- **Under the exclusive professional responsibility of a medical practioner**
- **Individual medical prescription**
- **for an individual patient (personalized medication)**

Hospital Exemption

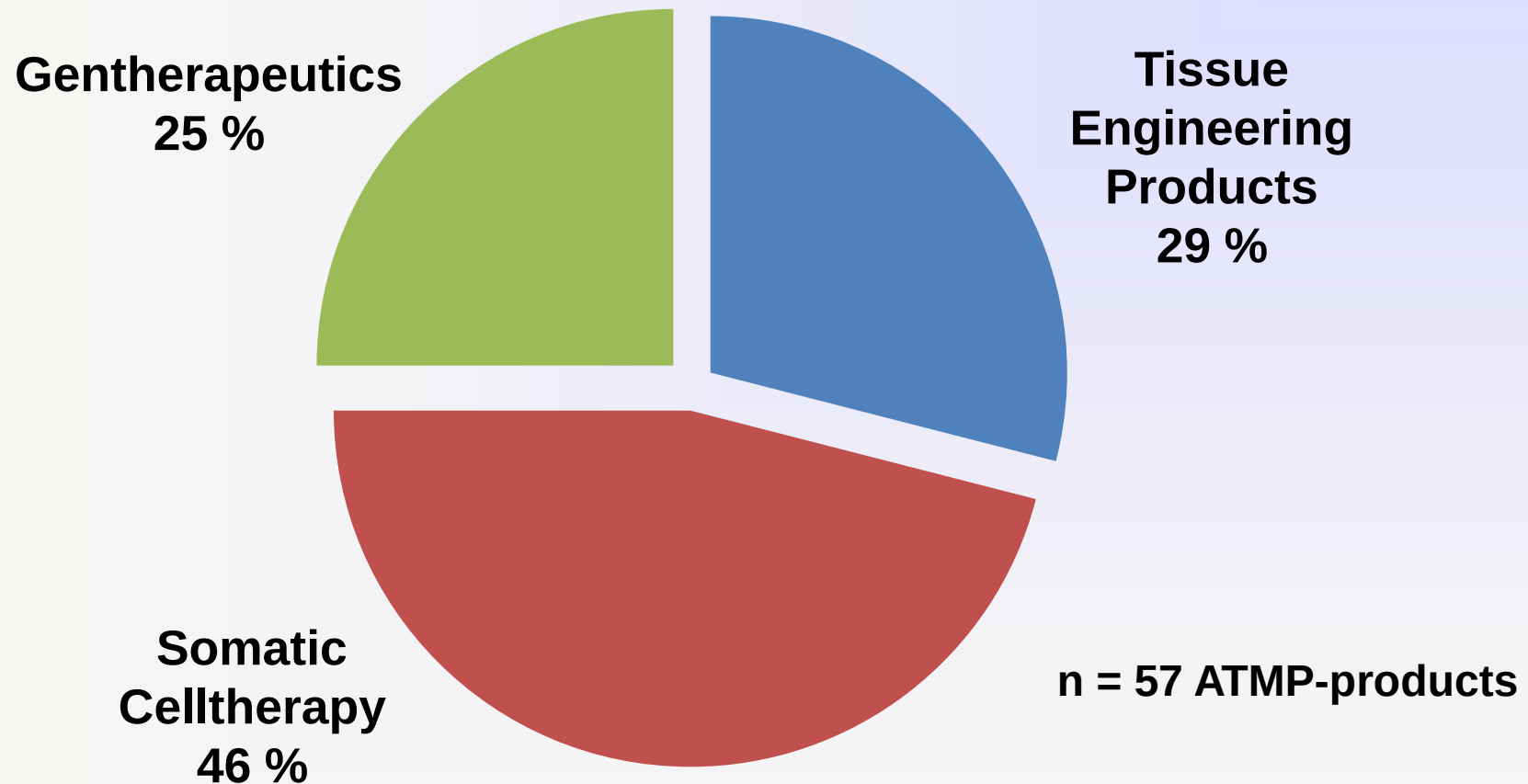
Manipulations not considered to be substantial:

- cutting
- grinding
- shaping
- centrifugation
- soaking in antibiotic or antimicrobial solutions
- sterilisation
- irradiation
- Cell separation
- Concentration or purification
- filtering
- lyophilization
- freezing
- cryopreservation
- vitrification

ATMP Drug Development



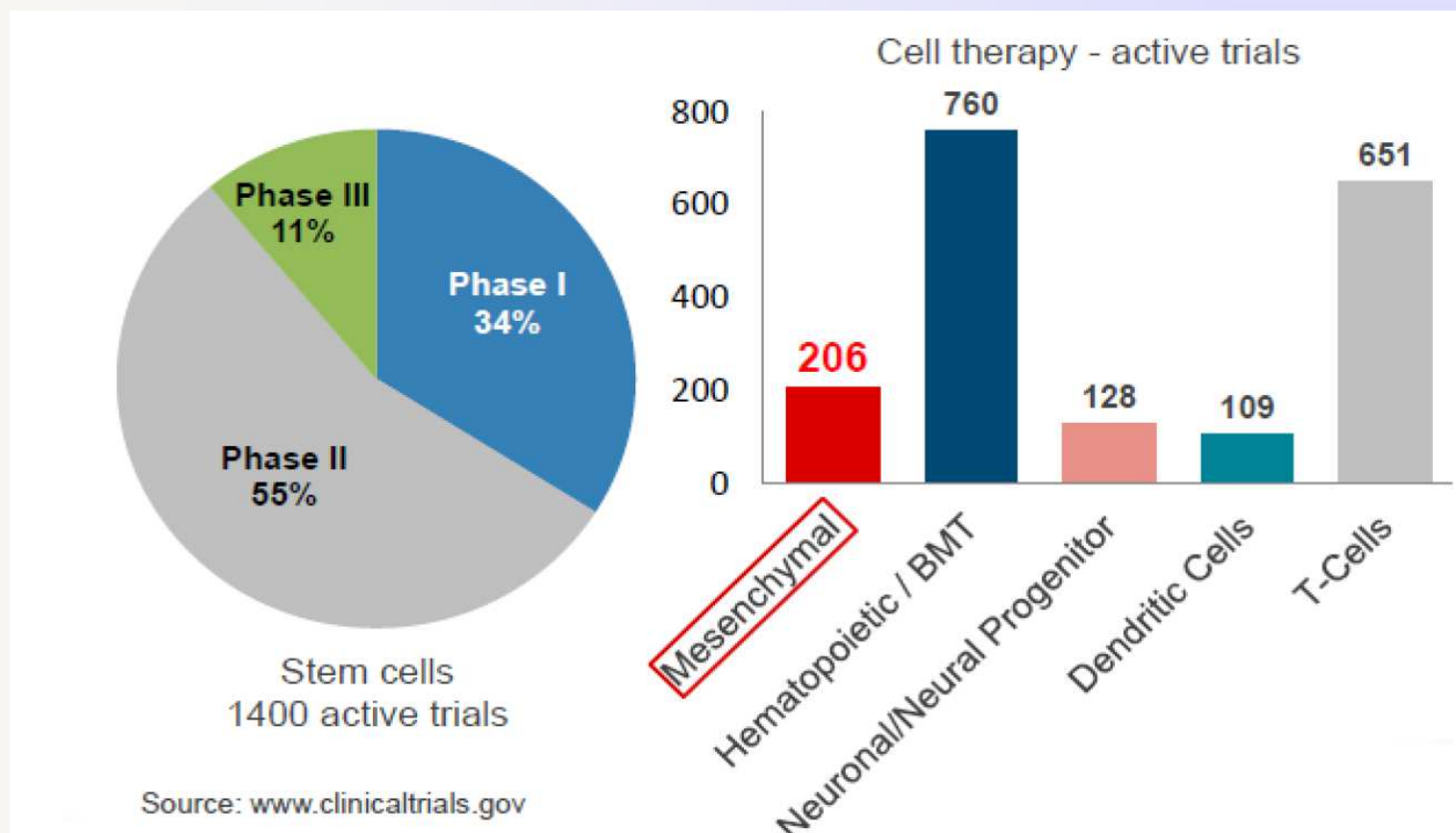
ATMPs developed by small pharmaceutical companies in 2010



Source: SME - office EMA

ATMPs development 2016

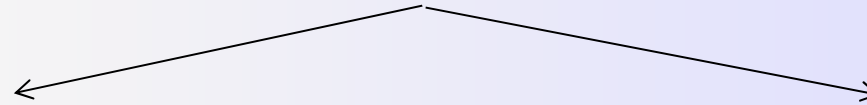
Most products are in early clinical phases



Cell-based Medicinal Products (autologous, allogeneic, xenogeneic)



- **Somatic Cell Therapy Products**
 - to treat, prevent or diagnose a disease through pharmacological, immunological or metabolic action of the cells
- **Tissue Engineering Products**
 - contains or consists of engineered cells or tissues
 - administered to human beings with a view to regenerating, repairing or replacing a human tissue



Regenerative Aspect:

Stem cell-based Transplantation

- autologous blood stem cells
(Neuroregeneration, heart attack, ...)
- allogenic blood stem cells
(Leukemia, other hematopoietic disease, Immundefects,)
- mesenchymale stem cells
(Bone Regeneration, Immunomodulation, ...)

NK – Natural Killer-Cell

CTL – Cytotoxic T-Lymphocyte

Immunological Aspect:

Immuno cell-based

- modified Stemcell-Preparation
- Donor Lymphocyte, (DLI)
- specific Cell Therapy
(virus-specific T-Cells)
- NK-, CTL-Cell Therapy
(Tumor Vaccination)

Cell Therapy Medicinal Products: Examples

- **Liver repair**

Allogenic liver cell suspension for treatment of acute sepsis or inherited metabolic liver failure

- **Type I Diabetes**

Allogenic pancreatic islet cell fraction to restore insulin production

- **Skin repair**

Autologous adipose-derived stem cells for treatment of burn- patients or anal fistula

- **Immunotherapeutics**

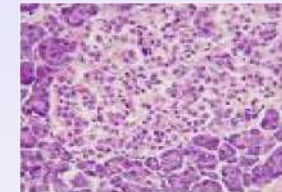
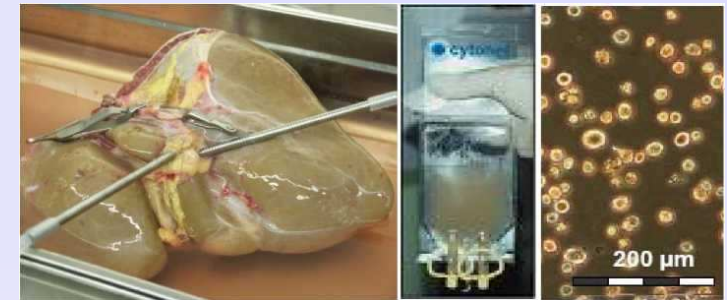
CTLs or NK cell transfer for adoptive immunotherapy

- **Cell-based therapeutic Vaccines**

Peptide-loaded DC used as tumor vaccines to induce immunity towards tumor-associated antigens

- **Haematopoietic stem cells**

HSC of different origin, e.g. for haematopoietic indications like Leukemia



DC - Dendritic Cells

Human Tissue Engineered Products: Examples

- **Cartilage repair**

Autologous chondrocyte transplantation (ACT)
1st & 2nd generation products

- **Skin regeneration**

Different skin cells (keratinocytes, fibroblasts) in combination with a sheet-like matrices/scaffolds Acute wounds, diabetic foot skin ulcers

- **Bone regeneration**

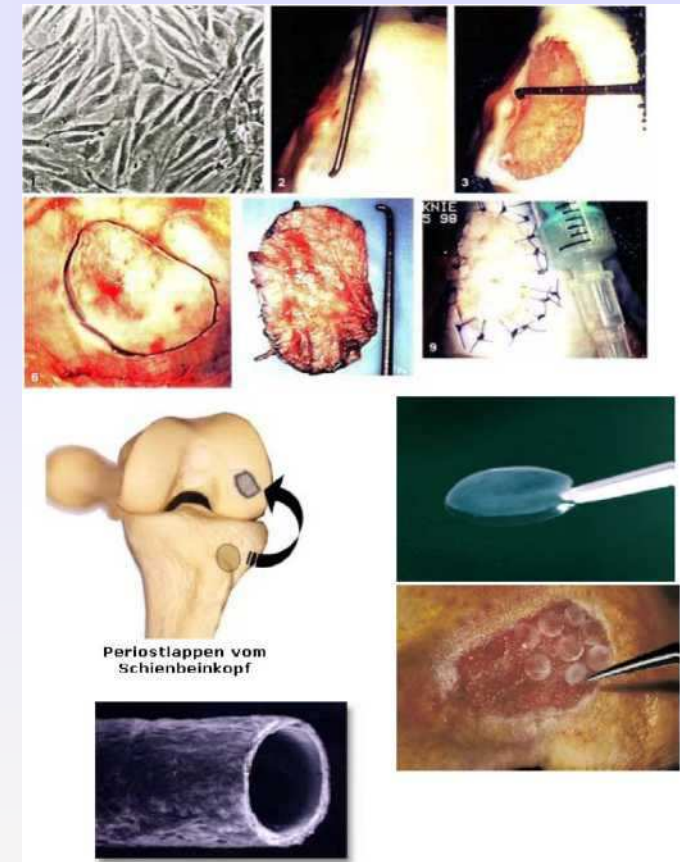
Osteoblasts or bone-marrow-derived stem cells combined with ceramic-based scaffolds or biomaterials

- **Cardiovascular regeneration**

Hematopoietic stem cells for heart muscle regeneration
Engineered autologous/allogeneic blood vessels or heart valves

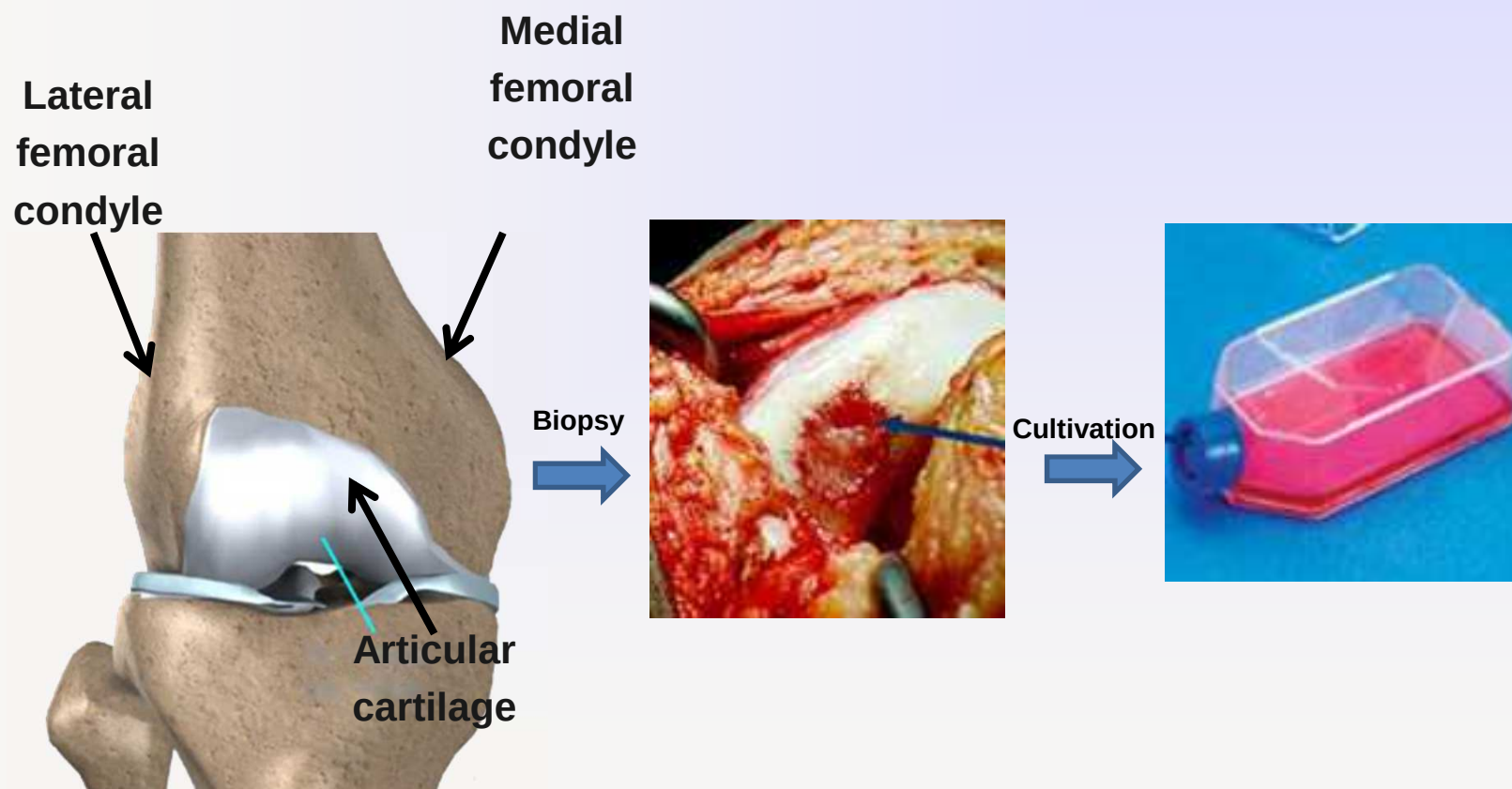
- **Complete organ engineering**

Artificial lymph node
Artificial liver

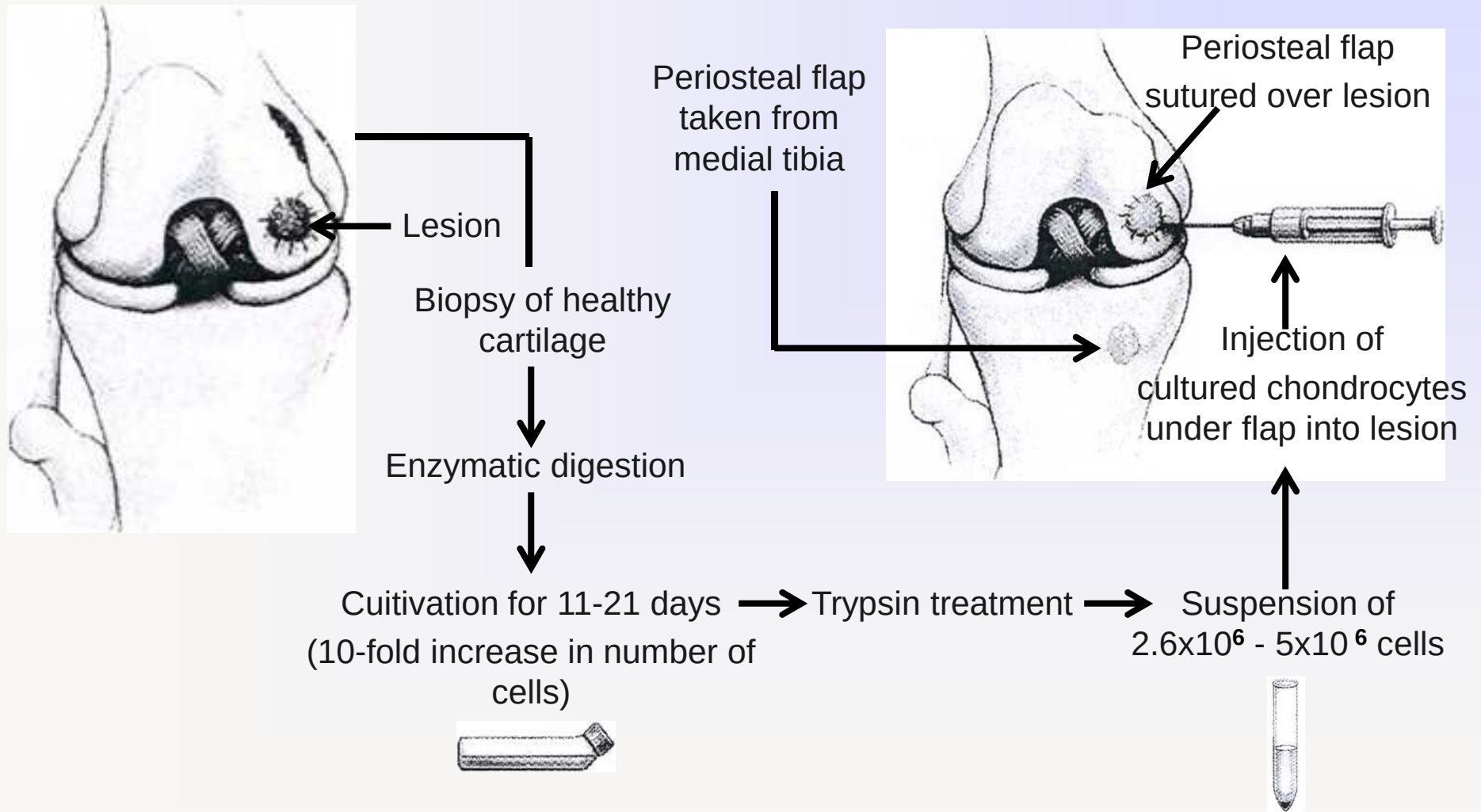


Chondrocytes

Autologous chondrocytes expanded in vitro for repairing defects in the cartilage of the knee caused by trauma



Autologous Chondrocyte Transplantation



ATMPs: State of the Art

Centralized Marketing Application



Initial Evaluation of Marketing Authorisation Applications (MAA) for ATMP								
	2009	2010	2011	2012	2013	2014	2015	Total
Submitted MAAs	3	1	2	3	2	2	0	13
Positive draft Opinion	1	0	1 ¹	1 ¹	2	1	0	6 Corresponding to 5 ATMPs
Withdrawals	1	1	0	0	2	0	0	4
Ongoing MAAs								4

¹ Same product (Glybera)

Scientific advice on Development of advanced therapy medicinal products								
	2009	2010	2011	2012	2013	2014	2015	Total
Submitted	22	19	12	17	20	28	11	132
Adopted	12	27	12	14	23	29	13	129

Source:
EMA 2016

Overview of Marketing Authorization of ATMPs until 2014



➡ Only 4 ATMPs have been granted a marketing authorization

- ☐ **ChondroCelect**
(autologous chondrocyte Transplantation)
- ☐ **Glybera**
(compensate for lipoprotein lipase deficiency by gene therapy)
- ☐ **Maci**
(matrix – induced autologous cultured chondrocytes)
- ☐ **Holoclar**
(Treatment of severe limbal stem-cell deficiency of eyes after burn by stem-cell therapy due to chemical burns)

➡ 4 marketing authorization applications have failed in phase I

➡ 1 marketing authorization was withdrawn by company

**„If people always do what they
always did,
they will get what they always got“**

(Albert Einstein)



Dresden, Frauenkirche, Münzgasse

**Thank you for your
attention!**



Questions?

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Management:**

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