TiGenix
Living Medicines

Wilfried Dalemans, PhD
Chief Technical Officer

DIA/MHRA ATMP Workshop

London – 18 November 2011

Demonstrating product comparability for a cell-based ATMP: a ChondroCelect case study

CHONDROCELECT

- **Characterized autologous** cartilage cells **expanded** *ex vivo* and expressing specific marker proteins
- **Medicinal product**
- Indication: **Repair** of single symptomatic **cartilage defects** of the femoral condyle of the knee (ICRS III or IV) in adults

3

ChondroCelect : First approved ATMP in Europe

COMMISSION OF THE EUROPEAN COMMUNITIES

Brussels, 5.10.2009
C(2009)7726

COMMISSION DECISION

of 5.10.2009

granting marketing authorisation under Regulation (EC) No 726/2004 of the European Parliament and of the Council for "ChondroCelect - Characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins", a medicinal product for human use

emea European Medicines Agency
Press office

London, 26 June 2009
Doc. Ref. EMEA/CHMP/394741/2009

PRESS RELEASE
European Medicines Agency recommends first marketing authorisation for an advanced therapy medicinal product

The European Medicines Agency has recommended the first marketing authorisation for an advanced therapy medicinal product, following a positive opinion from the Agency's Committee for Advanced Therapies (CAT) and the Committee for Medicinal Products for Human Use (CHMP).

4

Product comparability (CMC side)

A typical / classical approach:

“My new product meets the specifications”

5

Product comparability (CMC side)

- Three checkpoints
  - Your process
  - Your product
  - The science of the change
- Process
  - Critical parameters
  - Experience with your process
- Product
  - Quality attributes for release
  - Characterization assays

6

Product comparability (CMC side)

- The science of the change
- E.g. Cryopreservation
  - Cells undergo a physiological change
  - Addition of cryoprotectants (like DMSO)
  - Some cells may like it better than others
  - It is broadly used in the clinics (BM transplantation)
  - ....
- What are possible consequences on the product
  - Potency
  - Purity
  - Stability
- Pro-actively address these questions !

7

ChondroCelect product comparability approach

- Use an extensive and comprehensive series of parameters to evaluate
  - Manufacturing process data
  - Final product quality attributes (I, P, P, other release tests)
  - Product stability
  - Additional characterisation results
- CC is an autologous product
  - Start from a common biopsy to compare the processes
  - Compare for several donors
- First optimize the process and define its critical parameters. Then run the comparability.

8

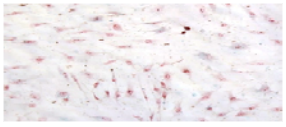
ChondroCelect assays

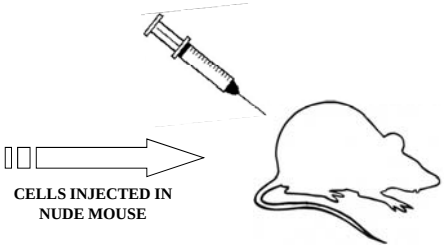
- Functional assays for cell characterization:
  - At the tissue level in small animal models (e.g. nude mice)
  - At the cellular level using 3-dimensional culture assays
  - At the molecular level by marker analysis
- Interrelationship between the assays and their correlation
- Totality of the functional assays describes the quality of the product

9

Evaluation of the cell quality at the tissue level: Nude mouse ectopic cartilage formation (ECFA)

EXPANSION OF CELL POPULATIONS USING DIFFERENT PROTOCOLS





CELLS INJECTED IN NUDE MOUSE

TISSUE HARVESTED AFTER 3-12 WEEKS

ECFA/HISTOLOGICAL SCORE (0 – 3)

0 – No extracellular matrix

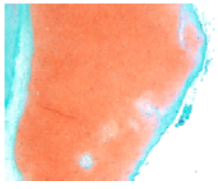
1 – Undifferentiated, fibrous tissue

2 – Differentiated cartilage

3 – Hyaline-like cartilage

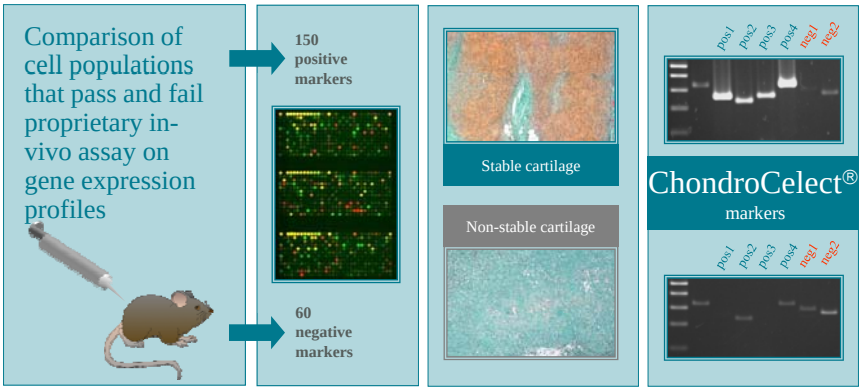
(Dell'Accio et al, 2001)

HISTOLOGICAL ASSESSMENT



1

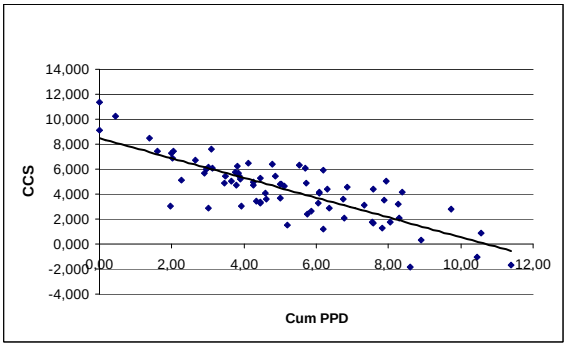
Evaluation of the cell quality at the molecular level: CC marker analysis



1

Evolution of the CC Score during expansion of the cells in monolayer

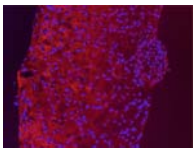
The gradual drop in CC Score during cell expansion in monolayer culture is indicative of a decreased chondrogenic capacity of the cells.

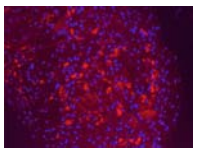


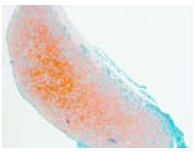
1

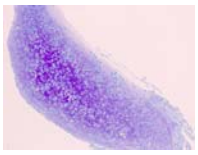
Evaluation of the cell quality at the cellular level
3D functional pellet culture assays

- Cells are expanded to various passages in monolayer culture prior to formulation into pellet cultures
- Functionality is assessed by histology, immunohistochemistry and biochemical analysis


Col II


Aggr

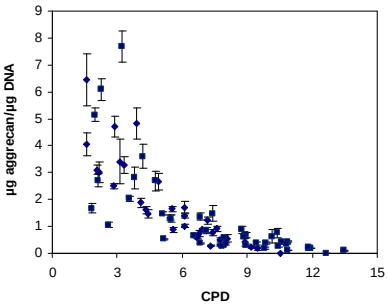

SafO

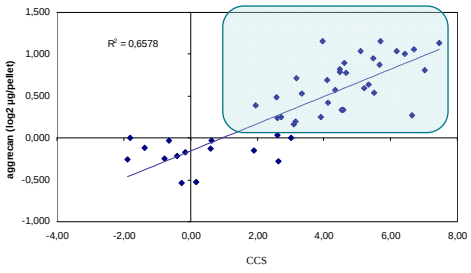

TB

1

Evaluation of the cell quality at the cellular level
3D functional pellet culture assays

The capacity of the cells to turn-over aggrecan in 3D pellet cultures diminishes with increasing expansion of the cells in monolayer culture





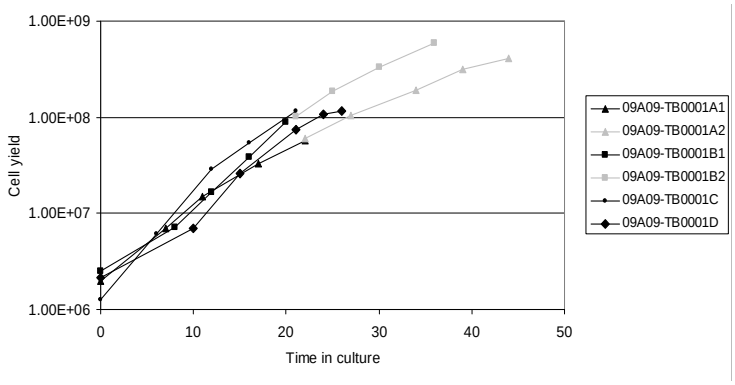
1

ChondroCelect product comparability approach

- Manufacturing process data
- Final product quality attributes (I, P, P, other release tests)
- Product stability
- Additional characterisation results

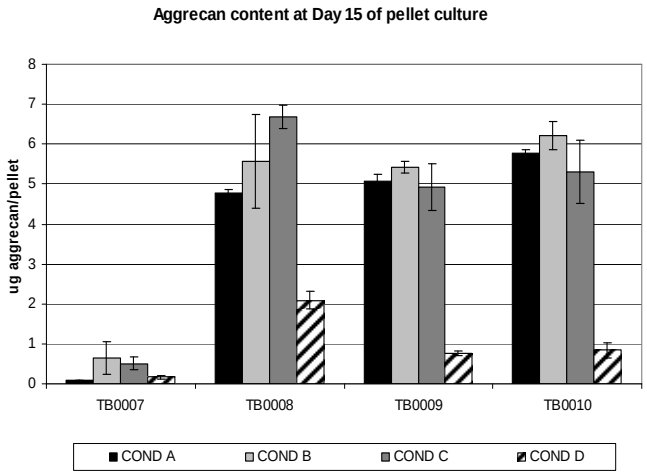
1

Product comparability: process data



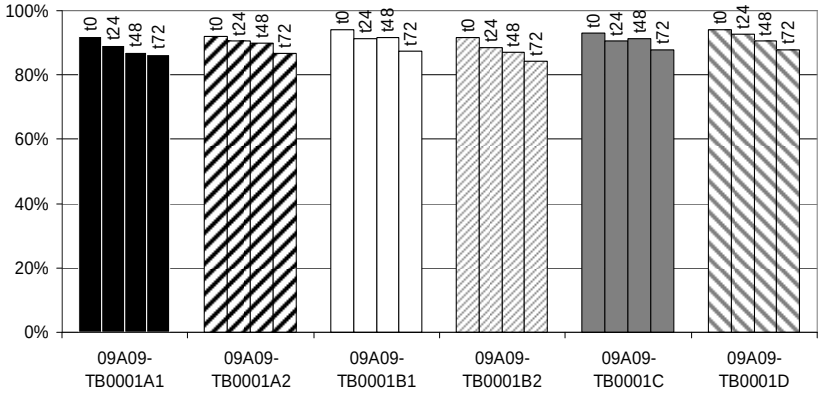
1

Product comparability: functionality characterization



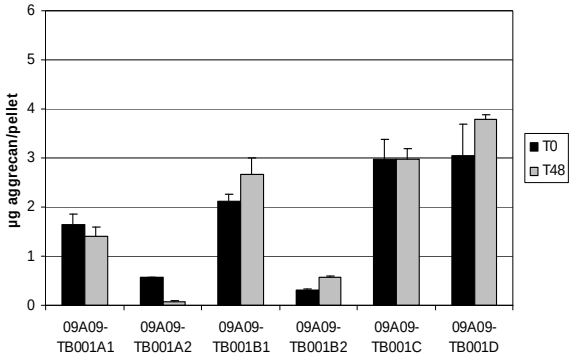
1

Product comparability: stability profile conditions



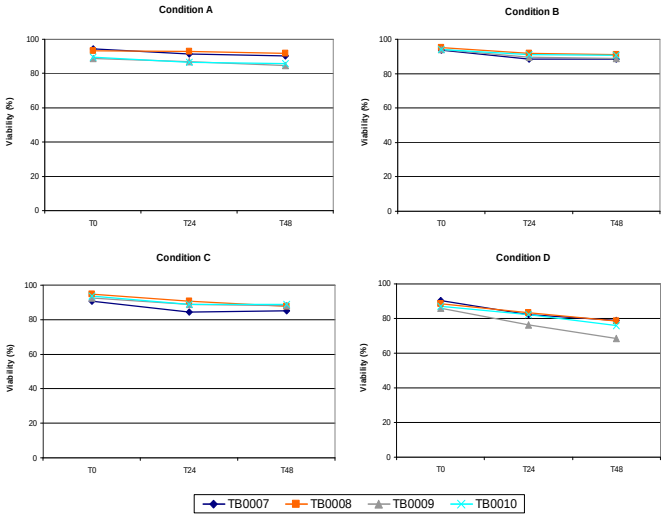
1

Product comparability: function stability



1

Product comparability: stability profiles donors



2

Conclusions

- Product comparability: Three (upfront) checkpoints
  - Your process
  - Your product
  - The science of the change
- Dissect and optimize the (new) process
- Product comparability
  - Extensive data package on process and product
- Depending on results and the remaining questions
  - Additional characterization assays development
  - Preclinical comparison
  - Clinical comparison

Thank you for your attention.