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Committee for Advanced Therapies (CAT) Scientific Workshop

Reducing the number of laboratory animals used in tissue engineering research - 11th October 2012 – European Medicines Agency, London

On 11th October, CAT held a scientific workshop on 'Reducing the number of laboratory animals used in tissue engineering research'. CAT members/alternates, CAT Interested Parties representatives and experts from Academia had a fruitful exchange of views on the animal testing requirements for cell-based medicinal products.

To initiate discussions on this topic, the CAT invited two experts in the field Dr Rob de Vries and Prof. Beatriz Silva Lima to give keynote lectures and address a series of questions with a panel of selected CAT experts and stakeholders.

The workshop was designed to foster direct interaction between regulators and CAT stakeholders by means of CAT roundtable and panel discussions on questions from participants.

The agenda of the workshop including the list of participants is available at:

http://www.ema.europa.eu/docs/en_GB/document_library/Agenda/2012/11/WC500134720.pdf

This report collects the issues and the views shared during the meeting under the key agenda points of the workshop. The report does not set out to draw final conclusions, neither as regards regulatory requirements nor on the issues raised in the context of the focus groups. It has also not been possible to reflect all individual views but rather, the report provides an overview of the main themes of the meeting.

1. Keynote lecture: Reducing the Number of Laboratory Animals Used in Tissue Engineering Research: standardisation of animal models and systematic reviews

Dr. Rob de Vries discussed the following research question which was addressed by his research group in the context of a wider project, funded by the Dutch Program Tissue Engineering, on the ethical aspects of tissue engineering (TE): *'Is it possible to reduce the number of animals used in TE research by selecting and using only those models that have greatest predictive value?'*. (for further details, see: R.B. de Vries, P. Buma, M. Leenaars, M. Ritskes-Hoitinga & B. Gordijn. 'Reducing the number of laboratory animals used in tissue engineering research by restricting the variety of animal models.



Articular cartilage tissue engineering as a case study' Tissue Eng Part B Rev. 2012 Jun 25. [Epub ahead of print]).

The research focussed on articular cartilage tissue engineering and was performed using literature searches and gathering the views of experts in the field with specific knowledge on various pre-clinical models.

The outcome of the research suggested that:

- the number of defect models used in articular cartilage tissue engineering research may be reduced and in particular small animal models (i.e. mouse/rat and rabbits) could be skipped because they are very probably less predictive of the human clinical situation than other, larger models (e.g., goat or horse). Due to the differences between humans and small animal models in the average thickness of the cartilage layer, the volume of the defects that can be created but also the nature of these defects (osteochondral rather than partial-thickness defects) and the load on the articular cartilage, the risk of overestimating the efficacy (treatment effect size) of a tissue engineering treatment in humans is much bigger when the estimation is based on studies in small rather than in large models.
- It would seem to be possible to reduce the number of large animal models used to only one model. In fact, it was found that several large animal models are being used (goat, sheep, pig, horse, and maybe dog) that, based on existing data, do not seem to differ significantly in the extent to which the findings can be extrapolated to the human situation.
- by avoiding duplication of experiments and by enabling direct comparison between results of studies conducted with different constructs, a reduction in the number of models is also likely to lead to a reduction in the overall number of laboratory animals used in the field of articular cartilage tissue engineering.

The evidence used in practice to support the choice of a model was debated. It was stressed that the choice of a model is often determined by other factors than the expected predictiveness, e.g. cost, availability, appropriate facilities needed, frequency of use in literature. A possible method to make the selection of animal models more evidence-based would be conducting systematic reviews and meta-analyses of studies already conducted in the field, using comprehensive search criteria and quality assessment (like it is common practice for clinical studies).

2. Keynote lecture: Cell-based products: evolution/revolution in safety testing

Prof. Beatriz Silva Lima presented an overview of the regulators' evolving role in ensuring safety, following cases like sulfanilamide, thalidomide and TGN1412, thus putting a large emphasis on safety but also leading to adjustment of regulatory documents like ICH S6 (e.g. species relevance reinforced, one species only possible, value of *in-vitro* tests increased, toxicology driven by pharmacodynamic).

She stressed that requirements on safety testing are impacted by innovative drugs development and recently the assessment of ATMPs proposes the use of the risk based approach assessment plus relevance of the respective animal model. This approach is therefore more driven by predictability of the study outcome.

Very advanced technologies are now available for chemical drug toxicity screenings which are not applicable to ATMPs, but test systems also evolve and progress in testing systems are linked to progress in innovative medicine development. Cells can also be test system themselves, e.g. differentiated cardiomyocytes for testing potential for QT prolongation. She highlighted the challenge to be faced by researchers to improve the knowledge on the validity of *in-vitro* models but also the need to link *in-vivo* to *in-vitro* results.

Concerning the question on whether *in-vivo* testing could be avoided she suggested that a reduction in studies may be possible and the use of only one model could be acceptable. Moreover hybrid proof of concept/safety studies should be encouraged.

She concluded that the reduction in the number of laboratory animals used in the ATMP field should be encouraged to discard redundant/non predictive studies, accelerate patients' access to medicinal products, reduce costs and ethical aspects. This would require accurate planning of the product development, use of all available experience from similar products, cross talk non-clinical with quality (and *in-vitro*), choice of the most appropriate model and protocol, reduce the model to one species if possible, incorporate safety in the proof of concept study, use of advanced technology (e.g. imaging techniques).

3. Panel discussion and CAT Tour de Table

The following points were raised during the panel discussion:

- availability of a relevant animal model is a critical factor especially for cell-based medicinal products, since the only "really" relevant species is the human;
- a common issue for developers may be that in early phase of development it is difficult to predict which problems will arise;
- a tick-box exercise has to be avoided;
- animal models may have to be evaluated also for their validity: frequent use in literature may not be a proof of their validity;
- large animal models may not always be available, e.g. when knock-out or knock-in models are required.

4. Wrap-up and conclusions

The following summary emerged from the discussions as a collection of significant points highlighted by CAT members and stakeholders:

- Animal data are an important and central part of ATMP development and can generate data on an incremental basis also to complement clinical knowledge.
- Approach to pre-clinical studies for ATMPs more driven by predictability and relevance (since relevance is important) than that for chemicals.
- The choice of animal model may depend on the study objective, also due to the complexity of the products and how they work:
 - functionality/potency: often small animal models;
 - efficacy or proof of concept: often large animals (especially for tissue engineered products), potentially combined with safety endpoints to maximize information;
 - biodistribution: depends on the availability of methods to detect the product (cells, genes) and on a risk-based approach;
 - disease model or healthy animals: disease model could be more informative, since they inform about efficacy and safety closer to the patient—relevant situation, and they may also allow for testing the route of administration (which can be a complex surgical procedure); however, measures for the protection of animals used for scientific purposes should be

observed according to Directive 2010/63/EU¹. In fact ethical aspects like suffering of the animals have to be part of the discussion; if the data, however are more relevant or even maximized, then this may also be seen as a supportive ethical factor favouring such approach.

- Factors other than predictability may be unavoidable, e.g. cost, ethical acceptability, feasibility, availability, need to generate statistically more expressive data. Also from logistical perspective: e.g. long-term follow-up of large animals.
- *In-vivo* results should be linked to *in-vitro* results also to learn more about validity of *in-vitro* models.
- Regulators also to reflect on how much repetition is needed and what can be extrapolated from other products or from literature.
- Consider innovative approaches like imaging techniques to avoid sacrificing animals (question is what level of “validation” should be required: for example the MRI debate in multiple sclerosis studies in humans is relevant in this context).
- Question on the level of validation required is also a valid one for any animal model itself.
- Totality of evidence approach may help closing gaps of validation.

5. Conclusion:

The CAT endorsed the need to reduce the number of animals in non-clinical testing but acknowledged that development of appropriate strategies for ATMPs, also avoiding unnecessary animal studies, will take time and requires evolution of the scientific knowledge. This change encompasses also understanding about both products and the animal models themselves, and has to go hand in hand with ethical considerations, both for animals and the patients which will be treated with the products.

The Chair thanked all participants for the fruitful discussions and closed the meeting.

¹ DIRECTIVE 2010/63/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 22 September 2010 on the protection of animals used for scientific purposes