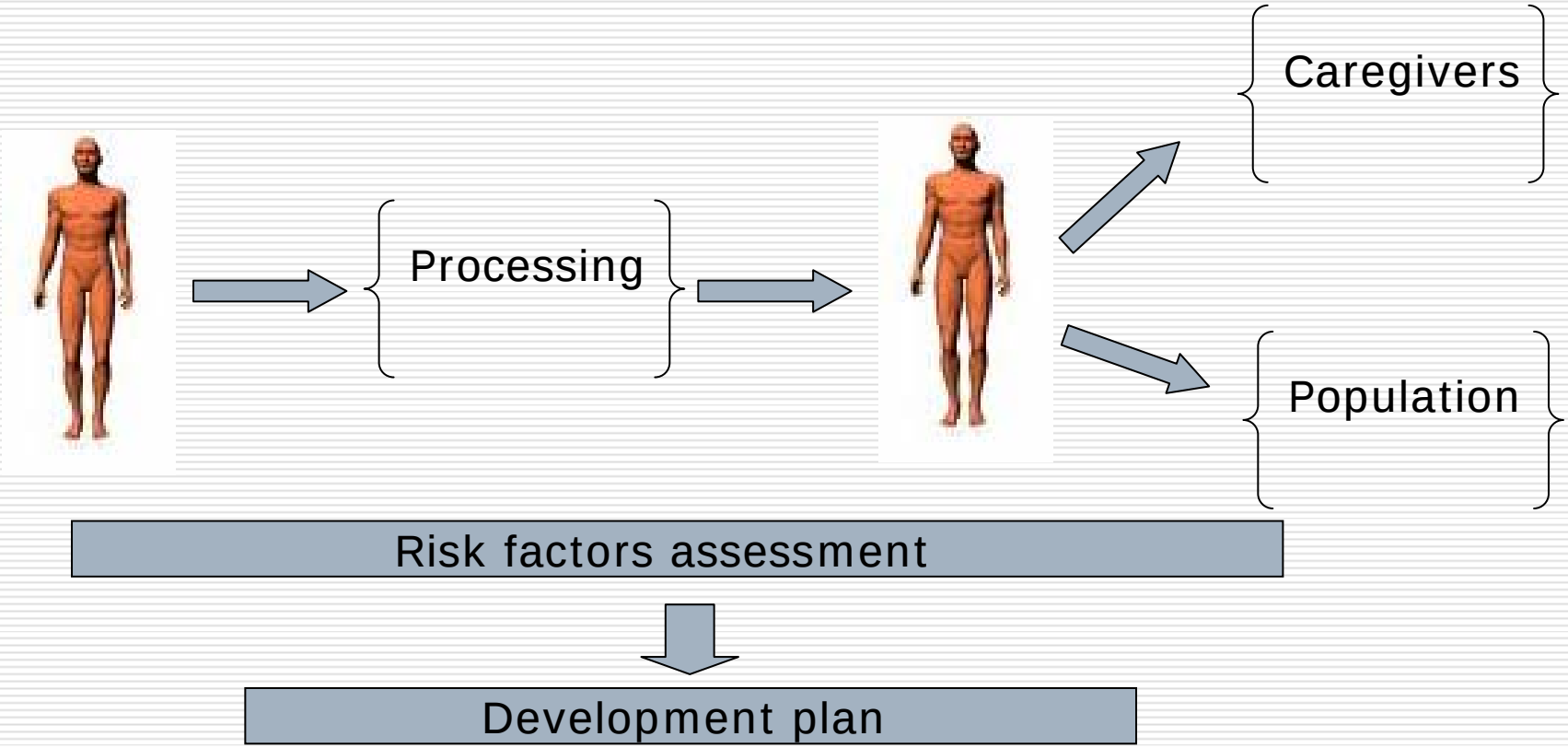
First Workshop on Advanced Therapy Medicinal products (ATMP)

Scientific requirements for cell therapy and tissue engineered products :Non clinical and clinical aspects

G. Migliaccio

Methodology: Risk analysis

- EMEA guideline on risk management systems for medicinal products for human use (EMEA/CHMP/96268/2005)



Risk factors

- The following general risk criteria can be used in the estimation of the overall risk of the product:
  - origin (autologous - allogeneic);
  - ability to proliferate and differentiate;
  - ability to initiate an immune response (as target or effector);
  - level of cell manipulation (in vitro/ex vivo expansion / activation / genetic manipulation);
  - mode of administration (ex vivo perfusion, local, systemic);
  - duration of exposure (short to permanent);
  - combination product (cells + bioactive molecules or structural materials)
  - availability of clinical data on or experience with similar products.

Non clinical development

- **Variability**
- The objectives of the non-clinical studies are to:
  - demonstrate proof-of-principle,
  - define the pharmacological and toxicological effects predictive of the human response.
- The goals of these studies include the following:
  - to provide information to select safe (*and efficacious*) doses for clinical trials,
  - to provide information to support the route of administration and the application schedule,
  - to provide information to support the duration of exposure and the duration of the follow-up time to detect adverse reactions,
  - to identify target organs for toxicity and parameters to monitor in patients receiving these therapies.

Primary Pharmacodynamics

- Reasonably justified markers of biological activity should be used to adequately identify the pharmacodynamic action of the CBMP in the host.
  - **Secondary pharmacology**
    - Potential undesirable physiological effects of human CBMP including their bioactive products should be investigated in an appropriate animal model. (But also migration and multiple target for released active substances)

Safety pharmacology

- Safety pharmacology should be considered on a case-by-case basis depending on the character of the cell-based medicinal product.
  - Cells may secrete pharmacologically active substances resulting in tissue/organ dysfunction.
  - Can they be toxic themselves? Negative effects of large concentration of active cells in a small area, vascular occlusion ?

Toxicology

- The type of toxicological studies depends on the product. However, as conventional study designs may not be appropriate, the scientific justification for the models used, or the omission of studies, shall be provided.

- Toxicity may evolve, for example, due to **unforecasted cellular alterations** developing during the manufacturing process such as altered adhesion patterns and in vivo behaviour.

- Other potential factors that may induce toxicity include the **allogeneic use** of the product, the presence of **components that are used in the manufacturing** process or are part of a structural component, or **proliferation of the applied cells** in an unwanted quantity or in an unwanted location.

Tumourigenicity

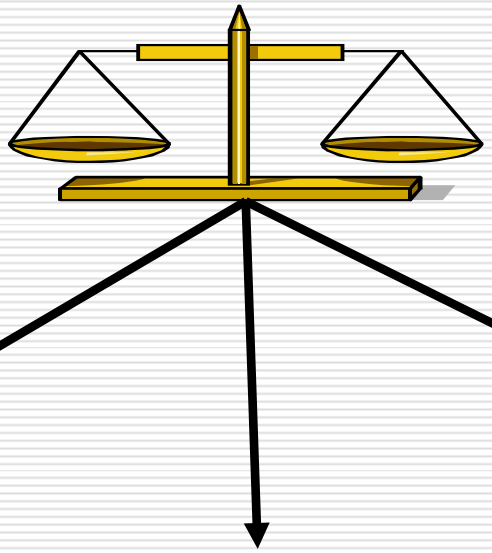
- As part of the safety testing, the possibility of tumourigenic transformation of the cells during the manufacturing process shall be analyzed.

Pharmacokinetics

- Conventional ADME studies are usually not relevant for human ATMP.
- Study requirements, possible methodologies and their feasibility shall be discussed, attention being paid to monitoring of :
  - viability,
  - proliferation-differentiation,
  - body distribution / migration and
  - functionality during the intended viability of the products.

Balance of Cell Proliferation

Cell proliferation



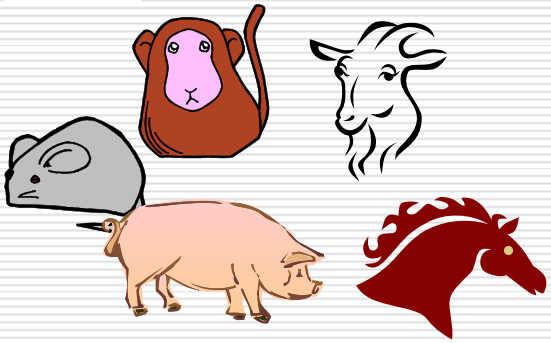
Undergrowth

Overgrowth

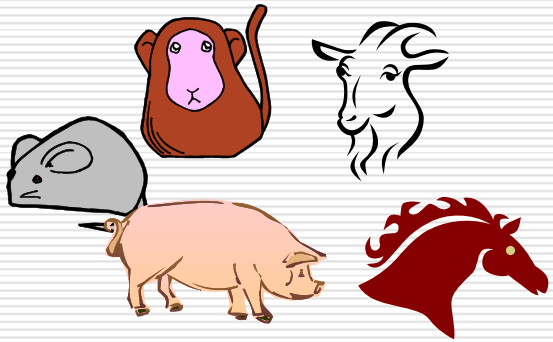
Correct effects or repair

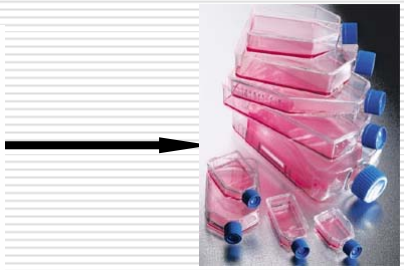
Non clinical studies and Animal homologous Models

Immunodepressed animals ?



Homologous models





In vitro

Primary pharmacodynamic

Possible approaches?

- Increase the controls at all levels of manufacturing
  - The practical approaches are limited, as many ATMPs will be prepared on demand for specific patient and might be of limited amount

- Move the development to the clinical stage
  - Due to the nature of ATMPs , Phase I studies will be conducted with patients and will be difficult to hypothesize a normal volunteer based trial

Purpose of a Phase I/II study with ATMP

- The initial studies should be adequate to demonstrate the "proof-of principle" of the ATMP unless this is obvious from the non-clinical studies or previous clinical studies with similar products. Also, some direct or surrogate parameters of efficacy should be obtained in these studies.
- Such markers may have been identified already in non-clinical studies.
- The use of markers and analytical assays in the initial studies may allow correlation with efficacy parameters in later stages of product development.
- The studies should be adequate to characterize the most frequent adverse effects resulting form the administration of the cell based product both with regard to acute toxicities and mid-term toxicities that appear within days and weeks after exposure.

Phase I/II studies with ATMP

- The product characterisation and its biological activity defined in the preclinical studies will contribute to the rationale for the clinical efficacy and safety studies.
- The clinical development plan should be justified in accordance with the pre-existing scientific clinical data. Especially, the clinical safety studies should address the concerns raised during the pharmaceutical and non-clinical development.
- Clinical studies should be tailored according to the specific properties of the product.

Dose finding studies

- The current system for the **definition of dose** for pharmaceuticals is not easily applicable to medicinal products containing cells.
- The **ATMPs** are often used as a single administration with the dosage defined by individual characteristics of the intended patient, such as body weight (i.e. cells/kg. of body weight), volume of missing tissue (i.e. bone defect reconstruction/ regeneration), or surface (i.e. skin replacement). ATMP may not have a clear dose-effect relationship;
- The selection of the dose should be based on the findings obtained in the quality development of the product and it should be linked with the potency of product.

Dose finding studies

- phase I/II studies should be designed to identify
  - a **Minimal Effective Dose**, defined as the lowest dose sufficient to obtain the intended effect or
  - an **Optimal Effective Dose Range**, defined as the largest dose range dose required to obtain the intended effect based on the clinical results for efficacy and tolerability., or to correct a pathology.
- If possible, it should be individuated also
  - the **Safe Maximal Dose**, defined as the maximal dose which could be administered on the basis of clinical safety studies without adverse effects.

Administration or concomitant procedures

- ATMP might require administration through specific surgical procedures, method of administration or the presence of concomitant treatments to obtain the intended therapeutic effect.

- The biological effects of ATMP are highly dependent on the *in vivo* environment, and may be influenced by the replacement process or the immune reaction either from the patient or from the cell based product.

Administration or concomitant procedures

- These requirements coming from the clinical development should be taken into account for the final use of these products. Their standardisation and optimisation should be an integral part of the clinical development studies.

- The therapeutic procedure as a whole, including the method of administration and required concomitant medication, such as immunosuppressive regimens need to be investigated and described in the product information, notably in the Summary of Product Characteristics (SPC).

Clinical Trial Design

- The suitable design of the trial will be determined by the disease and product characteristics, the existing alternative therapies and the possibility of using a placebo.
- Even in the most difficult scenario, a **randomised trial** versus the best standard care will always be preferable to an uncontrolled study design.
- A **blinded evaluation** of the clinical endpoints may be possible even when the blinding of the patient or the treating physician is not possible or feasible.
- **Demonstration of efficacy should be based on at least one robust randomised clinical trial**. Deviations from this approach should be justified.

Ethical aspects of ATMP's clinical studies

- It is unethical to perform a "bad" clinical study with a product that is not characterized and whose results will not be "strong enough" to support valid clinical conclusions.

- Due to the characteristic of the advanced therapy medicinal products it will be necessary to perform Phase I/II or "proof of concept" studies in human patients.

- Minimal requirements: A production process standardised and defined to produce a "consistent product" as GMP requires