LÆGEMIDDEL STYRELSEN

DANISH MEDICINES AGENCY

Objectives of the Focus group on non-clinical development of ATMPs and outcome of discussions in 2011

Session 1: Focus Group: non-clinical development of ATMPs

CAT Stakeholders workshop on Focus Groups

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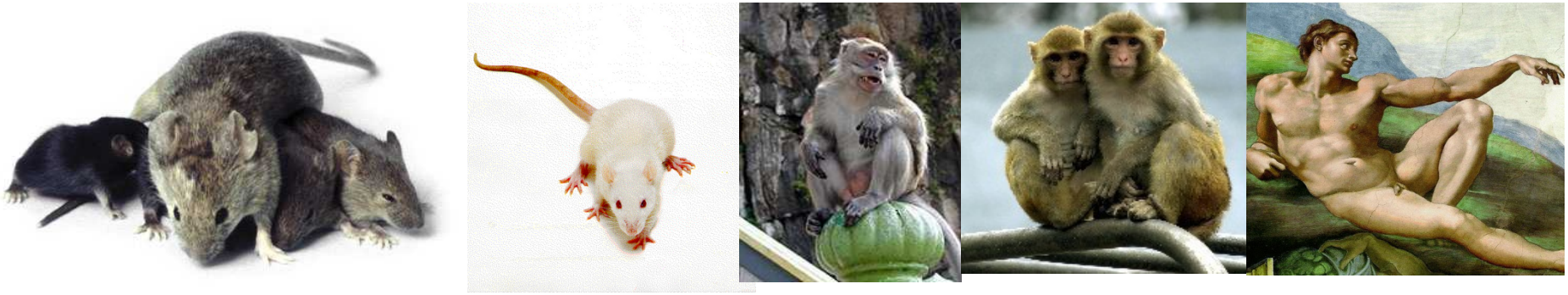
Committee for Advanced Therapies (CAT)
European Medicines Agency (EMA), London, UK

23. januar 2012



A relevant species is one in which the test material is pharmacologically active due to the expression of the receptor or an epitope (in the case of monoclonal antibodies)*.

*NfG on preclinical safety evaluation of biotechnology derived pharmaceuticals (CPMP/ICH/302/95; ICH S6)

- Cell surface molecules (receptors, integrins,…)
- Secreted factors like cytokines

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 March 2011
EMA/CAT/134694/2011
Patient Health Protection

Report from CAT-Interested Parties Focus Groups (CAT-IPs FG) on non-clinical development of ATMPs

9th February 2011 - 9:00 -13:00 (UK time)

Chair: Christian Schneider

Item	Draft agenda/Summary of discussions
1.	**Introduction of participants** (see list of participants at the end of the document)
2.	**Scope of CAT-IPs FGs and objective of the meeting** A summary document (EMA/CAT/769749/2010) explaining scope, role, composition, duration of the CAT-IPs FG was distributed to all participant.
3.	**Brainstorming:** **a) Non-clinical development of somatic cell therapy medicinal products and tissue engineered products** - Review of existing labelling techniques that can be used in biodistribution studies with cell-based medicinal products; - Conduct of toxicology and biodistribution studies for cell therapy products, especially products that are not injected but are transplanted (such as regenerative medicine combined products, cells and scaffolds) Presentation by EuropaBio **b) Non-clinical development of combined ATMPs** Presentation by Eucomed **c) Non-clinical development of gene therapy medicinal products** **d) Topics suggested in previous Interested Parties hearings/other items suggested by participants:**

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http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/03/WC500103895.pdf

Key points of discussion

- Individual products: Better come for Scientific Advice
- Principles for following regulatory non-clinical guidance:
  - Do not follow guidelines for the sake of following guidelines
  - Scrutinize study design: How relevant is the outcome expected to be? What will the shortcomings be?
  - Employ a risk-based approach
  - Remember 3R principles

Make use of regulatory resources

- CAT should explore the possibility of setting up a platform to share information with stakeholders on trends in non-clinical development of ATMPs.
  > See presentation by C Herberts and HT Vestergaard
- Use CAT/EMA incentives from early on:
  - Scientific Advice
  - ITF briefing meetings
  - ATMP **certification** (could be used as a "gap analysis")

Certification: What is it?

- *Art. 18: " Small and medium-sized enterprises developing an advanced therapy medicinal product may submit to the Agency all relevant quality and, where available, non-clinical data required in accordance with modules 3 and 4 of Annex I to Directive 2001/83/EC, for scientific evaluation and certification."*
- EMA procedureal guidance EMA/CAT/418458/2008/corr.: Not binding for future MA; not a Scientific Advice; not binding for National Agencies for Clinical Trial Authorisations.

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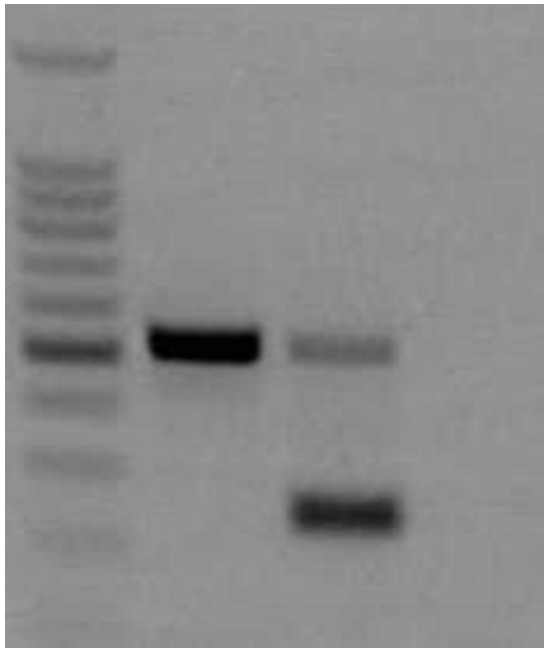
Certification

- What is a certification?



- Provides a snapshot / gap analysis
- NCA‘s have „moral obligation“ to follow certificate; CAT to scrutinize via its members in case NCAs deviate

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Advocation of a knowledge-based aproach

- CAT should reflect, when non-clinical studies are requested, on how far the experience from similar products and, if available, previous clinical experience can be taken into account.
  (example: dermal products with scaffolds)
- Developers do not request the establishment of a different standard to the evaluation of ATMPs legally on the EU market, but recognition of the long-standing.
- Clinical data may in part compensate for non-clinical studies (depends on quality/source of data/risks).

What animal model to chose?

- Use of smart *in-vitro* testing may in certain cases potentially complement or even substitute animal studies.
- Choice of animal model depends on purpose:
  - Proof-of-concept: usually homologous model
  - Toxicology: may also be necessary to test actucal medicinal product (in addition, or alternatively).
  - Could also be a disease model, if available.
- Intention: Generation of signals rather than quantitative (due to limitations of the known models) *(i.e., not necessarily confirmation of a risk that is already known?)*

Special scenarios

- Large animal models: Not by default, rather on a case-by-case basis, driven by the actual need for such data.
- Emerging specialised animal models may help.

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A Novel Small-Animal Model for Accelerated Investigation of Tissue-Engineered Aortic Valve Conduits

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The objective of the study was to describe a novel small-animal model of tissue-engineered aortic valve conduits and to investigate biological processes in an accelerated and inexpensive fashion. An isogenic Lewis-to-Lewis rat model was used to exclude immunological factors of graft deterioration. U-shaped aortic valvular grafts were decellularized and characterized morphologically. Acellular conduits were repopulated with labeled isogenic cells in a bioreactor under flow conditions. Grafts were anastomosed to the recipient's abdominal aorta in an end-to-side manner (n = 7). Native rat aortas were implanted as a control group (n = 7). Grafts were explanted after 28 days and characterized. After treatment with trypsin–ethylenediaminetetraacetic acid, no residual cells were visualized in the scaffold. Mean DNA content decreased from 0.347 to 0 μg/mg of DNA/tissue, and the content of collagenous connective tissue and proteoglycans appeared slightly reduced. Isolated aortic rat endothelial cells and myofibroblasts were repopulated on the acellularized scaffold, and florescent-labeled myofibroblasts were identified in the meshwork. Endothelial cells formed a monolayer on the luminal surface. Reseeded cells were viable as ascertained using a 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium assay. After implantation, Doppler and M-mode echography proved pulsatile cusp movement. All conduits were patent after 28 days. Examination of tissue-engineered explants revealed thickened aortic walls and incompetent valve function. Microscopically, aortic intima and media appeared normal, whereas the adventitia showed hyperproliferation of fibroblasts. Our new model leads to accelerated and reproducible results, suited to investigation of biological patterns of tissue engineering. The observed adventitial fibrosis emphasized the importance of careful selection of optimal cell types for repopulation in tissue-engineered constructs.

Introduction

AVAILABLE AORTIC VALVULAR prostheses and aortic valve conduits have several limitations. Mechanical valves require lifelong anticoagulation, which may cause bleeding or thromboembolic complications and bear a risk for prosthetic infection.[1,2] In contrast, nonviable biological valves have limited durability because of early tissue degradation and calcification.[3] Cryopreserved homografts contain viable tissue with excellent flow characteristics, but degeneration may occur early because of its immunogenicity, especially in children and patients with high immunological competence.[4] No available prostheses grow, requiring revision operations in growing children. The Ross operation takes these limitations into consideration, but possible autograft dilatation, as well as degeneration of the pulmonary homograft, increases the risk of repeat valvular graft replacements.[5] Furthermore, the demanding technique and prolonged operation times makes this procedure available only for selected patients.

The concept of tissue engineering may overcome the limitations of available valvular and vascular prostheses. Biodegradable matrices or decellularized tissue scaffolds of allo- or xenogenic origin are repopulated with autologous cells *in vitro*. These constructs are free of immunogenic cells and are supposed to be suitable for surgical implantation. The low-pressure system has been investigated in detail for more than 10 years, and tissue-regenerated pulmonary prostheses have been introduced into clinical practice.[6–8] Because acellularized scaffolds used for tissue regeneration are unsuitable for the high-pressure circuit because of its weak matrix composition, development of tissue-engineered (TE) aortic valved conduits requires use of *in vitro* reconstitution. Currently, the ideal decellularization protocol for aortic tissue, selection of proper cell types for recellularization, and optimal experimental

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[5]Department of Cardiology, Evangelische Krankenhaus, Hamm, Germany.

Duration of non-clinical studies

- In some cases, short-term toxicology may be more informative.
- Live-long follow-up in large animals may not be feasible.

Dose-finding

- Reduction of number of doses to be tested could be possible, but may have to be compensated by clinical testing.
- Combined ATMPs: May not be feasible nor informative.
- Distinguish between PoC (i.e., determinatio of an efficacious dose) and toxicology (i.e., determination of a maximum safe dose).

Risk-based approach

- Multifactorial
- Categorization ”low risk” and ”high risk” should be avoided (unnecessary stamp; may result in ambigous perception of a product; is too uni-dimensional).
- Clinical context including unmet medical need is an important factor to be considered.
- CAT to explore if experience gained with medical devices could be helpful.

Proposed actions

- ✓ CAT and SAWP to explore generation of a living experience document (what models used etc.).
- ✓ Ensure that NCA assessors have a consistent approach
- ✓ Risk-based approach:
  - CAT to pursue guideline;
  - Stakeholders to collect data on risks that they have already identified, and how one could address those risks (e.g., tumourigenicity with stem cells)
- ✓ Raise awareness of CAT on significant new approaches in non-clinical development