Advanced Therapy Medicinal Products:
from Promise to Reality

Regulatory path for translation of research
to commercial medicinal products

Nonclinical Development of Cell Based Medicinal Products

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Transition from NC to Clinical

Cell based products
vs
Biopharmaceuticals
vs
Small Molecules

Are Principles Different ?

Non Clinical Studies (NCEs)

Objectives

- To demonstrate proof-of-principle and Mode of Action,
- To address Fate (ADME)
- Define effects predictive of the human response
  - -pharmacological
  - -toxicological

Prior to initiation of clinical trials AND through clinical development

Non Clinical Studies (NCEs)

- **Proof of concept**
- **Safety Pharmacology**
- **Fate (ADME)**
- **Toxicology**

-Appropriate human extrapolation

-Safe administration of (First In) Human Doses

To BE Performed in Relevant Models

Non Clinical Studies (CBMPs)

Same Objectives

Same Goals

Same Principles

Different Strategies

Non Clinical Studies (CBMP)

Principles

- should be performed in **relevant (animal) models**.
- The rationale underpinning the NC development, and the criteria used to choose a specific (animal) model must be justified.
- Should reflect the inherent variability of some CBMP.
- Conventional studies may not be appropriate for CBMP. **(Adaptation needed)**

NC Program Supporting (FIH) Clinical Trials for CBP

Pharmacology

- proof of concept
- Secondary Pharmacodynamics
- Safety Pharmacology

Kinetics

- Cell migration from SOA
- Local and/or systemic exposure to Cell derived products
- Persistence and fate of CBP

Toxicology Studies

(duration, design, etc)

Information to be Collected for Human Risk Prediction (in vitro / in vivo)

- Engraftment, proliferation and/or differentiation pattern of
- Potential for and Pattern of “migration” from SOA
- Production of cell derived products
- Distribution and fate of cell derived products form SOA
- Ability to initiate an immune response (as target or efector);
- Duration of exposure or culture or life span of cell
- Availability of clinical data on or experience with similar products

Design of Non Clinical Studies
factors to consider

- Cell types in CBMP
- Cell Origin
- Type of Preparation/use

Design of Non Clinical Studies
factors to consider

Cell types in CBMP:

- self-renewing stem cells,
- Cell function (eg immunologically active)
- more committed progenitor cells
- or terminally differentiated cells exerting a specific defined physiological function.

The Risk Based Approach

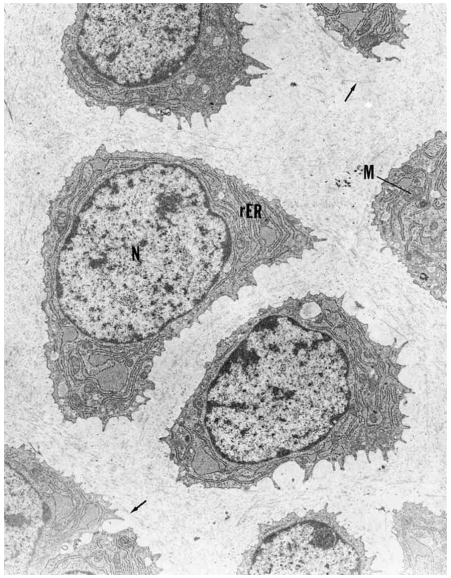
Risk Based Approach (for Advanced Therapies):

- Is based on the identification of risks and associated risk factors of an ATMP
- and the establishment of a specific profile for each risk.
- The Data presented for Marketing Authorization to be justified on the Identified Risks

Design and duration of Toxicity studies (single vs repeated; post-administration monitoring)

ChondroCelect: *Challenges with cell-based products*

- Cells are complex systems
  - Cells from biopsy are heterogeneous with various stages of differentiation
  - Cells are dependent on their environment
  - Cell cultures can become heterogeneous
  - Cells might de-differentiate (e.g. during longer cell culture)



=> Consequence:

√ Need for adequate characterization,

√ but also necessity to accept limitations

- Challenges:
  - Only short shelf-life => Thorough release testing not possible
  - „Renaissance“ of microbial safety (48 hours shelf life is a challenge!)
  - Differentiation to hyaline cartilage is the goal
  - Durability and long-term benefit => how to demonstrate?

C. Schneider, CHMP)

Design of Non Clinical Studies
factors to consider (exp.model)

Cell Origin:

autologous → homologous model ?

or allogeneic origin → in animal model? (incl. immunogenicity)

genetically modified → "NfG on the quality, preclinical and clinical aspects of gene transfer medicinal products"

Design of Non Clinical Studies
factors to consider

Type of Preparation/Use

The cells may be used alone

- or associated with biomolecules, chemical substances

- and combined with structural materials that alone might be classified as medical devices (combination products.

Principles for evaluation of combinations may apply and be considered

Design of Non Clinical Studies
factors to consider

non-viable cells and cellular fragments: underlying principles of CBP guideline apply

Case Example:

- Anti-tumour vaccine based on cellular lisate.
- Homologous material obtained from animal model
- model of disease used for prove of concept and safety aspects
- Initial doses based on *"in vitro"* (animal and human) and
- *"in vivo"* information

Translation: From NC into FIH

In vitro studies:

Cell (CBP) characterisation

(eg proliferation, differentiation, cell products):

- homologous cells (from human and **animal model***)
- alogeneic cells
- Genetically modified cells (from human and **animal model***)

In vivo studies (in relevant animal model):

- Proof of concept
- "Kinetics" (biodistribution)
- Safety (safety pharmacology; toxicology)

Outcome: "dose"-response relationships (in vitro & in vivo)

Translation: From NC into FIH

In vitro / vivo correlation (animals):

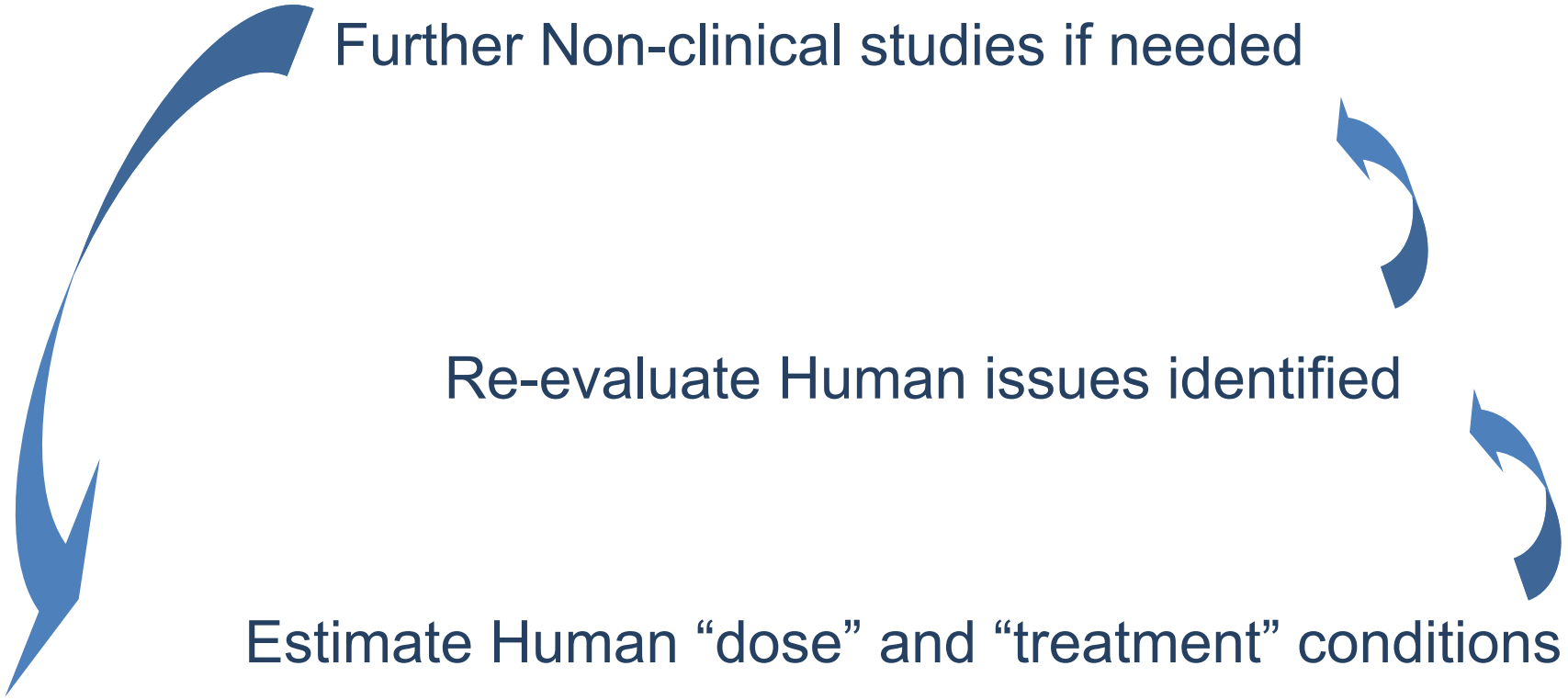
- *define the dose-response relationship*
  - *-for the intended effect*
  - *-for the potential safety concerns*
- **define the "in vitro"-"in vivo" relationship**

Use relationship to estimate in vivo human cell profile (from in vitro human cell data)

Estimate Human "dose" and "treatment" conditions

From NC into FIM

From NC into FIM into NC



Case Example: authologous cells for tissue regeneration

•**Proof of concept:**

• animal studies with authologous cells performed

Toxicology:

comparative growth pattern of human and animal cells studied *in vitro& in vivo* (animal model).

•human cells "implanted in immuno deficient animal model

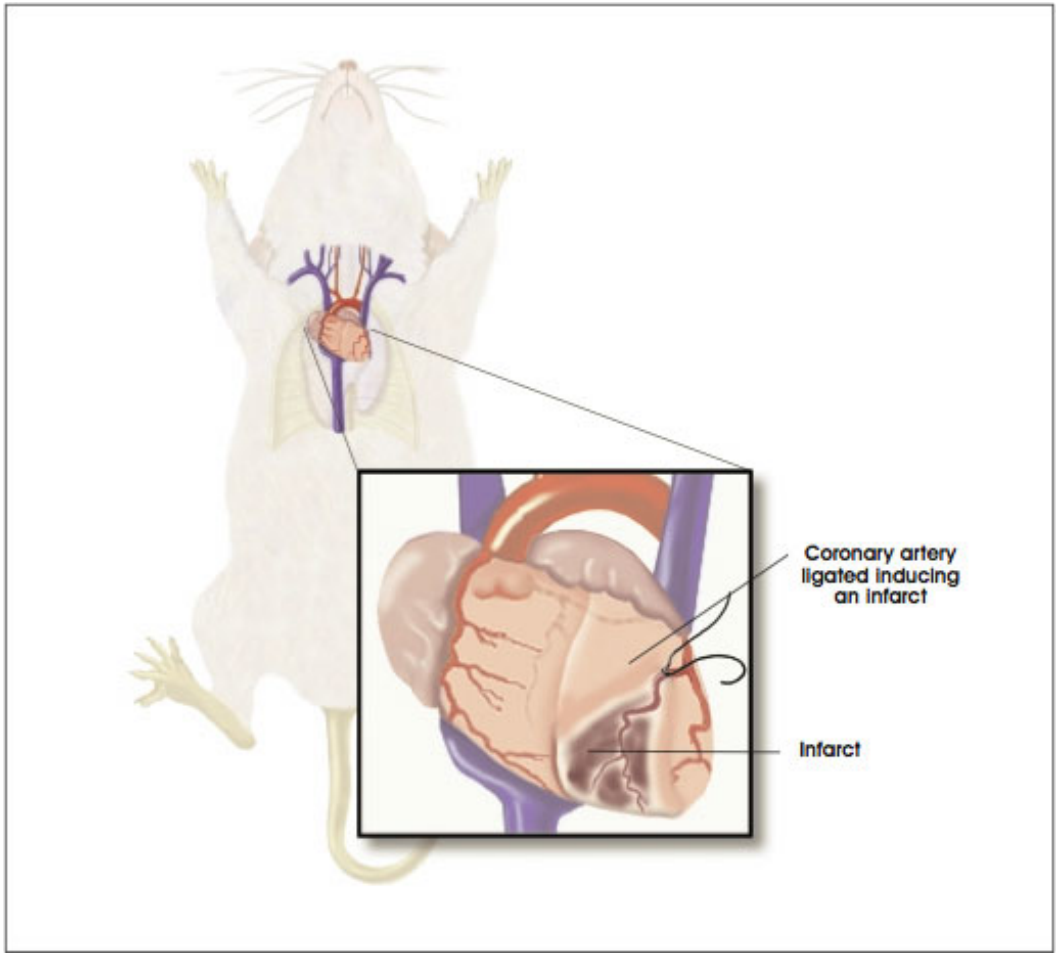
•Study duration adjusted (for potential for transformation & tumorigenesis)

•Dose levels selected based on estimated human doses

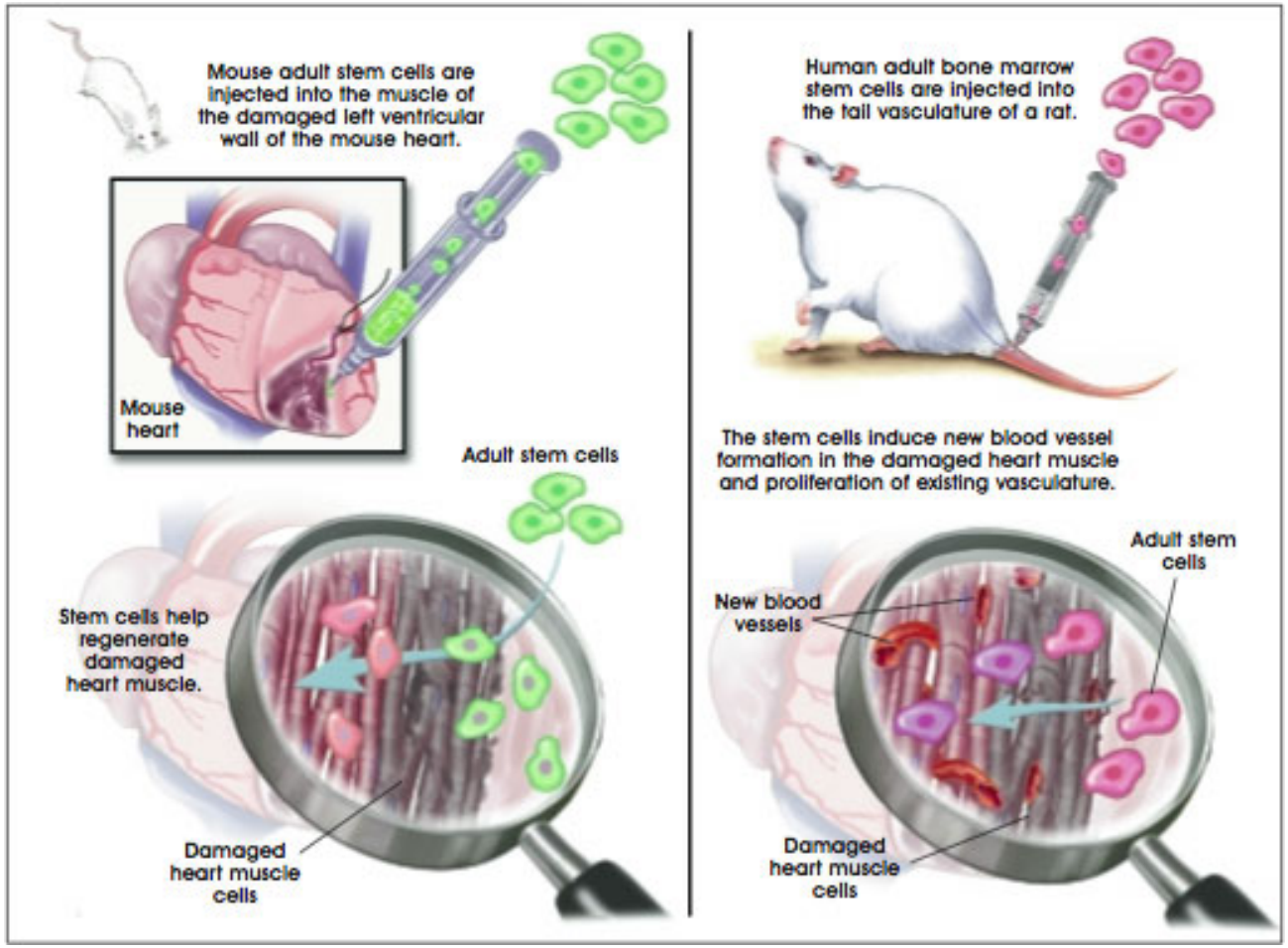
•Administration schedule adjusted to the human worse case scenario

(Dose levels and administration schedule in humans estimated based on patterns of human (and animal) cell division and differentiation)

Case Example (2)
from literature



Case Example (2)
from literature



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Mouse hematopoietic stem cells transplanted into the bone marrow

- responded to signals in the injured heart,
- migrated to the border region of the damaged area,
- and differentiated into several types of tissue needed for cardiac repair.

"This study suggests that mouse hematopoietic stem cells may be delivered to the heart through bone marrow transplantation as well as through direct injection into the cardiac tissue, thus providing another possible therapeutic strategy for regenerating injured cardiac tissue".

Possible Questions (RBA)

- Differentiated Cell types in the heart to be characterized
- Cell/tissue Functionality to be adressed
- Cell persistence “in situ” to be determined
- Their potential for senescence to be studied
- Stem cell “ectopic” engrafting to be studied
  - Sites of engraftment
  - Persistence
  - Senescence
  - Degenerescence
  - Tumorigenicity? (local/distant)
  - … …

Conclusions
NC Development of CBP

- Can only be defined in general terms
- Case by Case adjustments are needed depending on patterns of CBP and target population (healthy/patients →healthy animals / disease model)
- Relevant experimental models should be used
- Science based discussions between Regulators and Sponsors are encouraged
- Highly "Moving" Field, to be permanently adjusted according to the increasing (Human) experience and knowledge.

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THANK YOU