107TPDA04020

衛生福利部食品藥物管理署委辦計畫

「新興生醫產品 GMP 評鑑符合性管理制度之趨勢研析與建立」

新興生醫產品 GMP 訓練活動(5)

日　期　：民　國　１０７　年　６　月　１４　日

主辦單位：衛生福利部食品藥物管理署

承辦單位：TPDA 社團法人中華無菌製劑協會

講 師 資 料

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時 間 表

時 間	內 容	講 師
8:30-9:00	報 到	
9:00-9:10	長 官 致 詞	TFDA 風管組 代表
9:10-10:10	➢ Updated regulations of ATMPs in EU	Maria Cristina Galli, Ph.D
10:10-10:30	休 息	
10:30-11:30	➢ Introduction of EudraLex- Volume 4 Part Ⅳ: Guidelines on good manufacturing practice specific to advanced therapy medicinal products 2017.	Maria Cristina Galli, Ph.D
11:30-12:00	交 流 討 論 / 課 後 測 驗	TFDA 風管組代表 及講師

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一〇七年度

新興生醫產品GMP訓練活動(5)

社團法人中華無菌製劑協會

PRODUCTION AND DEVELOPMENT OF ADVANCED THERAPY MEDICINAL PRODUCTS

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Taipei (Taiwan), June 14, 2018

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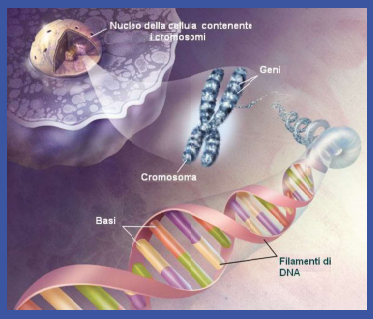
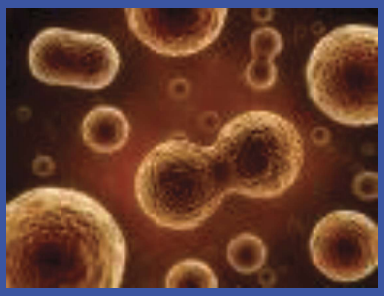
ADVANCED THERAPIES
EU Regulation 1394/2007

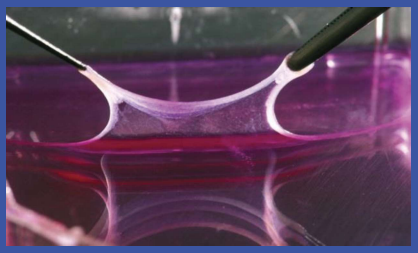
Gene Therapy Medicinal Products





Cell Therapy Medicinal Products

Tissue Engineering Medicinal Products



LEGAL FRAMEWORK FOR ATMP IN EU

ATMP are regulated as medicinal products:

- clinical development under EU Dir 2001/20 (near future: EU Reg 536/2014)
- European marketing authorization granted on the basis of quality, safety and efficacy criteria
- single assessment, authorization (or refusal) across EU
- specialized committee within EMA: the Committee for Advanced Therapies (CAT)
- specific GMP and pharmacovigilance obligations
- Art 28: hospital exemption

EU REG. 1394/2007: SPECIFIC ISSUES FOR ATMP

Committee for Advanced Therapies (**CAT**)

Definition of tissue engineered products

Combined products vs Medical Devices: **within pharmaceutical frame**

Post-marketing pharmacovigilance for **safety & efficacy**

30 yrs traceability

Special cases: products for hospital use only (art.28)

Classification procedure

Certification procedure

EU DEFINITION OF GTMP

Directive 2009/120/EC :

Gene therapy medicinal product means a **biological** medicinal product:

- (a) which 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.**

GTMP IN EU

Viral vectors e.g. AAV

Non viral vectors e.g. plasmids

Cells genetically modified with a vector e.g. with LV

Recombinant oncolytic viruses

Recombinant bacterial cells

Gene transfer acceptable only in SOMATIC cells

Germ line cells transduction unacceptable (EU dir. 2001/20, EU Reg.536/2014) → germ line manipulation by means of CRISPR technology not acceptable in EU

EU REG. 536/2014 ON CLINICAL TRIALS

Article 90

Specific requirements for special groups of medicinal products

No gene therapy clinical trials may be carried out which result in modifications to the subject's germ line genetic identity.

EU DEFINITION OF CTMP/TEP

A CTMP/TEP is a biological m.p.

containing **cells or tissues** that have been subject to **substantial** manipulation or that are **not intended to be used for the same essential function(s) in the recipient and the donor**

and

CTMP (Directive 2009/120/EC) : acting through **pharmacological, immunological or metabolic action** of its cells or tissues

TEP (EU.Reg 1394/2007): used to **regenerate, repair or replace a human tissue** (**Holoclar** on the EU market)

→they differ in the mechanism of action

MANIPULATIONS NOT CONSIDERED SUBSTANTIAL

Annex 1 EU Regulation 1394/2007

manipulations not considered substantial:

cutting, grinding, shaping, centrifugation, soaking in antimicrobial or antibiotic solution, sterilization, irradiation, cell separation, cell concentration, cell purification, filtering, lyophilisation, freezing, cryopreservation, vetrification

CAT CLASSIFICATION PROCEDURE

Incentive, open to all

Applicants can ask CAT **whether their product fulfils ATMP definition or not**

Product classified **according to legal definitions**, based on its characteristics as described by applicant

CAT scientific recommendation on classification issued in 60 days

EMA web site contains a list of ATMP classifications with summary information

CAT CLASSIFICATION: EXAMPLE (1)

HSV-1 containing human GM-CSF, for melanoma therapy
→CAT classification: **GTMP**

Adenoviral vector expressing a mutated HCV structural region, proposed for prevention and treatment of hepatitis C
→CAT classification: **not an ATMP** (intended for infectious disease)

Same vector i.e. adenoviral vector expressing GMC-SF for **cancer therapy**
→CAT classification: **GTMP**

CAT CLASSIFICATION: EXAMPLE (2)

Autologous lipo-aspirate containing non-manipulated adipocytes and stromal vascular fraction, for restoration of subcutaneous fat

→CAT classification: **NOT ATMP** (no manipulation, homologous use)

Autologous adipose tissue-derived mesenchymal stem cell, for treating degenerative arthritis, osteoarthritis, articular cartilage defects

→CAT classification: **TEP** (substantial manipulation, tissue regeneration)

TRACEABILITY REQUIREMENT

Reg.1394/2007:

MAH as well as hospital or clinics where the ATMP is used **shall establish and maintain** a **traceability system** that ensures tracking for **30 years after expiry date**

- product and its production process **including any reagent or material in contact with cells/tissue**
- patient and the ATMP received

Traceability must enable to track product to patient and vice-versa

► **traceability is an EU legal requirement for ATMP as well as for raw materials**

REG.1394/2007 ART.28 (1)

Market authorization is exempted for any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and **used within the same Member State♦ in a hospital** under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.

♦**no** market authorization =**no** free circulation of medicines within EU

REG.1394/2007 ART.28 (2)

Manufacturing of these products shall be **authorized by the competent authority of the Member State**.

Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards referred to in this paragraph are **equivalent** to those provided for at Community level in respect of advanced therapy medicinal products for which authorization is required pursuant to Regulation (EC) No 726/2004

ATMP ON EU MARKET

***Chondrocelect** (2009) **MACI** (2013) **Glybera** (2012) **Provenge** (2013)*

Holoclar (2015) →**TEP** (corneal tissue with autologous limbal stem cells for cornea regeneration)

Imlygic (2015) →**GTMP** (oncolytic virus for melanoma)

Strimvelis (2016) →**GTMP** (autologus CD34+ cells transduced with a retroviral vector encoding human ADA cDNA sequence, for treating ADA-SCID children)

Zalmoxis (2016) →**CTMP** (allogeneic T cells genetically modified with HSV-TK) for treatment of GVHD within a haploidentical haematopoietic stem cell transplant for various types of blood cancer)

Spherox (2017) →**TEP** (spheroids of chondrocytes to repair knee cartilage defects)

Alofisel (2017) →**CTMP** (allogeneic fat stem cells for treating complex anal fistulas in adults with Crohn's disease)

GENE THERAPY MEDICINAL PRODUCTS

viral vectors (e.g. ADV, AAV, HSV, RV, LV)

oncolytic viruses

non viral vectors (e.g. plasmids or liposomes carrying plasmids)

- *close to classical biologicals e.g. vaccines*

genetically modified cells (autologous, allogeneic)

- *new pharmaceutical entities*

In EU:

gene transfer is acceptable only in SOMATIC cells

Germ line cells transduction unacceptable: EU dir. 2001/20, EU Reg.536/2014

Gene therapy medicinal products shall not include vaccines against infectious diseases **(**Directive 2009/120/EC)

CELL THERAPY/ TISSUE ENGINEERED MEDICINAL PRODUCTS

Always comprised of cells, presented as:

- cell population suspended in a liquid
- cellular sheets/conglomerates/ tissue
- may be combined with a medical device

All are new pharmaceutical entities

ATMP VS TRANSPLANTS IN EU (1)

In EU, ATMP are regulated differently from cells/tissues/organ transplantation

ATMP are under the umbrella of medicine laws

►**Reg. 1394/2007**

→ regulated at **EMA** level

→ quality standards: GMP

Transplants are regulated by their own laws:

►**Directives on cells and tissues 2004/23/EC, 2006/17/EC, 2006/86/EC**

→ regulated at **national** level

→ quality standards other than GMP

ATMP VS TRANSPLANTS IN EU (2)

ATMP Reg. 1394/2007 art.3:

- Directives on cells and tissues are applicable **only to** donation, procurement and testing of **starting material** (e.g. cells or tissue from which the ATMP is produced)

GMP implications:

- GMP inspection will not cover donation, procurement and testing of starting material done at the Tissue Establishment (TE)
- GMP inspection will not cover TE cell repositories
- GMP inspection will cover the contract between QP and TE

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ATMP: GMP ISSUES SHARED WITH OTHER DRUGS

Injectable (GT, CT) or transplanted (TE) →sterile and apirogenic

- **Cell-based: aseptic production always needed**

Biological→ **potentially carrying pathogens** and optimal substrate for viruses, mycoplasma, bacteria, moulds during production

Genetically modified (GT) →**containment**, regional legal provisions for GMO risks

Batch release required before completion of some QC tests (e.g. sterility, such as for radiopharmaceuticals)

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ATMP SPECIFIC ISSUES

- iATMP production in academic facilities
- Patient specificity
- Donor status
- Limitations in cell quantity
- Cell fragility
- Legal requirements (traceability, leaflets)
- Limitations for recalled/returned ATMP
- Reconstitution of final product in the hospital

ALL are applicable to both DS/DP

ALL are present from early investigational stage

MAIN RISKS IN ATMP PRODUCTION

Biological contamination (bacteria, fungi, viruses, TSE)

Cross contamination between different products

Cross contamination between different lots of same product

Loss of donor/recipient identity

Loss/rejection of product

Loss of cells

RISK BASED APPROACH FOR ATMP PRODUCTION

EUDRALEX vol.4 EU GMP for ATMP

2.13 **The risk-based approach is applicable to all type of ATMP regardless of whether they are developed in a hospital, academic or industrial setting**

2.14 While the risk-based approach brings flexibility, it also implies that the **manufacturer is responsible to put in place the control/mitigation measures that are necessary to address the specific risks of the product and of the manufacturing process**.

2.15 The quality risks associated with an ATMP are highly dependent on the biological characteristics of the ATMP

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VIRAL SAFETY CONCEPTS

Overall strategy for risk minimization

Viral contaminant origin:

- starting materials, raw materials, manufacturing personnel

Entry port:

- any part of process where the above are present

Process ability of virus elimination: very few/none

Approach: **entry prevention**

This is applicable to investigational ATMP as well

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ATMP STARTING MATERIALS

CELLS OR TISSUES ARE THE STARTING MATERIAL FOR CELL-BASED ATMP

EU Reg. 1394/2007 art.3:

European Directives on cells and tissues

- 2004/23/EC, 2006/17/EC, 2006/86/EC

are applicable to donation, procurement and testing of starting material (e.g. cells or tissue from which ATMP is produced)

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GTMP STARTING MATERIALS: EU LEGAL DEFINITIONS

viral vectors:

→components from which the viral vector is obtained, i.e. master virus seed or plasmids used to transfect packaging cells/ MCB packaging cell line

non-viral vectors:

→ components used to generate the producing cell, i.e. plasmid, host bacteria, MCB of recombinant microbial cells

genetically modified cells:

→ components used to obtain the genetically modified cells, i.e. starting materials to manufacture the vector and the human/ animal cell preparations

Part IV, Annex I to Dir. 2001/83/EC (Dir.2009/120)

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PATIENT SPECIFICITY AND IDENTITY

Cell based products:

- autologous cells: **donor-recipient coincide**
- allogeneic cells: **donor matched to recipient**

GTMP

if transgene sequence is patient specific (e.g. tumor idiotype)

►**1patient=1product**

Legal problem: EU laws on patient data protection

→patient's code (not name/birth date)

NOTE: for donor as well as for **recipient**

PATIENT SPECIFICITY/IDENTITY: GMP IMPLICATIONS (1)

- ► need to have codes under tight control

  accuracy in tracking them paramount for patient's safety, not only for traceability
- ► donor identification code should be different from product lot code, also for autologous use, to distinguish starting material from product
- ► QC control for correct donor-to-recipient matching: more than a label check, it is part of product identity testing (now required in EU GMP guideline)

PATIENT SPECIFICITY/IDENTITY: GMP IMPLICATIONS (2)

For a classical drug, when producing two successive lots:

→risk of carryover, if it is the same drug

or

→risk of cross-contamination, if they are two different drugs

For a patient-specific ATMP:

- **two successive lots of same product have always the risk of cross-contamination**

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PATIENT SPECIFICITY/IDENTITY: GMP IMPLICATIONS (3)

To avoid cross contamination between two lots of patient specific ATMP:

- **cross contamination prevention measures are critical**: procedures/ personnel training/ QA control
- **handle one patient at a time** /LFH double occupancy only if 2 operators work on the same lot
- **separate lots** as much as possible **within incubators**
- between two successive lots=patients: **clean and clear the production suite as if it were two different products**

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DONOR STATUS: GMP IMPLICATIONS

If cell/tissue **donor** is **infected,** in order to minimize risk of cross contamination:

- manufacture of cell-based ATMP may take place **in a segregated area** of the facility e.g. separate cryostorage, separate production suite with separate HVAC, restriction for personnel to leave the segregated area without appropriate decontamination

→even if the product is the same as from non infected donors

- **need to know donor status when starting material enters the facility**

CELL-BASED PRODUCTS: GMP IMPLICATIONS

Closed systems wherever possible

Segregated areas and dedicated production equipment for cells from infected patients

Do not use multiple LFH stations in one room for more than one lot/product (small rooms are better than large ones)

CTMP production facility **separated** from GTMP production facility

Cell-based GTMP: **unidirectional flow** (personnel, materials etc.) from non-genetically modified cells area to gene-transduction areas

Validation to molecular level (e.g. detect transgene and/or vector) for cleaning procedures used at changeover

VIRAL VECTORS : GMP IMPLICATIONS (1)

Usually **not replication competent** for patient safety reasons

- oncolytic viruses: **replication competent** (Imlygic)

Cross contamination→it may result into resurgent replication competent vector

Where replication limited vectors are produced, measures to prevent introduction of wild-type viruses

Concurrent manufacture of not replication competent with replication competent vectors **not acceptable**

VIRAL VECTORS: GMP IMPLICATIONS (2)

Separated production facilities: s**egregated** areas and **dedicated** production equipment

Concurrent manufacture of different viral gene therapy vectors in the same area **not acceptable**

Closed systems wherever possible

Validation to molecular level (e.g. detect transgene and/or vector) for cleaning procedures

Emergency plan for dealing with accidental release of viable organisms

LIMITATIONS IN CELL QUANTITY

At sourcing level (i.e. in the starting material):

- Small biopsy or
- for clinical reasons cell donation can be obtained only once (e.g. infants) or at large time intervals (e.g. severe diseases)

At processing level:

- normal cell growth rate is limited

→it is possible that the process yields just the clinical dose + small QC sample

► possible ethical problem with rejecting a lot if starting material is not in stock (*with other drugs it is an economical issue*) (occurring particularly at investigational level when the process is not validated)

►unless putting at risk the clinical dose, a full testing program (i.e. identity, purity, quantity, activity) is not possible

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LIMITATIONS IN CELL QUANTITY: GMP IMPLICATIONS

►Control over the production process should be **maximized** even for investigational ATMP at phase I/II level

►Quality assurance is paramount

► If authorised by C.A., a reduced testing strategy may be applied

- enhanced understanding of product and process performance
- continuous assessment of the effectiveness of the quality assurance system

CELL FRAGILITY

starting material/ final product

- difficult to store even at ultralow temperature
- need to deliver quickly to patient for clinical reasons
- procurement/ treatment at distant sites

→ product with short shelf life

► **transport procedure validation is critical both for product and for starting material**

CELL QUANTITY/FRAGILITY: GMP IMPLICATIONS

QC AND ENVIRONMENTAL MONITORING

short shelf life and /or limited cell number in final product:

→ retention samples are not held in the same conditions as product or are not possible

→ results of some QC testing and environmental microbiological monitoring are available after lot release

► stepwise release procedure

► asepsis validation is critical

► retention samples may not be stored

STEPWISE BATCH RELEASE PROCEDURE

before and **after** all QC test results are available:

1. assessment of batch records and results from environmental monitoring, all deviations and the available analytical results, review and conditional certification by the Qualified Person
2. assessment of the final results, final product certification by the Qualified Person

► **SOP with measures to be taken** (including liaison with clinical staff) where unsatisfactory test results are obtained after product dispatch

Such events should be fully investigated, corrective and preventative actions taken to prevent recurrence

HOW TO ACHIEVE A COMMERCIAL ATMP

Efficient translation from research to medicinal product
Efficient transition through clinical development
Both essential for giving effective treatment options to patients
Delays of innovative medicine development caused by existing/perceived bottlenecks:

- at regulatory level
- at scientific level

REGULATORY LANDSCAPE

Regulatory requirements are also being adapted to new landscape
→early and continuous interaction with the regulatory bodies welcomed and expected

EMA and national regulatory agencies offer to developers different approval mechanisms including accelerated procedures and orphan drug designation, among others.

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SCIENTIFIC BOTTLENECKS FOR ATMP

Safety issues
- perceived as the major problem, much effort on it

Efficacy issues
- potentially underestimated

....if efficacy is poorly proven, safety issues take over….

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CHALLENGES FOR DEVELOPMENT

Common to both developers and regulators:

how to determine if data available for a given product are sufficient to allow progression from clinical trials to market

Regulatory help tools:

early interaction with most EU national regulatory agencies

EMA procedures

→ **an European consensus view** on a development path acceptable to regulators

►contribution to reduce waste of time and resources

MAIN RISKS FOR GTMP

Germ line transduction: unacceptable (**dir. 2001/20-EU Reg.536/2014**) → **germ line manipulation e.g. by means of CRISPR technology is not acceptable in EU**

Insertional mutagenesis→ oncogenesis

Replicating viral vector →target cell lysis / dissemination / shedding (ERA)

Oncolytic viruses→ ectopic replication

Transgene and/or vector immunogenicity→ impairment of clinical efficacy/immune-toxicity

Transgene disregulated expression→ toxicity/impairment of clinical efficacy

MAIN RISKS FOR CTMP/TEP

Infections (viruses, TSE)
Tumorigenicity
Failure to differentiate in vivo as expected for therapeutic effect
Distribution to unwanted sites
Unwanted/ectopic proliferation
Unwanted cell elimination e.g. because of immune/inflammatory reactions

HOW TO REDUCE RISK OF FAILURE

The following should be considered:

- product design
- appropriate animal model for the intended purpose
- delivery to the target tissues
- design of clinical trial

KNOW YOUR PRODUCT!

From the very beginning of development have clear in mind ***what the clinical product will be***

→design, develop and validate **an appropriate production process**

During development, any change in vector and /or production process may impact on the comparability of product across studies

→**carefully plan changes**

→consider possibility of starting development from the beginning

if targeting a rare disease, the number of available patients will not allow for a classical phase I-phase III transition

→probably little/no product development during clinical trial phase

GENE THERAPY MEDICINAL PRODUCT

Design of GTMP is critical

A clear understanding of GTMP molecular structure and biological characteristics is essential to design (=assess!) appropriate Q/NC/C studies

The *ideal* GTMP contains only sequences/proteins needed to achieve the intended clinical goal

The **real** GTMP contains also other sequences/proteins, heritage of early development construct and derived from production system

APPROPRIATE GTMP DESIGN SHOULD BALANCE SAFETY WITH SOUGHT CLINICAL EFFECT

-Deletion of sequences responsible for replication ability
Oncolytic viruses:
→replication designed and shown to be restricted to tumour cells
-Deletion of sequences responsible for integration ability
Integrative vectors needed to transduce stem/progenitor cells:
→ ex vivo approach, SIN vectors, cell copy number and MOI as low as transduction efficacy can allow
Minimal vector backbone to reduce toxicity

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BALANCING SAFETY-DRIVEN PRODUCT DESIGN WITH CLINICAL EFFICACY

Pay attention to:

- transduction (in)efficiency
- therapeutic gene expression level and/or persistence and/or restriction
- choice of (ir)relevant genes
- dosing
- potency testing

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CT/TE MEDICINAL PRODUCTS

Cells are living organisms!!

Process factors (e.g. growth factors, serum), conditions and duration of *in vitro* culture:

→ impact on cell composition, differentiation capacity *in vivo* and mode of action

Cell plasticity and product differentiation:

→ nonclinical and clinical studies should be performed with <u>well defined and characterized</u> product

Tumorigenicity risk:

→SC product should be shown to be lineage-committed before administration to the patient

DEVELOPING INFORMATIVE NON CLINICAL MODELS

To demonstrate proof of principle

To assess toxicity

To assess pharmacology

- for (rare) diseases
- homologous models

ISSUES FOR GT PRECLINICAL STUDIES

Specie-specificity (both vector & transgene): animal model selection
Transgenic/knockout/homologous animal models: relevance to human disease
Immunogenicity of human proteins in animals
Vector persistence
Tissue tropism of different serotypes/effect of associated treatment in clinical studies
Potential for reactivation of replicating AAV after recombination with WT-helper virus/after associated treatment
Germ-line transmission
ERA

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ISSUES FOR CT/TE PRECLINICAL STUDIES

Choice of animal model
Biodistribution and microenvironment (*niche*)
Ectopic tissue formation
Tumourigenicity
Differentiation in vivo
Immune rejection and persistence
→ more than one animal species/strain might be needed
→ i*n vitro* models may be additional and/or alternative
Potential inflammatory/immune response to SC product
→risk of stem cell elimination

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STEM CELLS TUMOURIGENICITY AND GENOMIC STABILITY

Inherent risk of tumor formation for pluripotent as well as somatic SC

- culture conditions (e.g. feeder cells and excipients) influence stem cells genomic stability
- iPSCs and hESCs have a relatively high potential risk

→presence of proliferative and pluripotent cells tolerated in final product should be limited and justified

→stem cell product should be evaluated for both tumorigenicity and chromosomal stability **before their initial clinical use**

→cytogenetic analysis, telomerase activity, proliferative capacity, senescence

KNOW YOUR TARGET DISEASE!

Lesson learned from practical experience

►importance of a deep knowledge of the target disease

→particularly for a rare disease with few available patients

Need to have

- well designed clinical endpoints
- validated appropriate biomarkers
- appropriate analysis of clinical data

in order to obtain robust clinical data

TAKE HOME MESSAGE FROM FIELD EXPERIENCE

Improve knowledge of disease clinical and biological features

→in order to choose relevant transgenes

→in order to design/validate appropriate/meaningful endpoints, appropriate/informative monitoring methods

Make systemic delivery more efficient

→ in order to reach the right cell target

Improve characterisation of the ATMP

→in order to design appropriate/meaningful testing methods, in particular for potency, to be correlated to clinical endpoints