PRESENT AND FUTURE OF CELL AND GENE THERAPY PRODUCT DEVELOPMENT

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DISCLAIMER

I attend this conference as an individual expert

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ATMP APPROVED FOR 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)

GENE THERAPY MOMENTUM

Three gene therapy medicinal products on the EU market (Glybera_Imlygic_Strimvelis)

Recently reported encouraging data in clinical trials with CART cells in cancer therapy

Increased industry interest in the field

New tools such as genome editing technology

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

Regulatory agencies offer to developers scientific advice as well as various approval mechanisms including accelerated procedures, priority programs, orphan drug designation, among others.

EMA EARLY ACCESS TOOLS

unmet medical needs, major public health interest, seriously debilitating or life-threatening or rare diseases

PRIME: priority medicine

Accelerate Assessment. reduced time (150 days)

Conditional Approval: earlier approval, less complete clinical data

All accessible for any type of medicine

EMA PRIME SCHEME

dedicated proactive regulatory guidance for generating robust benefit/risk data

- unmet medical need
- preliminary data of potential major therapeutic advantage (phase I/II)

continuos support by CAT rapporteur +experts

electronic application via website

kick-off meeting + Scientific Advice at key timepoints

fee waiver for SME & academia

About 2 yr experience, most applications are for ATMP

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….

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 regulatory agencies

EMA procedures:

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

►contribution to reduce waste of time and resources

EMA GUIDANCE FOR ATMP
Gene Therapy

Guidance on quality, preclinical and clinical aspects of gene transfer products (rev. 2014, out for consultation)

Guideline on follow up of patients administered with gene therapy (2010)

Guideline on risk based approach (Feb 2013)

Guideline on Development and manufacture of lentiviral vectors (2005)

Qual., Non Clin. & Clin. issues of adeno-associated viral vectors (2009)

Reflection paper on clinical risks deriving from insertional mutagenesis (2013)

ICH considerations – Oncolytic viruses (2009)

Guideline on MPs containing genetically modified cells (2012)

Scientific requirements for Environmental Risk Assessment (2008)

Reflection paper on design modifications of GTMPs during development (2012)

Non-clinical studies required before first clinical use (2008)

Non clinical testing of inadvertent of gene transfer vectors (2007)

EMA GUIDANCE FOR CELL-BASED ATMP

Reflection paper on stem-cell based MPs (2010)

Guideline on Risk Based Approach (Feb 2013)

Guideline on cell-based medicinal products (2008)

Clinical aspects to tissue engineered products

Guideline on MPs containing genetically modified cells (2012)

Potency testing of cell-based immunotherapy MPs for treatment of cancer (2007)

Guideline on Safety & Efficacy Follow-up – Risk Management of ATMPs (2008)

Reflection paper on Chondrocyte containing MPs for cartilage repair (2009)

Guideline on Xenogeneic CBMPs (2009)

MAIN RISKS FOR GTMP

Germ line transduction: **dir. 2001/20, EU Reg.536/2014 → germ line manipulation 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, but:

integrative vectors are 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

BALANCING SAFETY-DRIVEN PRODUCT DESIGN WITH CLINICAL EFFICACY

Pay attention to:

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

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 well defined and characterized product

Tumorigenicity risk:

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

STEM CELL-BASED MEDICINAL PRODUCT

SC-based product in a differentiated state:

→critical manufacturing steps to reach required differentiation stage **should be controlled** with relevant markers

SC-based product may still contain cells in an undifferentiated, proliferative state:

→potential for tumor formation

→during development appropriate tests to minimize risk of transformation and tumor formation, in particular with embryonic SC or iPSC.

MCG 2017

iPSC

Advantage: derived from autologous adult stem cells, can generate many cell types to produce clinically applicable products

however

unlimited potential for proliferation and differentiation

→from the regulatory point of view a major problem for safety

ISSUES FOR IPSC

- protocols for increasingly safer introduction of transgene
- testing methods for detecting appearance of genetic abnormalities both at reprogramming step and at subsequent expansion steps

still the tumour risk is considered by regulators an high priority

►undifferentiated cells in the final product are not welcomed

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: legal requirement in EU (EU Reg.726/2004)

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

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

DELIVERY TO THE TARGET TISSUES

To brain or heart or with muscle diseases or in cancer gene therapy

►still a challenge

Neutralizing antibodies can interfere with therapy

→research into viral vector tropism, novel capsids, improved vector delivery, redirecting immune-therapy to target antigens on tumor cells

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

CT CLINICAL ISSUES

Proof of concept/mode of action/dose finding

Ectopic presence of administered SC product

Safety and long term efficacy concerns

→need to develop and validate new non-invasive methods/ markers / tracers for tracking cells in clinical studies

Administration procedures, doses/cell numbers:

→addressed during nonclinical phase and confirmed during clinical studies

CLINICAL SAFETY

Ability to form teratomas

→in case of observed tumor, investigation (e.g. genetic analysis) whether due to SC product or to endogenous causes

Ectopic engraftment in non-target tissues

Number of circulating stem cells higher than physiologically

→ abnormal distribution

CLINICAL EFFICACY

To study tissue regeneration, repair or replacement:

→appropriate structural and morphological endpoints

Long term follow-up:

- duration
- safety issues
- efficacy issues: lack/impairment of efficacy

CLINICAL EFFICACY AND LONG TERM FOLLOW UP

LTFU: legal requirement in EU (Reg.1394)

Pay attention to:

- choice of (ir)relevant parameters
- timing of controls
- time length of controls
- invasiveness of controls
- methods for feasible patient tracking

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